Direct Synthesis of Previously Inaccessible Bridgehead Azabicyclics by Intramolecular Cyclization of α-Sulfonamido and α-Sulfonimido Radicals

Leo A. Paquette,* Choon Sup Ra,† Jeffrey D. Schloss, Silvana M. Leit,‡ and Judith C. Gallucci

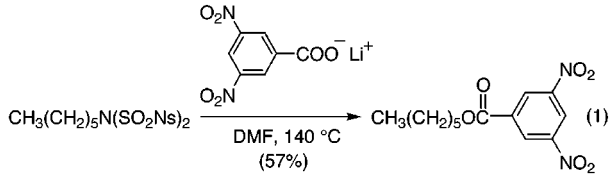
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Paquette.l@osu.edu

Received February 28, 2001

Syntheses of the first bridgehead sultams and the only known bridgehead disulfonimide are described. Both approaches capitalize on the electrophilicity of α-sulfonyl radicals and their propensity to undergo intramolecular ring closure. Where double bonds are concerned, 5-exo and 6-exo pathways operate preferentially as long as structural strain is not excessive. When the reaction center is a carbon−carbon triple bond, the first cyclization gives rise to vinyl radicals that hold sufficient reactivity to capture solvent benzene. In the case of **45**, this sequential reaction leads importantly to the introduction of a styrene functionality sufficiently activated to allow a second ring closure to be kinetically feasible. The solid-state structural features of **12** and **17** have been elucidated by X-ray crystallographic methods. Despite key differences from the norm in the alignment of the nitrogen lone pair relative to the adjacent sulfonyl groups, these compounds exhibit good hydrolytic stability. For **13**, generation of the α-sulfonamide carbanion is possible and regiospecific oxidation with chromyl acetate has been achieved.

Conformationally unconstrained sulfonamides **1** have held importance for many years in the analysis of amines,[1] as protected amino derivatives,[2,3] and most notably as antibacterial agents.[4,5] The structurally related disulfonimides **2**[6] have elicited interest because of the ease with which they undergo S_N2 displacement[7] and thermal or base-promoted elimination.[8] The nucleofugal capability of amino groups is so appreciably enhanced by activation in the manner defined by **2** that substitution occurs as readily as with tosylates in the alcohol series (eq 1).[9,10] Furthermore, the significant steric bulk of the disulfonimide functionality introduces nonbonded interactions that are conducive to overwhelmingly preferred terminal olefin formation (eq 2).[11] Both processes are notable for the expeditious manner in which they bring about deamination.



Cyclic variants of **1**, called sultams, have served as more geometrically defined scaffolds onto which a rich

* To whom correspondence should be addressed.

† On leave from the Department of Chemistry, Yeungnam University, Kyongsan 712-749, Korea.

‡ Present address: MethylGene Inc., 7220 Frederick-Banting, Montreal, Quebec, Canada H4S 2A1.

(1) Shriner, R. L.; Hermann, C. K. F.; Morrill, T. C.; Curtin, D. Y.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 7th ed.; John Wiley and Sons: New York, 1998.

(2) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; Chapter 6.

(3) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; Chapter 7.

(4) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, 1992.

(5) Bowman, W. C.; Rand, M. J. *Textbook of Pharmacology*, 2nd ed.; Blackwell: London, 1979; Chapter 34.

(6) (a) Bentz, F.; Nischk, G. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 66. (b) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Klein, S. A.; Baumgarten, R. J. *J. Org. Chem.* **1974**, *39*, 3525. (c) Pan, H.-L.; Fletcher, T. L. *Synthesis* **1975**, 39. (d) Bartsch, R. A.; Allaway, J. R.; Yandell, R. B.; Lee. J. G.; McCann, D. W. *J. Chem. Eng. Data* **1977**, *22*, 453. (e) Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412.

(7) (a) Andersen, N. H.; Uh, H.-S. *Synth. Commun.* **1972**, *2*, 297. (b) Hutchins, R. O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* **1975**, *40*, 2018. (c) Curtis, V. A.; Raheja, A.; Rejowski, J. E.; Majewski, R. W.; Baumgarten, R. J. *Tetrahedron Lett.* **1975**, 3107. (d) DeChristopher, P. J.; Adamek, J. P.; Klein, S. A.; Lyon, G. D.; Baumgarten, R. J. *J. Org. Chem.* **1975**, *40*, 3288. (e) Hutchins, R. L.; Kandasamy, D.; Dux, F., III.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259. (f) Glass, R. S.; Swedo, R. J. *J. Org. Chem.* **1978**, *43*, 2291. (g) Müller, P.; Thi, M. P. N. *Helv. Chim. Acta* **1979**, *62*, 1485. (h) Townsend, C. A.; Theis, A. B. *J. Org. Chem.* **1980**, *45*, 1697. (i) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Galante, J. J.; Haffner, H. E.; Boggio, R. J.; Baumgarten, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 2384.

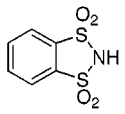
(8) Curtis, V. A.; Knutson, F. J.; Baumgarten, R. J. *Tetrahedron Lett.* **1981**, *22*, 199.

(9) Curtis, V. A.; Schwartz, H. S.; Hartman, A. F.; Pick, R. M.; Kolar, L. W.; Baumgarten, R. J. *Tetrahedron Lett.* **1977**, *23*, 1969.

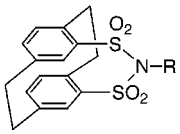
(10) Whereas the parent amines exhibit pK_a values in the range of ca. 35 and $PhSO_2NHPh$ has a pK_a of 9.65 [Dauphin, G.; Kergomard, A. *Bull. Soc. Chim. Fr.* **1961**, *3*, 486.], $(PhSO_2)_2NH$ (pK_a = 1.45) is approximtely as strong an acid as phosphoric acid and *N*,*N*-(*p*-nitrobenzene)sulfonimide is stronger yet (pK_a = 0.30).

10.1021/jo010216z CCC: $20.00
Published on Web 04/17/2001

variety of pharmacophores have been attached.[12,13] Many variants have been examined, including the strained four-membered β-sultams.[14] Numerous reagents possessing these structural elements have presently become part of common synthetic practice. Included in this group are the sulfonyloxaziridines,[15] 10,2-camphorsultams,[16] and saccharin-based electrophilic fluorinating agents.[17] In contrast, cyclic disulfonimides are relatively rare entities, the most well-known examples being 1,2-benzenedisulfonimide (**3**)[18] and [2.2]paracyclophane-4,15-disulfonimides of type **4**.[19]

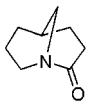


3

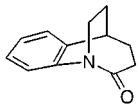


4

The further constraining of compounds of general formula **1** and **2** by positioning the nitrogen atom at a bridgehead site in a small bicyclic framework has not previously been accorded attention.[20] The appreciably heightened hydrolytic reactivity of lactams such as **5** and **6**[21] has been well documented.[22] This uncharacteristic behavior has been properly attributed to the effects of angle strain and enforced torsional distortion, the combined consequences of which are to orient the nonbonded nitrogen lone pair orthogonally to the C=O π bond and inhibit resonance interaction. Since amide resonance energy usually amounts to 16−22 kcal/mol[23] and N−C(=O)-overlap is subject to a cos θ relationship,[24] energy costs can be expected to rise steeply as resonance interaction is incrementally curtailed, and they do.

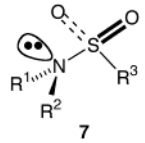


5

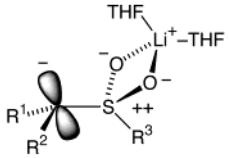


6

The corresponding scenario in substituted sulfonamides and disulfonimides is much less well defined, although it is recognized that stabilization is derived quite differently in these systems. Scrutiny of the crystallographic data for more than 200 sulfonamides of diverse type, with the geometry at N varying from distinctively pyramidal to near-planar, has revealed a decided preference for the lone pair to reside in the bisector of the O−S−O internuclear angle as in **7**.[25] α-Sulfonyl carbanions seemingly adopt a comparable staggered conformation. As seen in **8**, the lone pair orbital is likewise gauche to the two oxygens, both of which are ion-paired to the lithium ion.[26−28]

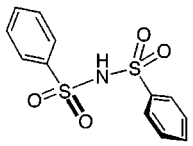


7

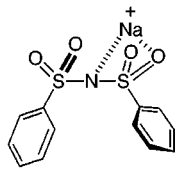


8

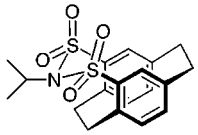
As it concerns disulfonimides, we are aware of a single study designed to evaluate the difference in structural features between the parent structure and an ionized form thereof.[29] Crystallographic analysis of dibenzenesulfonimide (**9**) and its sodium salt **10** demonstrated a major qualitative difference between them in the rotational orientation of the groups bound to the tetrahedral sulfur atoms. While the phenyl rings lie on opposite sides of the S−N−S plane in **9**, they populate the same side of this plane in **10**. The anti configuration is likely adopted to minimize global steric interactions within the neutral molecule. In the anion, the cis arrangement allows close approach of the electronegative nitrogen and oxygen atoms to the sodium ion.[30] The rotational orientation observed for **11** is unmistakingly structurally enforced.



