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Tandem Vinylogous 1,2-Addition/Anionic Oxy-Cope Reaction Leading from Butadiene Sulfone to an Orthogonally Functionalized Bicycle

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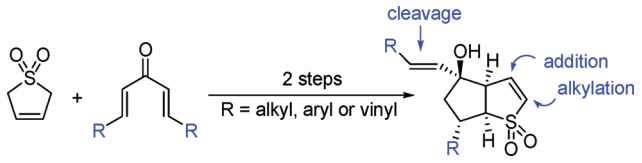


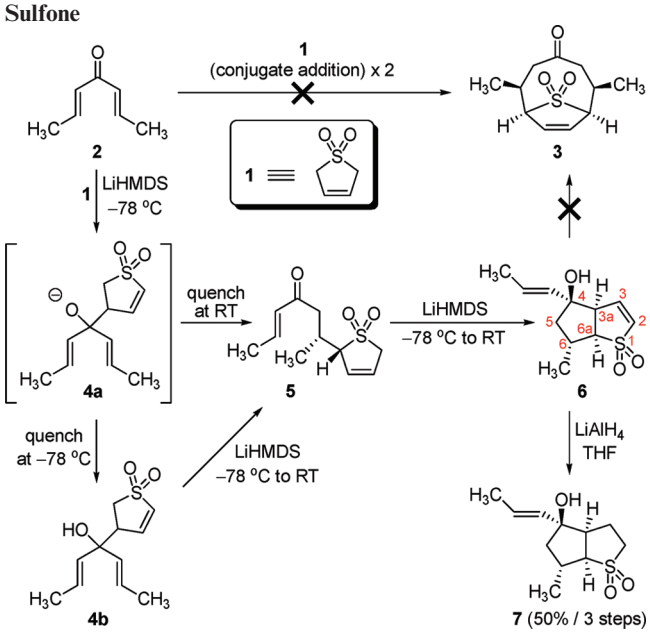
Here we present a transition metal-free synthesis of a rigid, orthogonally functionalized bicyclic sulfone, starting from readily available reagents. The transformation proceeds via a tandem vinylogous 1,2-addition/anionic oxy-Cope sequence, followed by a second vinylogous ketone addition. Stereochemical assignments suggest that the anionic oxy-Cope reaction proceeds exclusively through a boat-shaped transition state. The product of the two-step sequence can be further functionalized through subsequent chemo- and diastereoselective transformations, suggesting possible applications in medicinal chemistry or materials chemistry.

Butadiene sulfone (3-sulfolene, **1**) is an inexpensive (~10¢/g) 4-carbon building block that has been extensively used for the preparation of functionalized dienes, via deprotonation, alkylation, and cheletropic removal of SO_2.[1] The conjugate base of **1** has also been reported to participate in 1,4-addition reactions with a variety of simple Michael acceptors.[2] We hypothesized that the use of bifunctional electrophiles such as bis-alkylidene ketones might expand the range of structures accessible from **1**, by permitting cascade or tandem reactivity.[3]

To explore this possibility, we studied the reactivity of **1** with the readily available bis-alkylidene ketone **2**.[4] The presence of two Michael acceptors in **2** suggested that butadiene sulfone might engage in two sequential conjugate additions to afford meso-ketone **3**.[5] Alternatively, we considered that the reduced steric hindrance at the ketone in **2** (relative to other α,β-unsaturated carbonyl systems) might allow for a variety of transformations proceeding from nucleophilic attack at the carbonyl function.

