Studies on Nonconventionally Fused Bicyclic β-Lactams

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Described in this article are studies of structurally novel [3.2.0]bicyclic β-lactam ring systems that are isomeric to those of the penicillin, penem, and clavulanic acid families of antibiotics, but which have the lactam functionality arranged in alternative orientations within the four-membered ring. Semiempirical calculations indicate that the thermodynamic stabilities of the three alternative isomeric ring systems are similar to that of the classical penam or penem structure, and ab initio methods reveal that the LUMO energies of the two C-fused ring structures **11** and **12** are more than 1 eV lower than that of 2-azetidinone, but 0.22 to 0.73 eV higher than that of the penem ring **13**. The LUMO energy of the N−S fused penem structure **14** is about 0.2 eV lower than that of **13**. These studies also suggest that the N-fused bicyclic β-lactams are considerably more electrophilic than the corresponding C-fused compounds. Several of the new heterocyclic rings were synthesized using a two-step cyclization strategy to assemble the bicyclic core. First, the β-lactam ring was created by a Staudinger reaction of an acid chloride and α,β-unsaturated imine, and the sulfur heterocycle was closed through a halogen-promoted cyclization reaction of a sulfur substituent onto a neighboring alkenyl or alkynyl side chain. Using palladium catalysis, iodopenem adducts **18**, **31a**, and **56a** were converted to vinyl- and heteroaryl-substituted derivatives, carboxylic esters, and carboxylic acids. Four of the bicyclic β-lactams prepared in this study (**58b**, **80**, **87**, and **89**) showed weak levels of activity against *Staphylococcus aureus* or *Vibrio cholerae*.

Introduction

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors.[6] More recently, β-lactam compounds have become attractive starting materials and intermediates in a wide range of synthetic[7] settings and have demonstrated potential as inhibitors of various proteolytic enzyme systems.[8] The primary biological targets of the β-lactam drugs are the penicillin binding proteins, a group of transpeptidases anchored within the bacterial cellular membrane which mediate the final step of cell wall biosynthesis. In a key biochemical step, the D-alanine-D-alanine terminus of a peptidoglycan strand is enzymatically cleaved by a transpeptidase, and joined to another peptidoglycan residue within the bacterial cell wall. Penicillin and its structural relatives possess the unusual ability to interrupt this crucial cross-linking event by acylating the catalytic serine unit within the enzyme active site, resulting in bacteria having weakened or poorly formed cell walls. Over the years, numerous penicillin derivatives[9] have been prepared and examined for antibacterial activity. Additionally, a variety of new β-lactam-containing ring systems isolated from natural sources or from synthetic laboratories have been reported, including the penems,[10] carbapenems,[11] cephalosporins,[12] clavulanic

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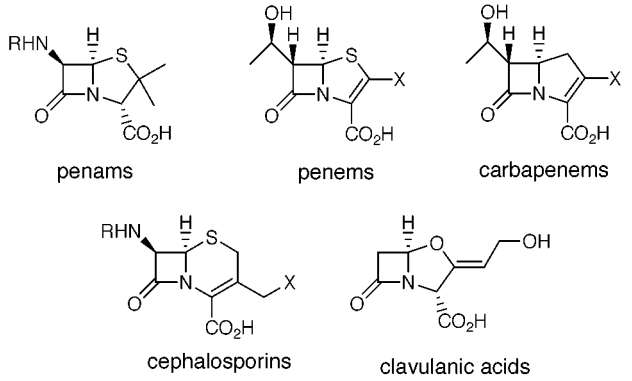
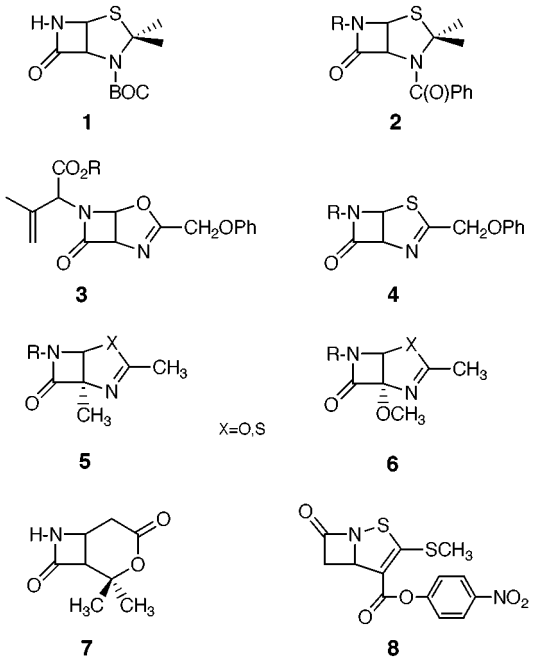
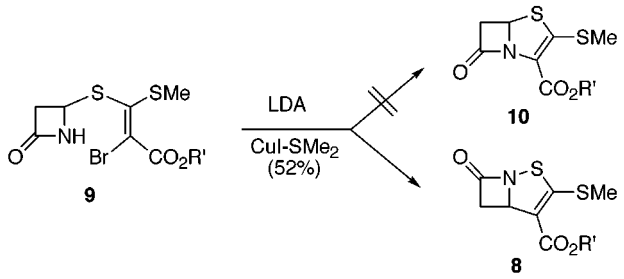
acids,[13] oxapenams,[14] oxacephams,[15] and monocyclic,[16] spirocyclic,[17] and multicyclic[18] analogues. The most common classes of β-lactam antibiotics are illustrated below. Perhaps it is not coincidental that all biologically active β-lactams, excluding the monocyclic compounds, contain a fused ring framework having the lactam nitrogen at the ring fusion, for it is the rigid conformational constraints and the highly pyramidalized nature of the nitrogen center in these fused ring systems that causes the lactam functionality to have diminished planarity and resonance stabilization. Consequently, the β-lactam ring within such structures has pronounced reactivity toward nucleophilic attack and subsequent ring opening.



To the best of our knowledge, there have not been any efforts to evaluate the properties of fused β-lactam ring systems whose lactam groups occupy "nonclassical" orientations within the four-membered ring. Although a handful of nonconventionally fused bicyclic β-lactams[19] such as structures **1**−**8** have previously been described in the literature, their chemical or biological properties have not been investigated. In fact, the majority of these compounds (**1**−**7**) have been utilized solely as intermediates in the synthesis of penicillins, carbapenems, and cephalosporins. The structurally unusual N-fused β-lactam derivative **8** was reported in 1980[20] as an unexpected product obtained[21] during an attempt to cyclize lactam **9** to penem **10** (Scheme 1).



Scheme 1



The purpose of our studies was to evaluate the properties of bicyclic β-lactam ring systems that have the lactam

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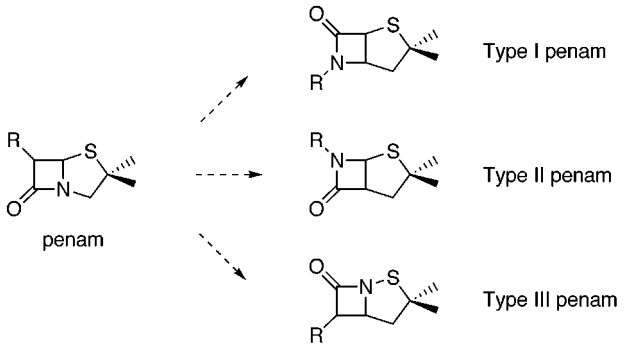
unit in different bonding arrangements compared to the classical N-fused compounds. In considering the penam ring system, for instance, three structural variants (designated types I, II, and III) can be conceived such that the lactam functionality occupies alternative positions within the bicyclic framework.



Since antibiotic activity among the β-lactams is, at least qualitatively, dependent on the presence of a reactive azetidinone ring, it was of interest to speculate about the possible effects of positioning the lactam group at other locations within the four-membered ring. Previous structural studies[22] confirm that "N-fused" β-lactam systems generally have a higher C=O stretching frequency than the "C-fused" structures, indicating a greater amount of ring strain and chemical reactivity toward nucleophiles. N-Fused lactams are highly respondent to the geometric constraints imposed by the second ring to which it is fused, as evidenced from the increase in the infrared absorption frequency for the lactam carbonyl as the size of the second ring is decreased (Figure 1). For C-fused rings, the size of the appended ring has little if any influence on the frequency of C=O absorption. This suggests a fundamental and potentially exploitable difference between N-fused and C-fused β-lactam rings.[23]

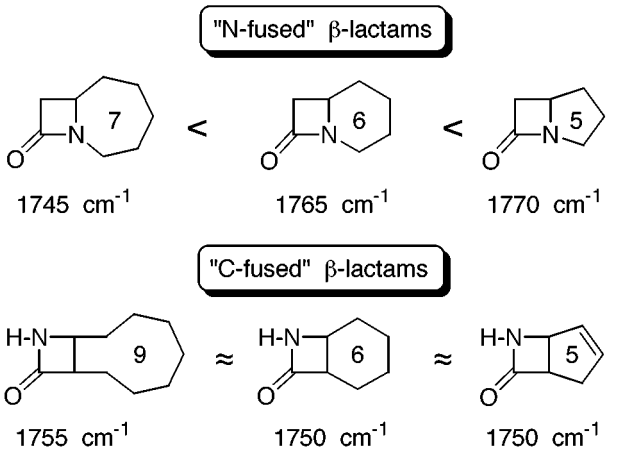


Figure 1. Effect of ring size on the infrared C=O absorption frequency of N-fused versus C-fused bicyclic β-lactams.

Results and Discussion

Computational Studies. AM1 semiempirical calculations were carried out on each of the four isomeric penam rings to gain further insight into their relative stabilities. In the calculations, a methyl group was placed on the β-lactam ring to preserve the tertiary nature of the lactam nitrogen, and the carboxylic acid group on the sulfur ring was omitted to avoid computational discrepancies due to hydrogen-bonding effects. Interestingly, these calculations suggest that all three of the isopenams have nearly the same thermodynamic stability as the classical penam ring system, based on their calculated gas phase heats of formation (Table 1). Whereas our type I and III penam analogues are of equal stability to the parent penam, the type II structure is about 1.4 kcal/mol thermodynamically more stable. Similar results were observed in our calculations within the penem series of structures shown at the bottom of Table 1.