9



10

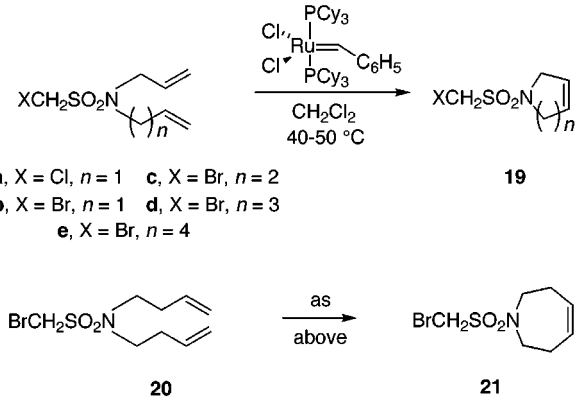


11

For the above reasons, it is not clear whether prescribed changes in the orientation of the nitrogen lone pair relative to the O−S−O internuclear angle will translate into altered reactivity. One way to address this

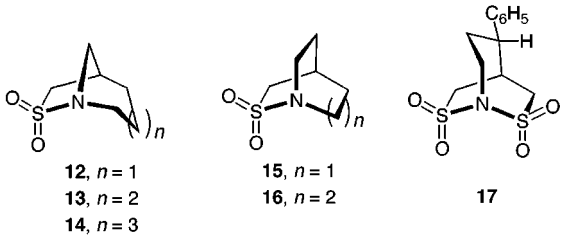
(11) Bartsch, R. A.; Allaway, J. R.; Ingram, D. D.; Lee, J.-G. *J. Am. Chem. Soc.* **1975**, *97*, 6873.
(12) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II* ; Elsevier: Oxford, 1996; Vols. 3 and 4.
(13) Buglass, A. J.; Tillett, J. G. *Chemistry of Sulfonic Acids, Esters, and their Derivatives*; John Wiley and Sons: Chichester, 1991; pp 789−878.
(14) Chanet-Ray, J.; Vessière, R. *Org. Prep. Proced. Int.* **1986**, *18*, 157.
(15) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(16) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241; **1988**, *60*, *39*.
(17) (a) Differding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248. (b) Differding, E.; Rüegg, G. M.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 1779.
(18) Blaschette, A.; Jones, P. G.; Hamann, T.; Näveke, M.; Schomburg, D. Cammenga, H. K.; Epple, M.; Steppuhn, I. *Z. Anorg. Allg. Chem.* **1993**, *619*, 912.
(19) van Lindert, H. C. A.; van Doorn, J. A.; Bakker, B. H.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 167.
(20) For a previous communication from this laboratory that outlines a portion of this investigation, consult Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126.
(21) (a) Yakhontov, L. N.; Rubtsov, M. V. *J. Gen. Chem. USSR (Engl. Trans.)* **1957**, *27*, 83. (b) Hall, H. K., Jr.; Shaw, R. G., Jr.; Deutschmann, A. *J. Org. Chem.* **1980**, *45*, 3722. (c) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. (d) Brehm, R.; Ohnhäuser, D.; Gerlach, H. *Helv. Chim. Acta* **1987**, *70*, 1981.
(22) (a) Blackburn, G. M.; Skaife, C. J.; Kay, I. T. *J. Chem. Res., Synop.* **1980**, *9*, 294. (b) Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676. (c) Wang, Q.-P.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5757.
(23) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169.
(24) Streitwieser, A. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961; pp 11−20.
(25) For a comparable search conducted some time ago, consult Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, O. S.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 787.
(26) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277 and relevant references therein.
(27) Raabe, G.; Gais, H.-J.; Fleischhauer, J. *J. Am. Chem. Soc.* **1996**, *118*, 4622 and earlier reports by the Gais group.
(28) Terrier, F.; Kizilian, E.; Goumont, R.; Faucher, N.; Wakselman, C. *J. Am. Chem. Soc.* **1998**, *120*, 9496.

Scheme 1



question is to prepare small bridgehead sultams and disulfonimides having rigid topography and incrementally modified geometric relationships.

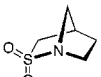
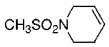
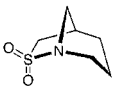
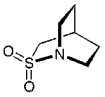
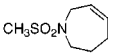
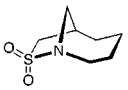
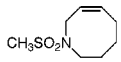
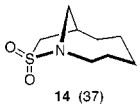
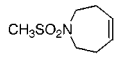
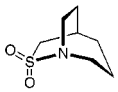
Weak basicity will certainly continue to be manifested.[31] In addition, a chemical robustness appreciably greater than that of the carbonyl analogues **5** and **6** can be anticipated. Described herein are protocols based on α-sulfonyl radical chemistry[32,33] that provide for direct entry to **12**−**17** and preliminary studies on the chemical reactivity of **13**.



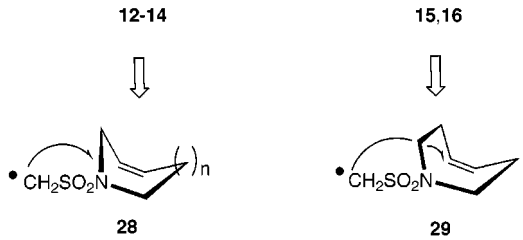
Bridgehead Sulfonamide Synthesis. A reliable protocol for the production of the bromo- and chloro-substituted sulfonamides **18** and **20** has been detailed elsewhere.[32a] Individual heating of these intermediates with the Grubbs catalyst[34] resulted in ring-closing metathesis[35] to deliver **19** and **21** efficiently (Scheme 1). Yields in excess of 95% were realized in all of these examples with the exception of **18e**. Formation of the unsaturated eight-membered ring was met with the generation of a 6.5:1 *Z*/*E* mixture (65% conversion).

The present strategy was to elucidate the propensity of **19** and **21** in their ability to experience radical-induced cyclization. α-Sulfonyl radicals are recognized not to be stabilized[36] and consequently to be prone to rapid intermolecular cyclization.[37] Notwithstanding, the heating of **19a** with tri-*n*-butyltin hydride and AIBN in benzene with syringe pump delivery resulted very predominantly in reductive dehalogenation to give **22** (Table 1). An increase in the ring size by one methylene group as in **19c** led to the first fruitful results. Although the reduced sulfonamide **24** was the major product (47%), the [3.2.1] bicyclic **12** and its [2.2.2] isomer **15** were formed in a ratio approximating 2:1. A further increase in ring size demonstrated that this process could be considered to be preparatively useful for the elaboration of the target molecules.

Table 1. Products of Free Radical Cyclization of Halomethylsulfonamides

compd	reduction prod (%)	cyclization prod (%)
19a	 **22** (74)	 **23** (0)
19c	 **24** (47)	 **12** (16) +  **15** (7)
19d	 **25** (12)	 **13** (69)
19e	 **26** (49)	 **14** (37)
21	 **27** (10)	 **16** (79)

Attention is called to the prominent workability of the 5-exo and 6-exo cyclization pathways as depicted in **28** and **29**.



Route to the Bridgehead Disulfonimide 17. Consistent with our goal of generating members of this

(29) Cotton, F. A.; Stokely, P. F. *J. Am. Chem. Soc.* **1970**, *92*, 294.

(30) For X-ray crystallographic analyses of other disulfonimide salts, see: (a) Xue, L.; Des Marteau, D. D.; Pennington, W. T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1331. (b) Jones, P. G.; Moers, O.; Blaschette, A. *Acta Crystallogr.* **1997**, *C53*, 1809. (c) Jones, P. G.; Moers, O.; Blaschette, A. *Acta Crystallogr.* **1997**, *C53*, 1811.

(31) (a) Laughlin, R. G. *J. Am. Chem. Soc.* **1967**, *89*, 4268. (b) Olavi, P.; Virtanen, I.; Maikkula, M. *Tetrahedron Lett.* **1968**, 4855.

(32) (a) Leit, S. M.; Paquette, L. A. *J. Org. Chem.* **1999**, *64*, 9225, (b) Schloss, J. D.; Leit, S. M.; Paquette, L. A. *J. Org. Chem.* **2000**, *65*, 7119 and relevant references cited in these papers.

(33) Review: Paquette, L. A. *Synlett* **2001**.

