Regiochemical and Stereochemical Studies on Halocyclization Reactions of Unsaturated Sulfides

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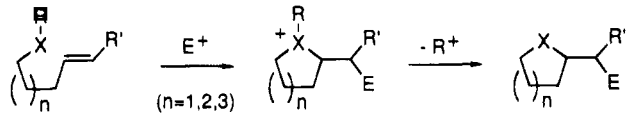
The regiochemistry and stereochemistry for the halocyclization reactions of unsaturated benzyl sulfides have been examined as a function of tether length, type of unsaturation (carbon–carbon double bond versus carbon–carbon triple bond), substituents, and halogenating agent. Alkenyl sulfides were found to react with iodine or bromine at room temperature to give five-membered ring cycloadducts exclusively over those having four-membered rings, while for larger systems, six-membered ring products are formed preferentially over their five-membered ring isomers and exclusively over the seven-membered ring adducts. The endo- versus exo-regioselectivity of these alkenyl sulfide ring closures most likely reflects the difference in thermodynamic stabilities of the β-halo sulfide cycloadducts, which are able to equilibrate via a common episulfonium intermediate. The efficiency of the cyclization process markedly drops off for these alkenyl sulfides as the tether length increases beyond four intervening carbon centers. Thus, while the halogenations of 3-butenyl sulfides and 4-pentenyl sulfides give high yields of cycloadducts, those of 5-hexenyl sulfides afford only small amounts of cyclized products and large quantities of acyclic dibromides. Conversely, the reactions of acetylenic sulfides with iodine give uniformly high yields and regiochemical control regardless of the tether length. Thus, 3-butynyl and 4-pentynyl sulfides cyclize cleanly to the five-membered ring while 5-hexynyl sulfides give exclusively the six-membered ring. The products arising from these alkynyl sulfide ring closures are believed to be formed under kinetic control. The methodology has been applied to the synthesis of unusual bicyclic β-lactams related to the penicillin family of antibiotics.

Introduction

The intramolecular addition of a heteronucleophile to a carbon–carbon double or triple bond in the presence of an electrophilic reagent represents one of the most fundamental methods for constructing heterocyclic rings.[1,2] This general class of reactions has proven particularly effective for those substrates **1** where the heteroatom X is O, NH, or S, although the vast majority of mechanistic and synthetic studies have thus far been limited to the oxygen and nitrogen systems. The overall reaction leading from unsaturated substrate **1** to heterocycle **3** can



1 **2** **3**

formally be viewed as a stepwise addition–dealkylation sequence proceeding through the intermediacy of cationic species **2**. The oxygen and nitrogen cyclizations are generally considered to follow kinetically controlled pathways that lead to adducts whose regiochemistry can usually be predicted using Baldwin's rules.[3] However, the larger atomic size, greater polarizability, and increased nucleophilicity of sulfur make it difficult to reliably predetermine the regiochemical outcome for sulfide cyclizations, which may be highly reversible and give products that can further rearrange. In the formulation of Baldwin's rules, it is explicitly pointed out that the rules are best applied to those systems containing only first row elements and that the introduction of second row atoms (sulfur in particular) into the system can lead to violations. Of the relatively limited number of sulfur cyclizations described in the literature, five-membered sulfur rings appear to be favored over other possible ring sizes.[4–13] For the majority of these examples, the heterosystem contains a divalent sulfur species and the cyclizations are limited to the construction of rigid, bicyclic 5.5-frameworks, wherein the observed 5-*exo-trig* regiochemistry is likely due to the rigidity of the ring system being formed.[4,5] These ring closures can occur through two distinctly different reaction pathways, depending on the nature of the sulfur R group and electrophile E^+. Most electrophile-promoted

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(1) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6, pp 342–404.

(2) (a) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978. (b) Glass, R. S. *Sulfur Centered Reactive Intermediates in Chemistry and Biology;* Chatgilialoglu, C., Asmus, K.-D., Eds.; Plenum Press: New York, 1990; pp 213–226. (c) For reviews on methods for constructing dihydrothiophenes, see: Blenderman, W. G.; Joullie, M. M. *Heterocycles* **1982**, *19*, 111.

(3) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(4) For examples of electrophile-promoted sulfur ring closures applied to the synthesis of thiaprostacyclins, refer to: (a) Nicolaou; K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3472. (b) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3480. (c) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3486. (d) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Chem. Soc., Chem. Commun.* **1978**, 375. (e) Nicolaou, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 7736. (f) Shibasaki; M.; Ikegami, S. *Tetrahedron Lett.* **1978**, *19*, 559.

(5) Sulfur cyclizations have been used as the key step in assembling the 5.5-fused bicyclic tetrahydrothiophene core of biotin. See: (a) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1975**, *97*, 5936. (b) Turos, E.; Parvez, M.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 1116. (c) Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865 and references cited therein.

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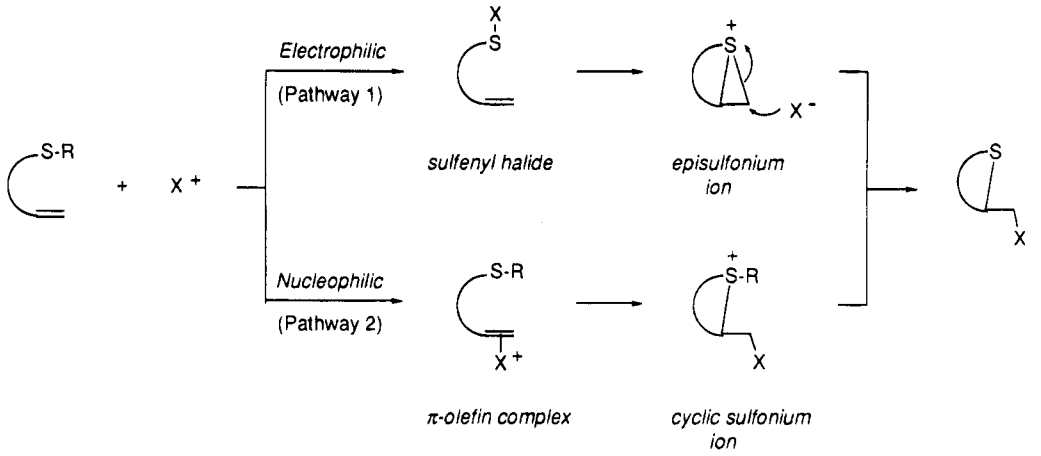
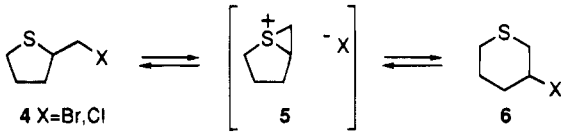
Scheme 1

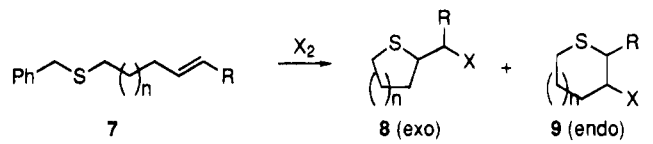


sulfur cyclizations are thought to take place via the initial generation of an electrophilic sulfur species such as a sulfenyl halide, which subsequently adds intramolecularly to the double bond to produce an episulfonium intermediate (pathway 1, Scheme 1).

Nucleophilic attack on this electrophilic species then affords the final cycloadduct. Less common are those cyclizations believed to proceed by the addition of a *nucleophilic* sulfur group onto an electrophilically-activated double bond, as shown in pathway 2 in Scheme 1. Regardless of which cyclization pathway is transversed, the final distribution of isolated products may simply reflect the thermodynamic stabilities of the β-halo sulfide cycloadducts, since these have a known propensity to rapidly equilibrate.[14] The interconversion of cyclic β-halo sulfides **4** and **6**, for example, has been shown to occur through formation and reopening of episulfonium ion **5** to give a 4:1 equilibrium mixture of compounds favoring the *larger* ring system **6**.[15]



To better understand the factors controlling the regiochemistry for electrophile-promoted sulfide cycloadditions, we have examined the exo versus endo selectivity of halogenation reactions of *acyclic* unsaturated benzyl sulfides **7** as a function of the alkyl tether length *n*, type of unsaturation (olefinic versus acetylenic), and substituents R. In this paper, we give a detailed account of these studies and provide rationale to account for the observed regiochemical and stereochemical trends.[16]



Results and Discussion

Selection and Preparation of Substrates. For these halogenation studies, unsaturated *benzyl* sulfides

(6) Proton-mediated additions of thiols to internal double bonds generally afford the Markovnikoff product. See: (a) Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* **1969**, *10*, 2453. Reactions of sulfenyl halides with olefins give adducts in which sulfur has been introduced in anti-Markovnikoff fashion. This striking reversal in regiochemistry has provided convincing proof of the involvement of an episulfonium ion. See: (a) Kartashov, V. R.; Skorobogatova, E. V.; Grudzinskaja, E. Yu.; Akimkina, N. F.; Zefirov, N. S.; Caple, R. *Tetrahedron* **1985**, *41*, 5219. (b) Smit, W. A.; Gybin, A. S.; Bogdanov, V. S.; Krimer, M. Z.; Vorobieva, E. A. *Tetrahedron Lett.* **1978**, *19*, 1085. (c) Mueller, W. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 482. (d) Lautenschlager, F.; Schwartz, N. V. *J. Org. Chem.* **1969**, *34*, 3991. (e) Mueller, W. H. *J. Am. Chem. Soc.* **1969**, *91*, 1223. (f) Wilder, P.; Feliu-Otero, L. A. *J. Org. Chem.* **1966**, *31*, 4264. (g) Wilder, P.; Feliu-Otero, L. A. *J. Org. Chem.* **1965**, *30*, 2560. (h) Corey, E. J.; Block, E. *J. Org. Chem.* **1966**, *31*, 1663. (i) Weil, E. D.; Smith, K. J.; Gruber, R. J. *J. Org. Chem.* **1966**, *31*, 1669.

(7) *tert*-Butyl thioethers have been shown to undergo electrophile-promoted addition to internal double bonds. (a) Hutchinson, J. H.; McEachern, E. J.; Scheigetz, J.; Macdonald, D.; Therien, M. *Tetrahedron Lett.* **1992**, *33*, 4713. (b) Eichinger, K.; Mayr, P.; Nussbaumer, P. *Synthesis* **1989**, 210.

(8) Cyclizations of unsaturated thioamides and thioureas in which sulfur acts as the nucleophile generally give the 5-*exo-trig* ring closure product. For examples and exceptions, see: (a) Engman, L. *J. Org. Chem.* **1991**, *56*, 3425. (b) Creeke, P. I.; Mellor, J. M. *Tetrahedron Lett.* **1989**, *30*, 4435. (c) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953. (d) Takahata, H.; Suzuki, T.; Maruyama, M.; Moriyama, K.; Mozumi, M.; Takamatsu, T.; Yamasaki, T. *Tetrahedron* **1988**, *44*, 4777. (e) Bernett, R. G.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 2048. (f) Tamaru, Y.; Mizutani, M.; Furukawa, S.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (g) McManus, S. P.; Ware, D. W.; Hames, R. A. *J. Org. Chem.* **1978**, *43*, 4288. (h) Lown, J. W.; Joshua, A. V. *Can. J. Chem.* **1977**, *55*, 122. (i) Lown, J. W.; Joshua, A. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2680. (j) Smith, P. A. S.; Sullivan, J. M. *J. Org. Chem.* **1961**, *26*, 1132.

(9) Jones and colleagues have examined the intramolecular additions of sulfenic acids to alkynes as an attractive synthetic route to cyclic α,β-unsaturated sulfoxides. The high regioselectivity and syn-selectivity of these reactions have been explained in terms of a concerted addition mechanism involving a five-center transition state (Bell, R.; Cottam, P. D.; Davies, J.; Jones, D. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2106).

(10) Rengevich, E. N.; Staninets, V. I.; Shilov, E. A. *Dokl. Akad. Nauk SSSR* **1962**, *146*, 111; *Dokl. Adad. Nauk. SSSR (Engl. Transl.)* **1962**, *146*, 787; *Chem. Abstr.* **1963**, *58*, 3285f.

(11) (a) Vedejs, E.; Buchanan, R. A.; Conrad, P. C.; Meier, G. P.; Mullins, M. J.; Schaffhausen, J. G.; Schwartz, C. E. *J. Am. Chem. Soc.* **1989**, *111*, 8421. (b) Vedejs, E.; Mullins, M. J. *J. Org. Chem.* **1979**, *44*, 2947.

(12) For examples of related sulfur cyclizations, see: (a) Kitamura, T.; Takachi, T.; Kawasato, H.; Kobayashi, S.; Taniguchi, H. *Tetrahedron Lett.* **1989**, *30*, 7445. (b) Kitamura, T.; Kawasato, H.; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1986**, 399. (c) McCabe, P. H.; Stewart, A. *J. Chem. Soc., Chem. Commun.* **1980**, 100.

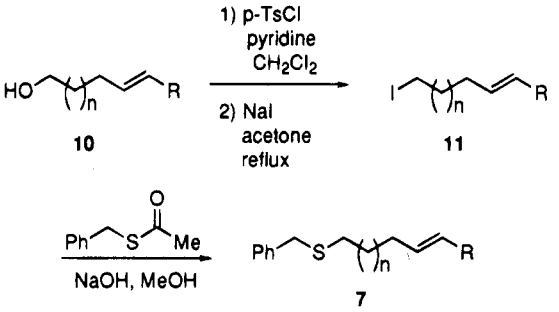
(13) For intramolecular Michael-type additions of thiolates to unsaturated functionality, see: (a) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727. (b) Vedejs, E.; Mullins, M. J.; Renga, J. M.; Singer, S. P. *Tetrahedron Lett.* **1978**, *19*, 519. (c) Stork, B.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1977**, *99*, 3850.

(14) (a) Ikegami, S.; Asai, T.; Tsuneoka, K.; Matsumura, S.; Akaboshi, S. *Tetrahedron* **1974**, *30*, 2087 and references cited therein. (b) Reike, R. D.; Bales, S. E.; Roberts, L. C. *J. Chem. Soc., Chem. Commun.* **1972**, 974. (c) Owsley, D. C.; Helmkamp, G. K.; Rettig, M. F. *J. Am. Chem. Soc.* **1969**, *91*, 5239. (d) Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2075. (e) Kharasch, N.; Buess, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 2724.

(15) (a) Leroy, C.; Martin, M.; Bassery, L. *Bull. Soc. Chim. Fr.* **1974**, 590. (b) Ikegami, S.; Ohishi, J.-i.; Shimizu, Y. *Tetrahedron Lett.* **1975**, *16*, 3923.

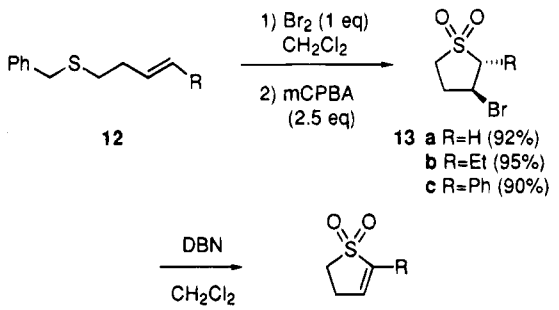
(16) For an earlier communication of our preliminary results, see: Ren, X. F.; Turos, E. *Tetrahedron Lett.* **1993**, *34*, 1575.

were chosen as substrates because of their increased resistance toward dimerization and oxidation, lower volatility, and strong UV activity compared to the corresponding thiols or methyl sulfides. Moreover, the presence of the benzyl moiety provides a convenient spectroscopic handle that allowed the progress of the reactions to be monitored by ^{1}H NMR. Thus, the disappearance of the signal for the PhCH_2S protons of benzyl sulfides **7** and the emergence of a singlet for benzyl halide generated during the reaction could be followed. The substrates required for these studies were prepared from the corresponding alcohols or alkyl halides using standard procedures, as illustrated for the alkenyl sulfides **7**.[17]



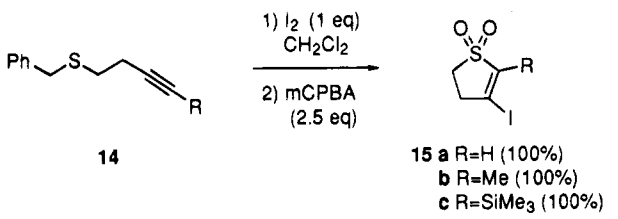
General Procedure for the Halocyclization Reactions. The halogenations were carried out by adding 1 molar equiv of Br_2 or I_2 to a solution of the unsaturated sulfide in CH_2Cl_2 at room temperature. Because of the volatility and chemical instability of some of the halo sulfide cycloadducts, particularly those of lower molecular weight, the crude products were immediately oxidized using *m*-chloroperoxybenzoic acid (*m*-CPBA) to their sulfone derivatives, which were isolated after purification by flash chromatography. The structures of the adducts were determined by comparing the ^{1}H and ^{13}C NMR spectra of the purified β-halo sulfones to those of the crude β-halo sulfides, with particular attention being paid to the chemical shifts of the protons α to sulfur before and after sulfonylation. The regiochemical assignments for the products from the alkenyl substrates were further supported by conversion of the halo sulfones to their vinyl sulfones. In most cases, the endocylic and exocylic double bonds in these elimination products could be readily distinguished and assigned in the NMR spectrum by the chemical shifts and splitting patterns of their vinyl protons.[18] Moreover, for two of the sulfone products (see **59b** and **69a**), single-crystal X-ray analysis confirmed the NMR structural assignments.