In the event, treatment of a solution of ketone **2** and sulfone **1** with LiHMDS at −78 °C resulted in attack from the γ-position of the sulfone anion directly to the ketone of **2** (Scheme 1).[6] When the reaction was quenched at low temperature, the major isolated product was the tertiary alcohol **4b**. Treatment of **4b** with a second equivalent of LiHMDS initiated an anionic oxy-Cope rearrangement,[7,8] affording keto-sulfone **5** as a single diastereomer. Further experimentation revealed that we could access **5** in a single step, by allowing the mixture of **1**, **2**, and LiHMDS to warm to room temperature prior to aqueous workup. While we cannot completely rule out the possibility that a portion of **5** was produced by the alternative conjugate addition pathway, both the high diastereomeric excess and our demonstration of **4** as a valid intermediate suggest that the majority of **5** was formed via the tandem vinylogous 1,2-addition/anionic oxy-Cope reaction indicated in Scheme 1.[9]

SCHEME 1. Rapid Access to Bicyclic Sulfone 6 from Butadiene Sulfone



(1) For leading references, see: (a) Chou, T.; Chang, L.-J.; Tso, H.-H. *J. Chem. Soc., Perkin Trans. I* **1986**, 1039–1042. (b) Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687–690. (c) Gries, R.; Khaskin, G.; Gotoh, T.; Schaefer, P. W.; Gries, G. *J. Chem. Ecol.* **2005**, *31*, 879–891. (d) Subramanian, T.; Chou, T.; Bhat, S. V. *Synth. Commun.* **2001**, *31*, 2787–2793. (e) Takayama, H.; Suzuki, T. *J. Chem. Soc., Chem. Commun.* **1988**, 1044–1045. (f) Yamada, S.; Ohsawa, H.; Suzuki, T.; Takayama, H. *J. Org. Chem.* **1986**, *51*, 4934–4940. (g) Chou, T.; Tso, H.-H.; Chang, L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 236–237.

(2) (a) Welcher, R. P. *J. Org. Chem.* **1963**, *28*, 1712–1713. (b) Yamada, S.; Suzuki, H.; Naito, H.; Nomoto, T.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1987**, 332–333.

(3) For a useful review of tandem reactions initiated by organolithium species, see: García, G. V.; Nudelman, N. S. *Org. Prep. Proced. Int.* **2003**, *35*, 445–500.

(4) Krabbenhoft, H. O. *J. Org. Chem.* **1979**, *44*, 4285–4294.

(5) For an alternative approach to medium-sized rings from butadiene sulfone, see: Chou, T.; Chang, C.-Y. *J. Org. Chem.* **1991**, *56*, 4560–4563.

(6) For other reports of vinylogous additions from butadiene sulfone, see: (a) Chou, T.; Tseng, H.-J. *Tetrahedron Lett.* **1995**, *36*, 7105–7108. (b) Chou, T.; Tso, H.-H.; Tao, Y.-T.; Lin, L. C. *J. Org. Chem.* **1987**, *52*, 244–246.

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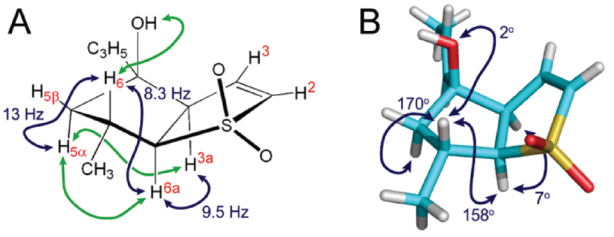


FIGURE 1. Structural information for **6**, obtained from solution- and solid-state analyses: (A) coupling constants (blue) and NOE enhancements (green) observed by NMR; (B) X-ray structure of **6**, showing the dihedral angles that correspond to the large vicinal coupling constants.