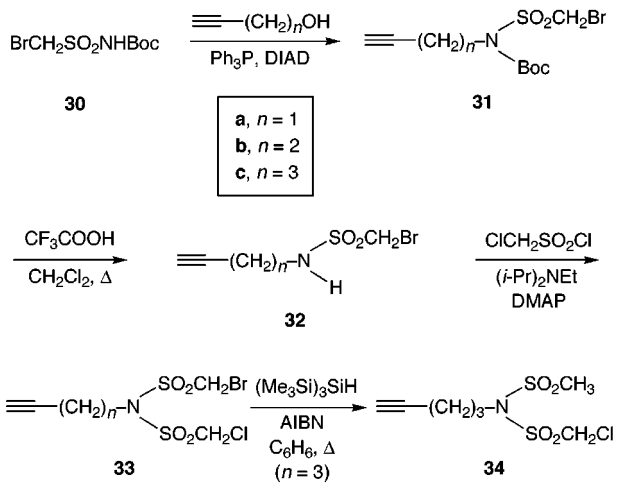
(34) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(35) (a) Cerezo, S.; Cortés, J.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869. (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761. (c) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743.

(36) Block, E. *Reactions of Organosulfur Compounds;* Academic Press: New York, 1978.

(37) (a) Oku, M.; Philips, J. C. *J. Am. Chem. Soc.* **1973**, *95*, 6495. (b) Ueno, Y.; Khare, R. K.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2637. (c) Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943. (d) Vacher, B.; Samat, A.; Allouche, A.; Laknifli, A.; Baldy, A.; Chanon, M. *Tetrahedron* **1988**, *44*, 2925. (e) Clive, D. L. J.; Boivin, T. L. B. *J. Org. Chem.* **1989**, *54*, 1997. (f) Reutrakul, V.; Poolsanong, C.; Pohmakotr, M. *Tetrahedron Lett.* **1989**, *30*, 6913. (g) Renaud, P.; Schubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433. (h) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (i) Renaud, P. *Tetrahedron Lett.* **1990**, *31*, 4601. (j) Tsai, Y.-M.; Ke, B.-W.; Lin, C.-H. *Tetrahedron Lett.* **1990**, *31*, 6047. (k) Tsai, Y.-M.; Ke, B.-W.; Yang, C.-T.; Lin, C.-H. *Tetrahedron Lett.* **1992**, *33*, 7895. (l) Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 3272. (m) Ke, B.-W.; Lin, C.-H.; Tsai, Y.-M. *Tetrahedron* **1997**, *53*, 7805. (n) Imboden, C.; Bourquard, T.; Corminboeuf, O.; Renaud, P.; Schenk, K.; Zahouily, M. *Tetrahedron Lett.* **1999**, *40*, 495.

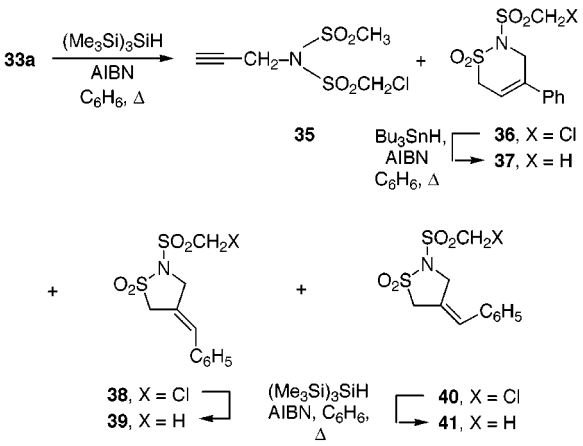
Scheme 2



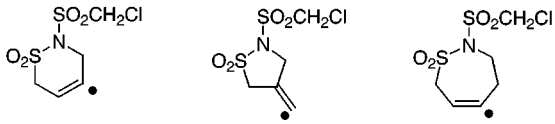
previously unknown structural class as economically and simply as possible, we proceeded to activate bromomethanesulfonamide[38] as its Boc derivative **30** (Scheme 2). Mitsunobu alkylation[39] of **30** with three homologous alkynols gave rise to **31a**−**c** in yields exceeding 90%. After the generation of **32** by conventional deprotection methodology, all attempts to introduce a second bromomethylsulfonyl residue were met with mediocre yields or no observable reaction. To remedy this situation, we turned to the less labile chloromethanesulfonyl chloride.[40] Its admixture with **32** in the presence of Hünig's base and DMAP did indeed furnish **33** in yields varying from 48% to 89% depending upon the number of methylene groups.

The time had come to evaluate the importance of chain length and polar effects on the desired 2-fold bicyclic ring closure. When the trimethylene example **33c** was heated with tris(trimethylsilyl)hydride[41] and AIBN in benzene, exclusive conversion to **34** (56% isolated) was seen to be operational. At the other end of the spectrum, analogous treatment of the smallest member of the series gave rise to four products (Scheme 3). While the major component of this mixture was again the monoreduction product, e.g., **35**, the remaining three were recognized on the basis of their NMR spectra to be *products of monocyclization in which a molecule of solvent had also been assimilated*. Quite unlike the cyclizations involving **19** and **21** where relatively unreactive cycloalkyl radicals[42,43] intervene, the more electrophilic[44] cycloalkenyl radicals **42** and **43** are energetic enough to attack benzene. The combined amounts of **36** and **38/40** produced (24% versus 20%/14%) are indicative that 5-exo ring closure is more kinetically favorable than the 6-endo pathway[45] The somewhat higher levels of **38** produced relative to **40** in these

Scheme 3



sequential reactions[46] can be understood on the basis of the minimization of nonbonded steric interactions during the attack on solvent benzene.



Since all three cyclic disulfonimides were amenable to chromatographic separation, it was possible to react each entity individually with a tin or silyl hydride in an effort to realize further ring closure. However, all attempts to induce bicyclization in this manner resulted exclusively in reduction to give **37**, **39**, and **41**, respectively. The resistance to intramolecular addition across the styrene-like double bond presumably reflects the kinetic deterrence to generation of [2.2.2]- and [2.2.1]bicyclic disulfonimide frameworks. The distinction between **38** and **40**, preliminarily assigned on the basis of their NMR spectral characteristics, was confirmed by an X-ray crystallographic analysis of **41** (Figure 1).

In light of the above findings and our awareness of the remarkable facility with which α-sulfonyl radicals engage in 7-endo cyclization to olefinic acceptors,[32] **33b** became increasingly regarded as the premier test substrate. Were the anticipated transition state to be kinetically dominant, conversion to vinyl radical **44** would be operative. Should this pathway operate in tandem with solvent capture, the formation of **45** would be observed. Indeed, **33b** proved to be subject to this sequential reaction and gave rise to **45** in 59% yield. The nonphenylated heterocycle **46** was also formed (Scheme 4).

When **45** was subsequently heated with tri-*n*-butyltin hydride and AIBN in refluxing benzene, smooth conversion to **17** materialized. This cyclization expectedly led to a single diastereomer as a direct consequence of the symmetry inherent in the benzylic radical precursor **47**. The quasi-equatorial projection of the phenyl substituent in **17** was ultimately confirmed by crystallographic methods.

Structural Features as Defined by Crystallographic Methods. The molecular structure of **41**, a

(38) Goralski, C. T.; Klinger, T. C. *J. Chem. Eng. Data* **1976**, *21*, 237.

(39) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(40) Paquette, L. A.; Wittenbrook, L. S. *Org. Synth.* **1969**, *49*, 18.

(41) (a) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681. (b) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678. (c) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

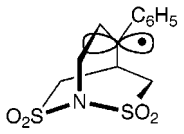
(42) (a) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960. (b) Münger, K.; Fischer, H. *Int. J. Chem. Kinetics* **1985**, *17*, 809.

(43) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon*−*Carbon Bonds*; Pergamon Press: Oxford, 1986; Chapter 5.

(44) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Chapter 4.1.

(45) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Verlag Chemie: Weinheim, 1996.

(46) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.



47

monocyclic disulfonimide, constitutes a useful reference compound. Three informative views of this molecule are provided in Figure 1. The near planarity of the nitrogen atom, best appreciated in views B and C, is evident by summing the associated angles. For **41**, the total is 358.2° (full planarity is present at 360°), indicating its near-planar status. When inspected down the S1−N1 bond (view B), the lone pair on N1 is seen to be positioned on the bisector of the O1−S1−O2 angle. Thus, the unconstrained sulfonyl group external to the ring orients itself in a manner often adopted by sulfonamides (see **7**). In contrast, the confines of the five-membered ring force the lone pair on N1 to eclipse the S2−O4 bond (view C).