To relate the reactivity and stability of a β-lactam compound to its antibacterial properties, a detailed knowledge of the catalytic mechanism of the penicillin binding proteins is essential. While it is not definitively known whether the initial acylation step of β-lactam hydrolysis in the β-lactamases is similar to that of the penicillin binding proteins, both families of enzymes are known to utilize an active site serine residue as the nucleophilic catalyst and both lead to the formation of a covalently attached acyl-enzyme intermediate.[24] Here we present the results of high-level ab initio calculations on a general model for the base-catalyzed nucleophilic addition of serine to a β-lactam. The model we have employed is similar to the one reported recently by Wladkowski[25] and co-workers, who carried out the optimization of the stationary points at the HF/6-31+G* level of theory and evaluated the energy of these points at the MP2/6-31+G*//6-31+G* level. However, in our experiments we elected to optimize all the stationary points at the higher MP2/6-31+G* level of theory, because the correlation energy effects on the transition structures are important. For our calculations, 2-azetidinone and 2-aminoethanol were used as models for the β-lactam substrate and the nucleophilic serine residue, respectively, and two molecules of NH_3 were employed as models for the active site lysine (acting as a general base) and alanine (which electrophilically assists catalysis) residues.[26] The geometries of the stationary points found in these calculations are shown in Figure 2. The point M is a minimum in the potential energy surface and corresponds to the starting complex in which the substrate is hydrogen-bonded to the amino group of the serine model and to the ammonia molecule simulating the alanine residue, in good agreement with the experimental evidence de-

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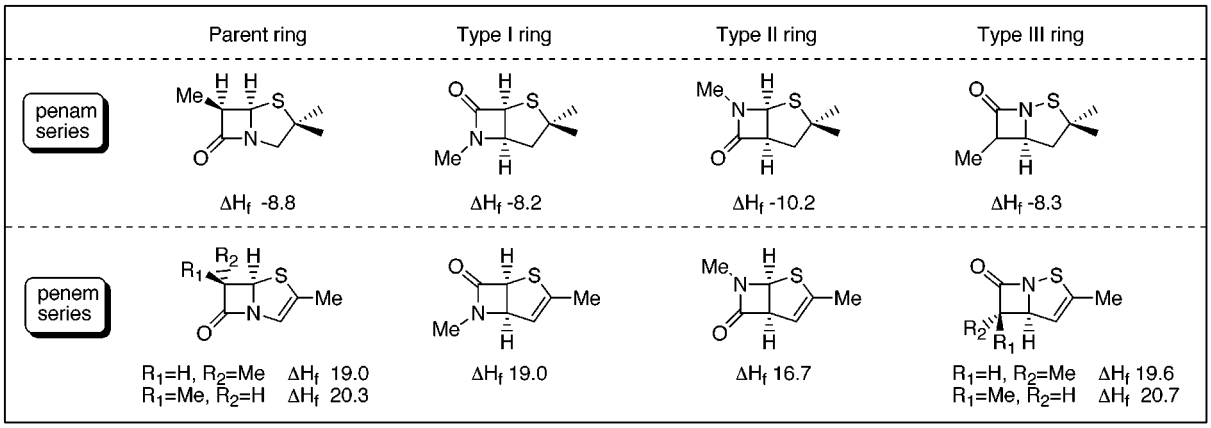
Table 1. Calculated Gas Phase Heats of Formation of Bicyclic β-Lactam Rings (kcal/mol)



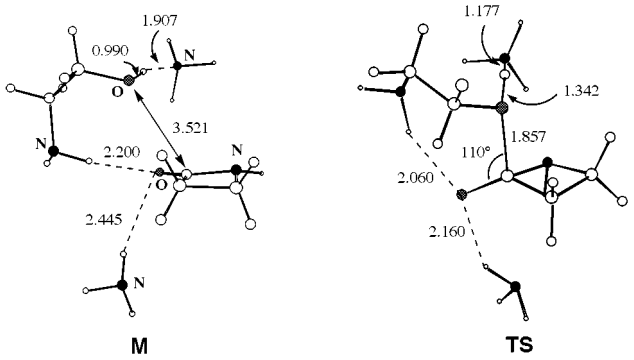


Figure 2. MP2/6-31+G* optimized geometries of the starting complex (M) and the transition structure (TS) for the catalyzed hydrolysis of 2-azetidinone (bond lengths are in angstroms).

rived from crystallographic studies.[27] The point TS is the transition structure for the formation of the tetrahedral intermediate during the β-lactam hydrolysis. In this transition structure, the distance between the oxygen of the serine and the carbonyl center of the β-lactam has been reduced to 1.857 Å, and the O−C−O angle is almost perfectly tetrahedral (110°). In addition, the distance between the hydrogen of the serine hydroxyl group and the lysine amino group is now only 1.177 Å, while the O−H distance has increased to 1.342 Å. Each of these changes reflect that the nucleophilic attack of the serine hydroxyl group to the β-lactam carbonyl is concerted, with hydrogen transfer taking place from the serine hydroxyl group to the nitrogen atom of the lysine residue. An interesting feature of the transition structure TS is the considerable degree of pyramidalization at the lactam nitrogen center, which now exhibits nearly sp^3 hybridization. It is interesting to relate this to the fact that most of the biologically active β-lactams are bicyclic and have the lactam nitrogen in an sp^3 hybridization state. According to the data from these MP2/6-31+G* calculations, the activation energy for the nucleophilic attack of the serine on 2-azetidinone is predicted to be 23.0 kcal mol^{-1}, which is slightly lower than the value obtained previously using a closely related model.[23] An important outcome of this computational experiment comes from the analysis of the Mulliken charges in the transition structure TS, which reveals a significant amount of charge (0.302 electrons) being transferred from the oxygen of the approaching serine nucleophile to the β-lactam carbonyl. This suggests that the addition of the catalytic serine to a β-lactam substrate within the active site is largely controlled by the interaction between the HOMO of the nucleophile (serine) and the LUMO of the electrophile (β-lactam). Thus, within a series of closely related β-lactam structures, the LUMO energy of the β-lactam can be a direct indicator of the compound's reactivity toward nucleophilic ring opening in the enzyme active site, providing that the geometry and binding parameters are not significantly perturbed.

Therefore, we thought it would be informative to calculate the LUMO energies of the four isomeric penem rings **11**−**14**. This was done at the HF/6-31G* level of theory. The optimized geometries obtained for these structures are shown in Figure 3, and their computed LUMO energy values are listed in Table 2. The main difference between the four isomers is in the degree of twisting within the β-lactam ring, as reflected by the $N-C_1-C_2-C_3$ dihedral angle D. For 2-azetidinone, the four centers of the ring all lie within a common plane. The C-fused lactams **11** and **12**, however, are slightly twisted out of planarity by 2−3°, and the N-fused rings **13** and **14** are contorted to an even greater extent. Another key structural difference between the four isomers is that the lactam nitrogen centers in **11** and in **12** are planar, while in **13** and **14** they are distinctly pyramidalized.

The calculated values of the LUMO energies for optimized structures **11**−**14** indicate that the electrophilicity of both C-fused bicyclic β-lactams (**11** and **12**) is significantly greater than that of 2-azetidinone but lower than that of the two N-fused bicyclic analogues (**13** and **14**). In comparing the two N-fused lactams **13** and **14**, the N−S fused isomer **14** has a somewhat lower LUMO energy value than the classical penem **13**. Thus, having a lactam-fused ring structure diminishes the LUMO energies and increases the electrophilicity of the β-lactam ring. One would then predict that the reactivity of these β-lactam rings toward nucleophilic addition would follow the trend **11** < **12** < **13** < **14**, despite the similarity of their thermodynamic stabilities.

Synthetic Studies. To construct the functionalized cores of our isomeric β-lactam structures, we developed a concise "double annulation" strategy shown in eq 1. In the first step of this procedure, the β-lactam ring is

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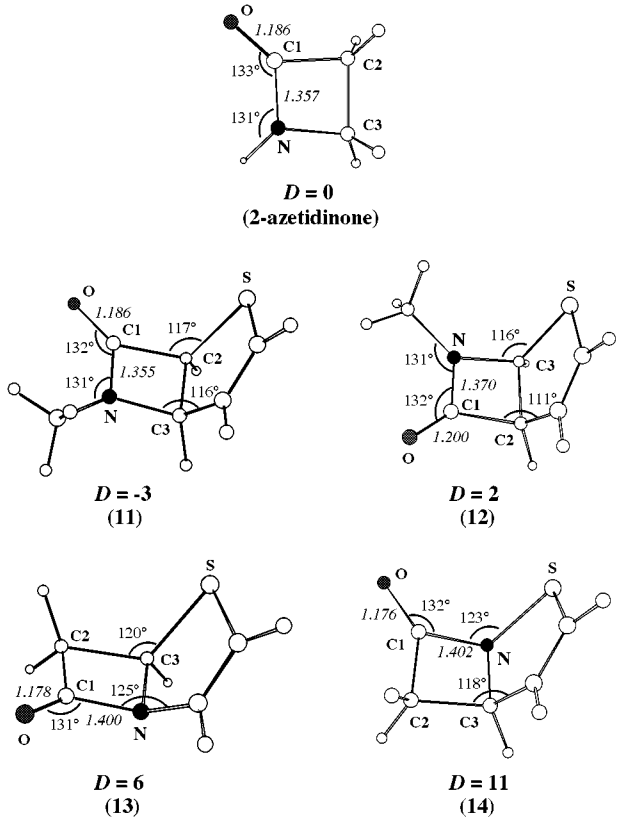
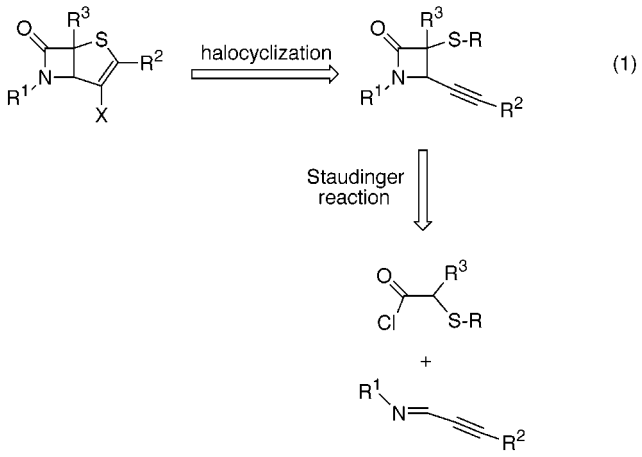