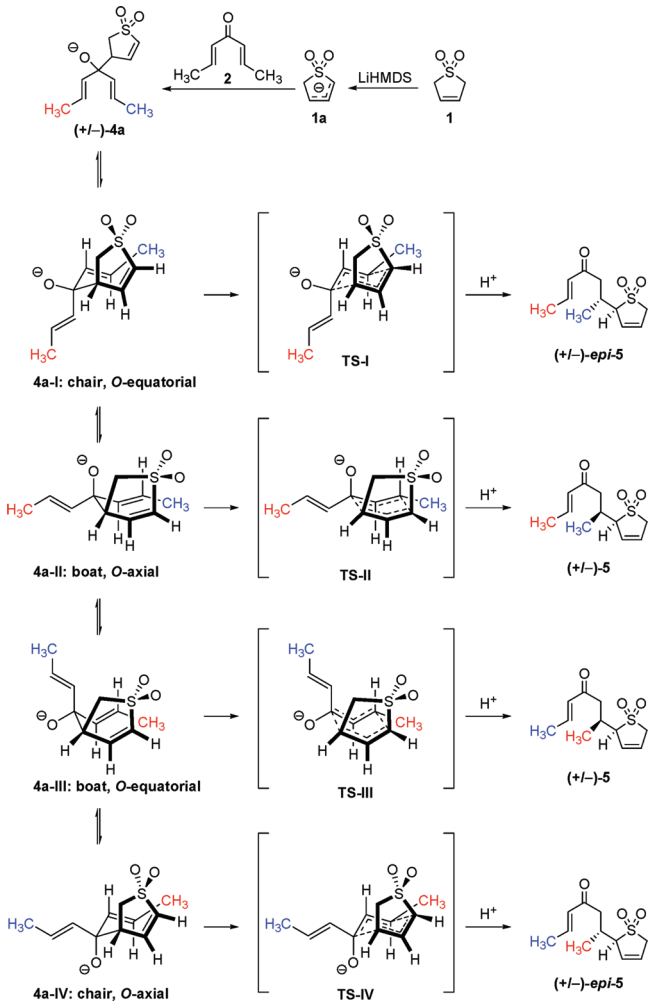
Reaction of keto-sulfone **5** with more LiHMDS resulted in a second attack from the γ-position of the sulfone to the ketone, leading to the formation of alcohol **6**, once again as a single diastereomer.[10] Sulfones **5** and **6** were somewhat sensitive to silica gel chromatography, complicating our attempts to document the overall yield. We therefore reduced the electrophilic vinyl sulfone function, affording **7** in a 50% yield over 3 steps (average of 79% per step).

Although the conjugate base of **6** could in principle engage in a second anionic oxy-Cope reaction (leading to **3**), this was not observed. Analysis of the structure of **6** (vide infra) suggests that the two olefins are too far removed from one another to participate in a concerted rearrangement.

The synthesis of structures like **6** from butadiene sulfone is unprecedented in the synthetic literature. Therefore, the connectivity and relative stereochemistry of this product was carefully established by a series of 1D and 2D NMR experiments. Particularly interesting from this data were the large coupling constants observed in several of the signals of the proton NMR spectrum, as well as several strong cross-peaks in the NOESY spectrum (Figure 1A). Taken together, our data suggested that the two bridgehead protons, as well as H-6, H-5α, and the hydroxyl group, occupied pseudoaxial positions around the alkyl ring. These assignments were supported by molecular modeling calculations, and were later confirmed by X-ray crystallographic analysis of a single crystal of **6**.[11] The presence of such large vicinal couplings in both **6** ($J_{6-5\alpha}$ = 13 Hz) and **7** ($J_{6-5\alpha}$ = 13 Hz; J_{3-2} = 13 Hz) also suggests that these structures are conformationally rigid, at least on the NMR time scale.

With the relative stereochemistry of **6** (and thus **5**) established, we considered the anionic oxy-Cope reaction that led to the formation of **5**. The two enantiomers of **4a** could conceivably engage in [3,3] sigmatropic rearrangement