The relevant structural parameters of bridgehead sultam **12** are displayed in Figure 2. This substance crystallizes with two molecules per asymmetric unit and as usual slightly different geometries are featured. The

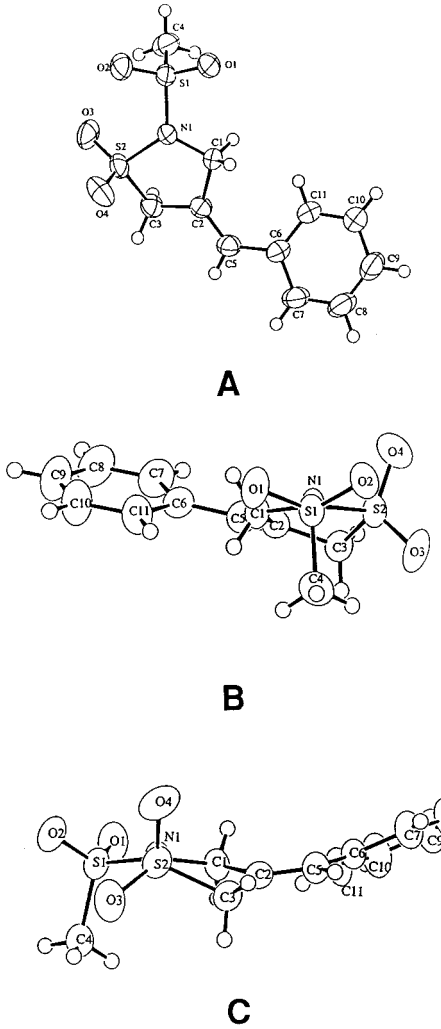


Figure 1. Three views of the molecular structure of **41** in the solid-state drawn with 50% probability displacement ellipsoids for the non-H atoms. A, From above the plane of the five-membered ring; B, down the S1−N1 bond; C, down the S2−N1 bond.

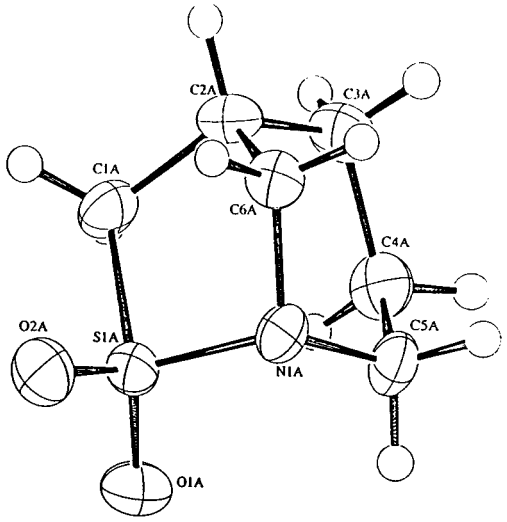
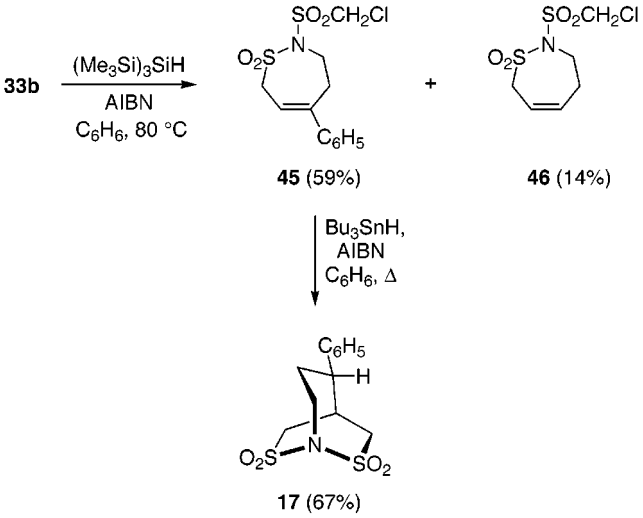


Figure 2. Molecular structure of **12** in the solid state.

Scheme 4



sums about the nitrogen atoms in these structures are 326.3° and 324.7°, reflecting the significant bending at the bridgehead position such that planarity cannot be approached. It is of some interest to determine the "position" of the lone pair of electrons on nitrogen in this example. To this end, the nitrogen atom was assumed to be sp^3-hybridized and a hydrogen was added to it at a calculated position. The hydrogen position was then assumed to be the position of the lone pair of electrons and the torsion angles compiled in Table 2 were calculated. In this instance, it is recognized that the nonbonded electron pair on nitrogen is projected at a right angle to the endo sulfonyl oxygen and in an approximate gauche relationship to the exo counterpart. Thus, the geometry inherent in **12** results in a significant distortion away from the equilibrium state represented by **7** and **41**.

The two molecules in the asymmetric unit of **17** (Figure 3) have sums of 345.6° and 346.0° about the N atoms and are therefore also not planar. The lesser strain imposed on this system is reflected in the adoption of less well-defined dihedral angle relationships across the disulfonimide functionality.

The >N−SO_2− and −SO_2−N−SO_2 motifs present in **12** and **17** are direct isosteres of the amide and imide

Table 2. Torsion Angles Calculated for 12 and 17

compd	atoms involved[a]	angle (degrees)
12	O1A−S1A−N1A−lone pair	−90
	O2A−S1A−N1A−lone pair	40
	O1B−S1B−N1B−lone pair	−90
	O2B−S1B−N1B−lone pair	39
17	O1−S1−N1−lone pair	−61
	O2−S1−N1−lone pair	67
	O3−S2−N1−lone pair	43
	O4−S2−N1−lone pair	−86
	O5−S3−N2−lone pair	76
	O6−S3−N2−lone pair	−55
	O7−S4−N2−lone pair	−82
	O8−S4−N2−lone pair	46

[a] The two structures in the asymmetric unit are distinguished as A and B.

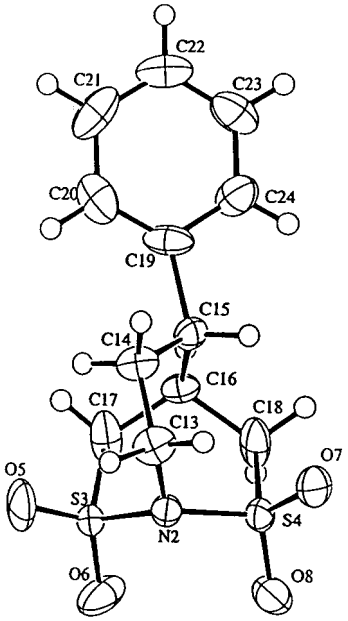


Figure 3. Molecular structure of **17** in the solid state.

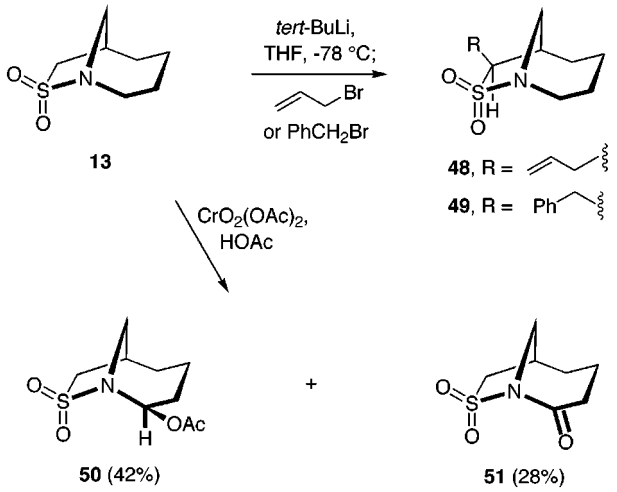
functional groups and display significantly different physical characteristics. Despite wide-ranging differences in the geometry at nitrogen, the sulfur-containing systems constitute hydrolytically stable analogues of the hydrolysis transition states of their carbonyl equivalents.

Preliminary Reactivity Studies. All five homologous sultams **12**−**16** and disulfonamide **17** are white, hydrolytically stable crystalline solids. No sign of hyperactivity is evident in any given example. When initial attempts to deprotonate **13** with a variety of bases failed, recourse was made to *tert*-butyllithium. Under these circumstances, regio- and stereoselective allylation and benzylation to give **48** and **49**, respectively, proceeded uneventfully (Scheme 5). Less reactive electrophiles were reluctant to engage in covalent bonding.

A particularly interesting reaction involves the action of chromyl acetate[47] on **13**. A rapid, exothermic reaction ensued to give the acetate **50** and the structurally novel keto sultam **51**. Although the combined yield of these two products (70%) allows for the possible formation of other positional isomers, none were found. Accordingly, the methylene group α to nitrogen in the largest bridge is inherently the most reactive toward this particular oxidant.

(47) Freeman, F. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995; p 1282.

Scheme 5



Discussion of Results. In keeping with previous trends involving radical intermediates free of sulfur, the bromomethyl sulfonamides **19c**−**e** experience ready 5-exo cyclization once they are transformed into the corresponding α-sulfonyl radicals. The 6-exo cyclization mode adopted by **21** is particularly efficient. The lone exception is **19a**, and we attribute its low-yield conversion into **23** to the elevated strain energy resident in this bridgehead sultam.