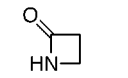
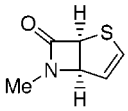
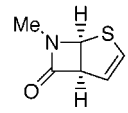
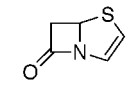
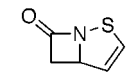
Figure 3. HF/6-31G* optimized geometries of 2-azetidinone and penems **11**−**14** (italicized bond lengths are in angstroms, and *D* is the N−C1−C2−C3 dihedral angle).

formed by a classical Staudinger reaction[28] between an α-(alkylthio)ketene equivalent and an α,β-unsaturated imine. The sulfur ring is subsequently closed onto the β-lactam unit by a halogen-promoted heterocyclization process.[29] The minimal number of steps required to access various types of [3.2.0]ring systems, and the opportunity to vary ring substituents R^1, R^2, R^3, and X, are attractive features of this methodology.[30]



Implementation of this strategy was first applied to the synthesis of type I penem **18**, as illustrated in Scheme 2. The sequence begins with treatment of an equimolar mixture of *S*-benzylthioacetyl chloride[31] (**15**) with propargylic imine **16** in the presence of a stoichiometric amount of Et_3N. Cycloadducts **17** were obtained as a 10:1 mixture of stereoisomers in 88% yield. Unfortunately, the predominant adduct in this crude composition was the undesired trans isomer, in contrast to the normally cis-selective [2 + 2]-cycloadditions of imines with α-alkoxy- and α-aminoacetyl chlorides.[32] Efforts to improve the cis-selectivity of these reactions by varying the reaction conditions or workup procedure were unsuccessful. However, the conversion of this mixture to a more favorable 1:2 cis:trans composition could be carried out by treating the unpurified β-lactam products with *n*-butyllithium at −78 °C followed by aqueous acetic acid. While the diastereomers of **17** could be separated by flash column chromatography, it was more convenient to simply carry the mixture on to the halogenation step, at which point the unreacted trans isomer could be easily retrieved. The halocyclization reaction of cis-**17** was effected using 1 equiv of I_2 in CH_2Cl_2 at room temperature, affording bicycloadduct **18** in better than 95% yield (based on the recovered amount of trans-**17**). From our previous studies on iodocyclization reactions of 3-butynyl benzyl sulfides, we ascertained that 5-endo cyclization

Table 2. Comparison of the Energies of the Lowest Unoccupied Molecular Orbital (LUMO) for 2-Azetidinone and β-Lactams 11−14

Structure		LUMO Energy (eV)
		5.784
	**(11)**	4.679
	**(12)**	4.174
	**(13)**	3.944
	**(14)**	3.755

increasing electrophilicity

(28) (a) Ren, X.-F.; Turos, E. *Tetrahedron Lett.* **1993**, 1575. (b) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468.

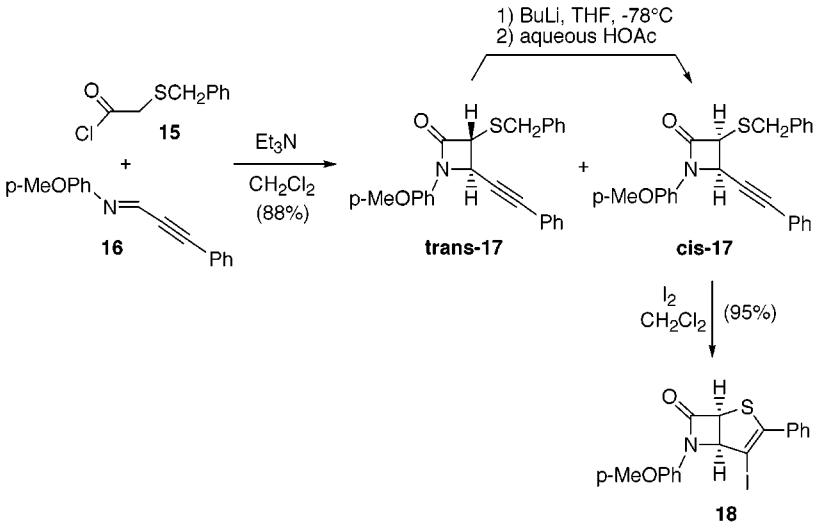
(29) [2 + 2]-cycloadditions of α-arylthioacetyl chlorides with imines have been reported previously. (a) Palomo, C.; Cossio, F. P.; Odiozola, J. M.; Oiarbide, M.; Ontoria, J. M. *Tetrahedron Lett.* **1989**, *30*, 4577. (b) Palomo, C.; Cossio, F. P.; Odiozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1991**, *56*, 4418. (c) Ishida, M.; Minami, T.; Agawa, T. *J. Org. Chem.* **1979**, *44*, 2069.

(30) This halocyclization procedure is somewhat reminiscent of the classical Morin isomerization of penicillin sulfoxides to cephams, a process thought to occur via intramolecular addition of an electrophilic sulfur group to an olefin. (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: (a) Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. I. For related methodology involving an intramolecular sulfenylation of an allene, see: Farina, V.; Kant, J. *Tetrahedron Lett.* **1992**, *33*, 3559.

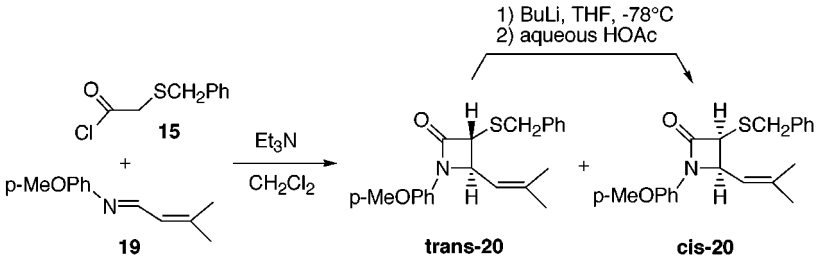
(31) This acid chloride can be easily prepared from the commercially available carboxylic acid by refluxing in thionyl chloride.

(32) For examples and discussions on the synthesis of α-alkoxy- and α-amino-substituted β-lactams, refer to ref 7b, Chapter 6, pp 295−368.

Scheme 2

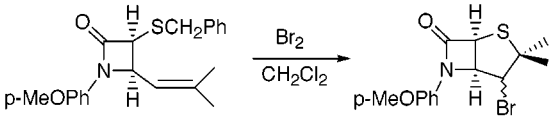


Scheme 3



products are formed exclusively over the 4-exo adducts, because of the significantly greater ring strain associated with forming the four- versus the five-membered sulfur ring.[28]

Using an analogous procedure, alkenyl β-lactams **20** were prepared from acid chloride **15** and the *N*-(4-methoxyphenyl)imine **19** of 3-methyl-2-butenal (Scheme 3). In this case, treatment of the initial product mixture according to the above-described deprotonation/protonation procedure gave a 1:3 mixture of cis:trans diastereomers in 77% overall combined yield. In the imine−acid chloride coupling reaction, an unidentified isomeric, non-β-lactam containing byproduct[33] was also obtained in amounts that varied depending on reaction and workup conditions. Bromination of the 1:3 mixture of alkenyl sulfides **20** with 1 molar equiv of Br_2 in CH_2Cl_2 solution led to the isolation of **21** (90% based on cis-**20**) as a 1:5 mixture of α:β bromo epimers, as well as products arising from bromination of the olefin centers in trans-**20** (eq 2). Assignment of relative stereochemistry in adducts **21** is based on comparison of the magnitude of the vicinal coupling constants for the proton at the brominated center in α-bromo ($J = 4.0$ Hz) and β-bromo ($J = 5.2$ Hz) compounds **21** with their Dreiding models.



(2)

Figure 4 shows two possible pathways for halocyclization of cis-**20**. Ring closure leading to the α-bromo product via transition state $A^{\neq}$ should be disfavored over the one producing the β-bromo isomer via transition state $B^{\neq}$, for several reasons. First, the $A_{1,3}$-type interactions of the vinyl methyl with the hydrogen at the ring fusion in $A^{\neq}$ should be more severe than the corresponding $A_{1,2}$-type interactions between the vinyl hydrogen and hydrogen at the ring fusion in $B^{\neq}$. Second, ring closure through $B^{\neq}$ is geometrically better suited with respect to the positioning of sulfur's nonbonding electron pairs[34] for attack at the terminus of the double bond.

We were interested in synthesizing β-lactams such as **25** that bear a large alkylthio substituent at the α-carbon. Heterosubstitution at the center α to the carbonyl on a β-lactam ring can often enhance the electrophilic properties and hydrolytic stability of the lactam carbonyl.[35] We envisioned that compounds **25** could best be accessed by

(33) We speculate that this isomeric material may be a [4 + 2]-cycloadduct that forms between the crotonimine and ketene, although no attempt was made to confirm this structure.

(34) Preliminary accounts of this research have been communicated in the following articles: (a) Ren, X.-F.; Turos, E. *J. Org. Chem.* **1994**, *59*, 5858. (b) Ren, X.-F.; Konaklieva, M. I.; Turos, E. *J. Org. Chem.* **1995**, *60*, 4980. (c) Konaklieva, I.; Shi, H.; Turos, E. *Tetrahedron Lett.* **1997**, *38*, 8647. Also, refer to ref 28b.

