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A Synthesis of Dihydrofuran-3(2*H*)-ones

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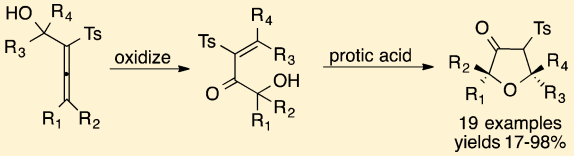
Supporting Information

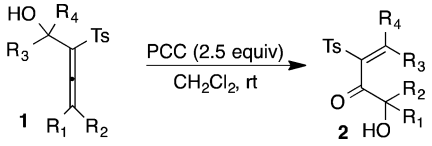
ABSTRACT: Treatment of readily available α′-hydroxyenones with a catalytic amount of strong acid in refluxing toluene affords the corresponding dihydrofuran-3(2*H*)-ones in excellent yields via a formal 5-endo-trig cyclization.



INTRODUCTION

We recently reported the reaction of allenols **1** with PCC to afford the corresponding enones (**2**) through what appeared to be a series of sigmatropic rearrangements (Scheme 1).[1] The

Scheme 1. Synthesis of a Hydroxyenone

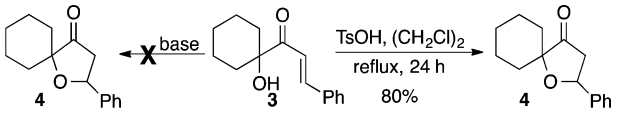


ease with which **2** and its congeners could be prepared and the facility of the reaction shown in Scheme 1 prompted us to consider various uses for these hydroxyenones. Among the possibilities considered was the acid- or base-catalyzed intramolecular cyclization of such species to the corresponding dihydrofuran-3(2*H*)-ones. In particular, we wondered if the electron-withdrawing group in **2** might provide a means of performing an intramolecular Michael reaction under conditions that were relatively mild and amenable in the future to asymmetric catalysis.

Furan-3(2*H*)-ones and their dihydro derivatives represent a substructure in many interesting natural products including jatrophone,[2] geiparvarin,[3] ascofuranone,[4] Furaneol,[5] bullatenone,[6] pseurotin,[7] longianone,[8] lychnophorolide A,[9] inotilone,[10] ciliarin,[11] chilenones,[12] and the eremantholides.[13] Compounds containing this substructure possess many important biological activities. These include antitumor activity, inhibitory activity against monoamine oxidase (MAO) and cyclooxygenase-2 (COX-2) as well as antiallergic activity.[3a,b,d,g,10,14,15]

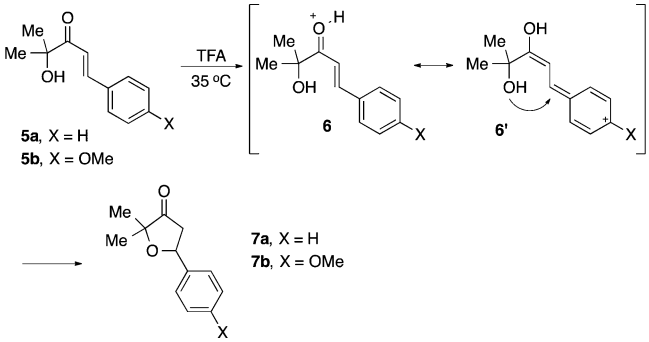
The base-catalyzed cyclization of hydroxyenones to the corresponding dihydrofuran-3(2*H*)-ones was established as generally inaccessible by Baldwin and co-workers in support of the predictions made by the rules that bear Baldwin's name.[16] Thus, treatment of **3** under a variety of basic conditions afforded only starting material (Scheme 2). On the other hand, the reaction of **3** with tosic acid in refluxing dichloroethane afforded the dihydrofuranone **4** in 80% isolated yield.

Scheme 2. A 5-Endo-Trig Cyclization



Johnson and co-workers demonstrated an electronic effect in this ring-closing process (Scheme 3).[17a] They compared the

Scheme 3. Johnson's Early Studies



cyclization of **5a** and **5b** and showed that the ring closure of the latter was faster than the former by approximately 2 orders of magnitude. The rationale for the increased reaction rate for **5b** was based on the greater contribution of resonance form **6′** for the protonated intermediate derived from **5b** relative to that derived from **5a**. Interestingly, these reactions, conducted in trifluoroacetic acid at 35 °C, did not go to completion, but rather came to an equilibrium in which significant amounts of starting materials remained. This is most likely due to the high concentration of acid (neat!) used in this particular study.

Later studies[17b] by Johnson demonstrated that the ρ value for the intramolecular addition step of the reaction was −2.23 as determined by correlation of reaction rates with σ^+ substituent constants from a total of six substrates, including **5a** and **5b**.[17b] This led to the conclusion that protonation of the

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carbonyl group in systems such as **5a** or **5b** led to significant twisting of the enone, facilitating intramolecular addition in what can be considered a 5-exo-trig fashion, a pathway allowed by Baldwin's rules.