Regiochemical Studies. To begin our studies, we first examined the bromination reactions of 3-butenyl benzyl sulfides **12**. Upon addition of Br_2, each of the substrates cyclized instantaneously to the five-membered ring β-bromo sulfides, which after *m*-CPBA oxidation afforded bromo sulfones **13** in excellent overall yields. Following these reactions by ^{1}H NMR in $CDCl_3$ solution, we were unable to observe the formation of any other halogenation products. Similar results were obtained using I_2 as the halogenating reagent, although the reactions proceeded more slowly and typically required several days to reach completion. Some of the iodosulfones were also susceptible toward formation of the vinyl sulfone by spontaneous elimination of HI during workup and purification. For each of the bromides **13a–c**, the proton at the Br-substituted center of the ring displayed a characteristic multiplet between 4.6 and 3.9 ppm in the NMR spectrum.[19] The trans relative stereochemistry of adducts **13b** and **13c** was inferred based on an anti addition to the olefin.[14] Moreover, each bromo sulfone



provided a single elimination product upon treatment with DBN whose NMR spectrum is indicative of a dihydrothiophene 1,1-dioxide ring system. For example, the ^{1}H NMR spectrum for the vinyl sulfone derived from **13a** showed AB multiplets at 6.73 and 6.64 ppm for the two vinyl protons, in accord with that reported[20a] for 4,5-dihydrothiophene *S,S*-dioxide. Similarly, the NMR spectrum obtained for the elimination product from **13b** agrees with the spectral data published by Chou et al. for 2-ethyl-4,5-dihydrothiophene *S,S*-dioxide.[20b]

In contrast to the high efficiency of these 5-*endo-trig* bromocyclizations, the brominations of 3-butynyl sulfides **14** gave complicated mixtures of products resulting from the rapid reaction of the vinyl sulfide cycloadducts with Br_2. To avoid overhalogenation, we therefore decided to use iodine as the electrophilic reagent and found to our satisfaction that the halocyclizations proceeded cleanly to give five-membered ring adducts **15** as the exclusive products. The acetylenic R substituent does not diminish the efficiency or the rate of the reactions.



The presence of an allylic or propargylic substituent on the alkyl tether does not interfere with the cyclizations. For example, the reactions of substituted sulfides **16** and **18** each give a single iodination product whose ^{1}H and ^{13}C NMR spectra are consistent with the five-membered ring structures **17** and **19**, respectively. The trans stereochemistry of **17** is evident from the fact that the proton α to the iodide is a doublet of a triplet (J = 5.9, 9.8 Hz), which suggests that **17** exists primarily in an envelope-like conformation having both the methyl

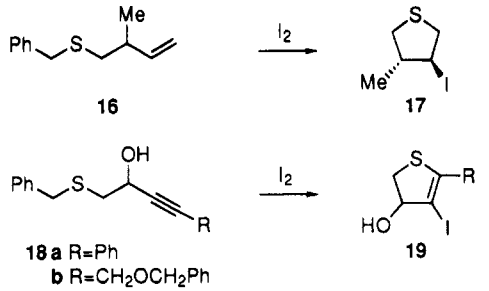
(17) The starting unsaturated alcohols or alkyl halides were purchased from commercial sources or prepared by Wittig olefination of the appropriate lactol.

(18) Deshielding of the vinyl proton syn to the sulfone center of an exocyclic vinyl sulfone usually separates the syn and anti protons in the NMR spectrum into well-separated geminally-coupled signals (Meyers, C. Y.; Sataty, I. *Tetrahedron Lett.* **1972**, *13*, 4323.).

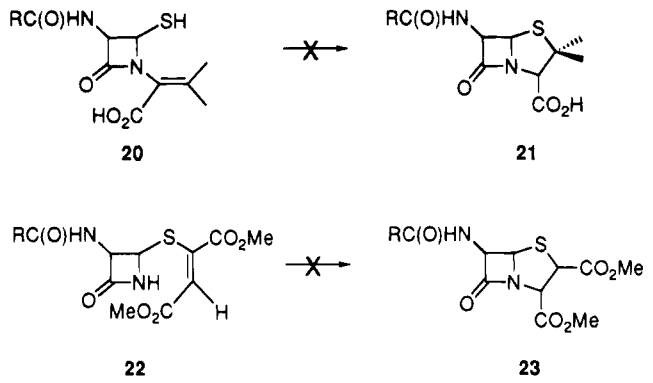
(19) The ^{1}H NMR data for these adducts are consistent with that reported for related halogenated cyclic sulfones. For reference, see: Tabushi, I.; Tamaru, Y.; Yoshida, Z.-i. *Tetrahedron Lett.* **1971**, *12*, 3893.

(20) The ^{1}H NMR spectra of the elimination products derived from **13a**, **13b**, and **43a** are in good agreement with the literature values. See: (a) Gianturco, M. A.; Friedel, P.; Flanagan, V. *Tetrahedron Lett.* **1965**, *6*, 1847. (b) Chou, T.-s.; Tso, H.-H.; Chang, L.-J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 515. (c) Kuhn, H. J.; Defoin, R.; Gollnick, K.; Kruger, C.; Tsay, Y.-H.; Liu, L.-K.; Betz, P. *Tetrahedron* **1989**, *45*, 1667.

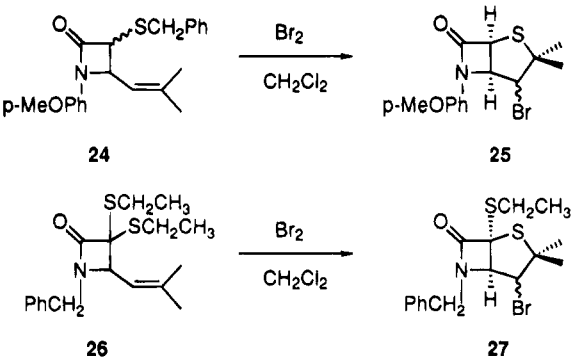
and iodide groups in equatorial positions with the two methine protons axially aligned.



The influence of an existing strained ring on the rate and regiochemical outcome of various ring-forming reactions has been cited previously, most notably for the cyclizations leading to the formation of bicyclic β-lactam rings.[21] In some instances, the reactions can be precluded due to the high conformational energy required to close the second ring. For example, Narisada and co-workers[22] have documented their unsuccessful attempts to execute 5-*endo-trig* ring closures on alkenyl β-lactam systems **20** and **22**, while the corresponding 5-exo or 6-endo cyclizations take place readily.[23,24]



We were therefore curious as to what effect the presence of a β-lactam ring might have on the efficiency and regioselectivity of 5-endo sulfide cyclizations. To examine this, alkenyl-substituted azetidinones **24** and **26** were prepared[25] and reacted with Br_2 under the usual reaction conditions. In each case, these substrates cyclized rapidly to the desired 4,5-fused bicyclic ring compounds **25** and **27**, respectively, in high yields. In the case of **24**, the cis isomer was quantitatively converted to a 5:1 mixture of cycloadducts **25** epimeric at the bromine-bearing carbon. On the other hand, the trans isomer of **24** failed to cyclize and instead gave products derived from olefin bromination. Dithio-substituted azetidinones **26** also underwent ring closure smoothly to quantitatively afford **27** as a 4:1 mixture of α:β Br epimers. The assignment of α and β relative stereochemistry in **25** and **27** is based on the assumption that the halogen would selectively add from the less hindered face of the olefin (syn to the allylic proton on the rings).



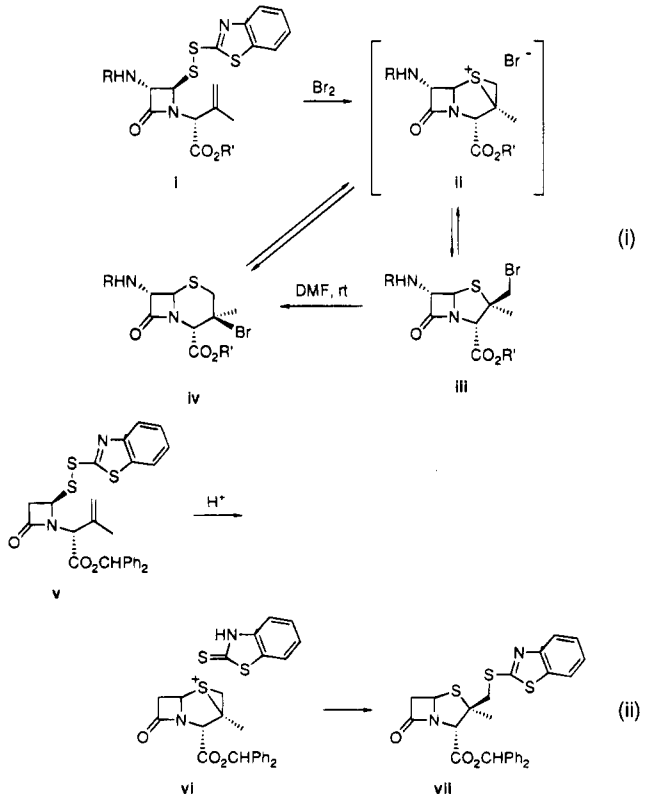
In similar fashion, acetylenic azetidinones **28** and **30** were converted in high yield to bicyclic β-lactams **29** and **31** upon iodination at room temperature. As above, the cis isomer of **28** cyclizes easily, while the trans stereoisomer of **28** is unreactive and can be recovered unchanged. The conversions of **26** to **27** and **30** to **31** are, to our knowledge, the first examples of a halocyclization involving an unsaturated dithiane.[26] The endo-regiospecificity and high yield associated with the formation of these 4.5-fused rings is further proof of the remarkable efficiency in which these cyclizations are able to render highly strained ring systems.

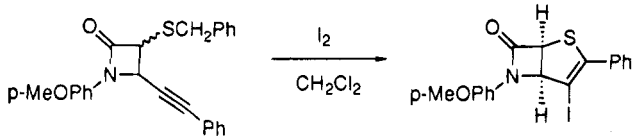
To briefly summarize these results, 3-alkenyl and 3-alkynyl sulfides each cyclize in the presence of a halogen to give exclusively the five-membered ring via a 5-endo ring closure process. The regiospecificity of these

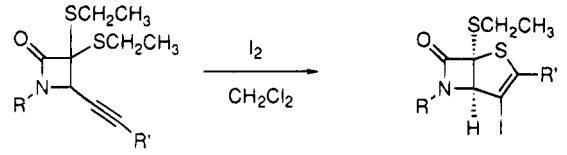
(21) The presence of an azetidinone ring can have a profound influence on the regiochemistry of radical ring closures. For examples, see: (a) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandraskaran, R. Y.; Finn, K.; De Meester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245. (b) Kametami, T.; Honda, T. *Heterocycles* **1982**, *19*, 1861. (c) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761. (d) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1982**, *23*, 2505. (e) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2693.

(22) Narisada, M.; Onoue, H.; Ohtani, M.; Watanabe, F.; Okada, T.; Nagata, W. *Tetrahedron Lett.* **1978**, *19*, 1755.

(23) For example, the bromination of disulfide **i** reportedly gives five-membered ring product **iii** in quantitative yield as the initially-formed product of the reaction (eq i). Upon standing at room temperature in solution, **iii** isomerizes cleanly to the six-membered ring **iv** through the episulfonium ion **ii** (Kamiya, T.; Teraji, T.; Saito, Y.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron Lett.* **1973**, *14*, 3001). Analogous behavior has been observed for the acid-catalyzed isomerization of azetidinyl disulfides such as **v** (eq ii). In this instance, protonation leads to the generation of an episulfonium species **vi** which undergoes nucleophilic ring opening to afford adduct **vii** (Alpegiani, M.; Giudici, F.; Perrone, E.; Borghi, D. *Tetrahedron Lett.* **1990**, *31*, 3509).



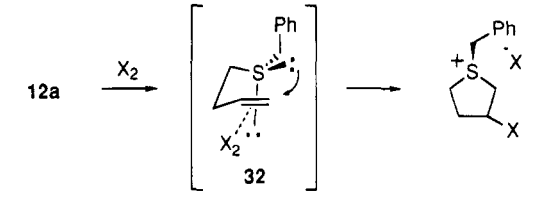


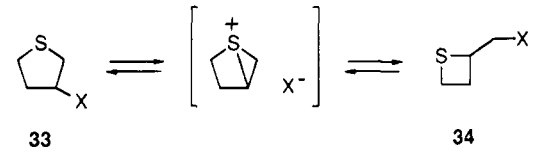


30 a R=*p*-MeOPh, R'=Ph
b R=CH_2Ph, R'=$SiEt_3$
c R=CH_2Ph, R'=Ph

31 a (88%)
b (95%)
c (98%)

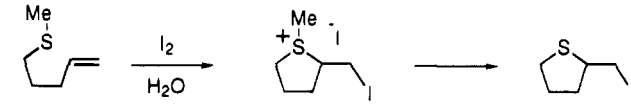
ring closures may be due, at least in part, to a kinetic preference for forming the less highly strained five-membered ring. From inspection of Dreiding models, the equatorial lone pair on sulfur in transition structure **32** appears to be better aligned with the *terminal* p-lobe of the olefin π-complex (leading to the five-membered ring sulfonium salt) rather than with the internal p-orbital (which would lead to the four-membered ring sulfonium ion). On this basis, the transition state for 5-endo cyclization should be considerably lower in energy than for the 4-exo mode. For the *alkenyl* cyclizations, the regioselectivity can also be explained on the basis of the greater thermodynamic stability of the S-dealkylated



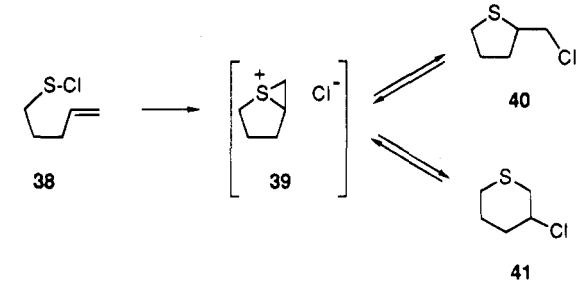


five-membered ring adduct **33** versus the more highly strained four-membered ring **34**, which could conceivably arise from **33** via an episulfonium intermediate.[27]

We next set out to examine the halogenations of 4-pentenyl sulfides under the same conditions as described above. Prior to carrying out these model reactions, we noted a brief study that appeared in 1962 by Rengevich and colleagues focusing on the kinetics for the iodocyclization of 4-pentenyl methyl sulfide (**35**) in aqueous media.[10] In this paper, the authors measured the

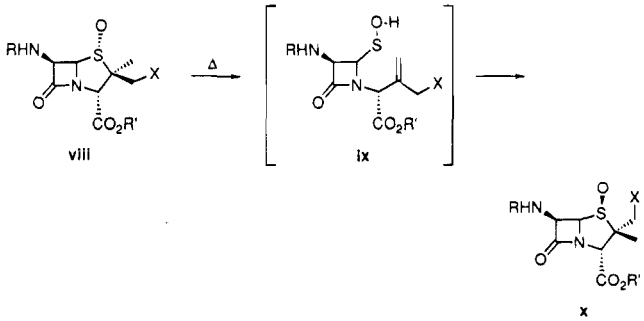


second order rate constant for the reaction to be on the order of 10^{-3} M^{-1} s^{-1} at 20 °C. More recently, however, Musker and colleagues independently determined that the rate of iodocyclization of **35** is at least 10^4 times faster than that originally reported.[8e] No attempt was made by these investigators to determine the structure of the cycloadduct, since, as they claimed, "the product of the iodocyclization of 4-pentenyl methyl sulfide was previously determined to be 2-(iodomethyl)tetrahydrothiophene." However, upon closer reading of the Rengevich paper, we failed to find convincing evidence that this is indeed the case. Rather, it is the initial product of the reaction, *S*-methyl-2-(iodomethyl)tetrahydrothiophene (**36**), and not the iodo sulfide **37**, that reportedly was isolated by Rengevich from the reaction. Furthermore, despite



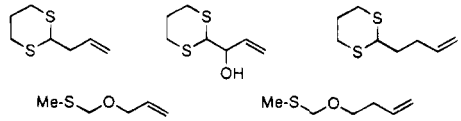
the statement made by Rengevich and co-workers that their cyclized product is a derivative of tetrahydrothiophene having a melting point greater than 320 °C and whose composition was "checked by analysis," no data was actually provided to confirm itsfive-membered ring structure. Therefore, it is not clear from these readings

(24) The thermal rearrangements first reported by Spry for the conversion of penicillin sulfoxides **viii** to **x** proceed via a tandem ring opening–cyclization mechanism involving sulfenic acid **ix** (Spry, D. O. *J. Am. Chem. Soc.* **1970**, *92*, 5006). This type of isomerization process has been utilized in the preparation of penicillin derivatives. (a) Barton, D. H. R.; Comer, F.; Grieg, D. G. T.; Sammes, P. G.; Cooper, C. M.; Hewitt, G.; Underwood, W.G. E. *J. Chem. Soc. C* **1971**, 3540. (b) Maiti, S. N.; Spevak, P.; Ogawa, K.; Micetich, R. G. *J. Org. Chem.* **1988**, *53*, 3803. These isomerizations are closely related to the classical Morin rearrangement of penicillin sulfoxides to cephalosporins, a process which involves the formation and cyclization of an electrophilic sulfur species onto a double bond. (Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896.) For discussions and references, see: (c) Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32. (d) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, **1982**; Vol. 1. For related reactions involving an intramolecular sulfenylation of an allenyl azetidinone system, see: Farina, V.; Kant, J. *Tetrahedron Lett.* **1992**, *33*, 3559.