(35) For instance, 7α-methoxylation of the cephalosporin ring system markedly enhances β-lactamase resistance. (a) Strominger, J. L.; Tipper, D. J. *Am. J. Med.* **1965**, *39*, 707. (b) Cama, L. D.; Leanza, W. J.; Beattie, T. R.; Christensen, B. G. *J. Am. Chem. Soc.* **1972**, *94*, 1408. (c) Stapley, E. O.; Birnbaum, J.; Miller, A. K.; Wallick, H.; Hendlin, D.; Woodruff, H. B. *Rev. Inf. Dis.* **1979**, *1*, 73 and references therein. (d) Nagarajan, R.; Boeck, L. D.; Gorman, M.; Hamill, R. L.; Higgens, C. E.; Hoehn, M. M.; Stark, W. M.; Whitney, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 2308. However, heterosubstitution on the penicillin core generally diminishes antibiotic activity (Bentley, P. H.; Clayton, J. P. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Elks, J., Ed.; Special Publication No. 28, The Chemical Society: London, 1977; pp 68−72), although the penicillin derivative temocillin seems to be an exception (Slocombe, B.; Basker, M. J.; Bentley, P. H.; Clayton, J. P.; Cole, M.; Comber, K. R.; Dixon, R. A.; Edmondson, R. A.; Jackson, D.; Merrikin, D. J.; Sutherland, R. *Antimicrob. Agents Chemother.* **1981**, *20*, 38).

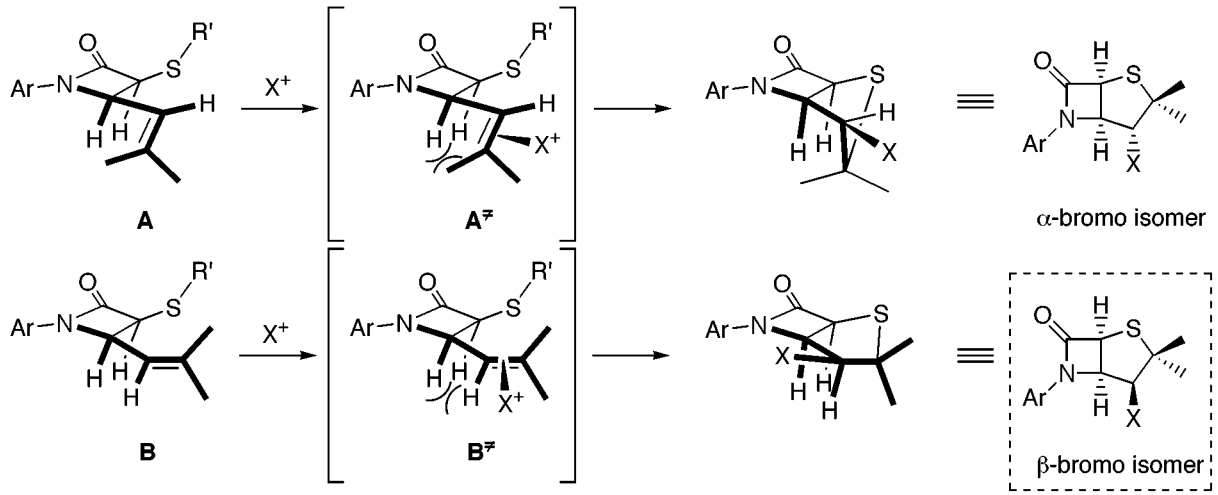
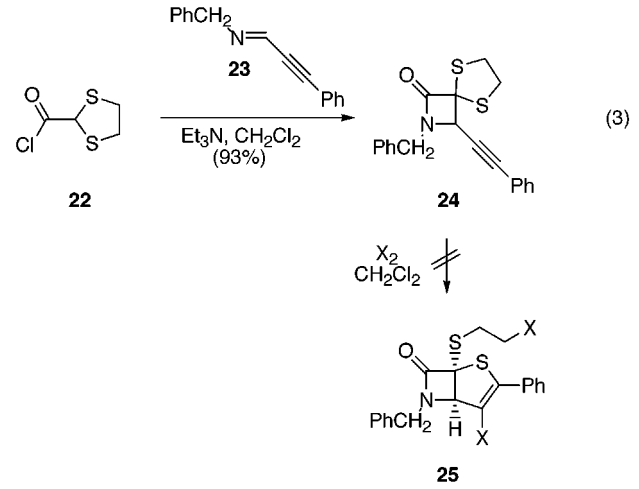


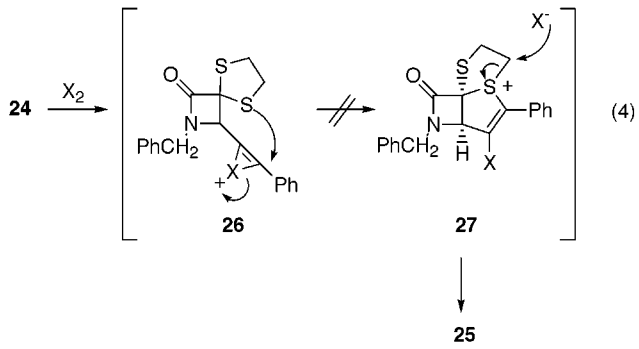
Figure 4. Comparison of geometries for the halocyclization of cis-**20**.

halocyclization of acetylenic dithiane **24**, which could be readily prepared from acid chloride **22** and imine **23** following the published method[36] of Sharma (eq 3).



(3)

Unfortunately, attempts to effect the halocyclization of spiro dithiane **24** were unsuccessful. The resistance of this substrate to undergo cyclization to **25** may be due to difficulty in forming tricyclic intermediate **27**, or in effecting its subsequent ring opening (eq 4).



(4)

In an attempt to circumvent this problem, an alternative route to α-thiosubstituted *β*-lactams was explored using bis(thioether) *β*-lactams **30** as substrates for the halocyclization procedure (Scheme 4). Dithianes **30** were prepared from [2 + 2]-coupling of bis(ethylthio)acetyl chloride[37] (**28**) and propargyl imines **29** and subsequently subjected to iodination using 1 molar equiv of I_2. Excellent yields of the desired bicycloadducts **31** were produced upon workup of the reaction. α-Thiosubstituted penam analogues **34** were similarly synthesized in two steps, starting from the condensation of acid chloride **28** and *N*-benzylimine **32**. Obtained from this reaction was *β*-lactam **33** in 58% yield, which upon bromination[38] afforded isopenicillin derivative **34** as a 1:4 mixture of α: *β* Br epimers. Relative stereochemical assignments for **34** are in accord with those made previously for *β*-lactam **21**. The conversion of **30** to **31** and **33** to **34** represents, to the best of our knowledge, the first examples of a halocyclization reaction in which a thioketal serves as the nucleophilic component.

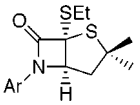
Our attention next turned to the synthesis of "inversely fused" penem and clavulanic acid analogues illustrated in Figure 5. The four boxed structures represent the formal hybridization of the penem/clavulanic acid ring systems with that of the monobactams, an intriguing class of monocyclic *β*-lactams whose potent antibacterial properties have been attributed to the strongly electron-withdrawing *N*-sulfato group.[39] In these hybridized ring structures, the *β*-lactam nitrogen is both at the ring fusion and directly bonded to sulfur, in an unusual bonding arrangement found only in one previously reported structure (see compound **8**).

Penem analogues **39**, whose interesting heterocyclic array contains five heteroatom-bearing ring carbons, were synthesized according to the procedure devised in Scheme 5. The requisite *cis*-alkenyl azetidinones **36** were

(36) Sharma, S. D.; Mehra, U.; Khurana, J. P. S.; Pandhi, S. B. *Synthesis* **1987**, 990.

(37) The synthesis of 3-bis(ethylthio)azetidinones has been reported previously. Cossio, F. P.; Ganboa, I.; Garcia, J. M.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 1945. Also see: Abramski, W.; Belzecki, C.; Chielewski, M. *Bull. Pol. Acad. Sci. Chem.* **1985**, *33*, 451.

(38) In the bromination reaction of **33**, a small amount of the proto derivative (shown below) can also be obtained, presumably from HBr-promoted ring closure.



(39) (a) Slusarchyk, W. A.; Dejneka, T.; Gordon, E. M.; Weaver, E. R.; Koster, W. H. *Heterocycles* **1984**, *21*, 191. (b) Cimarusti, C. M.; Sykes, R. B. *Med. Res. Rev.* **1984**, *4*, 1.