Shen and co-workers studied the same types of systems as the Johnson group, but in a more synthetic context.[18] For example, the reaction of **5a** with 5 mol % of $Cu(OTf)_2$ in the absence of solvent under microwave heating (final T = 143 °C) produced a 46% yield of **7a**. When TfOH was used as a catalyst the yield of **7a** was 78%. Five new examples of dihydrofuranones were reported in this paper; the others were known as a result of Johnson's work.[17b] Both studies used precursors in which, relative to **5a**, only variation of the aryl group on the enone was made. One might draw the conclusion that such substitution is necessary for the reaction to be successful. We demonstrate that this is not the case.

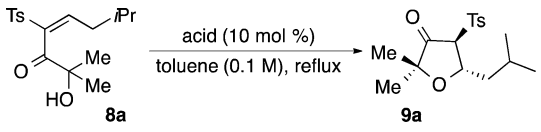
Overall, there appear to be only 13 unique compounds in the literature that have been prepared by this methodology. We provide here 19 more, results that begin to address how this reaction might be improved and how it might be subject to asymmetric catalysis.

RESULTS AND DISCUSSION

We thus began our work using Brønsted acids as catalysts for the process not only because we anticipated success using this approach but also because we anticipated that success might allow us to use chiral Brønsted acids[19] to generate enantiomerically enriched dihydrofuran-3(2*H*)-ones.

Based on the report of Shen and co-workers,[18] we anticipated a strong acid would be required for the desired cyclization to occur, but hoped that our precursors might be more reactive than those in the literature by virtue of the electron-withdrawing arylsulfonyl group on the double bond. While cyclization was successful, the presence of the arylsulfonyl group did not appear to provide any kinetic advantage to the intramolecular cyclization. Only a brief study was required; the results are shown in Table 1. Hydroxyenone **8a** was chosen as the test substrate. Note that this compound has an alkyl group, not an aryl group, at the β-position of the enone.

Table 1. Acid Screening for Dihydrofuranone Formation



8a **9a**

entry	acid	pK_a	time	yield (%)
1	$MeSO_3H$	−1.9	48 h	no reaction
2	TsOH	−2.3	48 h	46
3	TfOH	−12.0	10 h	68

We thought that a simple sulfonic acid might be effective in the cyclization. However, refluxing **8a** with 10 mol % of methanesulfonic acid in toluene (0.1 M) for 48 h returned only starting material with no evidence of cyclization (Table 1, entry 1). The slightly more acidic tosic acid produced better results, affording **9a** in 46% yield under the same reaction conditions. Finally, and in agreement with Shen's work,[18] triflic acid proved superior, giving the anticipated product **9a** in 68% yield after only 10 h of reflux.

With these reaction conditions in hand we set out to examine the scope of the reaction in the context of the hydroxyenones we had on hand from our previous work. The results are summarized in Table 2.

The conversion of starting materials bearing a single primary or secondary aliphatic group on the β-carbon of the enone system produced products in 68−86% yield (Table 2, entries 1−4). Interestingly, the substrate **8d** afforded the corresponding furanone in only 1 h, suggesting that a steric effect that helps twist the system may be beneficial in the process. When a single aryl or related substituent occupied the β-carbon of the enone, the reactions generally proceeded quickly and in high yield (68−89%, Table 2, entries 5−8). Comparing substrates **8e**, **8f**, and **8g** leads to the conclusion that electronic effects in this process are not as pronounced as one might imagine they could be. While aryl substitution favored product formation, an exception was seen with **8i**. We surmise that the inherent acid sensitivity of the furan group may have opened decomposition pathways that ultimately lowered the yield of the furanone product **9i** (Table 2, entry 9). However, a weaker acid (TsOH) could be used to effect the cyclization in high yield. Aliphatic disubstitution at the β-position favored cyclization, affording dihydrofuranones in 82−85% yield (Table 2, entries 10−12). Substrate **8l** consisted of a 1:0.33 mixture of isomers. The product **9l** was a 1:0.4 mixture of isomers as indicated by ^{1}H NMR. The stereochemistry of the major isomer was assigned via a NOESY experiment (see Supporting Information). When single alkenyl substituents were located at the β-position of the enone in the substrates, the cyclization reaction proceeded in variable yields (43−98%, Table 2, entries 13−18). The lower yields among these examples occurred with a simple vinyl substituent (entry 13), improved for systems with a propenyl substituent (entries 14−16), and were best with cinnamyl-type substituents (entries 17−18), suggesting a steric effect that perhaps impeded polymerization reactions that lowered yields in the other cases. Finally, substrate **8s** proved too fragile under the reaction conditions to be synthetically useful, the product **9s** being isolated in only 17% yield (Table 2, entry 19). Once again, the use of tosic acid improved the yield of the cyclization dramatically.

The structure of the products was deduced chiefly on the basis of proton and carbon NMR data. For example, in the conversion of **8a** to **9a**, there is a disappearance of the hydroxyl peak at 3.77 ppm in the ^{1}H NMR and of the sp^2-hybridized carbons of the α,β-unsaturated ketone. In the product **9a** there is the presence of a downfield doublet at 3.63 ppm and a downfield doublet of triplets at 4.67 ppm that couple with one another. In addition, in the ^{13}C NMR spectra of **9a**, there are two new downfield shifted aliphatic carbon peaks. This implies that the sp^2-hybridized carbons of the alkene have been converted into sp^3-hybridized carbons. Under these acidic conditions, the electrophilicity of the alkene would be increased such that the hydroxyl group could attack to form the furanone **9a** as detailed in the mechanism in Scheme 4.