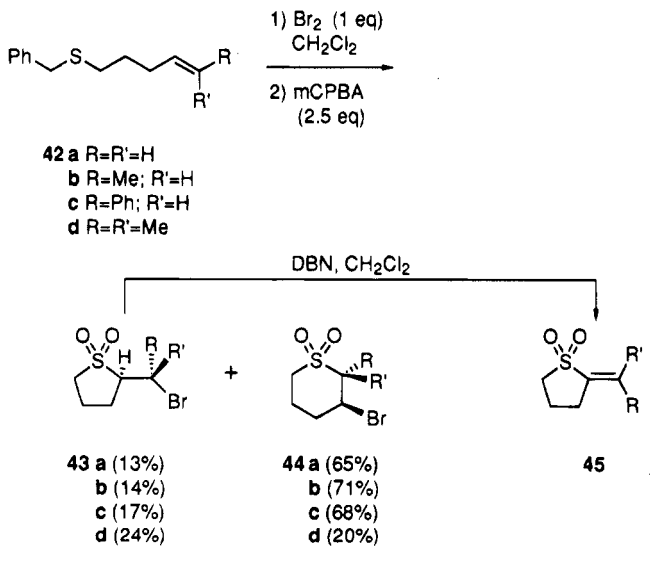
(25) Ren, X.-F.; Turos, E. *J. Org. Chem.* **1994**, *59*, 5858.

(26) To investigate whether halocyclizations of other types of unsaturated dithianes could be effected as a potential route to 2-heterosubstituted thiofurans and thiopyrans, the following substrates were tested in reactions with Br_2 or I_2. However, we were unable to identify any stable cyclization products from these halogenations.



(27) (a) For an example of a regiospecific and stereospecific 5-*endo-trig* ring closure of a sulfenyl acetate intermediate which is thought to proceed through such an intermediate, see ref 11. (b) For an example of a 5-*endo-dig* cyclization of an acetylenic *tert*-butyl thioether used as a method of preparing substituted thiophenes, see ref 7b.

whether the five-membered ring β-halo sulfide is the exclusive, or even favored, product of the reaction. This conclusion is further strengthened by considering the chemistry of β-halo sulfides, which are notoriously susceptible toward isomerization processes. For instance, it is known that the cyclization of sulfenyl chloride **38**, generated from the 4-pentenyl disulfide and Cl_2, provides a mixture of the five- and six-membered ring chloro sulfides **40** and **41**, respectively.[15b] When the reaction is run at low temperature, a 4:1 mixture of the five-:six-membered rings is obtained, but upon warming to room temperature, this mixture equilibrates via episulfonium intermediate **39** to favor the larger ring adduct **41**. Analogous behavior has been reported for the β-bromo sulfide derivatives of **40** and **41**.[15b] We have observed a similar outcome for our bromination reactions involving pentenyl sulfides **42**, which when done at room temperature give high yields of five- and six-membered ring regioisomers **43** and **44**, respectively.[28] On the basis of the work cited above, it would be reasonable to conclude that the mixtures of halo sulfone regioisomers isolated from these reactions corresponds to the thermodynamic ratios of the two *halo sulfide* adducts formed in the halocyclization prior to oxidation. Clearly, this mixture favors the larger (endocyclic) ring product. As demonstrated for the halocyclization of **42d**, disubstitution at the terminal site of the olefin apparently overrides this endo preference, albeit the lower yields. We speculate that the vinyl methyl groups in **42d** may destabilize the six-membered ring adduct due to strong diaxial interactions, such that the smaller (exo) cycloadduct having these groups removed from the ring now becomes favored. The structures of cycloadducts **43** and **44** were assigned from the ^1H NMR spectra of both the initially produced cyclic sulfides and their sulfone derivatives. Of particular importance was the downfield shift observed for the protons at the sulfur-bearing center of the ring upon oxidation to the sulfone.



42 a R=R'=H
b R=Me; R'=H
c R=Ph; R'=H
d R=R'=Me

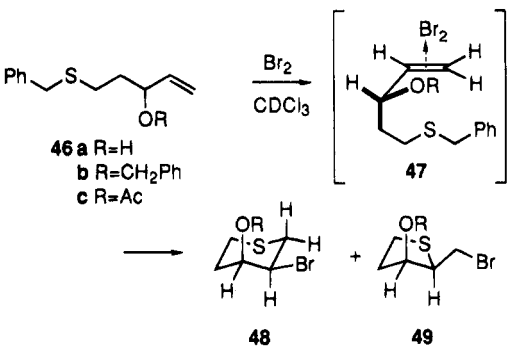
43 a (13%)
b (14%)
c (17%)
d (24%)

44 a (65%)
b (71%)
c (68%)
d (20%)

45

To gather additional proof of regiostructure for these cycloadducts, the mixtures of bromo sulfones **43** and **44** were treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to effect their elimination to the exocyclic and endocyclic vinyl sulfones, respectively. For the mixture of compounds **43a** and **44a**, the ^1H NMR spectrum obtained for the minor elimination product (from **43a**) gives a set of well-separated signals at 5.9 and 5.6 ppm matching that reported[9] for the exocyclic five-membered ring vinyl sulfone **45**, while the NMR data for the major elimination product (from **44a**) is in line with that expected for the α,β-unsaturated six-membered ring sulfone.[29] Similar attempts to convert the mixtures of **43/44b–d** to their respective vinyl sulfones using DBN resulted in the isolation of exocyclic vinyl sulfones **45** and complete recovery of compounds **44b–d**. The resistance of bromides **44b** and **44c** to undergo what would otherwise appear to be a facile E2 elimination (based on the ease in which the elimination of **44a** occurs) corroborates the trans stereochemistry of the R group and the bromide within these adducts, which must arise from an anti addition across the *E*-double bond of **42b** and **42c**.

To probe more deeply into the underlying features governing diastereofacial selectivity in these 5-exo versus 6-endo additions, the bromination reactions of α-substituted sulfides **46** were examined. The cyclizations of **46a** and **46b** proceed cleanly in the presence of 1 molar equiv of I_2 to produce the six-membered ring adducts **48** as the major products and minor amounts of a second compound we believe is the cis-disubstituted five-membered ring isomer **49**.[30] The cis stereochemistry of adducts **48** is



46 a R=H
b R=CH_2Ph
c R=Ac

47 **48** **49**

based on the observation that the axial proton at the halogenated center appears in the ^1H NMR spectrum as a doublet (J_{app} = 11.7 Hz) from strong vicinal coupling with one adjacent axial proton, which is broadened by weak coupling with two vicinal equatorial protons. Also, the equatorial proton at the oxygen-substituted carbon is a broadened singlet as a result of coupling with two adjacent equatorial protons and one axial proton. The cis-stereochemistry in **48** and **49** is in accord with the theoretical models of type A cyclizations put forth by Hehre and Chamberlain which state that the nucleophile preferentially adds to the olefin π-complex through a conformer having the allylic heterogroup coplanar with the olefin centers, as illustrated in **47**.[31]

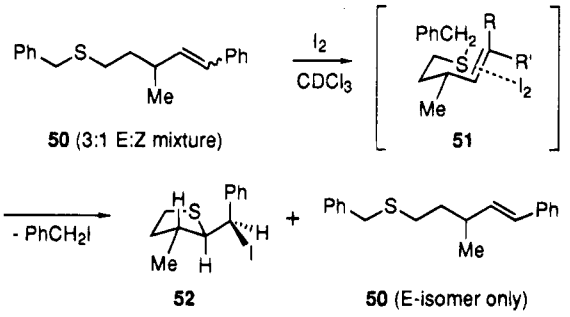
One additional experiment conducted using a 3:1 *E*:*Z* mixture of α-methyl-substituted sulfides **50** gave an unexpected result. Each isomer of **50** had been expected to cyclize via chairlike transition states to give five- and six-membered ring products. However, upon addition of 1 equiv of I_2 to the mixture, we found that the *Z*-isomer

(28) Small amounts (<10%) of acyclic dibromosulfones arising from halogenation of the olefin are also isolated from these reactions.

(29) This vinyl sulfone obtained from **44a** has been reported, but without NMR characterization (see ref 20c). Nevertheless, the overlapping AB pattern of signals at 6.40 ppm observed for this product is consistent with that expected for an endocyclic vinyl sulfone. For NMR data on a related structure, see: Becker, K. B.; Labhart, M. P. *Helv. Chim. Acta* **1983**, *66*, 1090: ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (m, 2H), 3.13 (m, 2H), 2.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 130.5, 51.0, 25.0, 20.5.

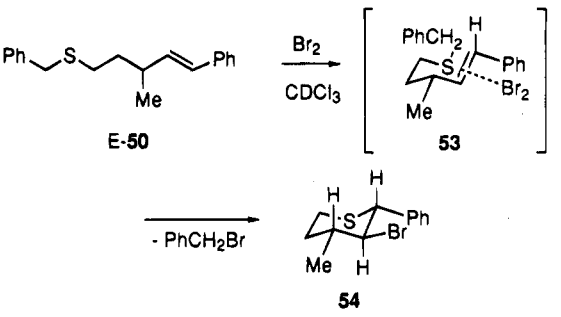
(30) For the reactions of **49c**, the initial mixture of bromination products rearranged upon standing overnight. No attempt was made to isolate or characterize these compounds.

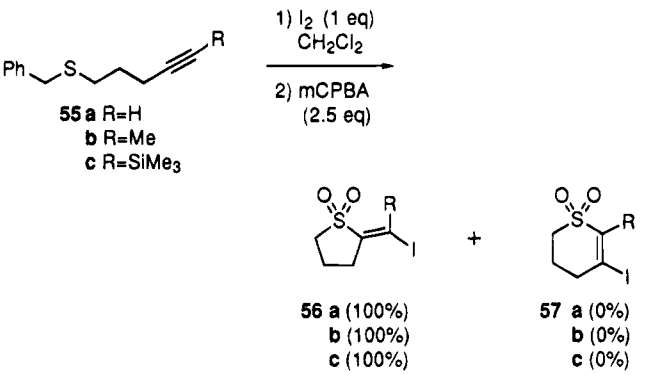
was slowly consumed over several days to afford five-membered ring product **52** as a single regio- and stereoisomer. On the other hand, the *E*-isomer was completely inert to I_2 and was recovered from the reaction unchanged. Structure **52** arising from (*Z*)-**50** was assigned based on the ^1H NMR chemical shifts and splitting patterns of the methine signals. Specifically, the benzylic methine proton appears as a doublet (J = 5.9 Hz) at 4.72 ppm and the methine ring proton alpha to sulfur is split into a doublet of a doublet (J = 5.9, 4.9 Hz) at 3.40 ppm. The exclusive formation of **52** from (*Z*)-**50** suggests that the difference in thermodynamic stabilities of the five- and six-membered ring regioadducts must be significantly large to force the equilibrium entirely to the five-membered ring. It would appear that placing the bulky iodobenzyl moiety exocyclic on the five-membered ring of **52** is energetically more favorable than having the methyl and iodo groups equatorial and the phenyl substituent axial on the six-membered ring. The lower reactivity of (*E*)-**50**, on the other hand, might be due to the increasing degree of $A^{1,3}$ interactions between the phenyl and allylic methyl groups in transition state **51** (R = H, R′ = Ph) which may weaken the π-coordination of I_2 to the olefin.



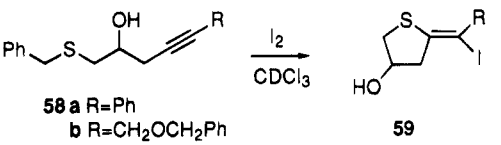
With the clean recovery of (*E*)-**50** from this reaction, we took the opportunity to attempt the cyclization under more forcing conditions. Treatment of (*E*)-**50** with Br_2 produced a single bromination product whose ^1H NMR spectrum is most consistent with six-membered ring structure **54**. In particular, we note that the benzyl methine proton of this adduct appearing as a doublet at 4.13 ppm has strong diaxial coupling (J = 11.7 Hz) with the methine proton α to the bromine, which is split into a doublet of doublets at 4.22 ppm with large vicinal J values (J = 11.7, 10.7 Hz). In this case, it seems that although an equilibrium should exist between **54** and its five-membered ring isomer, the six-membered ring compound having all three groups equatorial is apparently preferred.

As observed for the 3-butynyl substrates, reactions of 4-pentynyl sulfides **55** with Br_2 gave complex mixtures of bromination products, even if bromine is slowly added over a period of several hours. In contrast, the *iodocyclizations* of **55** proceeded cleanly to give the five-membered ring adducts in quantitative overall yield. An X-ray structure of **56b** was obtained that confirms both its five-membered ring structure and E-olefin geometry.[38] The structures of **56a** and **56c** are based on the close similarities of their ^1H and ^{13}C NMR spectra to those of **56b**.





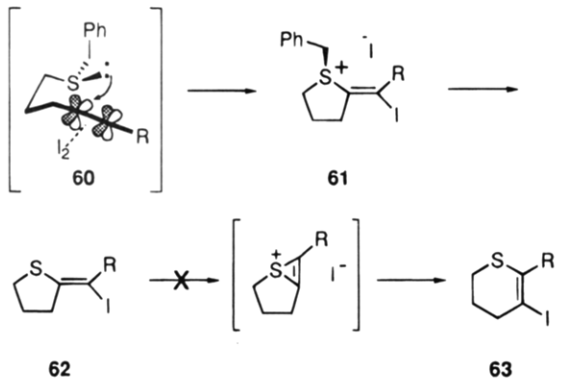
This 5-*exo-dig* ring closure pathway is also maintained for the iodinations of α-hydroxy-substituted sulfides **58a** and **58b**, which gave cycloadducts **59** as a single regioisomer.



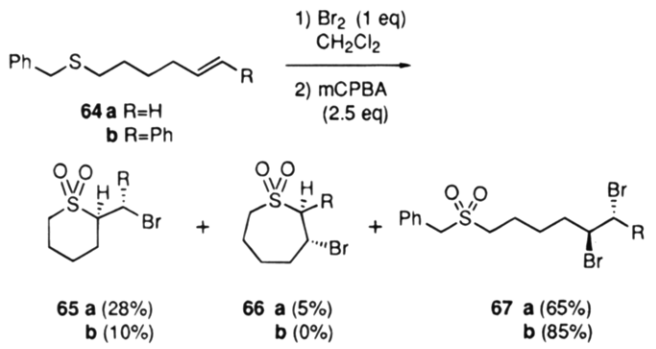
The fact that none of the six-membered ring regioadducts are obtained in these iodination reactions of *alkynyl* substrates **55** and **58** is somewhat surprising, given that the corresponding *alkenyl* cyclizations are endo-selective. This suggests that unlike the *5-exo-trig*/*6-endo-trig* ring closures which yield thermodynamic mixtures of products, these *5-exo-dig* cyclizations appear to be kinetically-controlled. This is reasonable since equilibration between the five- and the six-membered ring isomers (**62** and **63**) would necessarily proceed through an unsaturated episulfonium intermediate. The faster rate of ring closure for the *5-exo-dig* pathway relative to the *6-endo-dig* mode may be due in part to the internal p-lobe of acetylene–I_2 π-complex **60** having a more favorable alignment with the lone pair of the incoming sulfur nucleophile.

Finally, the endo/exo selectivity for the halocyclizations of 5-hexenyl and 5-hexynyl sulfides was investigated. In terms of the *efficiency* of these cyclizations, notable differences between the alkenyl and alkynyl systems were discovered. As an illustration, the bromination reactions of the 5-hexenylsulfides **64** provide acyclic dibromo sulfones **67** as the predominant product of the

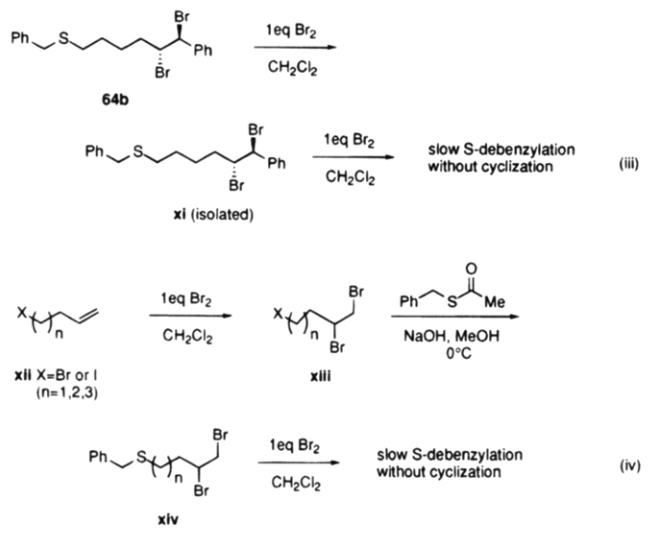
(31) The mechanism of the initial cyclization step has been the subject of much debate and speculation in recent years, particularly with regard to the role of the electrophile in the activation of the double bond. It now appears that while intermolecular additions of heteronucleophiles to electrophilically activated double bonds require the generation of an "onium-type" intermediate, such as in the bromination of olefins, intramolecular reactions can be triggered by the formation of a weakly associated electrophile–olefin π-complex. Hehre and Chamberlain have incorporated this mechanistic feature into theoretical models to explain differences in stereochemistry often observed for certain intermolecular and intramolecular additions to double bonds. Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.



reaction.[32] Although the amounts of cyclization adducts **65** and **66** from these additions are low, the major cycloadduct in each case is the six-membered ring **65**.