Although radical cyclizations onto carbon−carbon triple bonds, e.g., 5-hexynyl cyclizations, occur at rates somewhat slower than 5-hexenyl cyclizations,[48] many examples are known and synthesis has been well served by such transformations. Although α-sulfonyl radicals are inherently electrophilic and highly reactive, it remained to assess ring size effects during the intramolecular capture of these functional groups. As noted elsewhere,[46] the rates of 7-ring and 8-ring cyclizations onto double bonds are sufficiently slow to constitute the lower limit of synthetic utility in many cases. In addition, 7-octenyl radicals often exhibit reverse regioselectivity and cyclize via the 8-endo mode. We have demonstrated herein that the radical derived from **33a** prefers the 5-exo pathway leading to **43** over 6-endo closure resulting in the transient formation of **42**. The efficiency with which **33b** is converted into **45** and **46** suggests that the rate of 7-endo cyclization is especially high and therefore preparatively useful. Since we detected no cyclization with **33c**, eight-membered ring formation must be kinetically unfavorable.

The ability exhibited by alkenyl radicals **42**−**44** to effect homolytic aromatic substitution holds considerable importance in the context of the present study. The phenomenon has been oft-encountered in earlier work by others and attempts continue to be made to fully comprehend substituent effects and associated steric, stereoelectronic, and polar factors.[49] In particular, the route followed predominantly by **44** is to attack solvent benzene and deliver **45**. The styrene moiety thereby generated greatly facilitates the second-stage ring closure to deliver the target disulfonimide **17** with total control of regioselectivity. In essence, the solvent involved in the initial ring closure of **33b** provides the central topological control

(48) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
(49) Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1998**, *63*, 537 and relevant references therein.

element that guides the manner in which the bicyclic end-product is ultimately assembled.

The crystal structures of **12** and **17**, arrived at by X-ray diffraction analysis, provide the first in-depth glimpse of the spatial arrangements of the heteroatoms in the first known bridgehead sultams and disulfonimide. The exo and endo orientations of the sulfonyl oxygens are well defined. More significantly, although the N lone pair electrons cannot be precisely located, proper approximations have been made to show key differences relative to the neighboring O−S−O bonds.

Despite the significant distortions from the normal sulfonamide equilibrium state that are exhibited by the bridgehead systems obtained in the present study, the stability of these molecules is not compromised. The efficiency with which **13** is converted into **50** and **51** in the presence of the powerful oxidant known as chromyl acetate is noteworthy. This reagent is recognized to be capable of oxidizing unactivated C−H bonds in bicycloalkanes and polycycloalkanes to give alcohols, acetates, and ketones.[50,51] Typically, attack occurs at tertiary C−H bonds more rapidly than at methylene groups,[52] with methyl groups being unreactive. For **13**, the only tertiary hydrogen is positioned at the bridgehead site and is inert. The sultam functionality is also unaffected, the bridgehead nitrogen serving only to activate the neighboring CH_2 group of the tetramethylene bridge.

Experimental Section

General Considerations. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H NMR. The high-resolution electron impact mass spectra were recorded at The Ohio State University Campus Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA.

General Ring Closing Metathesis Procedure. A homogeneous orange-red solution of $RuCl_2(=CHPh)(PCy_3)_2$ (0.15−0.30 equiv) in anhydrous CH_2Cl_2 (5 mL) was added to a solution of **18** or **20** (1.0 equiv, 0.040−0.005 M) in the same medium under N_2. The mixture was stirred overnight at 45−50 °C, cooled, and evaporated to leave a residue that was chromatographed on silica gel (elution with 2:1−10:1 hexanes/ethyl acetate).

For **19a**: white solid, mp 82−83 °C (from ether) (98%); IR (CH_2Cl_2, cm^{-1}) 1467, 1387, 1352; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 2 H), 4.58 (s, 2 H), 4.32 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.3 (2C), 55.8 (2C), 54.0; EI MS *m*/*z* (M^+) calcd 182.9934, obsd 182.9911. Anal. Calcd for $C_5H_8ClNO_2S$: C, 33.06; H, 4.44. Found: C, 33.28; H, 4.47.

For **19b**: white solid, mp 125 °C (from ether) (95%); IR (CH_2Cl_2, cm^{-1}) 1466, 1376, 1351; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (s, 2 H), 4.47 (s, 2 H), 4.30 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.3 (2C), 55.9 (2C), 39.5; EI MS *m*/*z* (M^+) calcd 224.9459, obsd 224.9459. Anal. Calcd for $C_5H_8BrNO_2S$: C, 26.56; H, 3.57. Found: C, 27.05; H, 3.63.

For **19c**: white solid, mp 62−63 °C (96%); IR (CH_2Cl_2, cm^{-1}) 1456, 1430, 1372; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.84 (m, 1 H), 5.72−5.65 (m, 1 H), 4.40 (s, 2 H), 3.96−3.93 (m, 2 H), 3.56 (t, *J* = 5.7 Hz, 2 H), 2.29−2.22 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4, 123.0, 45.2, 43.3, 40.1, 25.5; EI MS *m*/*z* (M^+) calcd 238.9616, obsd 238.9637. Anal. Calcd for $C_6H_{10}BrNO_2S$: C, 30.01; H, 4.20. Found: C, 30.47; H, 4.24.

For **19d**: white solid, mp 125−126 °C (98%); IR ($CHCl_3$, cm^{-1}) 1450, 1433, 1372; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.81 (m, 1 H), 5.76−5.68 (m, 1 H), 4.39 (s, 2 H), 4.02−4.00 (m, 2 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 2.42−2.32 (m, 2 H), 1.94−1.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 127.3, 50.6, 47.1, 41.0, 27.3, 26.9; EI MS *m*/*z* (M^+) calcd 252.9772, obsd 252.9800. Anal. Calcd for $C_7H_{12}BrNO_2S$: C, 33.08; H, 4.76. Found: C, 33.21; H, 4.82.

For (*Z*)-**19e**: white solid, mp 79−81 °C (from ether) (65%, *Z*/*E* = 6.5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.83 (m, 1 H), 5.61−5.55 (m, 1 H), 4.41 (s, 2 H), 4.05 (d, *J* = 5.8 Hz, 2 H), 3.51 (br dd, *J* = 5.3, 5.1 Hz, 2 H), 2.44−2.37 (m, 2 H), 1.86−1.78 (m, 2 H), 1.67−1.57 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 125.1, 48.4, 46.5, 40.4, 26.5, 26.2, 24.4; EI MS *m*/*z* (M^+) calcd 266.9929, obsd 266.9903. Anal. Calcd for $C_8H_{14}BrNO_2S$: C, 35.83; H, 5.26. Found: C, 35.95; H, 5.32.

For **21**: white solid, mp 126 °C (98%); IR ($CHCl_3$, cm^{-1}) 1448, 1424, 1366; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (t, *J* = 3.2 Hz, 2 H), 4.41 (s, 2 H), 3.51−3.47 (m, 4 H), 2.41−2.37 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.0 (2 C), 49.3 (2 C), 40.5, 30.9 (2 C); EI MS *m*/*z* (M^+) calcd 252.9772, obsd 252.9799. Anal. Calcd for $C_7H_{12}BrNO_2S$: C, 33.08; H, 4.76. Found: C, 33.29; H, 4.81.

Prototypical Free Radical Cyclization Procedure. A solution of tri-*n*-butylstanne (1.1−1.5 equiv) and AIBN (0.07−0.30 equiv) in deoxygenated benzene (1−10 mL) was added over 2−16 h (manual or syringe pump) to a refluxing (0.091−0.001 M) solution of **19** or **21** (1 equiv) in deoxygenated benzene (3−260 mL). The reaction mixture was heated for another 3 h, cooled, treated with ether and 8% potassium fluoride solution, and stirred for 2 h. The separated organic layer was washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (elution with ethyl acetate in hexanes).

Sulfonamide **19a** was simply reduced to **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 2 H), 4.16 (s, 4 H), 2.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.6 (2 C), 54.9 (2 C), 34.5; EI MS *m*/*z* (M^+) calcd 147.0354, obsd 147.0348.

Sulfonamide **19c** afforded 47% of **24**, 16% of **12** and 7% of **15**. For **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.83 (m, 1 H), 5.72−5.67 (m, 1 H), 3.78−3.74 (m, 2 H), 3.36 (t, *J* = 5.7 Hz, 2 H), 2.80 (s, 3 H), 2.28−2.22 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4, 123.0, 44.6, 42.3, 35.4, 25.1; EI MS *m*/*z* (M^+) calcd 161.0511, obsd 161.0502.

For **12**: white solid, mp 214−215 °C (from CH_2Cl_2/hexanes). IR ($CHCl_3$, cm^{-1}) 1454, 1424, 1334; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62−3.51 (m, 2 H), 3.37 (dd, *J* = 13.1, 7.1 Hz, 1 H), 3.20 (dd, *J* = 13.0, 2.2 Hz, 1 H), 3.07 (dt, *J* = 13.1, 4.9 Hz, 1 H), 2.98 (br dd, *J* = 13.1, 2.3 Hz, 1 H), 2.89−2.84 (m, 1 H), 2.29−2.14 (m, 1 H), 1.98−1.77 (m, 2 H), 1.60−1.52 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1, 55.2, 51.0, 36.9, 29.6, 18.1; EI MS *m*/*z* (M^+) calcd 161.0511, obsd 161.0502.