The stereochemistry of certain products was assigned on the basis of the coupling constant observed for the proton on the carbon bearing the sulfonyl group, in those cases where a proton appeared on the adjacent carbon. This coupling constant ranged from 8.5 to 9.0 Hz, indicative of a *trans* relationship between the substituents on the dihydrofuranone ring.[20] Furthermore, we were able to obtain X-ray crystal structures on **9a**, **9e**, and **9f** in which this *trans* stereochemical relationship was unequivocally borne out.

A mechanism for this cyclization is shown in Scheme 4. Protonation of **8** produces **8′**, sufficiently reactive to intra-

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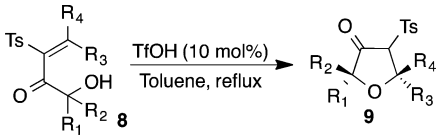
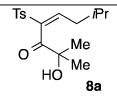
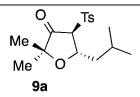
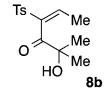
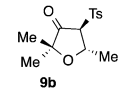
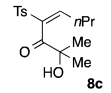
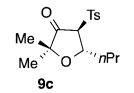
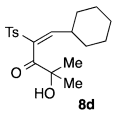
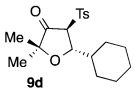
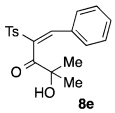
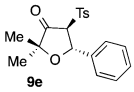
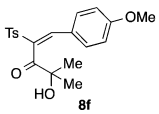
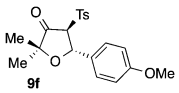
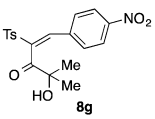
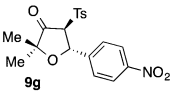
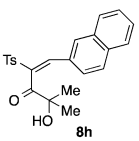
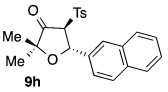
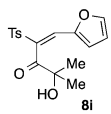
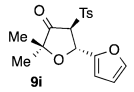
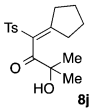
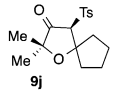
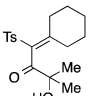
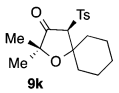
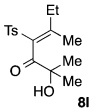
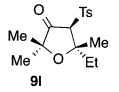
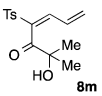
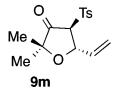
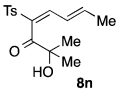
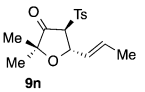
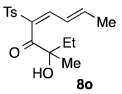
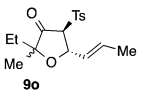
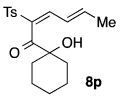
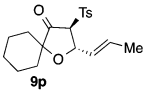
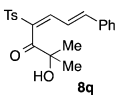
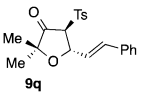
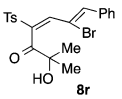
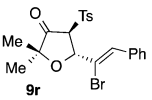
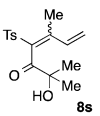
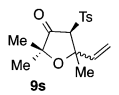
Table 2. Synthesis of Dihydrofuran-3(2*H*)ones



Entry	Starting Material	Product	Time, h	Yield (%)
1	 8a	 9a	10	68
2	 8b	 9b	8	86
3	 8c	 9c	8	80
4	 8d	 9d	1	69
5	 8e	 9e	1	89
6	 8f	 9f	0.3	80
7	 8g	 9g	0.3	85
8	 8h	 9h	2	68
9	 8i	 9i	1 4	30 88[a]
10	 8j	 9j	1	82
11	 8k	 9k	1	80
12	 8l	 9l	1	85[b]
13	 8m	 9m	1	43
14	 8n	 9n	3	54
15	 8o	 9o	1	61[c]
16	 8p	 9p	1	67
17	 8q	 9q	1	98
18	 8r	 9r	1	84
19	 8s	 9s	1 3	17[d] 58[a]

[a]10% TsOH was used as catalyst. [b]Stereochemistry of major product assigned by NOESY. Starting material ratio: 1:0.33; product ratio: 1:0.4 by ^{1}H NMR. [c]Product ratio: 1:0.8 by ^{1}H NMR. [d]Starting material ratio: 1:0.5; product ratio: 1:0.44 by ^{1}H NMR.

molecularly cyclize to produce **9′**. Loss of a proton and tautomerization leads to the observed product **9**.

Although Baldwin's work suggested that the cyclization reaction would not proceed with a base, we were curious to see if the presence of the arylsulfonyl group might enhance the reactivity of **8**.[21] To that end, we treated **8a** with strong bases such as KH and KO*t*Bu in THF. This furnished the furanone **9a** and the deconjugated isomerized isomer **8aa** in low yields. However, the treatment of **8a** with milder bases such as DBU and *i*Pr$_2$NEt exclusively produced isomerized product in good yield instead of cyclized furanone (Table 3).