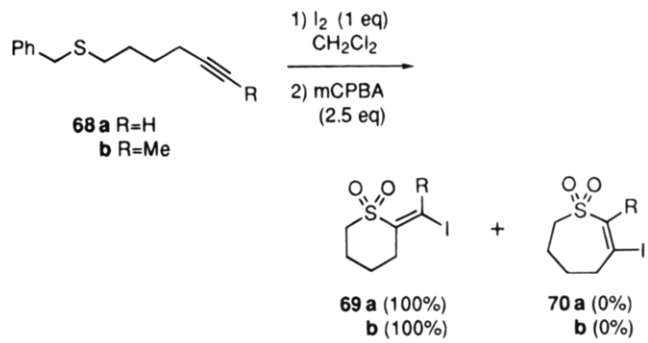


(32) (a) The isolation of large amounts of acyclic dibromides in these reactions made us speculate that perhaps these sulfide cyclizations may be proceeding regioselectively by an intramolecular S_N2 alkylation. To rule this out, we prepared *S*-benzyl dibromides **xi** from **64b** using 1 equiv of Br_2 (eq iii). After purification by flash chromatography, **xi** was treated with 1 equiv of Br_2 and the mixture was periodically examined by ^1H NMR. From the NMR spectrum, we observed that benzyl bromide was slowly being generated over several days, indicating the loss of the *S*-benzyl group. However, cyclization products were not being formed, since the protons α to the bromines of **xi** were unaffected. Similarly, dibromides **xiv** (prepared in two steps from the bromo- or iodo olefin **xii**) were found to gradually decompose in the presence of 1 equiv of Br_2 by loss of the *S*-benzyl moiety *without cyclization* (eq iv). (b) Mechanistic studies of intramolecular displacement reactions of sulfides have been reported(Jursic, B.; Ladika, M.; Sunko, D. E. *Gazz. Chim. Ital.* **1988**, *118*, 613). Since the rates of solvolysis for $PhCH_2S(CH_2)_{n-1}X$ decrease in the order of n = 6>5>3>4, formation of the six-membered cyclic sulfonium ion by intramolecular alkylation is favored kinetically over the five-membered ring. However, the presence of a second halide adjacent to the site of displacement in our systems (i.e., **xi** or **xiii**) apparently slows down the S_N2 reaction considerably. For an application of this alkylation procedure in the asymmetric synthesis of sulfur rings, see Urban, F. R.; Breitenbach, R.; Vincent, L. A. *J. Org. Chem.* **1990**, *55*, 3670.

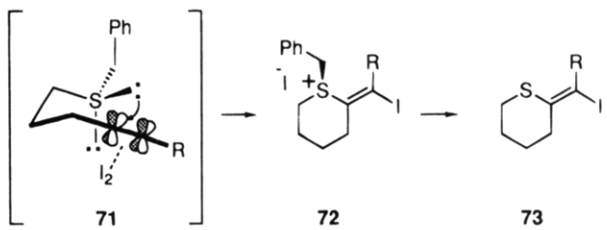


All of these addition products were obtained as single diastereomers whose structures were elucidated from their ^1H NMR spectra. Thus, while the diastereotopic protons at the brominated center in **65a** appear as individual doublets of doublets (J = 2.9, 10.7 Hz and J = 5.9, 10.7 Hz, respectively), the ring proton α to the bromine of **66a** is an unresolved multiplet. Similarly, the spectrum of **65b** shows a sharp doublet (J = 7.8 Hz) for the benzylic proton. Moreover, treatment of **65a** with DBN promotes the elimination to the exocyclic vinyl sulfone, while **66a** does not undergo elimination.[33] This demonstrates that the phenyl and bromide groups in **66a** are trans to each other.

To complete these studies, the iodination reactions of 5-hexynyl benzyl sulfides **68** were examined. We were pleased to find that these cyclizations took place without difficulty to give six-membered ring cycloadducts **69** as single products. None of the seven-membered ring product **70** or acyclic diiodides were isolated. The



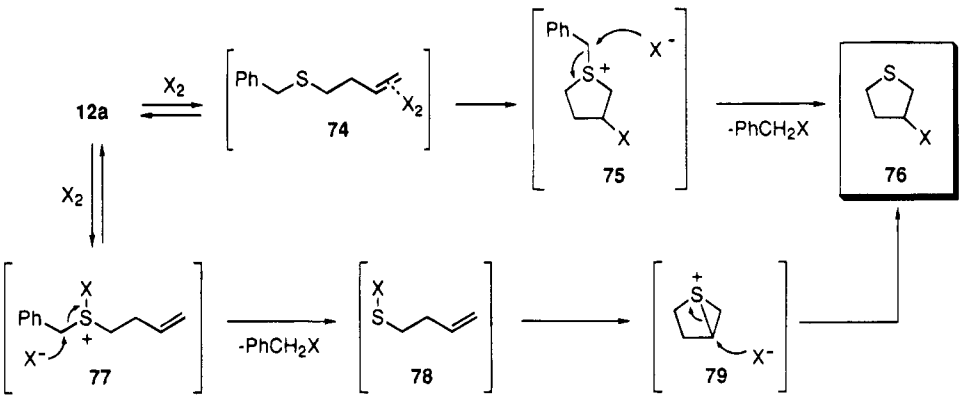
structure of **69a** was unambigously established by single-crystal X-ray analysis.[38] We attribute the high efficiency and regioselectivity of these *6-exo-dig* ring closures to entropic factors which favor the addition of sulfur to the internal center of the π-complex, whose alignment with the equatorial lone pair of sulfur may be reinforced by the linear arrangement of SP centers in **71**.



Mechanistic Considerations. As mentioned in the introductory section of this paper, electrophile-promoted cyclizations can potentially take place through the two mechanistic pathways illustrated in Scheme 1. These pathways differ by whether the sulfur group behaves as a nucleophile toward an electrophile–olefin complex (top pathway) or whether the sulfur group is first converted to an electrophilic species that is then attacked nucleophilically by the olefin (bottom pathway). To illustrate these possibilities, the two pathways for the iodination reaction of **12a** leading to cycloadduct **76** are shown in Scheme 2. The first possibility is that halogen would

(33) The ^1H NMR data for the vinyl sulfone generated from the elimination of **65a** agree closely with literature values (Hendrickson, J. B.; Palumbo, P. S. *Tetrahedron Lett.* **1985**, *26*, 2849 and ref 9): ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.60 (s, 1H), 3.0 (t, J = 5.9 Hz, 2H), 2.71 (t, J = 5.9 Hz, 2H), 2.16 (m, 2H), 1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 121.0, 54.0, 33.0, 26.6, 24.8.

Scheme 2



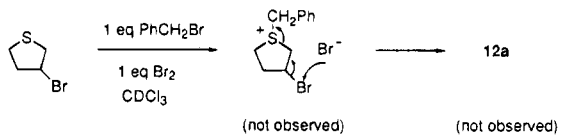
attack **12a** by coordinating to the olefin to produce π-complex **74**. Nucleophilic addition of the sulfide center to the halogen–olefin complex would give the cyclic benzylsulfonium ion **75**. Irreversible dealkylation[34] of **75** by halide ion would produce benzyl halide and the observed cycloadduct **76**. In the bottom pathway of Scheme 2 is shown an alternative scenario in which the halogenation occurs on the sulfur center of **12a**, producing halosulfonium salt **77**. Debenzylation of **77** provides sulfenyl halide **78**, which undergoes intramolecular addition to the double bond. Halide-induced ring opening of the resulting bicyclic episulfonium species **79** would afford cycloadduct **76**.

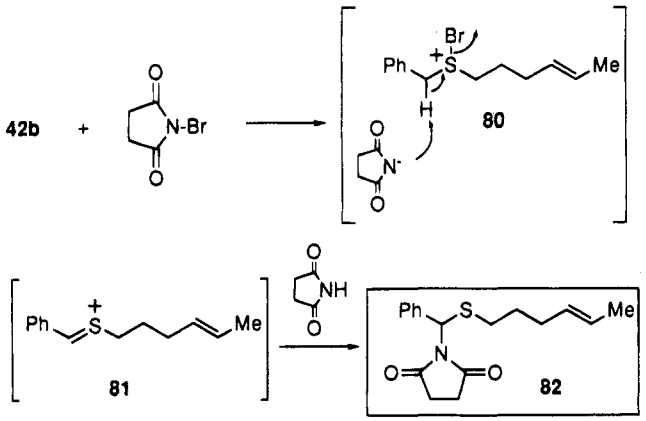
To distinguish between these two mechanistic pathways, the reaction of **12a** with iodine was followed spectroscopically. Upon addition of 1 equiv of I_2 to **12a** in $CDCl_3$ solution, the signals for the protons α to sulfur in **12a** are initially observed to broaden and shift slightly downfield. The remaining signals of **12a**, including those for the vinyl protons, are unaffected, suggesting that an equilibrium is rapidly established between **12a** and halosulfonium species **77**. The concentration of intermediate **77** in this equilibrium must be relatively small, since the downfield shift of the α-protons in the proton NMR spectrum is only about 0.1 ppm units relative to that in **12a**. Nevertheless, this raises the possibility that **77** can be an intermediate in the cyclization pathway by serving as a precursor to sulfenyl halide **78**, as shown in the bottom pathway of Scheme 2. Following the fate of the reaction further, the signals for the vinyl protons and the broadened CH_2S protons gradually disappear, and new signals corresponding to those of benzyl iodide and cycloadduct **76** emerge at approximately the same rate. While this would appear to support the latter mechanism involving formation of a sulfenyl halide **77**, more information is needed to ascertain whether the formation of benzyl iodide in the NMR spectrum is due to the debenzylation of halosulfonium ion **77** to give sulfenyl halide **78** or of benzylsulfonium ion **75** to produce **76**. To study this further, we examined the reaction of **64a** with iodine by ^1H NMR. Upon addition of 1 equiv of I_2 to **64a**, the signals for the protons α to sulfur were observed to broaden and shift to slightly lower field, again indicating the rapid formation of an equlibrium between sulfide **64a** and the halosulfonium species. However, the disappearance of the broadened benzyl proton signals and the formation of benzyl iodide occur very slowly, while the vinyl proton signals are unaffected even after several days. This suggests that the debenzylation of the halosulfonium ion to generate the sulfenyl halide requires at least several days. Consequently, the combination of these two experiments demonstrates that the sulfide cyclizations must take place by the top route shown in Scheme 2, since the generation of sulfenyl halide as a reactive intermediate (bottom pathway) under these conditions is too slow to account for the formation of the cycloadduct.[35] From these studies, we conclude that these halogen-induced sulfide ring closures resemble those of other electrophile-promoted heterocyclizations, which take place by the addition of a divalent heteronucleophile to an electrophilic olefin π-complex such as **74**.

One additional and rather surprising observation made during the course of our studies concerns the attempt to use *N*-bromosuccinimide (NBS) as an electrophilic reagent for these annulation reactions. Despite the fact that NBS and related halogen sources are commonly utilized to promote the addition of heteronucleophiles to unsaturated functionality, our experiments employing NBS to initiate these sulfide cyclizations (as shown for **42b**) produced *none* of the expected bromocyclization adducts. Instead, the succinimidyl-derived addition product **82** was the only observable product of the reaction of **42b** with 1 equiv of NBS. We suspect that the formation of this adduct is due to the increased basicity of succinimide anion (compared to bromide or iodide), which can lead to α-deprotonation of halosulfonium species **80**.[36] The resulting Pummerer-type intermediate **81** can then be captured, either reversibly by halide ion or irreversibly by succinimide, to give **82**. Further attempts to effect the halocyclization of **82** using I_2 or Br_2 were unsuccessful. From these investigations, it seems warranted to caution that NBS (and presumably other haloimide reagents) may not be effective at promoting halocyclization reactions of unsaturated sulfides.

Conclusion. These studies have revealed a number of interesting features of the halocyclization reactions of unsaturated sulfides. First and foremost, the regiochem-

(34) We confirmed that this final dealkylation step proceeds irreversibly under the reaction conditions by subjecting several of the β-bromo sulfides isolated from different bromocyclization reactions (such as that shown below) to possible reaction with 1 equiv of benzyl bromide and one additional equivalent of bromine in $CDCl_3$. Each of the mixtures were monitored by ^1H NMR. After several days, there was no visible changes in the NMR spectra that would indicate the re-formation of a benzylsulfonium species or the original starting unsaturated benzylsulfide. To effectively alkylate the sulfide center, more vigorous reaction conditions or stonger alkylating agents are typically required. For a closely related example, see Breau, L.; Oglivie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35.

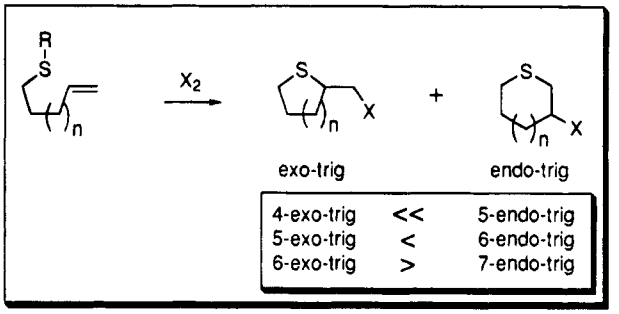




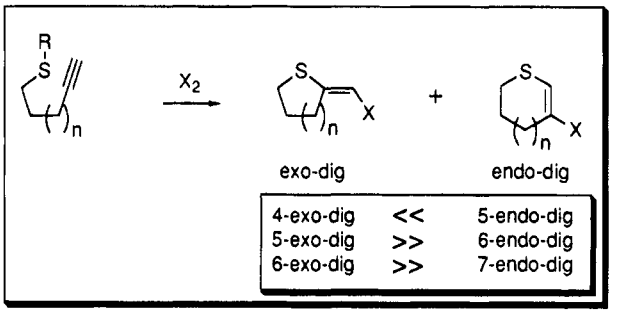
istry and regioselectivity for the intramolecular addition depends most critically on the type of unsaturation within the substrate and on the length of the alkyl tether. For the halocyclizations of *alkenyl* sulfides, five-membered rings are formed exclusively over four-membered rings, and six-membered rings are preferred over either five-membered or seven-membered rings. The regiochemical selectivities of these alkenyl ring closures most likely reflect the thermodynamic differences between the two possible β-halo sulfide regioadducts, which prior to their oxidation to sulfones can equilibrate under the reaction conditions through an episulfonium ion. As the length of the alkyl tether separating the sulfur center from the olefin moiety exceeds beyond three carbon units, however, the double bond becomes the predominate site of bromination. Scheme 3 summarizes these observed regiochemical trends, using the familiar terminology introduced by Baldwin.[3]

Scheme 3

Regiochemical Trends for Halocyclizations of Olefinic Sulfides



Regiochemical Trends for Halocyclizations of Acetylenic Sulfides

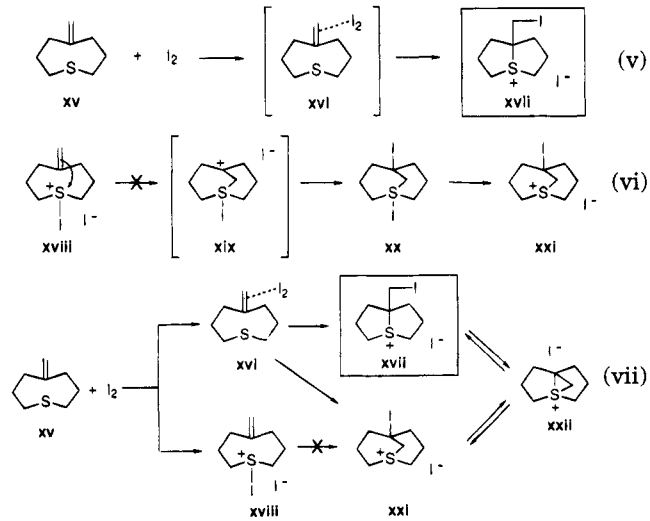


On the other hand, the halocyclizations of *acetylenic* sulfides show somewhat different behavior, in that the regioselectivity and efficiency of the ring closures are uniformly high regardless of whether the tether contains two, three, or four interconvening carbon centers. Furthermore, the products of these alkynyl cyclizations appear to be formed under kinetic control. Thus, five-membered rings are preferred exclusively over four-membered rings or six-membered rings, and six-membered rings are obtained without coformation of the seven-membered rings.