For **15**: IR ($CHCl_3$, cm^{-1}) 1454, 1424, 1334; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92−3.82 (m, 2 H), 3.31−3.25 (m, 4 H), 2.50−2.45 (m, 1 H), 1.88−1.77 (m, 2 H), 1.64−1.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.9 (2C), 45.7, 28.6, 22.2; EI MS *m*/*z* (M^+) calcd 161.0511, obsd 161.0502.

The structural assignment to **12** was confirmed by X-ray crystallographic analysis.

Sulfonamide **19d** furnished 12% of **25** and 69% of **13**. For **25**: white solid; IR ($CHCl_3$, cm^{-1}) 1472, 1453, 1418; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.72 (m, 2 H), 3.93 (br d, *J* = 4.9 Hz, 2 H), 3.55 (br dd, *J* = 6.1, 5.9 Hz, 2 H), 2.84 (s, 3 H), 2.35−2.32 (m, 2 H), 1.90−1.85 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 127.3, 49.8, 45.7, 38.6, 27.3, 26.8; EI MS *m*/*z* (M^+) calcd 175.0667, obsd 175.0673.

For **13**: white solid, mp 111−112 °C (from CH_2Cl_2/hexanes); IR ($CHCl_3$, cm^{-1}) 1473, 1451, 1419; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (ddd, *J* = 14.8, 12.1, 5.6 Hz, 1 H), 3.41 (ddd, *J* = 13.8, 4.7, 1.9 Hz, 1 H), 3.32 (dd, *J* = 13.6, 8.5 Hz, 1 H), 3.19 (dd, *J*

(50) Stewart, R. *Oxidation Mechanisms*; W. A. Benjamin, Inc.: New York, 1964; pp 50−55.
(51) Wiberg, K. B. In *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Chapter 2.
(52) Paquette, L. A.; Meehan, G. V.; Marshall, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 6779.

= 13.8, 1.5 Hz, 1 H), 3.13 (br dd, J = 14.8, 5.9 Hz, 1 H), 2.90 (m, 1 H), 2.65 (br d, J = 15.0 Hz, 1 H), 1.86−1.80 (m, 1 H), 1.75−1.39 (series of m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 49.2, 47.3, 39.3, 34.2, 27.6, 21.5; EI MS m/z (M^+) calcd 175.0667, obsd 175.0671.

Sulfonamide **19e** gave rise to 49% of **26** and 37% of **14**. For **26**: white solid; IR ($CHCl_3$, cm^{-1}) 1455, 1325, 1224; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.74 (m, 1 H), 5.56−5.49 (m, 1 H), 3.89 (d, J = 5.7 Hz, 2 H), 3.37 (br dd, J = 5.4, 5.1 Hz, 2 H), 2.79 (s, 3 H), 2.44−2.37 (m, 2 H), 1.89−1.78 (m, 2 H), 1.76−1.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 124.7, 47.5, 45.3, 37.1, 27.8, 26.7, 25.9; EI MS m/z (M^+) calcd 189.0824, obsd 189.0828.

For **14**: white solid; IR ($CHCl_3$, cm^{-1}) 1455, 1418, 1389; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70−3.61 (m, 1 H), 3.49 (ddd, J = 13.9, 4.7, 1.7 Hz, 1 H), 3.39 (dd, J = 13.6, 8.4 Hz, 1 H), 3.25 (br d, J = 13.5 Hz, 1 H), 3.19 (dd, J = 14.8, 5.7 Hz, 1 H), 3.02−2.99 (m, 1 H), 2.73 (br d, J = 13.6 Hz, 1 H), 2.03−1.48 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 49.2, 47.3, 39.3, 34.3, 27.6, 25.5, 21.5; EI MS m/z (M^+) calcd 189.0824, obsd 189.0823.

Sulfonamide **21** furnished **27** (10%) and **16** (79%). For **27**: white solid; IR ($CHCl_3$, cm^{-1}) 1403, 1330; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81−5.79 (m, 2 H), 3.38−3.35 (m, 4 H), 2.81 (s, 3 H), 2.39−2.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1 (2 C), 48.0 (2 C), 37.5, 30.4 (2 C); EI MS m/z (M^+) calcd 175.0667, obsd 175.0670.

For **16**: white solid, mp 228−229 °C (from CH_2Cl_2/hexanes); IR ($CHCl_3$, cm^{-1}) 1458, 1321, 1237; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (ddd, J = 10.0, 4.2, 0.9 Hz, 1 H), 3.93−3.83 (m, 1 H), 3.41−3.30 (m, 3 H), 3.10−3.01 (m, 1 H), 2.63−2.58 (m, 1 H), 1.97−1.75 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.2, 52.1 46.3, 31.3, 31.2, 24.4, 23.9; EI MS m/z (M^+) calcd 175.0667, obsd 175.0660.

***N*-(*tert*-Butoxycarbonyl)-bromomethanesulfonamide (30).** A solution of di-*tert*-butyl dicarbonate (4.39 g, 20.1 mmol) in dry CH_2Cl_2 (30 mL) was added to a solution of bromomethanesulfonamide (3.50 g, 20.1 mmol), DMAP (246 mg, 2.01 mmol), and triethylamine (3.05 g, 30.2 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 15 h, carefully washed with 10% HCl and brine, and then dried. Solvent evaporation and purification over silica gel (elution with 25% ethyl acetate in hexanes) gave **30** as a white solid (4.80 g, 87%), mp 99−100 °C; IR ($CHCl_3$, cm^{-1}) 1748; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 2 H), 0.82 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 85.2, 40.7, 27.7 (3 C); EI MS m/z $(M+H)^+$ calcd 273.9748, obsd 273.9713. Anal. Calcd for $C_6H_{12}BrNO_4S$: C, 26.29; H, 4.41. Found: C, 26.77; H, 4.32.

Prototypical Mitsunobu Alkylation of 30. To a cold (0 °C) solution of **30** (1.88 g, 6.86 mmol), triphenylphosphine (2.16 g, 8.23 mmol), and propargyl alcohol (442 mg, 7.88 mmol) in anhydrous THF (15 mL) was added dropwise over 10 min diisopropyl azodicarboxylate (1.66 g, 8.23 mmol) dissolved in dry benzene (10 mL). The magnetically stirred reaction mixture was allowed to warm slowly to room temperature during 15 h, at which point water (50 mL) was introduced and the product was taken up in ether (3 × 100 mL). The combined organic phases were washed with brine (2 × 30 mL), dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) gave **31a** as a colorless oil (2.06 g, 96%); IR (film, cm^{-1}) 1737, 1371, 1144; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 2 H), 4.44 (d, J = 2.4 Hz, 2 H), 2.32 t, J = 2.4 Hz, 1 H), 1.54 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 86.2, 78.1, 72.5, 41.9, 36.8, 27.8; ES MS m/z $(M+Na)^+$ calcd 333.9725, obsd 333.9732. Anal. Calcd for $C_9H_{14}BrNO_4S$: C, 34.53; H, 4.51. Found: C, 34.93; H, 4.51.

For **31b**: white solid, mp 51 °C (92%); IR ($CHCl_3$, cm^{-1}) 1728, 1368, 1140; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (s, 2 H), 3.87 (t, J = 7.3 Hz, 2 H), 2.60 (dt, J = 7.3, 2.7 Hz, 2 H), 2.03 (t, J = 2.7 Hz, 1 H), 1.56 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 85.8, 80.0, 70.7, 46.0, 42.0, 27.8, 19.8; ES MS m/z (M^+) or $(M + Na)^+$ too fleeting for accurate mass measurement. Anal. Calcd for $C_{10}H_{16}BrNO_4S$: C, 36.82; H, 4.94. Found: C, 36.94; H, 5.01.

For **31c**: colorless oil (92%); IR (film, cm^{-1}) 1727, 1456, 1362; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (s, 2 H), 3.79 (t, J = 7.5 Hz, 2 H), 2.24 (dt, J = 7.5, 2.4 Hz, 2 H), 1.98−1.87 (series of m, 3 H), 1.54 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 85.5, 82.8, 69.1, 47.4, 41.9, 28.8, 27.8, 15.8; ES MS m/z (M^+) or $(M + Na)^+$ too fleeting for accurate mass measurement. Anal. Calcd for $C_{11}H_{18}BrNO_4S$: C, 38.83 H, 5.33. Found: C, 38.58; H, 5.34.