CONCLUSION

In summary, we have developed an acid-catalyzed conversion of α'-hydroxysulfonylenones to furanones via a formal 5-endo-trig

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Scheme 4. Possible Cyclization Mechanism

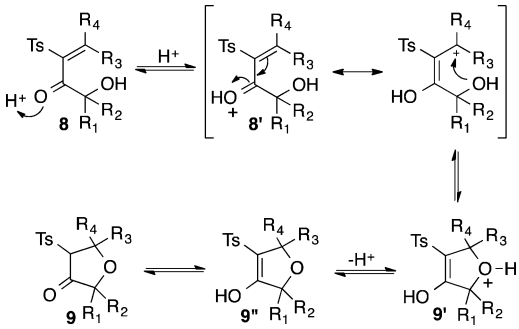
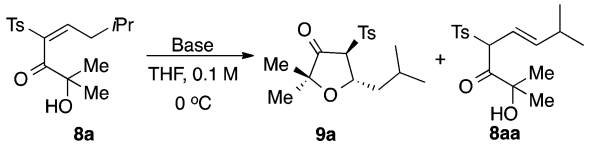


Table 3. Attempts at Base-Mediated Cyclization



entry	base (equiv)	time	yield (%) **9a**	yield (%) **8aa**
1	KH (1.1)	90 min	11	9
2	KOtBu (1.1)	10 min	10	9
3	DBU (1.1)	20 min	–	83
4	iPr_2NEt (2.2)	10 h	–	71

cyclization that extends the scope of the intramolecular Michael addition of alcohols to enones significantly, more than doubling the known number of examples of the process. This sets the stage for further methodological developments[22] as well as applications in total synthesis. Further results will be reported in due course.

EXPERIMENTAL SECTION

General Procedure. All reactions were carried out in oven-dried glassware under an argon atmosphere. Toluene and tetrahydrofuran were ordered and were distilled under a nitrogen atmosphere over sodium metal with benzophenone ketyl as an indicator. Dichloromethane was ordered and was distilled under a nitrogen atmosphere over calcium hydride. The starting material α'- hydroxyenones were prepared by the oxidation of allenyl alcohols by pyridinium chlorochromate (PCC).[1] Analytical thin layer chromatography was performed on silica gel plates with a UV indicator. Flash chromatography was carried out using 230−400 mesh silica gel with HPLC grade solvents. ^{1}H NMR and NOESY NMR spectra were recorded on a 300, 500, or 600 MHz spectrometer with chemical shifts reported in δ ppm with tetramethylsilane as an internal reference (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, etc.). ^{13}C NMR spectra were obtained on the same instruments at 75, 125, and 150 MHz, respectively, in $CDCl_3$ solution with $CDCl_3$ (77.0 ppm) as an internal reference. Melting points were determined with a melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR spectrometer. High-resolution mass spectra were acquired FTICR-MS with an ion cyclotron resonance analyzer (ICR) by electrospray ionization (ESI).

*(E)-4-Hydroxy-1-(4-methoxyphenyl)-4-methyl-2-tosylpent-1-en-3-one (**8f**).* Product was prepared by the literature method[1] and was isolated as a colorless oil in 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.56 (s, 1H), 2.43 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 161.9, 144.8, 140.6, 137.8, 136.6, 131.7, 129.8, 128.1, 124.5, 114.3, 78.8, 55.3, 27.5, 21.6; IR (cm^{-1}) 3387, 3056, 2970, 1768, 1597, 1511, 1270, 1147, 1074, 739; HRMS m/z calcd for $(C_{20}H_{22}O_5S)Na^+$ 397.1080, found 397.1076.

*(E)-4-Hydroxy-4-methyl-1-(4-nitrophenyl)-2-tosylpent-1-en-3-one (**8g**).* Product was prepared by the literature method[1] and was isolated as a yellow solid (mp = 170−172 °C) in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 9.0 Hz, 2H), 7.79 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 3.44 (s, 1H), 2.47 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 148.6, 145.8, 145.4, 138.4, 137.0, 135.1, 130.1, 128.5, 128.5, 123.9, 78.9, 27.5, 21.7; IR (cm^{-1}) 3521, 3056, 2974, 1703, 1601, 1527, 1348, 1266, 1143, 1082, 881, 730; HRMS m/z calcd for $(C_{19}H_19NO_6S)Na^+$ 412.0825, found 412.0823.

*(E)-4-Hydroxy-4-methyl-1-(naphthalen-2-yl)-2-tosylpent-1-en-3-one (**8h**).* Product was prepared by the literature method[1] and was isolated as a yellow solid (mp = 160−161 °C) in 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.91(dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.60−7.57 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 2.42 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 151.2, 147.7, 144.4, 137.0, 136.4, 133.4, 130.8, 130.0, 129.4, 129.2, 128.8, 128.3, 127.9, 126.6, 126.5, 124.2, 50.9, 27.9, 21.6; IR (cm^{-1}) 3517, 3060, 2982, 2933, 1764, 1707, 1670, 1597, 1544, 1466, 1315, 1258, 1147, 1078, 820, 739; HRMS m/z calcd for $(C_{23}H_{22}O_4S)Na^+$ 417.1131, found 417.1128.

General Procedure for the Synthesis of Furanones 9. To a stirred solution of the hydroxyenone **8a** (0.1 g, 0.30 mmol) in toluene (3 mL, 0.05M), TfOH (0.0027 mL, 0.03 mmol, 10 mol %) was added at room temperature. Then the reaction mixture was refluxed for 8 h. After completion of the reaction by TLC, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ and a brine solution and then dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation, and the crude product was purified by flash column chromatography over silica gel. The compound was eluted with 12−15% EtOAc/Hexane. The compound **9a** was obtained as a yellow colored solid (0.068 g, 68%).