Secondly, the type of unsaturation in the substrate dictates which halogenating agent should be used as the initiating reagent. For alkenyl sulfide cyclizations, Br_2 generally gives better results than I_2 because the brominations reach completion more rapidly and provide cycloadducts which, upon oxidation to the β-halo sulfones, can be isolated without spontaneously eliminating to the vinyl sulfones. On the other hand, I_2 is preferred over Br_2 for promoting the cyclizations of alkynyl sulfides because the iodocycloadducts are stable to the reaction conditions and can be obtained in quantitative yields. *N*-Bromosuccinimide is not an effective reagent for promoting these halocyclizations.

The ring closures have been postulated to proceed in two mechanistic steps: first, the intramolecular addition of a nucleophilic sulfur group onto an electrophilic olefin or acetylene π-complex, and second, irreversible dealkylation of the sulfonium intermediate to the cyclic sulfide. The extension and application of this methodology to the synthesis of other classes of functionalized sulfur rings and selected target structures such as novel β-lactams are areas being pursued in our laboratory at this time.

(35) This mechanism is different than that suggested by Musker and colleagues in their analysis of the reaction of 5-methylene-1-thiacyclooctane (**xv**) with I_2 (eq v). In this reaction, a single crystalline adduct was isolated whose structure was proven by X-ray analysis to be [5.5]-fused bicyclic compound **xvii**. The authors suggest that the formation of **xvii** arises from the nucleophilic addition of the sulfide to an I_2–olefin π-complex (see **xvi**) by an 5-*exo-trig* process. The fact that regioadduct **xvii** was the only product of the reaction led to the conclusion that the initial site of halogenation must be on the double bond. Furthermore, the authors reasoned that had the halogen first reacted with the sulfide center of **xv**, cyclization of the halosulfonium species (**xviii**) would have necessarily led to the formation of [3.3.1]-bridged tricyclic structure **xxi** via the formation of a tertiary carbocation (eq vi). Although the nature of this cation was not specified, we presume that its structure must correspond to the tetravalent sulfur species **xix**. We feel that this explanation fails to take into account that **xxi** could also be formed either by a 6-*endo-trig* cyclization of **xvi** or from the equilibration of **xvii** through episulfonium ion **xxii** (see eq vii below). To provide a more adequate rationale for these observations, we postulate that the halocyclization of **xv** is a thermodynamically-driven process favoring fused structure **xvii** having a primary iodide rather than the more labile tertiary iodide adduct **xxi**. We contend that even if I_2 were to react initially with sulfur to give iodosulfonium salt **xviii**, this process would be reversible. Thus, cyclization can occur from π-adduct **xvi** to give an equilibrium mixture of **xvii** and **xxi**, with adduct **xvii** being heavily favored thermodynamically.



(36) Unsymmetrical sulfides reportedly can undergo α-halogenation under similar conditions via the initial formation and deprotonation of a halosulfonium intermediate. (a) Tuleen, D. L.; Stephens, T. B. *J. Am. Chem. Soc.* **1969**, *34*, 31. (b) Tuleen, D. L. *J. Org. Chem.* **1967**, *32*, 4006.

Experimental Section

Caution: β-Halo sulfides are potent alkylating agents that should be handled with considerable care in well-vented hoods. All air- or moisture-sensitive reactions were performed under an argon atmosphere using glassware and syringes that were predried overnight in an oven at 120 °C and assembled while still hot. Reactions were generally followed by TLC using EM Reagents plates with fluorescence indicator (SiO_2-60, F-254). Flash chromatography was performed using J. T. Baker flash chromatography silica gel (40 μm). ^1H NMR spectra were recorded using a Varian 400 NMR instrument at 400 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded using a Varian Gemini 300 NMR spectrometer at 75 MHz in $CDCl_3$. IR spectra were obtained as a thin film on NaCl plates on a Perkin-Elmer 1310 spectrophotometer. Low-resolution and high-resolution mass spectra were run using electron impact or chemical ionization as indicated. Combustion analyses were performed by Atlantic Microlabs (Atlanta, GA). THF and Et_2O were distilled immediately prior to use from Na/benzophenone under argon, and CH_2Cl_2 was freshly distilled from CaH_2 under N_2. 3-Buten-1-ol, (*E*)-3-hexen-1-ol, (*E*)-4-hexen-1-ol, 5-hexen-1-ol, 3-butyn-1-ol, 3-pentyn-1-ol, epibromohydrin, phenylacetylene, 2-propyn-1-ol, bromoacetonitrile, 3-bromopropionitrile, benzyl bromide, and vinyl magnesium bromide were purchased from Aldrich Chemical Co. and used without further purification. The imines used for the synthesis of azetidinones **24**, **26**, **28**, and **30** were prepared by stirring a solution of the appropriate aldehyde and amine in refluxing benzene under Dean–Stark conditions.

Preparation of 3-(Benzyloxy)-1-propyne. To a solution of propargyl alcohol (1.12 g, 20 mmol) in THF was added slowly a slurry of NaH (1.0 g, 50%, 20.1 mmol, prewashed with anhydrous hexanes) in THF at 0 °C. The reaction mixture was stirred overnight until homogeneous. To this mixture was added dropwise benzyl bromide (3.50 g, 20.2 mmol). The reaction mixture was stirred for 4 h, and H_2O (50 mL) was added dropwise. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were combined and evaporated. Flash chromatography of the crude mixture gave 2.3 g (80%) of 3-(benzyloxy)-1-propyne as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.10 (s, 2H), 2.1 (s, 1H).

Preparation of 3-(Benzylthio)-1,2-epoxypropane. To an ice-cold mixture of epibromohydrin (2.04 g, 15 mmol) and benzylthioacetate (2.50 g, 15.1 mmol) in MeOH (75 mL) was added 0.5 M NaOH in MeOH (30 mL). The reaction mixture was stirred at 0 °C for 4 h and poured into H_2O (75 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 35 mL), and the organic layers were combined and evaporated. Flash chromatography gave 2.10 g (78%) of 3-(benzylthio)-1,2-epoxypropane: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.10 (s, 2H), 3.72 (s, 2H), 3.10 (m, 1H), 2.92 (m, 1H), 2.88 (m, 1H), 2.70 (m, 2H).

Preparation of 3-(Benzylthio)propionitrile. To a solution of 3-bromopropionitrile (2.70 g, 20.0 mmol) in MeOH (75 mL) at 0 °C were added slowly 0.5 M NaOH in MeOH (40 mL) and then a solution of benzyl thioacetate (3.32 g, 20.0 mmol) in MeOH (30 mL). The reaction mixture was stirred at room temperature for 24 h, poured into water, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 3.18 g (90%) of 3-(benzylthio)propionitrile as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.74 (s, 2H), 2.55 (t, J = 4.9 Hz, 2H), 2.42 (d, J = 4.9 Hz, 2H), 1.82 (m, 2H).

2-(Benzylthio)acetonitrile: 2.97 g (89%) prepared from 2.46 g of 2-bromoacetonitrile using an analogous procedure; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.70 (s, 2H), 2.98 (s, 2H).

Preparation of 3-(Benzylthio)propionaldehyde. To a solution of 3-(benzylthio)propionitrile (3.18 g, 18 mmol) in benzene at 0 °C was added slowly diisobutylaluminum hydride (13.1 mL, 1.5 M in toluene, 19.7 mmol). The reaction mixture was stirred for 2 h and quenched by dropwise addition of 1.0 M H_2SO_4 (36 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the organic layers were combined and evaporated. Flash chromatography gave 2.65 g (82%) of 3-(benzylthio)propionaldehyde as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.34 (m, 5H), 3.70 (s, 2H), 2.55 (t, J = 4.9 Hz, 2H), 2.42 (t, J = 4.9 Hz, 2H), 1.86 (m, 2H).

2-(Benzylthio)acetaldehyde: 2.32 g (79%) obtained from 2.70 g of 2-(benzylthio)acetonitrile using an analogous procedure; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.34 (m, 5H), 3.70 (s, 2H), 3.62 (s, 2H), 3.10 (s, 2H).

Representative Procedure for the Tosylation of Alcohols 10. To a solution of 3-buten-1-ol (1.47 g, 20.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added pyridine (1.74 g, 22.0 mmol) and *p*-toluenesulfonyl chloride (4.19 g, 22.1 mmol). The reaction mixture was stirred at rt for 12 h, poured into 5% aqueous HCl (30 mL), and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 4.38 g (95%) of 3-butenyl-1-tosylate as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 5.66 (m, 1H), 5.07 (m, 2H), 4.06 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 2.38 (dt, J = 6.8, 2.9 Hz, 2H).

(*E*)-3-Hexenyl-1-tosylate: 5.86 g (96%) obtained from 2.40 g of (*E*)-3-hexen-1-ol; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 5.49 (dt, J = 15.0, 7.8 Hz, 1H), 5.23 (dt, J = 15.0, 7.8 Hz, 1H), 4.00 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.31 (td, J = 7.8, 6.8 Hz, 2H), 1.95 (qd, J = 7.8, 6.8 Hz, 2H), 0.91 (t, J = 6.8 Hz, 3H).

2-Methyl-3-butenyl-1-mesylate: 3.2 g (91%) obtained from 1.7 g of 2-methyl-3-buten-1-ol by an analogous procedure using methanesulfonyl chloride; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.10 (m, 2H), 4.08 (m, 2H), 3.01 (s, 3H), 1.10 (d, J = 3.8 Hz, 3H).

(*E*)-4-Hexenyl-1-tosylate: 5.50 g (96%) obtained from 2.26 g of (*E*)-4-hexen-1-ol; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 5.29 (m, 2H), 3.98 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 1.98 (m, 2H), 1.66 (m, 2H), 1.56 (d, J = 5.9 Hz, 3H).

5-Hexenyl-1-tosylate: 8.31 g (93%) obtained from 3.52 g of 5-hexen-1-ol; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 5.72 (m, 1H), 4.95 (m, 2H), 4.01 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 2.0 (td, J = 6.8, 5.9 Hz, 2H), 1.62 (m, 2H), 1.4 (m, 2H).

3-Butynyl-1-tosylate: 10.28 g (90%) obtained from 3.57 g of 3-butyn-1-ol; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 4.10 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 1.98 (s, 1H).

3-Pentynyl-1-tosylate: 4.10 g (94%) obtained from 1.54 g of 3-pentyn-1-ol; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 4.05 (t, J = 8.0 Hz, 2H), 2.48 (m, 2H), 2.42 (s, 3H), 1.72 (s, 3H).

Representative Procedure for the Formation of Iodides. To a solution of 3-butenyl-1-tosylate (4.30 g, 19.2 mmol) in acetone was added NaI (4.27 g, 28.5 mmol). The mixture was heated at reflux overnight, cooled, and evaporated. The oily mixture was then added to water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 2.94 g (84%) of 4-iodo-1-butene (**11**, n = 0, R = H) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.12 (m, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.62 (dt, J = 6.8, 2.9 Hz, 2H).

(*E*)-1-Iodo-3-hexene (**11**, n = 0, R = Et): 3.98 g (83%) obtained from 5.80 g of (*E*)-3-hexenyl-1-tosylate; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dt, J = 15.0, 6.8 Hz, 1H), 5.37 (dt, J = 15.0, 7.8 Hz, 1H), 3.14 (t, J = 7.8 Hz, 2H), 2.55 (td, J = 7.8, 6.8 Hz, 2H), 2.01 (qd, J = 7.8, 6.8 Hz, 2H), 1.00 (t, J = 7.8 Hz, 3H).

(*E*)-1-Iodo-2-hexene (**11**, n = 1, R = Me): 3.79 g (85%) obtained from 5.40 g of (*E*)-4-hexenyl-1-tosylate; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (m, 1H), 5.38 (m, 1H), 3.20 (t, J = 6.8 Hz, 2H), 2.08 (m, 2H), 1.85 (m, 2H), 1.65 (d, J = 5.9 Hz, 3H).

(*E*)-5-Iodo-3-methyl-1-phenyl-1-pentene: ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.38 (m, 5H), 6.42 (d, J = 13.6 Hz, 1H), 6.00 (dd, J = 13.6, 4.2 Hz, 1H), 3.23 (m, 1H), 3.18 (m, 1H), 2.44 (m, 1H), 1.90 (m, 2H), 1.13 (d, J = 4.2 Hz, 3H).

5-Iodo-1-(trimethylsilyl)-1-pentyne: 1.98 g (81%) obtained from 2.85 g of 5-(trimethylsilyl)-4-pentynyl-1-tosylate;

colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (t, J = 6.8 Hz, 2H), 2.33 (t, J = 6.8 Hz, 2H), 1.96 (quintet, J = 6.8 Hz, 2H), 0.1 (s, 9H).

6-Iodo-1-hexene (**11**, n = 2, R = H): 3.08 g (88%) obtained from 4.23 g of 5-hexenyl-1-tosylate; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.98 (m, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.06 (td, J = 6.8, 5.9 Hz, 2H), 1.8 (m, 2H), 1.5 (m, 2H).

Representative Procedure for the Preparation of Benzyl Sulfides. To a solution of 4-iodo-1-butene (2.90 g, 15.9 mmol) in MeOH (75 mL) at 0 °C was added slowly 0.5 M NaOH in MeOH (32 mL) and then a solution of benzyl thioacetate (2.66 g, 16.0 mmol) in MeOH (30 mL). The reaction mixture was stirred at room temperature for 24 h, poured into water, and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 2.56 g (90%) of 4-(benzylthio)-1-butene (**12a**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 5.82 (m, 1H), 5.05 (m, 2H), 3.74 (s, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.33 (dt, J = 6.8, 2.9 Hz, 2H). Anal. Calcd for $C_{11}H_{14}S$: C, 74.16; H, 7.87; S, 17.98. Found: C, 74.23; H, 7.83; S, 17.95.

(*E*)-1-(Benzylthio)-3-hexene (**12b**): 3.30 g (93%) prepared from 3.63 g of (*E*)-1-iodo-3-hexene: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 5.49 (dt, J = 15.0, 6.8 Hz, 1H), 5.40 (dt, J = 15.0, 6.8 Hz, 1H), 3.73 (s, 2H), 2.45 (t, J = 7.8 Hz, 2H), 2.27 (td, J = 7.8, 6.8 Hz, 2H), 2.00 (qd, J = 7.8, 6.8 Hz, 2H), 0.97 (t, J = 7.8 Hz, 3H). Anal. Calcd for $C_{13}H_{18}S$: C, 75.73; H, 8.74; S, 15.53. Found: C, 75.70; H, 8.71; S, 15.55.

4-(Benzylthio)-1-butyne (**14a**): 1.74 g (88%) prepared from 2.02 g of 4-iodo-1-butyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 3.78 (s, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.43 (dt, J = 6.8, 3.0 Hz, 2H), 2.04 (d, J = 3.0 Hz, 1H). Anal. Calcd for $C_{11}H_{12}S$: C, 75.00; H, 6.82; S, 18.18. Found: C, 74.99; H, 6.80; S, 18.20.

5-(Benzylthio)-2-pentyne (**14b**): 2.68 g (90%) prepared from 3.04 g of 5-iodo-2-pentyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 3.76 (s, 2H), 2.55 (t, J = 7.8 Hz, 2H), 2.38 (t, J = 7.8 Hz, 2H), 1.78 (s, 3H). Anal. Calcd for $C_{12}H_{14}S$: C, 75.79; H, 7.37; S, 16.84. Found: C, 75.72; H, 7.39; S, 16.80.

4-(Benzylthio)-1-(trimethylsilyl)-1-butyne (**14c**): 2.11 g (83%) prepared from 2.58 g of 4-iodo-1-(trimethylsilyl)-1-butyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H), 3.76 (s, 2H), 2.55 (t, J = 7.8 Hz, 2H), 2.44 (t, J = 7.8 Hz, 2H), 0.22 (s, 9H). Anal. Calcd for $C_{14}H_{20}SiS$: C, 67.74; H, 8.06; S, 12.90. Found: C, 67.65; H, 8.15; S, 12.98.

4-(Benzylthio)-3-methyl-1-butene (**16**): 1.24 g (83%) obtained from 1.53 g of 4-iodo-3-methyl-1-butene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.74 (m, 1H), 5.0 (m, 2H), 3.70 (s, 2H), 2.45 (m, 1H), 2.35 (m, 2H), 1.06 (d, J = 6.0 Hz, 3H). Anal. Calcd for $C_{12}H_{16}S$: C, 75.00; H, 8.33; S, 16.67. Found: C, 74.87; H, 8.43; S, 16.58.

5-(Benzylthio)-1-pentene (**42a**): 3.41 g (89%) prepared from 2.98 g of 5-bromo-1-pentene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 5.80 (m, 1H), 5.05 (m, 2H), 3.74 (s, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.18 (td, J = 6.8, 2.9 Hz, 2H), 1.68 (quintet, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 138.5, 130.0, 129.6, 128.0, 116.0, 36.5, 33.2, 31.0, 28.2. Anal. Calcd for $C_{12}H_{16}S$: C, 75.00; H, 8.33; S, 16.67. Found: C, 75.12; H, 8.22; S, 16.73.