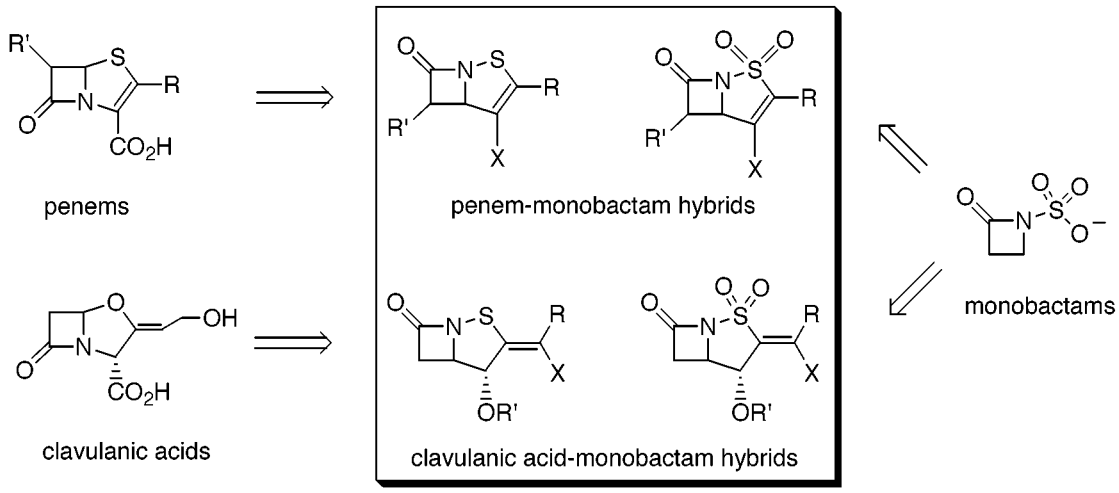
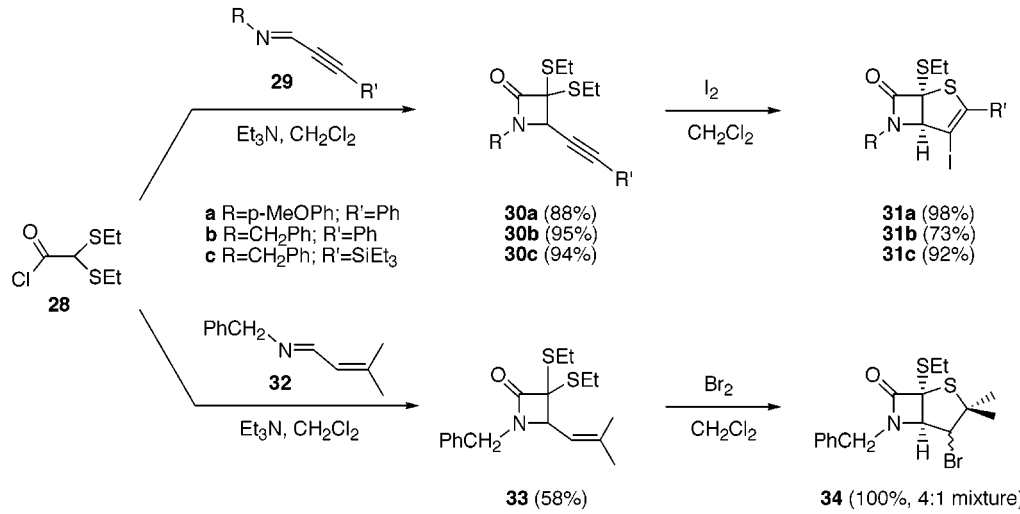
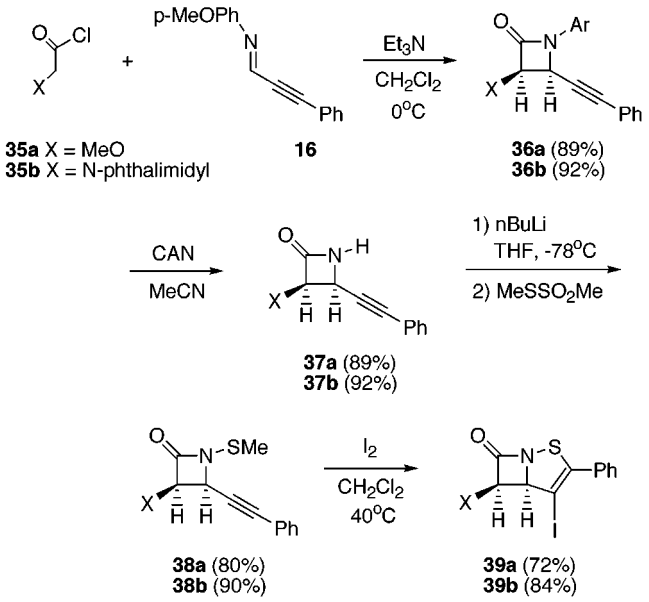


Figure 5. Novel penem−monobactam and clavulanic acid−monobactam hybrids.

Scheme 4



Scheme 5



prepared in about 90% yield by condensation of methoxyacetyl chloride (**35a**) or *N*-phthalimidoacetyl chloride (**35b**) with *N*-arylamine **16**. The cis relative stereochemistry of these adducts was evident from the ^{1}H NMR spectra, which showed characteristic doublets for the two ring protons with vicinal coupling constants of 4.8 Hz.[40] The aryl nitrogen protecting group of **36** was removed by oxidation with ceric ammonium nitrate[41] to give **37**. Deprotonation of **37** with n-BuLi at low temperature and subsequent trapping of the amide anion with methyl methanethiosulfonate[42] afforded *N*-(methylthio)-substituted β-lactams **38** in high overall yield.

In contemplating the possibility of forming isopenem ring system **39** via halogenation of substrate **38**, we realized that the use of an *N*-acylsulfenamide as a nucleophile in halocyclizations onto unsaturated centers is an unprecedented reaction. We had initial concerns that the lactam group might discourage ring closure by electronically deactivating the sulfur toward nucleophilic addition onto the π-system, or by introducing additional geometric constraints that could potentially interfere with the cyclization process. Despite these concerns, the cyclization of **38** proceeded cleanly using I_2 in dichloromethane to give **39** as a single bicyclic β-lactam having a C=O stretching band near 1790 cm^{-1}. The fact,

(40) Cis-disubstituted β-lactams characteristically show a vicinal coupling constant of 4.8−6.0 Hz, while for trans-disubstituted β-lactams this value is typically only 1−3 Hz.

(41) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(42) Shah, N. V.; Cama, L. D. *Heterocycles* **1987**, *25*, 221.

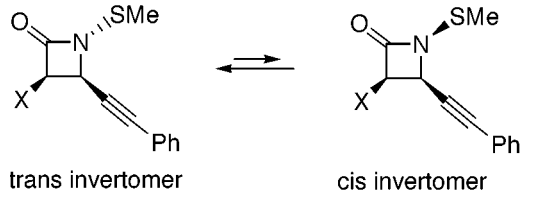


Figure 6. Nitrogen inversion in β-lactams **38**.

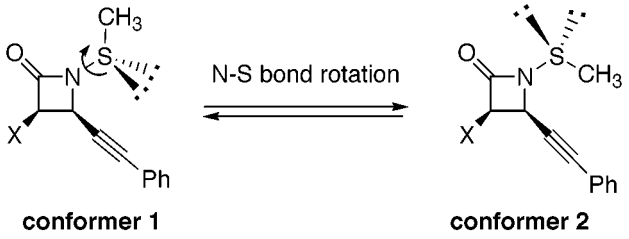


Figure 7. Sulfur−nitrogen bond rotation in β-lactams **38**.

however, that the ring closure proceeded sluggishly over several hours at an elevated temperature (40 °C) supports our initial speculation that *N*-acyl sulfenamide systems would be less prone to halocyclization than the corresponding thioether analogues (see **30** in Scheme 4), which halocyclize readily at room temperature. There are several likely reasons for this. First, the product of the reaction, N-fused lactam **39**, is conformationally more constrained than the corresponding C-fused analogues **31** formed in the thioether ring closures. Thus, the loss of amide resonance associated with increasing pyramidalization of the nitrogen center would discourage formation of the N-fused bicyclic lactam. Moreover, electron withdrawal by the *N*-acyl group of **38** would diminish nucleophilicity at sulfur. It is also conceivable that sulfur can slow the rate of configurational inversion at the nitrogen center (assuming some residual sp^3 character), establishing an equilibrium that favors the trans invertomer over the cis form required for cyclization (Figure 6), or that restricted isomerization around the N−S bond of **38** could orient sulfur's nonbonding orbitals away from the triple bond (see conformer 2 in Figure 7). Sulfenamides can have significant barriers to rotation around the sulfur−nitrogen single bond, generally in the range of 9−23 kcal/mol.[43] Miller and his colleagues have observed this behavior in their studies on the closely related thiamazin β-lactams, whose barrier to sulfur−nitrogen bond rotation was determined to be as high as 12 kcal/mol (Figure 8).[44] In examining the behavior of our β-lactams by variable temperature NMR, however, we found that lactams **38** exist as single compounds over a temperature range of −50 to +50 °C, which suggests that neither of the latter two isomerization phenomena is a factor in the cyclizations of our *N*-SMe β-lactams. Rather, the slow rate for halocyclization of these sulfenamides compared to the corresponding thioethers is most likely due to electron withdrawal by the *N*-acyl moiety and unfavorable geometric or stereoelectronic demands.

The difference in reactivity between the latter two β-lactam systems is also revealed in the ring-closing reactions of thioether lactam **33** and sulfenamide lactams **40** and **41**. Whereas alkenyl *thioether* **33** undergoes facile *5-endo-trig* cyclization upon reaction with bromine to provide bicyclic β-lactam **34** (refer to Scheme 4), alkenyl

(43) Raban, M. *Tetrahedron* **1984**, *40*, 3345.

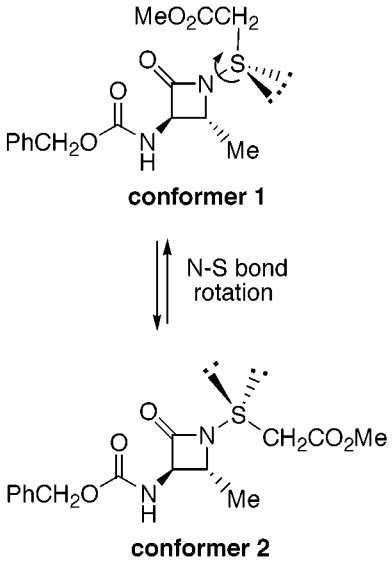
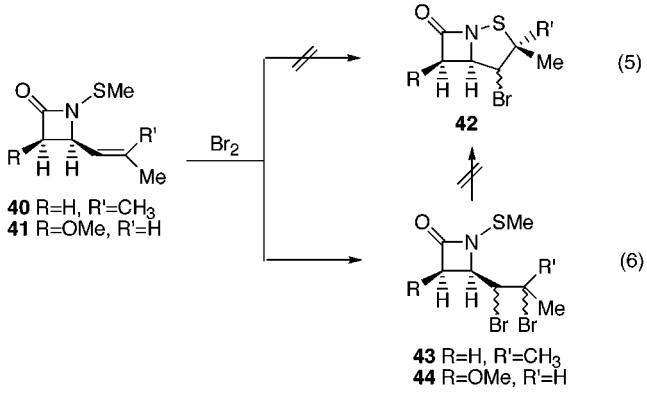


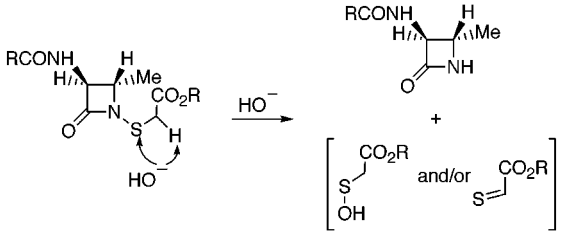
Figure 8. Sulfur-nitrogen bond rotation in thiamazins.

sulfenamides **40** and **41** fail to give the desired cyclization products **42** (eq 5). This would seem to indicate that the geometric/stereoelectronic constraints within **40** and **41** are even more prohibitive than those in the *acetylenic* substrates **38**, with the intramolecular addition of sulfur to the double bond now being energetically unfavorable. Consequently, diastereomeric mixtures of olefin bromination products **43** and **44** are instead produced from these halogenation reactions (eq 6).[45] Efforts to convert the unwanted dibrominated adducts **43** and **44** to heterocycles **42** under a variety of thermolytic conditions were unproductive.