*5-Isobutyl-2,2-dimethyl-4-tosyldihydrofuran-3(2H)-one (**9a**).* Product was prepared by the general procedure and was isolated as a white color solid (mp = 143−144 °C) in 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.67 (dt, J = 9.0 Hz, J = 3.0 Hz, 1H), 3.63 (d, J = 9.0 Hz, 1H), 2.47 (s, 3H), 1.96−1.90 (m, 1H), 1.74−1.63 (m, 1H), 1.23 (s, 3H), 1.14 (s, 3H), 0.96 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 145.7, 134.8, 129.8, 129.4, 81.5, 72.4, 71.6, 45.0, 24.5, 24.1, 23.5, 21.7, 21.4, 20.9; IR (cm^{-1}) 2949, 2921, 2872, 1760, 1597, 1466, 1318, 1151, 1087, 1060, 996, 813; HRMS m/z calcd for $(C_{17}H_{24}O_4S)Na^+$ 347.1287, found 347.1285.

*2,2,5-Trimethyl-4-tosyldihydrofuran-3(2H)-one (**9b**).* Product was prepared by the general procedure and was isolated as a dark tan solid (mp = 112−113 °C) in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.70 (dq, J = 9.0 Hz, J = 6.0 Hz, 1H), 3.63 (d, J = 9.0 Hz, 1H), 2.47 (s, 3H), 1.55 (d, J = 6.0 Hz, 3H), 1.24 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 145.7, 134.7, 129.8, 129.4, 81.7, 73.3, 69.6, 23.9, 21.7, 21.4, 20.7; IR (cm^{-1}) 3066, 2990, 2939, 2887, 1767, 1592, 1453, 1322, 1139, 1084, 980, 674; HRMS m/z calcd for $(C_{14}H_{18}O_4S)Na^+$ 305.0818, found 305.0816.

*2,2-Dimethyl-5-propyl-4-tosyldihydrofuran-3(2H)-one (**9c**).* Product was prepared by the general procedure and was isolated as a dark tan solid (mp = 116−117 °C) in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.64 (td, J = 8.5 Hz, J = 3.0 Hz, 1H), 3.68 (d, J = 8.5 Hz, 1H), 2.47 (s, 3H), 1.95−1.89 (m, 1H), 1.74−1.67 (m, 1H), 1.61−1.44 (m, 4H), 1.23 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 145.7, 134.7, 129.8, 129.3, 81.5, 71.7, 37.6, 20.4, 21.7, 21.0, 18.2, 13.8; IR (cm^{-1}) 2959, 2927, 2871, 1763, 1588, 1318, 1143, 1087, 813; HRMS m/z calcd for $(C_{16}H_{22}O_4S)Na^+$ 333.1131, found 333.1131.

*5-Cyclohexyl-2,2-dimethyl-4-tosyldihydrofuran-3(2H)-one (**9d**).* Product was prepared by the general procedure and was isolated as a white solid (mp = 108−110 °C) in 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 4.35 (dd, J = 4.5 Hz, J = 4.5 Hz, 1H), 3.86 (d, J = 7.5 Hz, 1H), 2.47 (s, 3H),

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1.80−1.63 (m, 6H), 1.31−1.16 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 145.6, 134.7, 129.8, 129.3, 81.3, 69.4, 41.5, 29.7, 26.2, 26.1, 25.8, 24.2, 21.9, 21.7; IR (cm^{-1}) 2979, 2931, 2851, 1755, 1596, 1445, 1318, 1155, 1084, 813; HRMS m/z calcd for $(C_{19}H_{26}O_4S)Na^+$ 373.1440, found 373.1441.

2,2-Dimethyl-5-phenyl-4-tosyldihydrofuran-3(2H)-one (**9e**). Product was prepared by the general procedure and was isolated as a white solid (mp = 145−147 °C) in 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.44−7.42 (m, 2H), 7.38−7.31 (m, 5H), 5.67 (d, J = 8.5 Hz, 1H), 4.04 (d, J = 8.5 Hz, 1H), 2.44 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 145.7, 138.4, 134.6, 129.7, 129.3, 128.8, 128.6, 126.7, 82.3, 75.0, 74.0, 24.0, 21.7, 21.2; IR (cm^{-1}) 3051, 2982, 1756, 1593, 1417, 1327, 1262, 1151, 1066, 890; HRMS m/z calcd for $(C_{19}H_{20}O_4S)Na^+$ 367.0974, found 367.0972.

5-(4-Methoxyphenyl)-2,2-dimethyl-4-tosyldihydrofuran-3(2H)-one (**9f**). Product was prepared by the general procedure and was isolated as a white color solid (mp = 179−180 °C) in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.32 (dd, J = 8.5 Hz, J = 7.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.60 (d, J = 8.5 Hz, 1H), 4.01 (d, J = 9.0 Hz, 1H), 3.30 (s, 3H), 2.43 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 159.8, 145.6, 134.7, 130.8, 129.7, 129.2, 128.1, 114.0, 82.2, 74.7, 73.8, 55.2, 23.9, 21.6, 21.1; IR (cm^{-1}) 3052, 2986, 1761, 1610, 1518, 1422, 1327, 1258, 1153, 1074, 1031, 892, 744; HRMS m/z calcd for $(C_{20}H_{22}O_5S)Na^+$ 397.1080, found 397.1077.