(*E*)-6-(Benzylthio)-2-hexene (**42b**): 2.87 g (90%) prepared from 3.25 g of (*E*)-6-iodo-2-hexene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.40 (m, 2H), 3.65 (s, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.05 (m, 2H), 1.60 (m, 5H). Anal. Calcd for $C_{13}H_{18}S$: C, 75.73; H, 8.74; S, 15.53. Found: C, 75.80; H, 8.61; S, 15.65.

6-(Benzylthio)-2-methyl-2-hexene (**42d**): 3.19 g (87%) prepared from 3.73 g of 6-iodo-2-methyl-2-hexene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.05 (t, J = 7.8 Hz, 2H), 3.70 (s, 2H), 2.40 (t, J = 6.8 Hz, 2H), 2.05 (m, 2H), 1.65 (m, 2H), 1.60 (m, 6H).

5-(Benzylthio)-1-pentyne (**55a**): 2.91 g (92%) prepared from 3.23 g of 5-iodo-1-pentyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5H), 3.71 (s, 2H), 2.53 (t, J = 6.8 Hz, 2H), 2.29 (t, J = 6.8 Hz, 2H), 1.95 (s, 1H), 1.77 (quintet, J = 6.8 Hz, 2H). Anal. Calcd for $C_{12}H_{14}S$: C, 75.79; H, 7.37; S, 16.84. Found: C, 75.82; H, 7.42; S, 16.88.

6-(Benzylthio)-2-hexyne (**55b**): 2.56 g (91%) prepared from 2.87 g of 6-iodo-1-hexyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 3.76 (s, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.24 (t, J = 6.8 Hz, 2H), 1.76 (m, 5H). Anal. Calcd for $C_{13}H_{16}S$: C, 76.47; H, 7.84; S, 15.69. Found: C, 76.62; H, 7.69; S, 15.59.

5-(Benzylthio)-1-(trimethylsilyl)-1-pentyne (**55c**): 1.66 g (85%) prepared from 1.98 g of 5-iodo-1-(trimethylsilyl)-1-pentyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 3.76 (s, 2H), 2.54 (t, J = 6.8 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H), 1.76 (quintet, J = 6.8 Hz, 2H), 0.15 (s, 9H). Anal. Calcd for $C_{15}H_{22}SiS$: C, 68.70; H, 8.40; S, 12.21. Found: C, 68.72; H, 8.39; S, 12.25.

6-(Benzylthio)-1-hexene (**64a**): 2.47 g (92%) prepared from 2.74 g of 6-iodo-1-hexene; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.82 (m, 1H), 5.0 (m, 2H), 3.73 (s, 2H), 2.44 (t, J = 7.8 Hz, 2H), 2.06 (td, J = 6.8, 5.9 Hz, 2H), 1.61 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 139.8, 129.9, 129.6, 127.5, 115.5, 36.6, 33.9, 31.6, 29.0, 28.2. Anal. Calcd for $C_{13}H_{18}S$: C, 75.73; H, 8.74; S, 15.53. Found: C, 75.72; H, 8.72; S, 15.53.

6-(Benzylthio)-1-hexyne (**68a**): 1.95 g (92%) prepared from 2.16 g of 6-iodo-1-hexyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 3.76 (s, 2H), 2.42 (t, J = 6.8 Hz, 2H), 2.20 (t, J = 6.8 Hz, 2H), 1.65 (m, 2H), 1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 129.9, 129.6, 128.0, 84.2, 69.0, 36.1, 31.0, 28.1, 27.8, 18.0. Anal. Calcd for $C_{13}H_{16}S$: C, 76.47; H, 7.84; S, 15.69. Found: C, 76.52; H, 7.89; S, 15.80.

7-(Benzylthio)-2-heptyne (**68b**): 1.36 g (90%) prepared from 1.54 g of 7-iodo-2-heptyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 3.76 (s, 2H), 2.41 (t, J = 6.8 Hz, 2H), 2.12 (t, J = 6.8 Hz, 2H), 1.76 (s, 3H), 1.65 (quintet, J = 6.8 Hz, 2H), 1.56 (quintet, J = 6.8 Hz, 2H). Anal. Calcd for $C_{14}H_{18}S$: C, 77.06; H, 8.26; S, 14.68. Found: C, 77.00; H, 8.30; S, 14.56.

The following sulfides were prepared from the corresponding alcohols[37] in the manner described above except that the alkyl tosylate or alkyl iodide intermediates were not characterized.

(*E*)-4-(Benzylthio)-1-phenyl-1-butene (**12c**): 3.33 g (85%) prepared from 2.28 g of (*E*)-1-phenyl-1-buten-4-ol; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H), 6.40 (d, J = 15.0 Hz, 1H), 6.19 (td, J = 15.0, 6.8 Hz, 1H), 3.75 (s, 2H), 2.55 (t, J = 6.8 Hz, 2H), 2.46 (td, J = 7.8, 6.8 Hz, 2H). Anal. Calcd for $C_{17}H_{18}S$: C, 80.31; H, 7.09; S, 12.60. Found: C, 80.33; H, 7.05; S, 12.58.

(*E*)-5-(Benzylthio)-1-phenyl-1-pentene (**42c**): 1.65 g (83%) prepared from 1.20 g of (*E*)-5-phenyl-4-penten-1-ol; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 10H), 6.38 (d, J = 16.6 Hz, 1H), 6.17 (dt, J = 16.6, 6.8 Hz, 1H), 3.72 (s, 2H), 2.46 (t, J = 6.8 Hz, 2H), 2.28 (dt, J = 7.8, 6.8 Hz, 2H), 1.73 (quintet, J = 6.8 Hz, 2H); MS (EI) m/z (relative intensity) 269 (61, M + 1), 231 (19), 211 (87), 193 (55), 177 (100). Anal. Calcd for $C_{18}H_{20}S$: C, 80.60; H, 7.46; S, 11.94. Found: C, 80.58; H, 7.49; S, 11.92.

(*E*)-5-(Benzylthio)-3-methyl-1-phenyl-1-pentene (**50**): 2.04 g (69%) obtained from 1.85 g of (*E*)-3-methyl-5-phenyl-4-penten-1-ol; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 10H), 6.40 (d, J = 15.6 Hz, 1H), 6.08 (dd, J = 15.6, 8.8 Hz, 1H), 3.76 (s, 2H), 2.50 (m, 3H), 1.71 (m, 2H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 138.3, 138.2, 136.1, 129.9, 129.8, 129.6, 127.8, 127.6, 127.0, 36.9, 36.8, 36.7, 29.5, 21.0. Anal. Calcd for $C_{19}H_{22}S$: C, 80.85; H, 7.80; S, 11.35. Found: C, 80.80; H, 7.71; S, 11.45.

(*E*)-6-(Benzylthio)-1-phenyl-1-hexene (**64b**): 1.65 g (64%) prepared from 1.61 g of (*E*)-6-phenyl-5-hexen-1-ol; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H), 6.38 (d, J =

(37) These compounds were prepared by Wittig olefination of the lactol using the ylid generated upon treatment of benzyl triphenylphosphonium bromide with nBuLi. After aqueous workup, the alcohol was vacuum distilled at 0.1 Torr.

(38) The author has deposited atomic coordinates for **56b** and **69a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EQ, UK.

15.6 Hz, 1H), 6.20 (dt, J = 15.6, 6.8 Hz, 1H), 3.73 (s, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.22 (q, J = 6.8 Hz, 2H), 1.68–1.54 (m, 4H). Anal. Calcd for $C_{19}H_{22}S$: C, 80.85; H, 7.80; S, 11.35. Found: C, 80.65; H, 7.69; S, 11.49.

Representative Procedure for the Preparation of Monocyclic β-Lactams 24, 26, 28, and 30. To a stirred solution of Et_3N (1.25 mL, 8.97 mmol) and (*E*)-3-phenyl-2-propenal *N*-(4-methoxyphenyl)imine (2.11 g, 8.90 mmol) in THF (60 mL) at −78 °C was added via canula a solution of *S*-benzylthioacetyl chloride (1.80 g, 9.0 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 30 min, warmed to rt, and then poured into 5% aqueous HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give a dark brown oil. Flash chromatography (2:1 CH_2Cl_2:hexanes then CH_2Cl_2) of the crude material afforded 3.14 g (88%) of azetidinones **28** as a 1:10 mixture of cis:trans isomers.

To a stirred solution of the above product mixture (3.14 g, 7.87 mmol) in THF (80 mL) at −78 °C was added n-BuLi (4.80 mL, 1.8 M solution in hexanes, 8.64 mmol). The reaction mixture was stirred for 15 min, poured into 5% aqueous HOAc, and extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and then evaporated. Flash chromatography of this material gave 3.12 g (99%) of **28** as a 2:1 mixture of cis:trans isomers: ^{1}H NMR (400 MHz, $CDCl_3$) (cis:trans mixture) δ 7.25–7.45 (m, 12H), 6.94 (d, 2H, J = 8.4 Hz, cis isomer), 6.91 (d, 2H, J = 8.4 Hz, trans isomer), 5.00 (d, 1H, J = 4.9 Hz, cis isomer), 4.39 (d, 1H, J = 4.9 Hz, cis isomer), 4.32–4.29 (AB m, 2H, trans isomer), 4.06–4.08 (AB m, 2H, cis isomer), 3.95 (s, 2H, trans isomer), 3.79 (s, 3H, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$) (trans isomer) δ 162.1, 157.6, 138.0, 132.4, 131.2, 129.9, 129.8, 129.5, 128.1, 128.0, 122.1, 119.1, 115.0, 88.4, 83.9, 58.0, 55.9, 51.0, 35.9; IR (thin film) 1750 cm^{-1} (C=O). Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.19; H, 5.26. Found: C, 75.25; H, 5.17.

3-(Benzylthio)-*N*-(4-methoxyphenyl)-4-(2-methyl-1-propenyl)azetidinone (24): 1.28 g (38%, 2:1 cis:trans mixture) prepared as described above from 1.80 g of 3-methyl-2-butenyl N-(4-methoxyphenyl)imine and 1.95 g of *S*-benzylthioacetyl chloride; ^{1}H NMR (400 MHz, $CDCl_3$) (cis:trans mixture) δ 7.21–7.36 (m, 7H), 6.82 (d, 2H, J = 8.8 Hz, both isomers), 5.30 (d, 1H, J = 9.6 Hz, cis isomer), 5.06 (d, 1H, J = 9.8 Hz, trans isomer), 4.75 (dd, 1H, J = 9.6, 4.9 Hz, cis isomer), 4.23 (dd, 1H, J = 9.8, 2.0 Hz, trans isomer), 3.85 (m, 2H), 3.80 (s, 3H, cis isomer), 3.75 (s, 3H, trans isomer), 1.80 (s, 3H, cis isomer), 1.78 (3H, cis isomer), 1.67 (s, 3H, trans isomer), 1.65 (s, 3H, trans isomer); ^{13}C NMR (75 MHz, $CDCl_3$) (cis isomer) δ 163.5, 157.0, 140.1, 138.4, 132.0, 130.0, 129.2, 127.9, 122.0, 119.0, 114.8, 58.2, 56.4, 55.9, 35.6, 26.1, 18.6; IR (thin film): 1750 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{21}H_{24}NO_2S$ (M + 1) 354.1528, found 354.1551.

***N*-Benzyl-3,3-bis(ethylthio)-4-(2-methyl-1-propenyl)-azetidinone (26)**: 2.33 g (58%) obtained from 2.30 g of 3-methyl-2-butenal *N*-benzylimine and 2.38 g of bis(ethylthio)-acetyl chloride; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.35 (m, 5H), 5.24 (d, 1H, J = 9.6 Hz), 4.65 (d, 1H, J = 14.8 Hz), 4.15 (d, 1H, J = 9.6 Hz), 3.93 (d, 1H, J = 14.8 Hz), 2.64–2.90 (m, 4H), 1.76 (s, 3H), 1.44 (s, 3H), 1.19-1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 142.2, 136.0, 129.5, 129.0, 128.1, 119.1, 70.4, 63.5, 44.3, 26.2, 24.3, 24.1, 18.5, 14.5, 14.4; IR (thin film) 1760 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{18}H_{26}NOS_2$ (M + 1) 336.1456, found 336.1452.

3,3-Bis(ethylthio)-*N*-(4-methoxyphenyl)-4-(2-phenylethynyl)azetidinone (30a): 4.46 g (88%) prepared from 3.00 g of 3-phenylpropynal *N*-(4-methoxyphenyl)imine and 2.53 g of bis(ethylthio)acetyl chloride; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.54 (m, 7H), 6.89 (d, 2H, J = 8.8 Hz), 4.95 (s, 1H), 3.74 (s, 3H), 2.89–3.14 (m, 4H), 1.31–1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 157.5, 132.6, 131.0, 129.9, 129.6, 122.1, 119.6, 115.1, 91.5, 81.9, 70.0, 58.0, 55.5, 24.6, 24.5, 14.4, 14.2; IR (thin film) 1752 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{22}H_{24}NO_2S_2$ (M + 1) 398.1249, found 398.1265.

***N*-Benzyl-3,3-bis(ethylthio)-4-[2-(triethylsilyl)ethynyl]-azetidinone (30b)**: 4.03 g (98%) prepared from 2.11 g of 3-(trimethylsilyl)-2-propynal *N*-benzylimine and 1.98 g of bis-(ethylthio)acetyl chloride; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.35 (m, 5H), 4.65 (d, 2H, J = 15.6 Hz), 4.15 (s, 1H), 4.09 (d, 2H, J = 15.6 Hz), 2.86–2.95 (m, 1H), 2.72–2.84 (m, 3H), 1.19-1.28 (m, 6H), 0.99 (t, 9H, J = 8.0 Hz), 0.59 (q, 6H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 135.6, 129.8, 129.0, 128.5, 98.9, 94.8, 70.1, 58.0, 42.9, 25.0, 24.9, 14.8, 14.1, 7.8, 4.2; IR (thin film) 1770 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{22}H_{34}NOS_2Si$ (M + 1) 420.1851, found 420.1833.

***N*-Benzyl-3,3-bis(ethylthio)-4-(2-phenylethynyl)azetidinone (30c)**: 3.59 g (95%) prepared from 2.17 g of 3-phenyl-2-propynal *N*-benzylimine and 2.00 g of bis(ethylthio)acetyl chloride; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.44 (m, 10H), 4.78 (d, 1H, J = 14.8 Hz), 4.42 (s, 1H), 4.23 (d, 1H, J = 14.8 Hz), 2.80–3.04 (m, 4H), 1.25–1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 135.5, 132.5, 129.9, 129.7, 129.0, 128.5, 127.5, 122.2, 95.0, 82.0, 70.9, 58.0, 45.0, 25.1, 25.0, 14.5, 14.2. IR (thin film): 1765 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{22}H_{24}NOS_2$ (M + 1) 382.1299, found 382.1301.

Representative Procedure for the Preparation of Benzyl Sulfides 18a, 18b, and 46a. To a solution of phenylacetylene (0.80 g, 7.8 mmol) in THF (50 mL) at −78 °C under nitrogen was added nBuLi (5.5 mL, 1.50 M in hexanes, 8.3 mmol), and the mixture was stirred for 30 min. To a solution of (benzylthio)acetaldehyde (1.25 g, 7.5 mmol, generated by DIBAL reduction of (benzylthio)acetonitrile as described above) in THF (50 mL) at −78 °C under nitrogen was added slowly via cannula the above freshly prepared organolithium reagent. The reaction mixture was stirred for 30 min, warmed to rt, and poured into 5% aqueous NH_4Cl solution (20 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 1.52 g (76%) of 4-(benzylthio)-3-hydroxy-1-phenyl-1-butyne (**18a**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 10H), 4.66 (dd, J = 6.8, 5.9 Hz, 1H), 3.88 (s, 2H), 2.86 (d, J = 4.9 Hz, 2H). Anal. Calcd for $C_{17}H_{16}OS$: C, 76.12; H, 5.97; S, 11.94. Found: C, 75.99; H, 6.09; S, 11.86.

1-(Benzyloxy)-5-(benzylthio)-4-hydroxy-2-pentyne (18b): 1.99 g (84%) prepared from 1.26 g of (benzylthio)acetaldehyde and 1.15 g of 3-(benzyloxy)-1-propyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 2H), 4.48 (m, 1H), 4.20 (s, 2H), 3.82 (s, 1H), 2.78 (d, J = 4.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.5, 128.1, 86.5, 82.0, 72.1, 61.9, 57.9, 39.2, 37.2. Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.08; H, 6.41; S, 10.26. Found: C, 73.02; H, 6.39; S, 10.30.