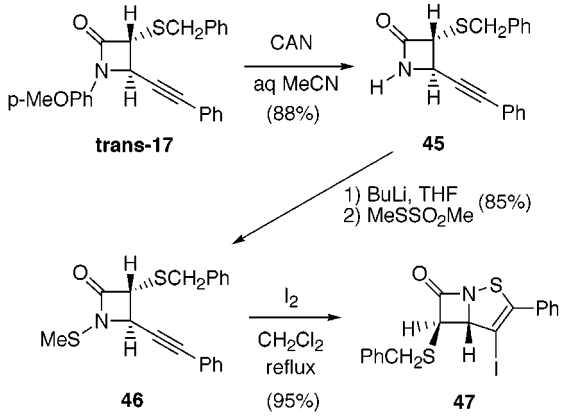


The necessity of having the two reactive groups involved in the halocyclization, the sulfur and unsaturated

(44) (a) Woulfe, S. R.; Miller, M. J. *J. Med. Chem.* **1985**, *28*, 1447. (b) Woulfe, S. R.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 3133. (c) Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528. In this paper, the authors report that approximately 50% of the thiamazin undergoes decomposition at pH 11 by cleavage of the nitrogen−sulfur bond, at a rate of 0.35 h^{-1}. This process occurs through hydroxide ion attack on the sulfur center as well as via deprotonation of the SCH_2CO_2R group.



Scheme 6



ring substituents, cis on the β-lactam ring suggests the possibility of being able to direct the cis and trans β-lactam isomers to regioisomeric ring adducts. For example, the iodocyclization shown previously in Scheme 2 involving a cis/trans mixture of β-lactams **17** led to cyclization of only the cis compound, producing the C-fused bicycloadduct **18**. With the recovered trans isomer from this reaction, we were able to prepare the *N*-methylthio β-lactam **46**. Iodination of **46** in refluxing CH_2Cl_2 solution provided the N-fused ring compound **47** (Scheme 6).

We intended to utilize a similar halocyclization protocol for the synthesis of clavulanic acid analogues **53** (Scheme 7). The requisite β-lactam starting materials **48** were obtained by reaction of acetyl chlorides **35a** or **35b** with crotonaldehyde imine in the presence of a stoichiometric amount of triethylamine at 0 °C. The cis stereochemistry of adducts **48** was assigned on the basis of a ^{1}H NMR *J* coupling value of 4.8 Hz for the two protons on the β-lactam ring. Ozonolysis of **48** at room temperature provided cis aldehydes **49** in high yield without any detectible epimerization. To incorporate the required acetylenic side chain onto the β-lactam ring of intermediate **50**, an acetylide anion addition to aldehyde precursor **49** was carried out. Addition of lithium phenylacetylide to **49** proceeded stereoselectively to give the alcohol adducts, which afforded acetates **50** upon acetylation under standard conditions. Compound **50a** was isolated as a 1:5 mixture of α:β stereoisomers in 55% combined yield after flash chromatography, while **50b** was obtained in 69% overall yield as a 1:2 mixture of α:β diastereomers. Deprotection of the *N*-methoxyphenyl group of **50** and installment of the methylthio moiety onto the lactam nitrogen proceeded smoothly. The minor stereoisomers of **52** could be chromatographically separated at this juncture. Iodocyclization of **52a** and **52b** was effected with I_2 in CH_2Cl_2 at room temperature to give **53a** and **53b**, respectively, in high yield. These bicycloadducts are unusual in that they contain six contiguous and uniquely heterosubstituted carbon centers within their backbone. In light of our previous studies[46] which demonstrated the overwhelming preference of alkynyl sulfides to undergo 5-exo-dig ring closure, adducts **53** have been assigned to have an exocyclic olefin with the *E* geometry arising from stereospecific trans addition to the triple bond. The relative configuration of the allylic acetate center in **53** is of particular interest, since it originates from a stereoselective addition of acetylide anion to chiral aldehydes **49**. The stereochemistry of this nucleophilic addition can be rationalized using the Felkin−Anh[47] model, as illustrated in Figure 9. In this conformation having the electron-withdrawing nitrogen of the β-lactam ring orthogonal to the carbonyl group, attack of the lithium acetylide anion would occur more readily from the less congested α-face of the aldehyde, leading to alcohol **54**.

In the case of methoxy-substituted aldehyde **49a**, the ratio of α:β acetate products can be inverted by conducting the acetylide addition reaction in the presence of a stoichiometric amount of $MgCl_2$. We speculate that in this case the addition occurs preferentially by approach of the acetylide from the less hindered face of a chelated magnesium complex, with the metal ion coordinating the oxygens of the methoxy and aldehyde moieties, to give alcohol **55** (Figure 10).

From the infrared spectra of β-lactams **53**, it is readily apparent that the lactam carbonyl is electrophically enhanced by the lactam nitrogen being both at the site of ring fusion and bonded to the electronegative sulfur atom. The stretching absorption frequency for the carbonyl in these analogues appears at a considerably higher wavenumber ($\upsilon_{C=O}$ 1780 cm^{-1}) than that observed for the C-fused analogues **31** and **34** ($\upsilon_{C=O}$ 1750−1760 cm^{-1}) and is within the same range as the biologically active penems ($\upsilon_{C=O}$ 1775−1785 cm^{-1}). Despite their unusually high electrophilicities, these N−S-fused lactams appear to be quite resistant toward hydrolytic conditions and can be easily isolated from aqueous sodium bisulfite solution and purified by silica gel flash chromatography without any apparent decomposition. They tolerate prolonged exposure to aqueous media ranging from pH 4 to 10 and are thus comparable to the monocyclic thiamazins that have been reported by Miller to be hydrolytically stable below pH 11.[44]

Listed in Table 3 are the carbonyl stretching frequencies recorded for the various bicyclic β-lactam derivatives from our study. Comparison of the observed carbonyl infrared absorption frequencies indicates that the simple C-fused penem and penam analogues **31** and **34** ($\upsilon_{C=O}$ 1750−1760 cm^{-1}) are somewhat less electrophilic than the parent antibiotics ($\upsilon_{C=O}$ 1775−1785 cm^{-1}), which is in agreement with earlier studies which show that N-fused β-lactams absorb at about 15 cm^{-1} higher than the C-fused rings (vide supra). Since biological activity of β-lactam antibiotics is attributable to a highly electrophilic carbonyl carbon, we thought that the electrophilicity of these compounds could be enhanced through oxidation of the sulfur atom(s).[48] This was demonstrated by converting β-lactams **31** and **34** to their disulfone

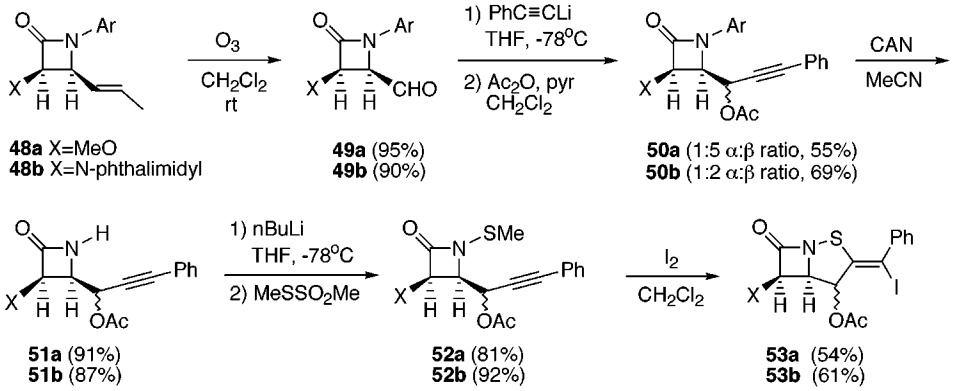
(45) The proton NMR spectra of the adducts **43** and **44** from bromination of trans-**40** and trans-**41** shows the retention of the azetidinyl *S*-Me groups (appearing as separate singlets for the two diastereomers).

(46) For more detailed discussions on stereoelectronic requirements in sulfur halocyclizations, see the papers cited in ref 28 as well as the following article on related cyclization chemistry. Ren, X.-F.; Konaklieva, M. I.; Turos, E.; Krajkowski, L. M.; Lake, C. H.; Janik, T. S.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6484.

(47) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

(48) Oxidation of penicillins and cephalosporins to their sulfoxides and sulfones increases the β-lactam carbonyl stretching frequency by 15 and 45 cm^{-1}, respectively. (See: Demarco, P. V.; Nagarajan, R. In *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed., Academic Press: New York, 1972; pp 315−320). Penicillin sulfones lack antibiotic activity but show β-lactamase inhibition. (For insight into their mechanism of action and lead references, see: Fink, A. L.; Ellerby, L. M.; Bassett, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 6871).