2,2-Dimethyl-5-(4-nitrophenyl)-4-tosyldihydrofuran-3(2H)-one (**9g**). Product was prepared by the general procedure and was isolated as a white color solid (mp = 170−171 °C) in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 2H), 7.75−7.73 (m, 4H), 7.37 (d, J = 8.5 Hz, 2H), 5.84 (d, J = 8.5 Hz, 1H), 3.94 (d, J = 8.5 Hz, 1H), 2.46 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 148.0, 146.2, 146.1, 134.1, 129.9, 129.4, 127.8, 123.8, 82.7, 73.8, 73.7, 23.9, 21.7, 21.3; IR (cm^{-1}) 3053, 2989, 1763, 1647, 1524, 1419, 1351, 1266, 1153, 895, 751; HRMS m/z calcd for $(C_{19}H_{19}NO_6S)Na^+$ 412.0825, found 412.0822.

2,2-Dimethyl-5-(naphthalen-2-yl)-4-tosyldihydrofuran-3(2H)-one (**9h**). Product was prepared by the general procedure and was isolated as a white color solid (mp = 156−158 °C) in 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.87 (m, 2H), 7.80−7.78 (m, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.53−7.49 (m, 3H), 7.27−7.25 (m, 4H), 5.80 (d, J = 8.5 Hz, 1H), 4.14 (d, J = 8.5 Hz, 1H), 2.35 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 145.7, 135.9, 134.6, 133.4, 132.9, 129.7, 129.2, 128.1, 127.7, 126.6, 126.5, 126.3, 123.6, 82.4, 75.4, 73.8, 24.0, 21.6, 21.7; IR (cm^{-1}) 3055, 2979, 2930, 1765, 1594, 1505, 1383, 1317, 1149, 1067, 955, 866, 817, 738; HRMS m/z calcd for $(C_{23}H_{22}O_4S)Na^+$ 417.1131, found 417.1128.

5-(Furan-2-yl)-2,2-dimethyl-4-tosyldihydrofuran-3(2H)-one (**9i**). Product was prepared by the general procedure and was isolated as a dark tan solid (mp = 137−138 °C) in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 6.36 (d, J = 3.5 Hz, 1H), 6.31 (dd, J = 3.0 Hz, J = 2.0 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 8.0 Hz, 1H), 2.44 (s, 3H), 1.318 (s, 3H), 1.311 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 149.7, 145.7, 143.3, 134.5, 129.8, 129.1, 110.7, 110.3, 82.3, 70.0, 68.7, 24.0, 21.7, 21.4; IR (cm^{-1}) 3056, 2982, 1768, 1593, 1425, 1266, 1147, 898, 755; HRMS m/z calcd for $(C_{17}H_{18}O_5S)Na^+$ 357.0767, found 357.0765.

2,2-Dimethyl-4-tosyl-1-oxaspiro[4.4]nonan-3-one (**9j**). Product was prepared by the general procedure and was isolated as a white solid (mp = 174−175 °C) in 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.04 (s, 1H), 2.69−2.62 (m, 1H), 2.47 (s, 3H), 2.14−1.74 (m, 7H), 1.39 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 145.3, 135.9, 129.6, 129.2, 88.7, 81.0, 73.4, 42.1, 35.0, 26.4, 25.0, 23.7, 22.5, 21.7; IR (cm^{-1}) 3050, 2979, 1755, 1596, 1413, 1322, 1262, 1147, 1076, 909, 750; HRMS m/z calcd for $(C_{17}H_{22}O_4S)Na^+$ 345.1131, found 345.1129.

2,2-Dimethyl-4-tosyl-1-oxaspiro[4.5]decan-3-one (**9k**). Product was prepared by the general procedure and was isolated as a white solid (mp = 194−195 °C) in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 3.80 (s, 1H), 2.46 (s, 3H), 2.22−2.14 (m, 2H), 2.07−2.01 (m, 1H), 1.84−1.68 (m, 5H), 1.60−1.57 (m, 1H), 1.40 (m, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 145.2, 136.4, 129.5, 129.2, 81.6, 80.2, 76.3, 39.9, 33.3, 27.4, 25.4, 24.8, 21.8, 21.7, 21.1; IR (cm^{-1}) 3054, 2990, 2943, 2855, 1767, 1600, 1421, 1326, 1258, 1155, 897, 750; HRMS m/z calcd for $(C_{18}H_{24}O_4S)Na^+$ 359.1287, found 359.1285.