5-(Benzylthio)-3-hydroxy-1-pentene (46a): 2.25 g (78%) prepared from 2.5 g of 3-(benzylthio)propanal (generated by DIBAL reduction of 3-(benzylthio)propionitrile as described above) and 1.5 mL of vinylmagnesium bromide (1.0M in THF): colorless oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5H), 5.81 (ddd, J = 12.7, 11.7, 3.9 Hz, 1H), 5.21 (d, J = 12.7 Hz, 1H), 5.12 (d, J = 11.7 Hz, 1H), 4.21 (m, 1H), 3.70 (s, 2H), 2.52 (t, J = 6.8 Hz, 2H), 1.80 (td, J = 6.8, 3.9 Hz, 2H). Anal. Calcd for $C_{12}H_{16}OS$: C, 69.23; H, 7.69; S, 15.38. Found: C, 69.28; H, 7.69; S, 15.37.

Preparation of 3-(Benzyloxy)-5-(benzylthio)-1-pentene (46b). To a solution of alcohol **46a** (0.60 g, 2.9 mmol) in THF (75 mL) was added NaH (150 mg, 3.7 mmol, 60% suspension in mineral oil, washed with anhydrous hexanes prior to use) in a slurry in THF (50 mL) via cannula, and the reaction mixture was stirred for 8 h. To this mixture was added dropwise benzyl bromide (540 mg, 3.2 mmol) and a catalytic amount of nBu_4NI. The reaction mixture was stirred overnight and then poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 0.76 g (88%) of **46b** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 10H), 5.70 (ddd, J = 11.7, 9.8, 7.8 Hz, 1H), 5.21 (m, 2H), 4.57 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 11.7 Hz, 1H), 3.86 (m, 1H), 3.69 (s, 2H), 2.50 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 139.5, 139.4, 129.9, 129.7, 129.6, 128.6, 128.2, 118.8, 118.0, 79.8, 70.6, 36.5, 35.5, 27.8. Anal. Calcd for $C_{19}H_{22}OS$: C, 76.51; H, 7.38; S, 10.74. Found: C, 76.72; H, 7.39; S, 10.66.

Preparation of 3-Acetoxy-5-(benzylthio)-1-pentene (46c). To a solution of **46a** (1.25 g, 6.0 mmol) in Et_3N (2.5 mL, 18 mmol) and a catalytic amount of DMAP was added

anhydrous acetic anhydride (0.92 g, 9.0 mmol). The reaction mixture was stirred overnight and then poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 1.37 g (91%) of **46c** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 5.72 (ddd, J = 11.7, 9.8, 7.8 Hz, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 4.10 (m, 1H), 3.70 (s, 2H), 2.40 (t, J = 6.8 Hz, 2H), 2.02 (s, 3H), 1.86 (m, 2H). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.20; H, 7.20; S, 12.80. Found: C, 67.05; H, 7.29; S, 12.71.

Representative Procedure for the Preparation of Acetylenic Benzyl Sulfides 58a and 58b. To a solution of phenylacetylene (0.80 g, 7.8 mmol) in THF (50 mL) at −78 °C under nitrogen was added nBuLi (5.5 mL, 1.50 M in hexanes, 8.3 mmol). The mixture was stirred for 30 min, and to this mixture was added dropwise $BF_3{\cdot}Et_2O$ (1.1 mL, 8.9 mmol). To a solution of 3-(benzylthio)-1,2-epoxypropane (1.4 g, 7.8 mmol, prepared from benzylthiolate displacement of epibromohydrin as described above) in THF (50 mL) at −78 °C under nitrogen was added slowly via cannula the above freshly prepared solution. The reaction mixture was stirred for 30 min with warming to rt and poured into 5% NH_4Cl solution (25 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 1.73 g (79%) of 5-(benzylthio)-1-phenyl-1-pentyn-4-ol (**58a**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 10H), 3.89 (m, 1H), 3.76 (s, 2H), 2.84–2.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 132.5, 129.8, 129.6, 129.0, 128.8, 128.0, 124.0, 86.0, 83.8, 68.8, 38.0, 36.8, 27.4. Anal. Calcd for $C_{18}H_{18}OS$: C, 76.60; H, 6.38; S, 11.35. Found: C, 76.72; H, 6.39; S, 11.32.

1-(Benzyloxy)-6-(benzylthio)-2-hexyn-5-ol (58b): 2.30 g (82%) prepared from 1.55 g of 3-(benzylthio)-1,2-epoxypropane and 1.30 g of 3-(benzyloxy)-1-propyne; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.38 (s, 2H), 4.15 (s, 2H), 3.75 (s, 2H), 2.72 (dd, J = 11.7, 3.9 Hz, 1H), 2.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.2, 129.9, 129.8, 129.4, 129.0, 128.8, 128.0, 83.1, 79.2, 72.1, 68.6, 58.0, 38.0, 36.6, 26.4. Anal. Calcd for $C_{20}H_{22}O_2S$: C, 73.62; H, 6.75; S, 9.82. Found: C, 73.72; H, 6.79; S, 9.82.

Representative Procedure for the Halocyclization Reactions and Subsequent Sulfonylation. To a solution of 4-(benzylthio)-1-butene (**12a**, 1.42 g, 8.0 mmol) in CH_2Cl_2 (50 mL) at rt was added dropwise Br_2 (410 μL, 8.1 mmol). The mixture was allowed to stir overnight or until the ^{1}H NMR spectrum of the crude reaction mixture showed that the reaction was completed. To a stirred solution of the above reaction mixture in CH_2Cl_2 was added in one portion m-CPBA (6.9 g, 50–60%, approximately 20.0 mmol). The mixture was stirred for 12 h and poured into 5% aqueous $NaHSO_3$ solution (60 mL). The mixture was stirred for 8 h until the layers separated, and the organic layer was washed with 5% aqueous $NaHCO_3$ solution (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture afforded 1.46 g (92%) of 3-bromotetrahydrothiophene 1,1-dioxide (**13a**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (m, 1H), 3.61 (dd, J = 6.8 Hz, 1H), 3.40 (m, 2H), 3.14 (m, 1H), 2.78 (m, 1H), 2.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.5, 50.5, 40.0, 34.1. Anal. Calcd for $C_4H_7O_2SBr$: C, 24.12; H, 3.52; S, 16.08. Found: C, 24.09; H, 3.55; S, 16.12.

***trans*-3-Bromo-2-ethyltetrahydrothiophene 1,1-dioxide (13b)**: 0.363 g (95%) obtained from 0.347 g of **12b** (R = Et); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (ddd, J = 5.9, 4.9, 3.9 Hz, 1H), 3.33 (ddd, J = 6.8, 5.9, 4.9 Hz, 1H), 3.02 (m, 2H), 2.72 (m, 1H), 2.44 (m, 1H), 1.91 (m, 2H), 1.17 (t, J = 7.8 Hz, 3H). Anal. Calcd for $C_6H_{11}O_2SBr$: C, 31.72; H, 4.85; S, 14.10. Found: C, 31.56; H, 4.88; S, 14.12.

***trans*-3-Bromo-2-phenyltetrahydrothiophene 1,1-dioxide (13c)**: 0.460 g (90%); obtained from 0.472 g of **12c** (R = Ph); white solid; mp 118–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.35 (m, 5H), 4.55 (dt, J = 11.7, 5.9 Hz, 1H), 3.49 (m, 1H), 3.27 (m, 1H), 2.92 (m, 1H), 2.63 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.2, 130.1, 129.8, 128.1, 74.2, 52.1, 44.0, 32.0; MS (CI, isobutane) m/z (relative intensity) 278 (11), 277 (96, M + 1), 276 (11), 275 (93, M + 1), 212 (7), 210 (7), 195 (60), 131 (100); MS (EI) m/z (relative intensity) 276.0 (2), 274.0 (2), 212.0 (7), 210.0 (6), 184.0 (20), 182.0 (17), 131.1 (35), 104.1 (100, M^+), 91.1 (25, M^+); HRMS (EI) m/z calcd for $C_{10}H_{11}O_2SBr$ 273.9663, found 273.9700. Anal. Calcd for $C_{10}H_{11}O_2SBr$: C, 43.64; H, 4.00; S, 11.64. Found: C, 43.66; H, 4.11; S, 11.60.

4,5-Dihydro-3-iodothiophene 1,1-dioxide (15a): 0.284 g (100%) obtained from 0.205 g of **14a** (R = H); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 3.34 (t, J = 6.0 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 107.2, 51.0, 39.2; MS (EI) m/z (relative intensity) 247 (5), 246 (5), 245 (100, M+1). Anal. Calcd for $C_4H_5O_2SI$: C, 19.67; H, 2.05; S, 13.11. Found: C, 19.72; H, 2.15; S, 13.32.

4,5-Dihydro-3-iodo-2-methylthiophene 1,1-dioxide (15b): 0.388 g (100%) obtained from 0.286 g of **14b** (R = Me); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, J = 8.8 Hz, 2H), 3.22 (t, J = 8.8 Hz, 2H); 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 105.0, 48.2, 36.5, 12.5; MS (EI) m/z (relative intensity) 261 (6, M + 1), 260 (7, M + 1), 259 (100, M + 1), 258 (4), 133 (8), 109 (3); HRMS (EI) m/z calcd for $C_5H_7O_2SI$ 257.9212, found 257.9160. Anal. Calcd for $C_5H_7O_2SI$: C, 23.26; H, 2.71; S, 12.40. Found: C, 23.35; H, 2.69; S, 12.32.

4,5-Dihydro-3-iodo-2-(trimethylsilyl)thiophene 1,1-dioxide (15c): 0.385 g (100%) obtained from 0.302 g of **14c** (R = $SiMe_3$); colorless oily solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (t, J = 7.0 Hz, 2H), 3.24 (t, J = 7.0 Hz, 2H), 0.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 117.0, 51.2, 43.5, −0.8; MS (EI) m/z (relative intensity) 315.9 (5), 300.9 (100), 226.9 (20), 184.9 (57), 73.0 (24); HRMS (EI) m/z calcd for $C_7H_{13}O_2SiSI$ 315.9451, found 315.9446.

2-(Bromomethyl)tetrahydrothiophene 1,1-dioxide (43a): 0.035 g (13%) obtained from 0.242 g of **42a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dd, J = 8.8, 3.9 Hz, 1H), 3.39 (m,1H), 3.21 (m, 1H), 3.04 (m, 1H), 2.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 52.5, 30.0, 27.5, 20.0.

3-Bromotetrahydro-2*H*-thiopyran 1,1-dioxide (44a): 0.175 g (65%) obtained from 0.242 g of **42a**; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (m, 1H), 3.37 (m, 1H), 3.30 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.45 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.5, 50.5, 41.5, 36.0, 22.4; HRMS (EI) m/z calcd for $C_5H_9O_2SBr$ 212.9585, found 212.9556. Anal. Calcd for $C_5H_9O_2SBr$: C, 28.17; H, 4.23; S, 15.02. Found: C, 28.16; H, 4.29; S, 15.12.

***trans*-3-Bromo-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (44b)**: 0.120 g (71%) obtained from 0.153 g of **42b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (dt, J = 11.7, 3.9 Hz, 1H), 3.16 (m, 2H), 3.0 (m, 1H), 2.53 (m, 1H), 2.12–2.01 (m, 3H), 1.60 (d, J = 6.8 Hz, 3H). Anal. Calcd for $C_6H_{11}O_2SBr$: C, 31.72; H, 4.85; S, 14.10. Found: C, 31.77; H, 4.79; S, 14.09.

2-(1-Bromo-1-phenylmethyl)tetrahydrothiophene 1,1-dioxide (43c): 0.066 g (17%) prepared from 0.357 g of **42c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (dt, J = 11.7, 3.9 Hz, 1H), 4.22 (d, J = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131–128 (5 signals), 67.0, 54.0, 51.8, 32.0, 19.5; MS (EI) m/z (relative intensity) 292 (11), 291 (100, M + 1), 290 (12), 289 (94, M + 1), 209 (93), 145 (32), 117 (22).

***trans*-3-Bromo-2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide (44c)**: 0.262 g (68%) prepared from 0.357 g of **42c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, J = 10.7 Hz, 1H), 3.85 (dt, J = 10.7, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131–128 (5C), 74.8, 52.0, 48.0, 37.2, 23.8; MS (EI) m/z (relative intensity) 292 (11), 291 (100), 290 (12), 289 (94), 209 (93), 145 (32), 117 (22); HRMS (EI) m/z calcd for $C_{11}H_{13}O_2S$ (M − Br) 209.0636; found: 209.0623. Anal. Calcd for $C_{11}H_{13}O_2SBr$: C, 45.67; H, 4.50; S, 11.07. Found: C, 45.70; H, 4.39; S, 11.12.

2-(1-Bromo-1-methylethyl)tetrahydrothiophene 1,1-dioxide (43d): 0.106 g (24%) prepared from 0.405 g of **42d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (dd, J = 11.7, 7.8 Hz, 1H), 3.10 (m, 1H), 2.95 (m, 1H), 2.42 (m, 1H), 2.20–2.00 (m, 3H), 1.98 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.2, 63.5, 54.0, 34.0, 32.0, 28.0, 19.5.

3-Bromo-2,2-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (44d): 0.089 g (20%) prepared from 0.405 g of **42d**; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (dd, J = 11.7, 3.9 Hz, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.20–1.95 (m, 4H),

1.38 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.4, 56.4, 46.1, 32.0, 23.0, 19.8, 17.6; MS (EI) m/z (relative intensity) 243.0 (100, M + 1), 241.0 (92, M + 1), 161.1 (51, M − Br); HRMS (EI) m/z calcd for $C_7H_{14}SO_2Br$ (M + 1) 240.9898, found 240.9902.

(*E*)-2-(Iodomethylene)tetrahydrothiophene 1,1-dioxide (56a): 0.213 g (100%) isolated from 0.157 g of **55a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 3.18 (t, J = 7.8 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.22 (quintet, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 87.3, 51.8, 31.2, 17.8; MS (EI) m/z (relative intensity) 259 (100, M + 1), 258 (5, M$^+$). Anal. Calcd for $C_5H_7O_2SI$: C, 23.26; H, 2.71; S, 12.40. Found: C, 23.25; H, 2.73; S, 12.42.

(*E*)-2-(1-Iodoethylidene)tetrahydrothiophene 1,1-dioxide (56b): 0.385 g (100%) isolated from 0.289 g of **55b**; white solid; mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (t, J = 6.8 Hz, 2H), 2.85 (s, 3H), 2.67 (t, J = 6.8 Hz, 2H), 2.21 (quintet, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 108.2, 54.8, 36.8, 29.8, 18.4; MS (CI, isobutane) m/z (relative intensity) 275 (5) 274 (8) 273 (100), 272 (3), 145 (13); HRMS (EI) m/z calcd for $C_6H_9O_2SI$ 271.9368, found 271.9372. Anal. Calcd for $C_6H_9O_2SI$: C, 26.47; H, 3.31; S, 11.77. Found: C, 26.50; H, 3.40; S, 11.73.

(*E*)-2-[1-Iodo-1-(trimethylsilyl)methylene]tetrahydrothiophene 1,1-dioxide (56c): 0.344 g (100%) isolated from 0.273 g of **55c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (t, J = 6.8 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.19 (quintet, J = 6.8 Hz, 2H), 0.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 124.5, 54.2, 41.9, 18.2, 1.8. Anal. Calcd for $C_8H_{15}O_2SSiI$: C, 29.09; H, 4.55; S, 9.70. Found: C, 29.38; H, 4.60; S, 9.65.

2-(Bromomethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (65a): 0.096 g (28%) isolated from 0.313 g of **64a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.0 (dd, J = 10.7, 2.9 Hz, 1H), 3.36 (dd, J = 10.7, 5.9 Hz, 1H), 3.05−3.18 (m, 2H), 2.93 (td, J = 10.7, 4.9 Hz, 1H), 2.50 (m, 1H), 2.04 (m, 2H), 1.98−1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.0, 52.2, 29.0, 26.2, 24.5, 23.8; HRMS (EI) m/z calcd for $C_6H_{12}O_2SBr$ (M + 1) 226.9741, found 226.9759.

Benzyl 5,6-dibromohexyl sulfone (67a): 0.393 g (65%) isolated from 0.313 g of **64a**; white solid; mp 84−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 4.23 (s, 2H), 3.82 (dd, J = 10.7, 4.9 Hz, 1H), 3.61 (dd, J = 10.7, 9.8 Hz, 1H), 2.84 (t, J = 7.8 Hz, 2H), 2.13 (m, 1H), 1.88−1.70 (m, 4H), 1.65 (m, 1H), 1.55 (m, 1H). Anal. Calcd for $C_{13}H_{18}O_2SBr_2$: C, 39.20; H, 4.52; S, 8.04. Found: C, 39.16; H, 4.60; S, 8.05.

2-(1-Bromo-1-phenylmethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (65b): 0.022 g (10%) isolated from 0.214 g of **64b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.30 (m, 5H), 5.45 (d, J = 7.8 Hz, 1H), 3.40 (m, 1H), 3.0 (m, 2H), 2.85 (m, 1H), 2.70 (m, 1H), 2.01 (m, 4H), 1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 129.8, 129.4, 128.5, 67.5, 54.0, 50.1, 30.5, 24.6, 24.4; MS (CI, isobutane) m/z (relative intensity) 305.0 (14), 303.0 (15), 284.0 (65), 223.1 (100), 159.1 (21), 111.1 (37); HRMS (CI, isobutane) m/z calcd for $C_{12}H_{16}O_2SBr$ (M + 1) 303.0054, found 303.0078.