SCHEME 2. Possible Transition States Leading from 4a to 5

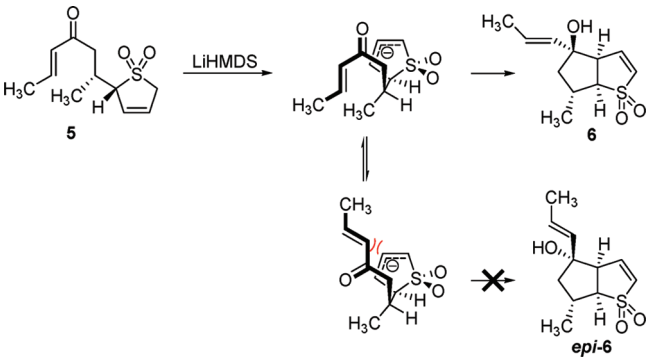


through a total of 8 different transition states (i.e., 2 enantiomeric sets of 4). One enantiomeric series of these is shown in Scheme 2,[12] wherein the two allylic methyl groups in **4a** have been arbitrarily colored blue and red to emphasize the fact that two of the transition states (I and II) involve a different diastereotopic alkene to the other two (III and IV).

While one might have predicted the two chair-shaped transition states (TS-I and TS-IV) to be more favored,[13] the observed product (**5**) suggests that the reaction proceeds through one of two possible boat-shaped transition states (TS-II or TS-III). The experiment described here does not allow a distinction between the relative energies of the *O*-equatorial or *O*-axial transition states. However, we note that TS-II is best oriented to benefit from stabilization through chelation (via the alkoxide and one of the sulfone oxygen atoms) to the lithium counterion.[14] Additional

(7) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
(8) For reviews of the anionic oxy-Cope reaction, see: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971–14020. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Permagon Press: Oxford, UK, 1991; Vol. 5, Chapter 7.1.
(9) For other examples of tandem ketone-addition/anionic oxy-Cope reactions, see: (a) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *J. Org. Chem.* **1998**, *63*, 6905–6913. (b) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201–205. (c) Paquette, L. A. *Eur. J. Org. Chem.* **1998**, 1709–1728.
(10) Treatment of **1** and **2** with LiHMDS for extended periods did not result in the direct formation of **6**, suggesting that the enolate formed following the anionic oxy-Cope is not able to deprotonate the sulfone moiety.
(11) Supplementary crystallographic data for compounds **6** and **9** have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 766248 and 766249. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.
(12) For a similar treatment of a different system, see: White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901–14904.
(13) Chair-shaped transition states generally predominate in [3,3]-sigmatropic rearrangements of acyclic substrates. See: Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67–74. However, conformational constraints in cyclic substrates can lead to a preference for boat-shaped transition states. See ref 8a for a more extensive discussion.
(14) For other examples of chelation-controlled anionic oxy-Cope reactions, see: (a) Rutherford, A. P.; Hartley, R. C. *Tetrahedron Lett.* **2000**, *41*, 737–741. (b) Seki, K.; Tooya, M.; Sato, T.; Ueno, M.; Uyehara, T. *Tetrahedron Lett.* **1998**, *39*, 8673–8676.

SCHEME 3. Proposed Origin of the Diastereoselective Preference for the Transformation from 5 to 6



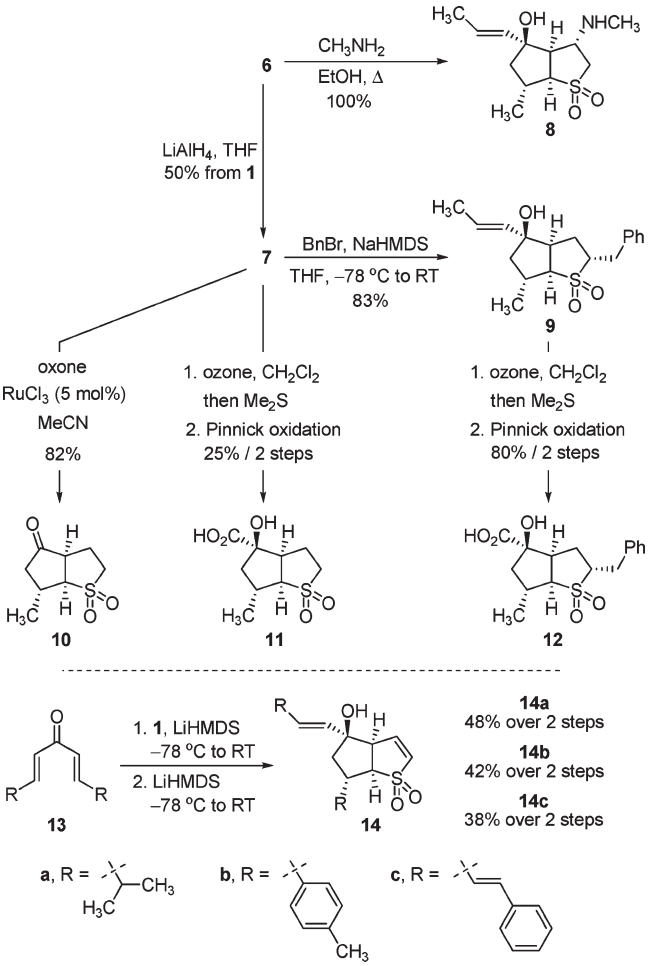
support for the involvement of a chelated lithium counterion comes from the observation that **1** and **2** fail to react cleanly in the presence of NaHMDS, KHMDS, or KHMDS with 18-crown-6.[15]