5-Ethyl-2,2,5-trimethyl-4-tosyldihydrofuran-3(2H)-one (**9l**). Product was prepared by the general procedure and was isolated as a white solid (mp =145−147 °C) in 85% yield as a mixture of isomers in a ratio of 1.0:0.4. Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 4.01 (s, 1H), 2.47 (s, 3H), 1.87 (q, J = 7.5 Hz, 2H), 1.72 (s, 3H), 1.40 (s, 3H), 1.18 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 145.34, 136.6, 129.67, 129.17, 82.09, 80.3, 72.6, 35.0, 26.7, 25.5, 24.2, 21.7, 7.8; Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 9.0 Hz, 2H), 4.03 (s, 1H), 2.46 (s, 3H), 2.16−2.02 (m, 2H), 1.62 (s, 3H), 1.36 (s, 3H), 1.19 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 145.32, 136.9, 129.63, 129.15, 82.4, 80.1, 76.8, 29.4, 27.6, 26.6, 24.7, 7.1; IR (cm^{-1}) 3058, 2979, 2895, 1767, 1628, 1608, 1457, 1381, 1302, 1262, 1147, 1087, 984; HRMS m/z calcd for $(C_{16}H_{22}O_4S)Na^+$ 333.1131, found 333.1129.

2,2-Dimethyl-4-tosyl-5-vinyldihydrofuran-3(2H)-one (**9m**). Product was prepared by the general procedure and was isolated as a white color solid (mp = 84−85 °C) in 43% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 5.97 (ddd, J = 16.5 Hz, J = 10.5 Hz, J = 5.5 Hz, 1H), 5.49 (d, J = 17.0 Hz, 1H), 5.30 (dd, J = 10.5 Hz, J = 3.0 Hz, 1H), 5.10−5.07 (m, 1H), 3.81 (d, J = 9.0 Hz, 1H), 2.46 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 145.8, 135.3, 134.7, 129.8, 129.3, 118.5, 81.8, 73.5, 72.1, 23.9, 21.7, 21.1; IR (cm^{-1}) 3049, 2986, 2937, 2864, 1761, 1597, 1459, 1380, 1320, 1261, 1146, 1070, 936, 813, 748; HRMS m/z calcd for $(C_{15}H_{18}O_4S)Na^+$ 317.0818, found 317.0817.

2,2-Dimethyl-5-((E)-prop-1-en-1-yl)-4-tosyldihydrofuran-3(2H)-one (**9n**). Product was prepared by the general procedure and was isolated as a white solid (mp = 115−116 °C) in 54% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 5.86 (qd, J = 15.0 Hz, J = 7.0 Hz, 1H), 5.52 (qd, J = 8.5 Hz, J = 2.0 Hz, 1H), 4.97 (t, J = 8.0 Hz, 1H), 3.79 (d, J = 9.0 Hz, 1H), 2.46 (s, 3H), 1.68 (dd, J = 6.5 Hz, J = 1.0 Hz, 3H), 1.27 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 145.6, 134.8, 131.8, 129.7, 129.3, 128.1, 81.5, 73.9, 71.9, 23.9, 21.7, 21.0, 17.7; IR (cm^{-1}) 3058, 2986, 1763, 1592, 1421, 1258, 1151, 1060, 893, 754; HRMS m/z calcd for $(C_{16}H_{20}O_4S)Na^+$ 331.0974, found 331.0973.

2-Ethyl-2-methyl-5-((E)-prop-1-en-1-yl)-4-tosyldihydrofuran-3(2H)-one (**9o**). Product was prepared by the general procedure, and two inseparable diastereomers were isolated as a colorless oil in 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 4H), 7.38 (m, 4H), 5.84 (m, 2H), 5.50 (m, 2H), 4.95 (m, 2H), 3.78 (d, J = 15.0 Hz, 1H), 3.70 (d, J = 15.5 Hz, 1H), 1.73−1.47 (m, 10H), 1.21 (s, 3H), 1.17 (s, 3H), 0.89 (t, J = 12.5 Hz, 3H), 0.80 (t, J = 12.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 205.4, 145.66, 145.62, 135.0, 134.8, 13.7, 131.4, 129.7, 129.37, 129.33, 129.2, 128.3, 128.2, 127.5, 84.6, 84.1, 77.4, 73.9, 73.8, 72.8, 71.9, 68.4, 30.3, 26.0, 21.7, 20.6, 19.8, 17.7, 7.7, 6.9; IR (cm^{-1}) 3007, 2985, 2864, 1760, 1591, 1410, 1261, 1140, 1055, 880, 762; HRMS m/z calcd for $(C_{17}H_{22}O_4S)Na^+$ 345.1131, found 345.1129.

2-((E)-Prop-1-en-1-yl)-3-tosyl-1-oxaspiro[4.5]decan-4-one (**9p**). Product was prepared by the general procedure and was isolated as a colorless oil in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 5.84 (ddd, J = 14.7 Hz, J = 6.6 Hz, J = 6.3 Hz, 1H), 5.53 (qd, J = 15.0 Hz, J = 1.8 Hz, 1H), 4.96 (dd, J = 8.4 Hz, J = 7.2 Hz, 1H), 3.78 (d, J = 8.9 Hz, 1H), 2.46 (s, 3H), 1.73−1.47 (m, 12H), 1.38−1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 145.5, 134.9, 131.3, 129.7, 129.3, 128.5, 83.2, 73.8, 72.4, 32.6, 28.7, 24.8, 21.7, 21.2, 20.6, 17.7; IR (cm^{-1}) 3052, 2937, 2851, 1758, 1679, 1597, 1492, 1449, 1327, 1268, 1153, 1037, 962, 813,

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734, 665; HRMS m/z calcd for $(C_{19}H_{24}O_4S)Na^+$ 371.1287, found 371.1286.