Deprotection of 31a−c. A solution of **31a** (630 mg, 2.02 mmol) and trifluoroacetic acid (296 mg, 2.60 mmol) in CH_2Cl_2 (15 mL) was refluxed for 10 h, cooled, and quenched with 1 N $NaHCO_3$ solution (1 mL). The product was taken up in CH_2Cl_2 (3 × 30 mL) and the organic phase was washed with brine (20 mL) prior to drying and solvent evaporation. The residue was purified chromatographically (silica gel, elution with 30% ethyl acetate in hexanes) to furnish oily **32a** (389 mg, 91%); IR (film, cm^{-1}) 3287, 1429, 1335; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (br s, 1 H), 4.55 (s, 2 H), 4.03 (dd, J = 6.3, 2.4 Hz, 2 H), 2.42 (t, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.0, 73.7, 42.2, 33.0; ES MS m/z $(M + Na)^+$ calcd 233.9200, obsd 233.9202. Anal. Calcd for $C_4H_6BrNO_2S$: C, 22.65 H, 2.85. Found: C, 22.95; H, 2.82.

For **32b**: white solid, mp 59 °C (90%); IR ($CHCl_3$, cm^{-1}) 3285, 1328, 1142; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (br s, 1 H), 4.46 (s, 2 H), 3.37 (dd, J = 11.7, 6.3 Hz, 2 H), 2.51 (dt, J = 6.3, 2.6 Hz, 2 H), 2.10 (t, J = 2.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.1, 71.2, 42.5, 41.9, 20.5; EI MS m/z $(M - C_3H_3)^+$ calcd 185.9927, obsd 185.9927. Anal. Calcd for $C_5H_8BrNO_2S$: C, 26.56; H, 3.57. Found: C, 26.70; H, 3.57.

For **32c**: white solid, mp 59 °C (95%); IR (film, cm^{-1}) 3291, 1430, 1331; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (br s, 1 H), 4.44 (s, 2 H), 3.31 (t, J = 6.3 Hz, 2 H), 2.32 (m, 2 H), 2.02 (t, J = 2.6 Hz, 1 H), 1.81 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.7, 69.8, 42.8, 41.3, 28.5, 15.6; ES MS m/z $(M + Na)^+$ calcd 261.9513, obsd 261.9497.*Anal.* Calcd for $C_6H_{10}BrNO_2S$: C, 30.01; H, 4.20. Found: C, 30.03; H, 4.39.

Choromethylsulfonylation of 32a−c. A cold (0 °C) solution of **32a** (940 mg, 4.43 mmol) in CH_2Cl_2 (10 mL) containing Hunig's base (1.26 g, 9.75 mmol) and DMAP (108 mg, 0.89 mmol) was treated dropwise with chloromethanesulfonyl chloride (1.32 g, 8.86 mmol) dissolved in CH_2Cl_2 (10 mL). Stirring was maintained for an additional 1.5 h at this temperature, saturated $NaHSO_4$ solution (20 mL) was added, and the product was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with 1 N HCl (2 × 30 mL), water (20 mL), and brine (2 × 30 mL) prior to drying. The concentrate was subjected to flash chromatography (silica gel, elution with 10% ethyl acetate in hexanes) to furnish **33a** as a colorless oil (1.28 g, 89%); IR (film, cm^{-1}) 1369, 1164; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (s, 2 H), 4.89 (s, 2 H), 4.66 (d, J = 2.4 Hz, 2 H), 2.58 (t, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.0, 75.4, 58.7, 44.0, 40.5; ES MS m/z $(M + Na)^+$ calcd 345.8586, obsd 345.8587. Anal. Calcd for $C_5H_7BrClNO_4Si$: C, 18.50; H, 2.17. Found: C, 18.82; H, 2.26.

For **33b**: colorless oil (33%; 88% based on recovered **32b**); IR (film, cm^{-1}) 1367, 1161; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 2 H), 4.91 (s, 2 H), 4.11 (t, J = 7.0 Hz, 2 H), 2.71 (dt, J = 7.0, 2.6 Hz, 2 H), 2.15 (t, J = 2.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.2, 72.0, 58.5, 50.1, 43.8, 20.8; ES MS m/z $(M + Na)^+$ calcd 359.8743, obsd 359.8739.

For **33c**: colorless oil (25%; 72% based on recovered **32c**); IR (film, cm^{-1}) 1394, 1365, 1160; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 2 H), 4.03 (t, J = 7.6 Hz, 2 H), 2.28 (dt, J = 7.0, 2.3 Hz, 2 H), 2.09−2.00 (series of m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.0, 69.7, 58.2, 51.3, 43.6, 29.4, 15.6; ES MS m/z (M^+) or $(M + Na)^+$ too fleeting for accurate mass measurement.

Radical Behavior of 33c. A magnetically stirred solution of **33c** (130 mg, 0.37 mmol) in degassed refluxing benzene (10 mL) was gradually treated during 2 h via a syringe pump with a solution of tris(trimethylsilyl)silane (202 mg, 0.81 mmol) and AIBN (12 mg, 0.11 mmol) in benzene (10 mL). After three additional hours of heating, the concentrated solution was chromatographed on silica gel (elution with 20% ethyl acetate in hexanes) to give **34** as a colorless oil: IR (film, cm^{-1}) 1371, 1161; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 2 H), 3.93 (m, 2

H), 3.32 (s, 3 H), 2.26 (m, 2 H), 2.03−1.96 (series of m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.1, 69.6, 58.2, 49.7, 43.9, 29.1, 15.6; ES MS *m/z* $(M + Na)^+$ calcd 295.9794, obsd 295.9789.

Radical Behavior of 33a. Comparable reaction of **33a** (138 mg, 0.43 mmol) with tris(trimethylsilyl)silane (316 mg, 1.28 mmol) and AIBN (12 mg, 0.12 mmol) in benzene (total volume 40 mL) afforded following chromatography 35% of **35**, 24% of **36**, 20% of **38**, and 14% of **40**.For **36**: white solid, mp 92−93 °C; IR (film, cm^{-1}) 1385, 1350, 1150; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 5.90 (m, 1 H), 4.98 (m, 4 H), 4.15 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 136.3, 128.9, 128.8, 126.0, 115.7, 58.6, 51.7, 49.5; ES MS *m/z* $(M + Na)^+$ calcd 343.9794, obsd 343.9811. Anal. Calcd for $C_{11}H_{12}ClNO_4S_2$: C, 41.06; H, 3.76. Found: C, 41.47; H, 3.95.

For **38**: white solid, mp 78−79 °C; IR (film, cm^{-1}) 1352, 1173; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 3 H), 7.20 (m, 2 H), 6.83 (m, 1 H), 4.95 (s, 2 H), 4.79 (d, J = 1.4 Hz, 2 H), 4.36 (d, J = 1.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 131.5, 128.9, 128.8, 128.4, 119.3, 57.1, 55.5, 53.8; ES MS *m/z* $(M + Na)^+$ calcd 343.9794, obsd 343.9484. Anal. Calcd for $C_{11}H_{12}ClNO_4S_2$: C, 41.06; H, 3.76. Found: C, 40.99; H, 3.78.

For **40**: white solid, mp 155−156 °C; IR ($CHCl_3$, cm^{-1}) 1382, 1360, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 3 H), 7.19 (m, 2 H), 6.79 (t, J = 1.7 Hz, 1 H), 4.96 (s, 2 H), 4.92 (d, J = 1.8 Hz, 2 H), 4.28 (d, J = 1.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 132.4, 129.0, 128.6, 119.3, 57.2, 57.1, 53.5 (1 C not observed); ES MS *m/z* $(M + Na)^+$ calcd 343.9794, obsd 343.9802. Anal. Calcd for $C_{11}H_{12}ClNO_4S_2$: C, 41.06; H, 3.76. Found: C, 41.44; H, 3.87.

Reduction of 36. To a solution of **36** (14 mg, 0.04 mmol) in degassed refluxing benzene (5 mL) was added a mixture of tri-*n*-butyltin hydride (25 mg, 0.09 mmol) and AIBN (1 mg, 0.01 mmol) dissolved in benzene (5 mL) during 10 h via a syringe pump. After an additional 3 h of stirring, the concentrated material was purified by flash chromatography (silica gel, elution with 15% ethyl acetate in hexanes) and gave **37** as a white solid (8.0 mg, 64%), mp 140−141 °C; IR (film, cm^{-1}) 1342, 1157; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 5.87 (m, 1 H), 4.95 (dd, J = 3.5, 1.7 Hz, 2 H), 4.13 (m, 2 H), 3.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.1, 128.81, 128.78, 126.1, 116.1, 50.6, 48.6, 44.7; ES MS *m/z* $(M + Na)^+$ calcd 310.0184, obsd 310.0183.

Reduction of 38. Analogous processing of **38** (20 mg) afforded 14 mg (79%) of **39** as a colorless oil; IR (film, cm^{-1}) 1355, 1172, 1147; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.36 (series of m, 3 H), 7.19 (m, 2 H), 6.83 (d, J = 1.6 Hz, 1 H), 4.62 (d, J = 1.5 Hz, 2 H), 4.30 (d, J = 1.6 Hz, 2 H), 3.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 131.2, 128.9, 128.8, 128.4, 120.0, 53.6, 52.7, 40.8; ES MS *m/z* $(M + Na)^+$ calcd 310.0184, obsd 310.0196.