Scheme 7



48a X=MeO
48b X=N-phthalimidyl

49a (95%)
49b (90%)

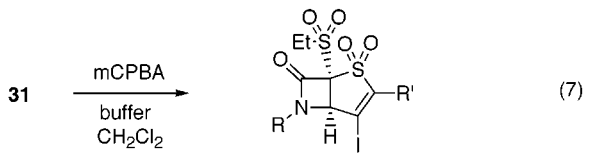
50a (1:5 α:β ratio, 55%)
50b (1:2 α:β ratio, 69%)

51a (91%)
51b (87%)

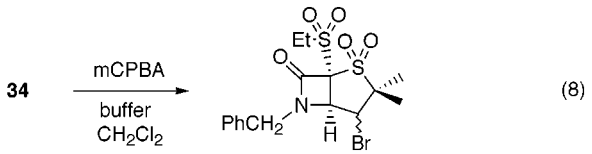
52a (81%)
52b (92%)

53a (54%)
53b (61%)

derivatives **56** and **57**, respectively, using *m*-chloroperoxybenzoic acid (mCPBA)[49] in CH_2Cl_2 solution buffered with $Na_2HPO_4-NaH_2PO_4$ (eqs 7 and 8). As anticipated, the electron-withdrawing influence of the twin α-disulfone groups on the lactam carbonyl can be observed by the shift in the infrared absorption frequency for the

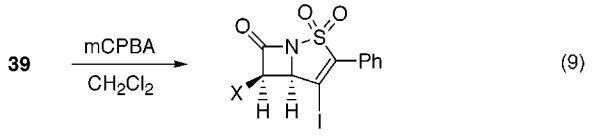


56a R=p-MeOPh, R'=Ph (86%)
56b R=$PhCH_2$, R'=Ph (45%)
56c R=$PhCH_2$, R'=$SiEt_3$ (72%)



57 (1:4 α:β Br epimers)

C=O bond from 1750−1760 cm^{-1} (for sulfides **31** and **34**) to 1775−1785 cm^{-1} (for disulfones **56** and **57**). Similarly, peracid oxidation of sulfenamides **39** afforded sulfonamides **58** whose infrared absorption band near 1800 cm^{-1} confirms both the survival of the β-lactam ring during the oxidation and workup procedures and the unusually short C=O bond (eq 9). These highly electrophilic bicyclic disulfone and sulfonamide derivatives are stable to aqueous $NaHSO_3$ and $NaHCO_3$ workup conditions and to silica gel chromatography and show no tendency to hydrolyze under neutral or mildly basic conditions.



58a X=MeO (82%)
58b X=N-phthalimidyl (87%)

Functionalization of β-Lactam Core Structures. With a selection of new β-lactam core structures available to us, our attention turned to the preparation of derivatized compounds for preliminary antimicrobial testing experiments. Since all "conventional" penicillin antibiotics and β-lactamase inhibitors contain an ionizable group[50] (such as a carboxylic acid) on the thiazolidine

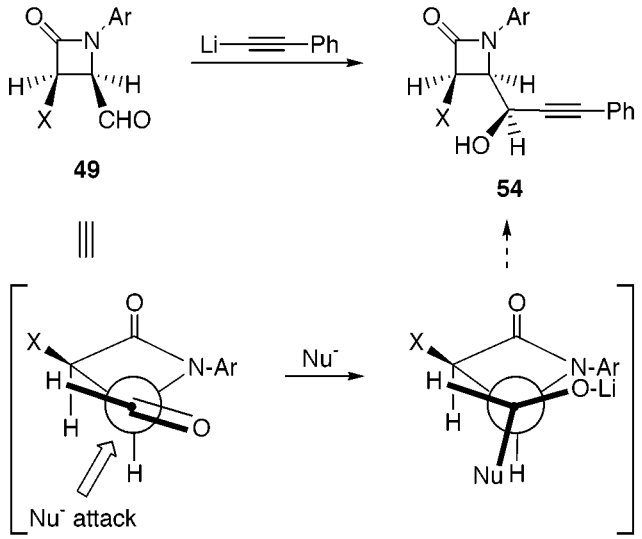


Figure 9. Stereochemistry of lithium acetylide addition to **49**.

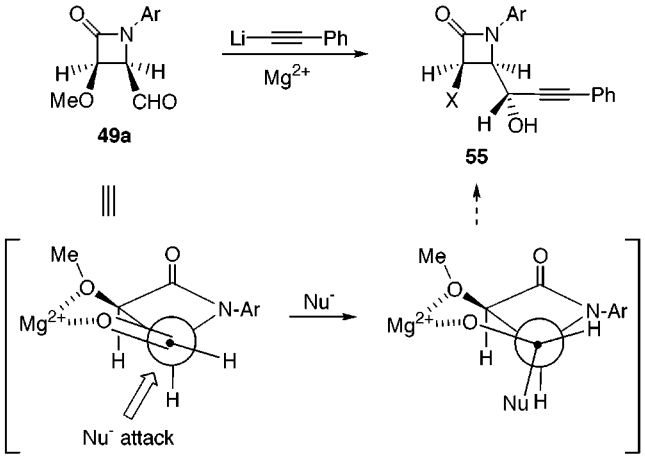
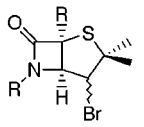
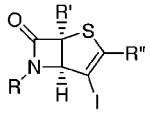
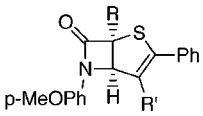
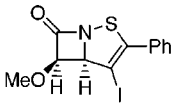
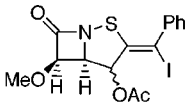


Figure 10. Stereochemistry of lithium acetylide addition to **49a** in the presence of $MgCl_2$.

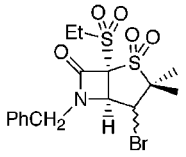
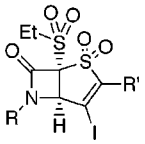
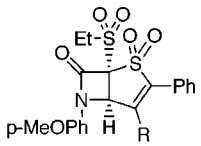
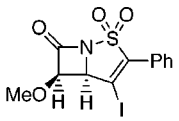
ring, it seemed desirable to begin these investigations by studying methods for derivatizing some of our β-lactam core structures with more polar, and possibly ionizable, functionality. In considering the various options for modifying our β-lactam rings, we felt that the halogen

(49) (a) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408. (b) Cooper, R. D. G.; DeMarco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1969**, *91*, 1528.

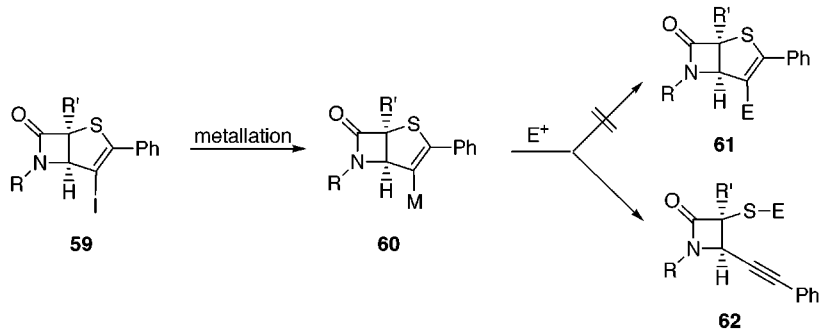
Table 3. Infrared C=O Stretching Frequency for β-Lactams

Structure	Compound	ν (cm^{-1})
	**21** (R=H, R'=p-MeOPh) **34** (R=SEt, R'=PhCH$_2$)	1760 1755
	**18** (R=p-MeOPh, R'=H, R"=Ph) **31a** (R=p-MeOPh, R'=SEt, R"=Ph) **31b** (R=PhCH$_2$, R'=SEt, R"=Ph) **31c** (R=PhCH$_2$, R'=SEt, R'=SiEt$_3$)	1750 1760 1752 1753
	**74a** (R=H, R'=vinyl) **74b** (R=H, R'=2-furanyl) **75** (R=H, R'=CO$_2$Me) **76** (R=H, R'=CO$_2$CH$_2$CH=CH$_2$) **77** (R=SEt, R'=CO$_2$CH$_3$) **78** (R=H, R'=CO$_2$H) **80** (R=SEt, R'=CO$_2$H)	1750 1750 1750 1750 1755 1750 1755
	**39a** **39b**	1790 1790
	**53a** **53b**	1780 1780

[O]

Structure	Compound	ν (cm^{-1})
	**57**	1775
	**56a** (R=p-MeOPh, R'=SEt, R"=Ph) **56b** (R=PhCH$_2$, R'=SEt, R"=Ph) **56c** (R=PhCH$_2$, R'=SEt, R'=SiEt$_3$)	1780 1785 1785
	**76** (R=CO$_2$CH$_3$) **79** (R=CO$_2$H)	1780 1785
	**58a** **58b**	1801 1800

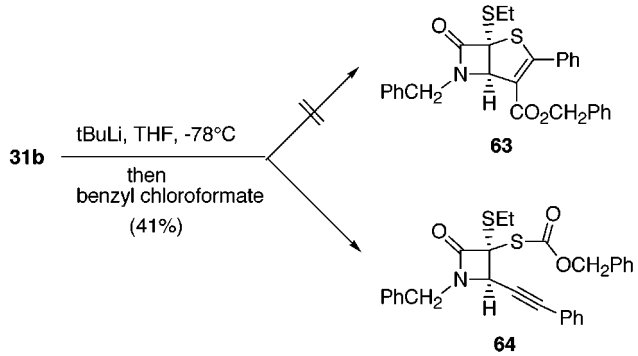
Scheme 8



could serve as the most direct means to introduce other functionality via a metal−halogen exchange and reaction with a suitable electrophile (Scheme 8). However, it soon became apparent that this would be more difficult than first envisioned, due to the fact that the halide in these C-fused penems is both β to and antiperiplanar to a sulfur leaving group.