*2,2-Dimethyl-5-((E)-styryl)-4-tosyldihydrofuran-3(2H)-one (**9q**).* Product was prepared by the general procedure and was isolated as a yellow tan color solid (mp = 114−116 °C) in 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.32−7.25 (m, 5H), 6.66 (dd, J = 18.5 Hz, J = 1.5 Hz, 1H), 6.18 (dd, J = 16.0 Hz, J = 6.0 Hz, 1H), 5.18 (ddd, J = 9.0 Hz, J = 6.5 Hz, J = 1.5 Hz, 1H), 3.90 (d, J = 9.0 Hz, 1H), 2.36 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 145.8, 135.6, 134.7, 133.6, 129.9, 129.2, 128.5, 128.2, 126.7, 125.8, 81.9, 73.8, 72.2, 23.9, 21.0; IR (cm^{-1}) 3058, 3023, 2973, 2930, 1761, 1329, 1151, 1063, 962, 901, 808, 661; HRMS m/z calcd for $(C_{21}H_{22}O_4S)Na^+$ 393.1131, found 393.1125.

*5-((Z)-1-Bromo-2-phenylvinyl)-2,2-dimethyl-4-tosyldihydrofuran-3(2H)-one (**9r**).* Product was prepared by the general procedure and was isolated as a yellow tan color solid (mp = 137−139 °C) in 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.0 Hz, 2H), 7.37−7.33 (m, 5H), 7.01 (s, 1H), 5.21 (d, J = 8.0 Hz, 1H), 4.41 (d, J = 8.5 Hz, 1H), 2.33 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 146.1, 134.3, 134.0, 130.0, 129.8, 129.2, 129.0, 128.9, 128.1, 122.8, 82.5, 79.4, 70.0, 23.9, 22.0, 21.6; IR (cm^{-1}) 3058, 2979, 2927, 2881, 1761, 1600, 1495, 1449, 1324, 1264, 1166, 1064, 813, 734, 652; HRMS m/z calcd for $(C_{21}H_{21}BrO_4S)Na^+$ 471.0236, found 471.0232.

*2,2,5-Trimethyl-4-tosyl-5-vinyldihydrofuran-3(2H)-one (**9s**).* The product was prepared by the general procedure, and two inseparable diastereomers were isolated as a colorless oil in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) Major isomer: δ 7.86−7.83 (m, 2H), 7.39−7.37 (m, 2H), 6.19 (dd, J = 17.0 Hz, J = 10.5 Hz, 1H), 5.40 (d, J = 17.0 Hz, 1H), 5.18 (d, J = 10.5 Hz, 1H), 4.06 (s, 1H), 2.46 (s, 3H), 1.84 (s, 3H), 1.44 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 143.3, 136.2, 129.6, 129.2, 113.6, 81.0, 80.8, 74.7, 26.5, 25.4, 24.5, 21.7; Minor isomer: δ 7.86−7.83 (m, 2H), 7.39−7.37 (m, 2H), 6.53 (dd, J = 17.0 Hz, J = 10.5 Hz, 1H), 5.57 (d, J = 17.0 Hz, 1H), 5.34 (d, J = 10.5 Hz, 1H), 4.03 (s, 1H), 2.46 (s, 3H), 1.68 (s, 3H), 1.39 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 145.4, 137.6, 129.5, 129.3 116.2, 81.5, 80.9, 76.1, 30.6, 27.1, 24.9, 21.7; IR (cm^{-1}) 3157, 3049, 2993, 2930, 2255, 1761, 1633, 1597, 1321, 1268, 1146, 1083, 902, 748, 652; HRMS m/z calcd for $(C_{16}H_{20}O_4S)Na^+$ 331.0974, found 331.0973.

*(E)-2-Hydroxy-2,7-dimethyl-4-tosyloct-5-en-3-one (**8aa**).* To a stirred solution of **8a** (0.100 g, 0.300 mmol) in THF (3 mL, 0.1 M) was added 1,8-diazabicycloundec-7-ene (0.051 g, 0.330 mmol) at 0 °C under an argon atmosphere. The reaction was stirred for 20 min at 0 °C and monitored by TLC. Upon reaction completion by TLC, the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were dried over anhydrous sodium sulfate and concentrated on the rotary evaporator. The crude product was purified by flash column chromatography (15% EtOAc/Hexane). The product was isolated as a colorless oil (0.083 g) in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.57 (dd, J = 9.5 Hz, 1H), 5.56 (d, J = 6.5 Hz, 1H), 5.42−5.37 (m, 1H), 3.67 (s, 1H), 2.46 (s, 3H), 2.26 (septet, J = 7.0 Hz, 1H), 1.49 (s, 3H), 1.26 (s, 3H), 0.91 (d, J = 3.5 Hz, 3H), 0.90 (d, J = 3.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 148.0, 145.5, 133.2, 129.9, 129.3, 115.9, 71.5, 31.2, 26.3, 25.9, 21.7, 21.6, 21.5; IR (cm^{-1}) 3305, 3056, 2970, 2877, 1767, 1590, 1511, 1260, 1130, 1043, 739; HRMS m/z calcd for $(C_{17}H_{24}O_4S)Na^+$ 347.1287, found 347.1291.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR data for new compounds; X-ray crystal structure data for compounds **9a**, **9e**, and **9f**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01076.

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Notes

The authors declare no competing financial interest.

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