The second vinylogous attack at the ketone is also of interest, given the high level of diastereoselectivity observed in the conversion of **5** into **6**. As illustrated in Scheme 3, the preferential selection of one diasteotopic face of the ketone is likely due to steric factors. In the most probable reaction pathway leading to the observed product (**6**), the allylic anion can easily approach the carbonyl group. By contrast, in the most likely pathway leading to the other possible diastereomer of the observed product (i.e., *epi*-**6**), the β-position of the sulfone would suffer an unfavorable contact with the alkene. Chelation may play a role here as well, by helping to position the carbonyl group in **5** close to the two sulfone oxygen atoms.

The apparent rigidity of **6**, together with its orthogonal functionalization, suggests that it could be a useful intermediate for the generation of structurally predictable (or at least easily calculable) targets for use in medicinal chemistry, functional materials, or supramolecular systems. We therefore explored the further functionalization of the periphery of the bicyclic structure. We found that conjugate addition of methyl amine to the vinyl sulfone function in **6** occurred smoothly to afford a single diastereomer of product (**8**), as anticipated on steric grounds.[16] Similarly, deprotonation of the saturated alkyl sulfone (**7**) and reaction with benzyl bromide led to a single diastereomer of **9**. Protection of the alcohol was not required. The orientation of the benzyl substituent was confirmed by X-ray crystallography,[11] and is consistent with an *exo* approach by the electrophile.

Turning our attention toward functionalization of the carbocyclic ring, we found that we could cleanly remove the allylic alcohol function by treatment with $RuCl_3$ and oxone[17] to provide ketone **10** in good yield. This intermediate could lead to a variety of derivatives functionalized at both C-4 and C-5. Alternatively, we found that a two-stage

SCHEME 4. Chemoselective Functionalization of the Bicyclic Sulfone



ozonolysis/Pinnick[18] procedure preserved the stereogenic center at C-4, affording the α-hydroxy acids **11** and **12**. The low overall yield for the preparation of **11** is largely due to purification issues; the less polar acid **12** was isolated in substantially improved yield.

Finally, we explored the installation of functional groups other than methyl at C-6. Many different bis-alkylidene ketones can be accessed following simple procedures;[19] reaction with sulfone **1** by the protocol described here should lead to a variety of differently substituted bicyclic sulfones. To test this hypothesis, we examined the reaction of **1** with both a more sterically demanding bis-alkylidene ketone (**13a**) and a diaryl bis-alkylidene ketone (**13b**). Both reactions provided the expected products (**14**, Scheme 4) in similar overall yield to that observed for **6**. Remarkably, even the bis-dienyl ketone **13c** was a competent substrate for this reaction, affording tetraene **14c** in modest yield over two steps.