Reduction of 40. Comparable treatment of **40** (12.5 mg) furnished 8.0 mg (72%) of **41** as a white solid, mp 173−174 °C, and returned 4 mg of starting material.

For **41**: IR (film, cm^{-1}) 1363, 1331, 1266; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.33 (series of m, 3 H), 7.16 (m, 2 H), 6.76 (m, 1 H), 4.72 (s, 2 H), 4.23 (s, 2 H), 3.27 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 129.0, 128.8, 128.5, 119.7, 56.6, 50.6, 40.8 (one C not observed); ES MS *m/z* $(M + Na)^+$ calcd 310.0184, obsd 310.0173. The structural assignment to **41** was confirmed by X-ray crystallographic analysis.

Radical Behavior of 33b. Reaction of **33b** (95 mg, 0.28 mmol) in the predescribed manner with tris(trimethylsilyl)-silane (174 mg, 0.70 mmol) and AIBN (7 mg, 0.03 mmol) in hot benzene (10 mL total) afforded 56 mg (59%) of **45** and 10 mg (14%) of **46**.

For **45**: colorless wax; IR (film, cm^{-1}) 1377, 1162; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.96 (t, J = 7.0 Hz, 1. H), 4.96 (s, 2 H), 4.41 (d, J = 7.0 Hz, 2 H), 4.23 (m, 2 H), 3.03 (t, J = 5.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 142.4, 128.7, 128.3, 126.2, 115.8, 59.0, 56.1, 50.8, 34.5; ES MS *m/z* $(M + Na)^+$ calcd 357.9950, obsd 357.9942. Anal. Calcd for $C_{12}H_{14}ClNO_4S_2$: C, 42.92; H, 4.20. Found: C, 42.93; H, 4.20.

For **46**: white solid, mp 90−91 °C; IR (film, cm^{-1}) 1372; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (m, 1 H), 5.75 (m, 1 H), 4.94 (s, 2 H), 4.27 (d, J = 6.1 Hz, 2 H), 4.09 (m, 2 H), 2.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 118.4, 58.9, 55.8, 50.4, 30.7; ES MS *m/z* $(M + Na)^+$ calcd 281.9637, obsd 281.9650.

Cyclization of 45. A solution of **45** (50 mg, 0.15 mmol) in deoxygenated refluxing benzene (5 mL) was treated during 6 h via a syringe pump with a solution of tri-*n*-butytin hydride (65 mg, 0.22 mmol) and AIBN (5 mg, 0.03 mmol) in benzene (5 mL). After an additional 2 h of heating, the complete consumption of starting material was noted (TLC analysis). The concentrated residue was chromatographed on silica gel (elution with 25% ethyl acetate in hexanes) to furnish **17** (30 mg, 67%) as a white solid, mp 203−204 °C; IR ($CHCl_3$, cm^{-1}) 1387, 1170, 1156; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (series of m, 3 H), 7.18 (d, J = 1.6 Hz, 2 H), 4.27 (m, 1 H), 3.88 (m, 2 H), 3.74 (dt, J = 14.2, 1.6 Hz, 1 H), 3.67 (dd, J = 4.5, 2.5 Hz, 1 H), 3.51 (m, 2 H), 3.08 (m, 1 H), 2.46 (m, 1 H), 1.05 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.4, 127.7, 125.9, 55.8, 54.7, 47.9, 43.2, 37.9, 30.4; ES MS *m/z* $(M + Na)^+$ calcd 324.0340, obsd 324.0346. Anal. Calcd for $C_{12}H_{15}NO_4S_2$: C, 47.82; H, 5.02. Found: C, 47.82; H, 5.01. The structural assignment to **17** was confirmed by X-ray crystallographaphy.

Allylation of 13. A cold (−78 °C), magnetically stirred solution of **13** (51 mg, 0.29 mmol) in dry THF (3 mL) was treated dropwise with *tert*-butylithium in pentane (0.18 mL, 0.31 mmol). The reaction mixture was stirred at this temperature for 15 min prior to the introduction of allyl bromide (0.04 mL, 0.44 mmol). After 2 h, the mixture was warmed to room temperature, diluted with ether, and quenched with saturated NH_4Cl solution. The separated organic phase was washed with water and brine, then dried and concentrated in advance of chromatography on silica gel. Elution with 15% ethyl acetate in hexanes gave **48** (49 mg, 78%) as a colorless oil; IR (film, cm^{-1}) 1371, 1329, 1259; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85−5.77 (m, 1 H), 5.18−5.10 (m, 2 H), 3.62 (ddd, J = 14.8, 11.8, 5.2 Hz, 1 H), 3.39 (ddd, J = 13.9, 4.8, 1.6 Hz, 1 H), 3.16 (dd, J = 14.7, 5.0 Hz, 1 H), 3.11 (d, J = 13.9 Hz, 1 H), 2.78 (m, 1 H), 2.71 (m, 1 H), 2.52 (br d, J = 1.6 Hz, 1 H), 2.35 (m, 1 H), 1.89−1.84 (m, 1 H), 1.82−1.77 (m, 1 H), 1.68−1.43 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 118.1, 63.2, 47.2, 47.1, 45.4, 34.2, 34.1, 27.3, 22.2; EI MS *m/z* (M^+) calcd 215.0980, obsd 215.0985. Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96. Found: C, 55.86; H, 8.02.

Benzylation of 13. A 48.3 mg (0.28 mmol) sample of **13** was deprotonated with *tert*-butyllithium (0.18 mL, 0.30 mmol) in the predescribed manner and alkylated with benzyl bromide (0.05 mL, 0.4 mmol) to provide 48.2 mg (66%) of **49** as a colorless oil; IR (film, cm^{-1}) 1454, 1315, 1140; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5 H), 3.66 (ddd, J = 14.8, 11.5, 5.2 Hz, 1 H), 3.49 (dd, J = 14.0, 4.8 Hz, 1 H), 3.39 (dd, J = 14.2, 5.1 Hz, 1 H), 3.21−3.15 (m, 2 H), 3.06 (ddt, J = 10.3, 5.2, 1.5 Hz, 1 H), 2.83 (dd, J = 14.2, 10.3 Hz, 1 H), 2.55 (br d, J = 3.3 Hz, 1 H), 1.92−1.82 (m, 1 H), 1.80−170 (m, 1 H), 1.66−1.33 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.7 (4 C), 126.8, 64.7, 47.3, 47.1, 45.2, 35.7, 34.3, 27.2, 22.1; EI MS *m/z* (M^+) calcd 265.1137, obsd 265.1136. Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22. Found: C, 63.59; H, 7.16.

Chromyl Acetate Oxidation of 13. Chromium trioxide (581 mg, 5.81 mmol) was added to a mixture of acetic acid (2.9 mL) and acetic anhydride (2.9 mL) and the resulting dark red solution was stirred for 30 min prior to the introduction of **13** (509 mg, 2.90 mmol) in one portion. The exothermic reaction was cooled in a water bath as necessary. After 18 h of stirring, the dark green solution was diluted with CH_2Cl_2, washed with water, dried, and evaporated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes) afforded 282 mg (42%) of **50** and 155 mg (28%) of **51**.

For **50**: colorless oil; IR (film, cm^{-1}) 1741, 1668, 1323; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, J = 10.4, 5.6 Hz, 1 H), 3.55 (d, J = 14.2 Hz, 1 H), 3.46−3.35 (m, 2 H), 2.97 (br d, J = 3.0 Hz, 1 H), 2.81 (d, J = 13.7 Hz, 1 H), 2.26−2.20 (m, 1 H), 2.04 (s, 3 H), 1.81−1.72 (m, 3 H), 1.63−1.26 (series of m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 81.9, 53.9, 46.8, 38.4, 34.2, 31.8, 21.1, 18.4; EI MS *m/z* (M^+) calcd 233.0722, obsd 233.0698.

Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.34; H, 6.48. Found: C, 46.11; H, 6.37.

For **51**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (dd, J = 14.7, 1.2 Hz, 1 H), 3.70 (ddd, J = 14.8, 5.2, 1.7 Hz, 1 H), 3.55 (dd J = 13.6, 8.6 Hz, 1 H), 3.12−3.07 (m, 1 H), 3.03 (dt, J = 13.5, 1.8 Hz, 1 H), 2.90 (ddd, J = 15.0, 13.0, 1.9 Hz, 1 H), 2.60−2.53 (m, 1 H), 2.02−1.87 (m, 3 H), 1.84−1.67 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 54.2, 50.2, 36.9, 36.7, 32.9, 19.3; EI MS m/z (M^+) calcd 189.0460, obsd 189.0428. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86. Found: C, 44.02; H, 5.85.

Acknowledgment. S.M.L. thanks the Universidad de Buenos Aires, Argentina for the award of a René Thalmann postdoctoral fellowship.

Supporting Information Available: Crystallographic experimental details for **41**, **12**, and **17** including tables of bond lengths, bond angles, atomic coordinates, and isotropic/anisotropic displacement parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010216Z