Benzyl 5,6-dibromo-6-phenylhexyl sulfone (67b): 0.306 g (85%) isolated from 0.214 g of **64b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.32 (m, 10H), 5.05 (d, J = 10.7 Hz, 1H), 4.50 (dt, J = 10.7, 2.0 Hz, 1H), 4.25 (s, 2H), 2.90 (t, J = 6.8 Hz, 2H), 2.41 (m, 1H), 2.0−1.60 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 131.6, 131.5, 129.9, 129.8, 129.6, 128.9, 128.6, 60.0, 58.0, 57.8, 51.5, 36.5, 26.0, 21.2; MS (EI) m/z (relative intensity) 395 (5, M − Br), 314 (70, −2Br), 157 (72), 117 (78), 91 (100), 65 (69). Anal. Calcd for $C_{19}H_{22}O_2SBr_2$: C, 48.10; H, 4.64; S, 6.75. Found: C, 48.11; H, 4.60; S, 6.65.

(*E*)-2-(Iodomethylene)tetrahydro-2*H*-thiopyran 1,1,-dioxide (69a): 0.460 g (100%) obtained from 0.345 g of **68a**; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 2.95 (t, J = 5.9 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.10 (tt, J = 6.8, 5.9 Hz, 2H), 1.69 (tt, J = 6.8, 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 92.5, 54.0, 34.1, 26.0, 24.5; MS (EI) m/z (relative intensity) 271.9 (90, M$^+$), 145.0 (82), 91.1 (82), 79.1 (82), 41.0 (100); HRMS (EI) m/z calcd for $C_6H_9O_2SI$ 271.9368, found 271.9372. Anal. Calcd for $C_6H_9O_2SI$: C, 26.47; H, 3.31; S, 11.77. Found: C, 26.44; H, 3.30; S, 11.70.

(*E*)-2-(1-Iodo-1-phenylmethylene)tetrahydro-2*H*-thiopyran 1,1,-dioxide (69b): 0.366 g (100%) obtained from 0.279 g of **68b**; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.0 (m, 4H), 2.05 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 131.0, 56.0, 42.5, 32.1, 26.0, 24.5; MS (EI) m/z (relative intensity) 286 (15), 159 (100), 67 (44), 53 (47), 41 (47); HRMS (EI) m/z calcd for $C_7H_{11}O_2SI$ 285.9525, found 285.9547. Anal. Calcd for $C_7H_{11}O_2SI$: C, 29.37; H, 3.85; S, 11.19. Found: C, 29.44; H, 3.80; S, 11.30.

^{1}H NMR data was obtained for the following compounds prepared by reaction of the appropriate sulfide with 1.1 molar equiv of bromine or iodine in $CDCl_3$ solution. The *m*-CPBA oxidation was omitted, and no attempt was made to isolate or further characterize the product.

***trans*-3-Iodo-4-methyltetrahydrothiophene (17)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (m, 1H), 3.32 (m, 2H), 2.96 (m, 1H), 2.55 (m, 1H), 2.31 (m, 1H), 1.22 (d, J = 5.9 Hz, 3H).

4,5-Dihydro-4-hydroxy-3-iodo-2-phenylthiophene (19a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 5.02 (dd, J = 6.8, 2.9 Hz, 1H), 3.75 (dd, J = 12.7, 6.8 Hz, 1H), 3.38 (dd, J = 12.7, 2.9 Hz, 1H).

4,5-Dihydro-4-hydroxy-3-iodo-2-phenylthiophene (19b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, J = 6.9, 2.9 Hz, 1H), 4.56 (s, 2H), 4.30 (s, 2H), 3.56 (dd, J = 12.7, 7.8 Hz, 1H), 3.25 (dd, J = 12.7, 2.9 Hz, 1H).

***cis*-3-Bromo-4-hydroxytetrahydrothiophene (48)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (broadened d, J = 11.7 Hz, 1H), 4.10 (m, 1H), 3.44 (dd, J = 12.7, 11.7 Hz, 1H), 3.05 (broadened dd, J = 11.7, 10.7 Hz, 1H), 2.68 (broadened d, J = 12.7 Hz, 1H), 2.32 (m, 2H), 2.10 (m, 1H).

***trans*-2-(1-Iodo-1-phenylmethyl)-3-methyltetrahydrothiophene (52)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 4.72 (d, J = 5.9 Hz, 1H), 3.40 (dd, J = 5.9, 4.9 Hz, 1H), 2.80 (m, 2H), 2.30 (m, 1H), 2.11 (m, 1H), 1.70 (m, 1H), 0.78 (d, J = 6.8 Hz, 3H).

3-Bromo-4-methyl-2-phenyltetrahydrothiopyran (54): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, J = 11.7, 10.7 Hz, 1H), 4.13 (d, J = 11.7 Hz, 1H), 2.80 (m, 2H), 2.64 (m, 1H), 2.23 (m, 1H), 1.81 (m, 1H), 1.30 (d, J = 6.8 Hz, 3H).

(*E*)-4-Hydroxy-2-(1-iodo-1-phenylmethylene)tetrahydrothiophene (59a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.24 (m, 5H), 4.60 (m, 1H), 3.40 (dd, J = 11.7, 3.9 Hz, 1H), 3.26 (dd, J = 11.7, 2.0 Hz, 1H), 2.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 143.6, 143.5, 129.9, 129.0, 128.8, 72.6, 53.2, 44.1; IR (thin film) 3600-3200 cm^{-1} (OH).

(*E*)-2-[2-(Benzyloxy)-1-iodoethylidene]-4-hydroxytetrahydrothiophene (59b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 4.58 (m, 1H), 4.51 (s, 2H), 4.23 (s, 2H), 3.42 (dd, J = 11.7, 3.9 Hz, 1H), 3.32 (dd, J = 11.7, 1.0 Hz, 1H), 2.90 (dd, J = 16.6, 1.0 Hz, 1H), 2.78 (dd, J = 16.6, 3.9 Hz, 1H).

Representative Procedure for the Halocyclization of Monocyclic β-Lactams. To a solution of azetidinone **30c** (3.80 g, 9.97 mmol) in CH_2Cl_2 (100 mL) at rt was added in one portion I_2 (2.60 g, 10.2 mmol). The mixture was allowed to stir overnight and evaporated. Flash chromatography of the crude material gave 4.20 g (88%) of cycloadduct **31c** as a white solid: mp 105−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.42 (m, 10H), 4.80 (d, 1H, J = 15.6 Hz), 4.71 (s, 1H), 4.60 (d, 1H, J = 15.6 Hz), 2.80−2.85 (m, 2H), 1.28 (t, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 148.9, 136.0, 134.3, 132.0, 130.5, 129.5, 129.2, 129.0, 128.9, 128.8, 82.4, 70.2, 45.6, 25.3, 14.9; IR (thin film) 1752 cm^{-1} (C=O); HRMS (EI) m/z calcd for $C_{20}H_{19}NOS_2I$ (M + 1) 479.9953, found 479.9940.

Penicillin Analogue 25. Major isomer: 0.279 g (56%) obtained from 0.520 g of a 2:1 cis:trans mixture of azetidinones **24**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 5.02 (dd, 1H, J = 4.0, 4.8 Hz), 4.73 (d, 1H, J = 4.8 Hz), 4.37 (d, 1H, J = 4.0 Hz), 3.79 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 157.2, 129.4, 119.2, 115.2, 69.0, 62.7, 60.8, 55.8, 55.6, 28.7, 28.0; IR (thin film) 1760 cm^{-1} (C=O); MS (CI, isobutane) m/z (relative intensity) 342 (94, M + 1), 264 (33), 232 (32), 190 (52), 167 (14),149 (52), 129 (33), 113 (52).

Minor isomer: 0.056 g (11%) isolated from 0.520 g of a 2:1 cis:trans mixture of azetidinones **24**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 5.15 (dd, 1H, J = 5.2, 4.8 Hz), 4.52 (d, 1H, J = 5.2 Hz), 4.13 (d, 1H, J = 4.8 Hz), 3.82 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 163.9, 157.5, 130.7, 121.1, 114.5, 68.5, 64.4, 58.7, 55.8, 53.7, 29.1, 28.2; IR (thin film) 1760 cm^{-1} (C=O); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NO_2SBr$ (M + 1) 342.0163; found 342.0078.

Thio-substituted penicillin analogue 27: 0.099 g (100%, 4:1 mixture of α:β bromo isomers) isolated from 0.086 g of azetidinone **26**; ^1H NMR (400 MHz, $CDCl_3$) (mixture of isomers) δ 7.34-7.38 (m, 5H), 4.90 (d, 1H, *J* = 15.6 Hz, β-isomer), 4.75 (d, 1H, *J* = 15.6 Hz), 4.31 (d, 1H, *J* = 15.6 Hz, β-isomer), 4.29 (d, 1H, *J* = 4.8 Hz), 4.18 (d, 1H, *J* = 15.6 Hz), 4.16 (d, 1H, *J* = 4.8 Hz), 4.15–4.16 (buried signal, 1H, β-isomer), 4.08 (d, 1H, *J* = 4.8 Hz, β-isomer), 2.71 (q, 2H, *J* = 5.9 Hz), 1.64 (s, 3H), 1.39 (s, 3H), 1.24 (t, 3H, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (α-bromo isomer) δ 165.7, 135.2, 129.5, 129.1, 128.7, 75.5, 71.7, 64.0, 60.1, 45.5, 27.5, 27.1, 26.2, 14.4; HRMS (EI) *m/z* calcd for $C_{16}H_{21}NOS_2Br$ (M + 1) 386.0248; found 386.0137.

Penem analogue 29: 0.068 g (64%) plus 0.032 g of recovered *trans*-**28** obtained from 0.098 g of a 2:1 mixture of azetidinones **28**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.72 (m, 7H), 6.90 (d, 2H, *J* = 8.8 Hz), 5.59 (d, 1H, *J* = 4.8 Hz), 5.02 (d, 1H, *J* = 4.8 Hz), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 157.9, 149.8, 137.5, 134.8, 130.6, 130.0, 129.4, 122.9, 121.6, 114.6, 76.0, 70.5, 56.0; IR (thin film) 1750 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{14}NO_2SI$: C, 49.66; H, 3.22; S, 7.36. Found: C, 49.85; H, 3.11; S, 7.59.

Thio-substituted penem analogue 31a: 0.138 g (98%) obtained from 0.113 g of azetidinone **30a**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.8 Hz), 7.36–7.50 (m, 5H), 6.92 (d, 2H, *J* = 8.8 Hz), 5.32 (s, 1H), 3.80 (s, 3H), 2.93 (q, 2H, *J* = 5.8 Hz), 1.38 (t, 3H, *J* = 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 157.9, 150.9, 134.4, 130.6, 130.2, 129.5, 129.2, 121.6, 114.8, 72.9, 69.6, 55.9, 53.9, 25.6, 14.9; IR (thin film) 1760 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{18}NO_2S_2I$: C, 48.48; H, 3.64; S, 12.93. Found: C, 48.59; H, 3.61; S, 12.73.

Thio-Substituted Penem Analogue 31b: 0.142 g (92%) obtained from 0.125 g of azetidinone **30b**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 4.78 (d, 2H, *J* = 15.6 Hz), 4.56 (s, 1H), 4.40 (d, 2H, *J* = 15.6 Hz), 2.70–2.82 (m, 2H), 1.25 (t, 3H, *J* = 6.8 Hz), 0.97 (t, 9H, *J* = 8.0 Hz), 0.85 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 150.5, 136.0, 129.5, 129.0, 128.5, 84.4, 79.0, 74.8, 45.8, 25.0, 15.0, 7.8, 3.1; IR (thin film) 1753 cm^{-1} (C=O); HRMS (EI) *m/z* calcd for $C_{20}H_{29}NOS_2SiI$ (M + 1) 518.0505, found 518.0617.

Preparation of *N*-Succinimidyl Sulfide Derivative 82. To a solution of **42b** (1.03 g, 5.0 mmol) in CH_2Cl_2 (50 mL) at rt was added in one portion *N*-bromosuccinimide (NBS) (0.98 g, 5.5 mmol). The mixture was stirred for 4 h and then poured into 5% aqueous $NaHSO_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture provided 1.26 g (83%) of **82** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.8 Hz, 2H), 7.35–7.28 (m, 3H), 6.24 (s, 1H), 5.38 (m, 2H), 2.68 (d, *J* = 5.9 Hz, 4H), 2.60 (m, 2H), 2.04 (m, 2H), 1.65–1.60 (m, 5H); IR (thin film) 1771, 1705 cm^{-1} (C=O stretching). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.33; H, 6.93; S, 10.56; N, 4.62. Found: C, 67.34; H, 6.90; S, 10.70; N, 4.65.

Representative Procedure for the Elimination of β-Halo Sulfones. To a solution of 3-bromotetrahydrothiophene 1,1-dioxide (**13a**, 1.39 g, 7.0 mmol) in THF (20 mL) at rt was added DBN (0.90 g, 7.2 mmol). The mixture was stirred for 4 h, poured into 5% aqueous HCl solution (20 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture gave 0.800 g (97%) of 4,5-dihydrothiophene 1,1-dioxide[20a] as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (m, 1H), 6.64 (m, 1H), 3.21 (t, *J* = 6.3 Hz, 2H), 2.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 133.0, 48.0, 26.8; MS (EI) *m/z* (relative intensity) 118 (36), 89 (100), 70 (10), 61 (20), 53 (24); HRMS (EI) *m/z* calcd for $C_4H_6SO_2$ 118.0112; found: 118.0084.

4,5-Dihydro-2-ethylthiophene 1,1-dioxide:[20b] 0.685 g (88%) obtained from 1.21 g of **13b**; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (t, *J* = 1.9 Hz, 1H), 3.23 (t, *J* = 8.8 Hz, 2H), 2.77 (m, 2H), 2.43 (q, *J* = 9.9 Hz, 2H), 1.21 (t, *J* = 9.9 Hz, 3H).

4,5-Dihydro-2-phenylthiophene 1,1-dioxide: 0.625 g (82%) obtained from 1.08 g of **13c**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.39 (m, 3H), 6.72 (t, *J* = 3.2 Hz, 1H), 3.38 (t, *J* = 6.8 Hz, 2H), 2.90 (dt, *J* = 6.8, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 132.8, 130.2, 129.9, 128.2, 127.8, 49.1, 24.0; MS (CI, isobutane, m/e) 197 (6), 196 (12), 194 (6), 195 (100); MS (EI) *m/z* (relative intensity) 194.0 (35), 129.1 (35), 105.0 (52), 102.0 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{10}SO_2$ 194.0402; found 194.0401.

4,5-Dihydro-2-methylenethiophene 1,1-dioxide (**45a**): 0.019 g (13%) obtained from 0.235 g of the mixture of **43a:44a**; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 2.0 Hz, 1H), 5.59 (d, *J* = 2.0 Hz, 1H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.76 (m, 2H), 2.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.6, 116.1, 50.0, 27.0, 19.0.

3,4-Dihydro-2*H*-thiopyran 1,1-dioxide:[20c] 0.095 g (65%) obtained from 0.235 g of the mixture of **43a:44a**; ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (m, 2H), 3.13 (m, 2H), 2.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 130.5, 51.0, 25.0, 20.5.

(*E*)-4,5-Dihydro-2-ethylidenethiophene 1,1-dioxide (**45b**): 0.015 g (14%) obtained from 0.167 g of the mixture of **43b:44b**; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (m, 1H), 3.0 (m, 2H), 2.65 (m, 2H), 2.16 (m, 2H), 1.78 (s, 3H).

(*E*)-4,5-Dihydro-2-isopropylidenethiophene 1,1-dioxide (**45d**): 0.022 g (24%) obtained from 0.137 g of the mixture of **43d:44d**; ^1H NMR (400 MHz, $CDCl_3$) δ 3.05 (t, *J* = 7.8 Hz, 2H), 2.65 (m, 2H), 2.12 (m, 5H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 134.0, 52.3, 27.4, 23.2, 20.0, 19.0.

(*E*)-2-Methylenetetrahydrothiopyran 1,1-dioxide: 0.065 g (88%) obtained from 0.114 g of **65a**; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.60 (s, 1H), 3.01 (t, *J* = 5.9 Hz, 2H), 2.71 (t, *J* = 5.9 Hz, 2H), 2.16 (m, 2H), 1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 121.0, 54.0, 33.0, 26.6, 24.8.

(*E*)-2-Phenylmethylenetetrahydrothiopyran 1,1-dioxide: 0.093 g (81%) obtained from 0.156 g of **65b**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43–7.30 (m, 5H), 3.13 (t, *J* = 5.9 Hz, 2H), 2.98 (t, *J* = 5.9 Hz, 2H), 2.22 (tt, *J* = 5.9, 2.9 Hz, 2H), 1.74 (tt, *J* = 5.9, 2.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 134.5, 134.0, 129.8, 129.6, 129.5, 54.1, 28.0, 26.1, 24.5; MS (EI) *m/z* (relative intensity) 222.1 (20), 143.1 (23), 91.1 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{14}O_2S$ 222.0715, found 222.0708.

Supporting Information Available: Copies of ^1H and selected ^{13}C NMR spectra (97 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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