Although only a handful of derivatizations of **6** are presented here, it is nonetheless apparent that a wide range of potentially useful structures can be accessed efficiently. For example, β-amino sulfones (such as **8**) are of interest in medicinal chemistry applications due to the greatly attenuated basicity

(15) Alkoxides become increasingly dissociated from their metal counterions moving down the series Li < Na < K. See: Msayib, K. J.; Watt, C. I. F. *Chem. Soc. Rev.* **1992**, *21*, 237–243. For the effect of 18-crown-6 see refs 7 and 8.

(16) For other conjugate additions to isomerized butadiene sulfones, see: Argyle, C. S.; Goadby, S. C.; Mason, K. G.; Reed, R. A.; Smith, M. A.; Stern, E. S. *J. Chem. Soc.* (*C*) **1967**, 2156–2170.

(17) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814–4818.

(18) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(19) (a) Arnold, A.; Markert, M.; Mahrwald, R. *Synthesis* **2006**, 1099–1102. (b) Conrad, C. R.; Dolliver, M. A. *Org. Synth. Collect.* **1943**, *2*, 167–169.

of the amine nitrogen, relative to other secondary amines.[20] Similarly, γ-carbonyl sulfones (such as **10**) can potentially be converted to sulfonamides by the procedure of Sellstedt and Almqvist;[21] sulfonamides are found in a large number of successful drug molecules. Finally, molecular docking studies in our laboratory[22] suggest that bicyclic α-hydroxy acids of the kind typified by **11** and **12** (but containing amine or guanidine groups at C-6) might be useful inhibitors of sialidase enzymes. We are currently investigating these potential inhibitors.

Experimental Section

1. Synthesis of 5. Butadiene sulfone (**1**) (4.20 g, 35.6 mmol) and ketone **2** (4.80 g, 43.6 mmol) were dissolved in tetrahydrofuran (300 mL), and the solution was cooled to −78 °C. A freshly prepared solution of LiHMDS (39.2 mmol) in tetrahydrofuran (60 mL) was added via cannula. The reaction mixture was stirred for 30 min at −78 °C, then removed from the cooling bath and stirred 1 h at room temperature. The reaction was quenched by the addition of 10% aqueous HCl (50 mL), and the mixture was partially concentrated in vacuo at 30 °C. The resulting yellow solution was partitioned between 10% aqueous HCl and chloroform. The organic fraction was washed with brine and dried with Na_2SO_4 then concentrated in vacuo at 30 °C to provide 7.80 g of sulfone **5** as a yellow oil. The crude product was carried to the next step with no further purification. IR (film) 1694, 1303, 1133, 971 cm^{-1}; ^1H NMR (500 MHz) δ 6.89 (dq, J = 16, 7 Hz, 1 H), 6.12 (dq, J = 16, 2 Hz, 1 H), 6.11−6.00 (m, 2 H), 3.78−3.63 (m, 3 H), 2.92 (dd, J = 16, 5 Hz, 1 H), 2.74−2.65 (m, 1 H), 2.55 (dd, J = 16, 8 Hz, 1 H), 1.89 (dd, J = 7, 2 Hz, 3 H), 1.14 (d, J = 7 Hz, 3 H); ^{13}C NMR (125 MHz) δ 198.6 (C), 144.0 (CH), 132.1 (CH), 129.1 (CH), 124.2 (CH), 69.1 (CH), 56.6 (CH_2), 43.1 (CH_2), 29.9 (CH), 18.5 (CH_3), 16.8 (CH_3); MS (ES+) m/z 253 (4), 251 (100); HRMS calcd for $C_{11}H_{16}O_3S$ (M + Na) 251.0718, found 251.0715.

2. Synthesis of 6. Compound **5** (crude, 7.80 g, 34.2 mmol) was dissolved in tetrahydrofuran (400 mL), and the solution was cooled to −78 °C. A freshly prepared solution of LiHMDS (37.6 mmol) in tetrahydrofuran (60 mL) was added via cannula. The reaction mixture was stirred for 30 min at −78 °C then removed from the cooling bath and stirred 5 h at room temperature. The reaction was quenched by the addition of 10% aqueous HCl (100 mL), and the mixture was partially concentrated in vacuo. The resulting red solution was partitioned between 10% aqueous HCl and chloroform. The organic fraction was washed with brine, dried with Na_2SO_4, and concentrated in vacuo at 30 °C to provide 8.20 g of crude vinylsulfone **6** as a yellow oil. The crude product was typically carried to the next step with no further purification. Alternatively, an analytically pure sample could be obtained through flash-column chromatography (dichloromethane:ethyl acetate 10:1) followed by recrystallization from a minimum amount of ethyl acetate and diethyl ether. Mp 107−110 °C; IR (film) 3485 (br), 1282, 1132 cm^{-1}; ^1H NMR (500 MHz) δ 6.52 (dd, J = 7, 2 Hz, 1 H), 6.49 (dd, J = 7, 3 Hz, 1 H), 5.79 (dq, J = 15, 6 Hz, 1 H), 5.58 (dq, J = 15, 2 Hz, 1 H), 3.53 (ddd, J = 10, 3, 2 Hz, 1 H), 3.19 (dd, J = 10, 8 Hz, 1 H), 2.97−2.85 (m, 1 H), 2.02 (dd, J = 13, 6 Hz, 1 H), 1.71 (dd, J = 6, 2 Hz, 3 H), 1.70 (t, J = 13 Hz, 1 H), 1.24 (d, J = 6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 137.1 (CH), 133.7 (CH), 132.7 (CH), 125.9 (CH), 80.6 (C), 67.8 (CH), 57.8 (CH), 51.6 (CH_2), 33.6 (CH), 19.6 (CH_3), 17.8 (CH_3); MS (ES+) m/z 253 (4), 251 (100); HRMS calcd for $C_{11}H_{16}O_3S$ (M + Na) 251.0718, found 251.0715.

3. Synthesis of 7. Compound **6** (crude, 4.50 g, 19.7 mmol) was dissolved in tetrahydrofuran (300 mL). The solution was cooled to 0 °C and $LiAlH_4$ (1.87 g, 49.3 mmol) was added in three portions over 5 min. The solution was warmed to room temperature and stirred for 2.5 h. Wet sodium sulfate was added in small portions over 5 min until gas evolution desisted. The reaction mixture was filtered and washed with ethyl acetate and methanol. The filtrate was concentrated in vacuo to provide 4.20 g of crude sulfone **7** as yellow residue. Flash-column chromatography of a 1.10 g sample of crude material (ethyl acetate:dichloromethane:methanol 20:20:1) afforded 600 mg (50% over 3 steps) of **7** as a thick yellow oil. IR (film) 3484 (br), 1290, 1102, 972 cm^{-1}; ^1H NMR (500 MHz) δ 5.72 (dq, J = 15, 6 Hz, 1 H), 5.44 (dq, J = 15, 2 Hz, 1 H), 3.28 (ddd, J = 13, 13, 7 Hz, 1 H), 2.93 (dd, J = 10, 10 Hz, 1 H), 2.87 (ddt, J = 13, 7, 2 Hz, 1 H), 2.82−2.76 (m, 2H), 2.11 (dd, J = 13, 7 Hz, 1 H), 1.97 (dddd, J = 13, 13, 8, 7 Hz, 1 H), 1.83 (dd, J = 13, 6 Hz, 1 H), 1.68 (dd, J = 6, 2 Hz, 3 H), 1.45 (t, J = 13 Hz, 1 H), 1.18 (d, J = 7 Hz, 3 H); ^{13}C NMR (125 MHz) δ 134.4 (CH), 125.1 (CH), 82.3 (C), 69.4 (CH), 50.8 (CH_2), 50.5 (CH), 49.9 (CH_2), 35.9 (CH), 19.5 (CH_3), 19.4 (CH_2), 17.8 (CH_3); MS (ES+) m/z 253 (4), 251 (100); HRMS (ES+) calcd for $C_{11}H_{18}O_3S$ (M + Na) 253.0874, found 253.0869.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data for compounds **6** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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