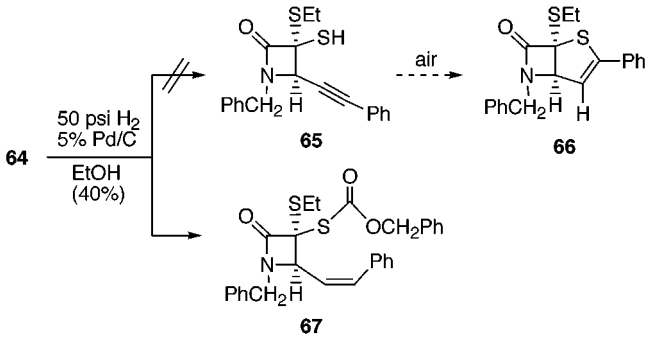
Our initial attempts to carry out low-temperature metalation reactions on **59** using tBuLi or Mg°, with subsequent alkylation or aldol reaction, led only to products **62** derived from opening of the dihydrothiophene or β-lactam rings. The reaction shown in Scheme 9 illustrates one unsuccessful attempt to esterify iodide **31b** by lithiation and trapping with benzyl chloroformate, which results instead in the formation of ring-opened adduct **64** by β-elimination. In an effort to revert this unwanted material back to a bicyclic derivative of **31b**, we attempted to selectively reduce off the benzyl thiocarbonate moiety to release the free thiol, with the expectation that cyclization of **65** to give **66** would occur spontaneously upon aerobic workup (Scheme 10). However, the only product observed by proton NMR to form upon catalytic hydrogenation of **64** was *Z*-olefin **67**, resulting from partial reduction of the triple bond side chain.

Scheme 9



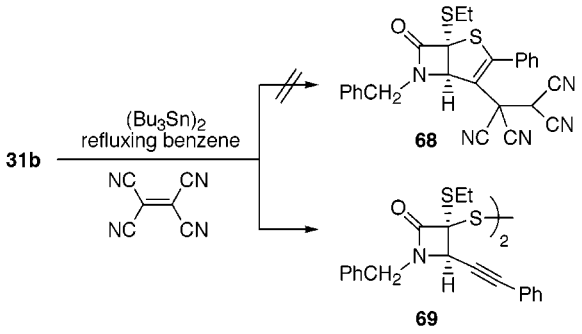
(50) (a) Imtiaz, U.; Billings, E.; Knox, J. R.; Manavathu, E. K.; Lerner, S. A.; Mobashery, S. *J. Am. Chem. Soc.* **1993**, *115*, 4435. (b) Knox, J. R.; Moews, P. C. *J. Mol. Biol.* **1991**, *220*, 435. (c) Moews, P. C.; Knox, J. R.; Dideberg, O.; Charlier, P.; Frere, J. M. *Proteins* **1990**, *7*, 156. (d) Herzberg, O.; Moult, J. *Science* **1987**, *236*, 694.

Scheme 10

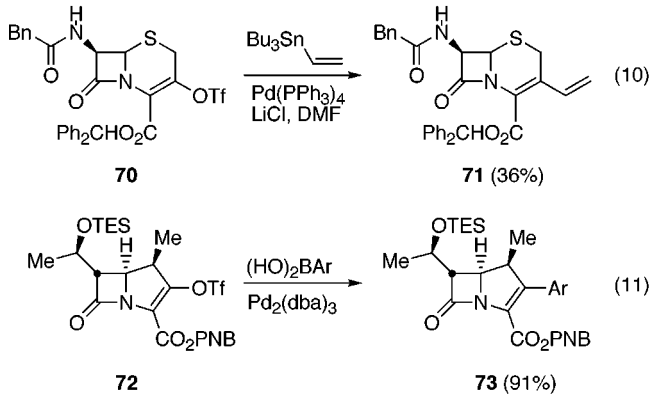


Similar efforts to generate and trap a vinyl radical intermediate from β-lactam **31b** also failed to provide the desired substitution products. For instance, upon reaction of vinyl iodide **31b** with Bu_3SnH/AIBN or $(Bu_3Sn)_2$ in the presence of various radical trapping agents, only disulfide product **69** was obtained instead of the olefin addition product **68**. The dimeric structure of **69** was confirmed by mass spectrometry. This product undoubtedly arises from a rapid elimination[51] of thiyl radical from a β-thiosubstituted vinyl radical intermediate, and dimerization to give the disulfide (Scheme 11).

Scheme 11



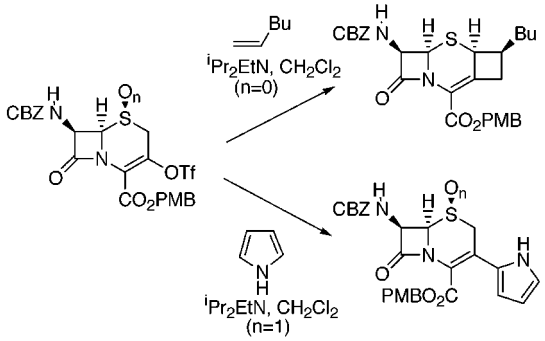
The sensitivity of compound **31b** toward elimination in metal-mediated halogen exchange reactions prompted us to consider the use of palladium-catalyzed processes. The Stille cross-coupling reaction[52] of unsaturated halides and triflates with organostannanes has become a reliable synthetic method whose mild nature often enables even difficult transformations to be carried out successfully. However, only a limited number of reports of Pd(0)-promoted reactions involving β-lactam frameworks or functionality similar to that presented in the structures of our substrates have appeared in the literature.[53] The most pertinent examples are the palladium-catalyzed couplings of cephem triflates with organotin compounds used in the preparation of 3-alkenyl, 3-alkynyl, and 3-arylcephem derivatives (eq 10) and the related reactions of carbapenem triflates (eq 11).[54]



(10)

(11)

We were encouraged to find that isopenem iodide **18** underwent Stille cross-coupling cleanly with some representative organotin reagents using 3 mol % of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) in the presence of 6 mol % of triphenylphosphine (Table 4). For example, reaction of **18** with tributylvinyltin in anhydrous DMF provided an 80% yield of adduct **74a**. Employing $Pd(OAc)_2$ as the catalyst, the yield of **74a** improved to 87%. Heteroaromatic rings can also be introduced onto the bicyclic core of **18**, as illustrated in



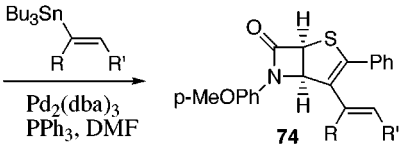
(51) The rate of elimination of a thiyl radical from a β-thioalkyl radical is on the order of 10^8 L mol^{-1} s^{-1} at room temperature (Wagner, P.; Sedon, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579). For a β-thiovinyl radical, the expulsion of thiyl radical should occur even more rapidly. See: (a) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnola, P. *J. Org. Chem.* **1994**, *59*, 2818. (b) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273.

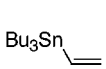
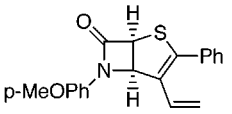
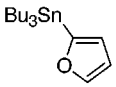
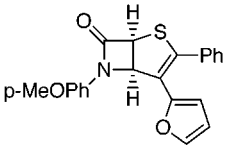
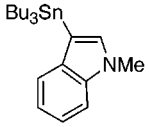
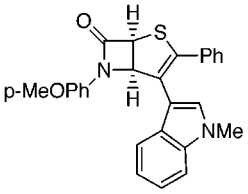
(52) (a) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (e) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(53) For examples of palladium-catalyzed reactions on β-lactam ring systems, see: (a) Barrett, D.; Terasawa, T.; Okuda, S.; Kawabata, K.; Yasuda, N.; Kamimura, T.; Sakane, K.; Takaya, T. *J. Antibiot.* **1997**, *50*, 100. (b) Armitage, M. A.; Lathbury, D. C.; Sweeney, J. B. *Tetrahedron Lett.* **1995**, *36*, 775. (c) Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.; Sridharan, V.; Hughes, M. *Tetrahedron Lett.* **1995**, *36*, 9053. (d) Rano, T. A.; Greenlee, M. L.; DiNinno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853. (e) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H.; Munroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828. (f) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962. (g) Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 5739. (h) Farina, V.; Baker, S. R.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043. (i) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH Publishers: New York, 1993; pp 121−196. (j) Researchers at SmithKline Beecham have patented (world patent number WO 9318044-A) interesting chemistry of cephalosporin triflates where, in the presence of Hunig's base, novel [4 + 2]-cycloadducts or substitution products are obtained. For reactions involving pyrrole, only the substitution product is observed. For these reactions, an allenyl intermediate is presumed, and regiochemistry of addition to this species is dependent on the oxidation state of sulfur (n = 0 or 1). Readers may refer to the following articles: (a) Elliott, R. L.; Nicholson, N. H.; Peaker, F. E.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1994**, *59*, 1606. (b) Elliott, R. L.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1993**, *58*, 6954.

(54) (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833. (b) Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 5438. (c) Narukawa, Y.; Nishi, K.; Onoue, H. *Tetrahedron* **1997**, *53*, 539. (d) Meurer, L. C.; Guthikonda, R. N.; Huber, J. L.; DiNinno, F. *BioMed. Chem. Lett.* **1995**, *5*, 767. (e) Yasuda, N.; Xavier, L.; Reiger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron* **1993**, *34*, 3211. (f) Rano, T. A.; Greenlee, M. L.; DiNinno, F. *Tetrahedron Lett.* **1990**, *31*, 2853.

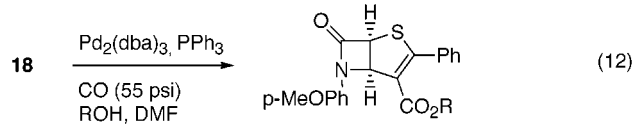
Table 4. Palladium-Promoted Cross-Coupling Reactions of β-Lactam 18 with Organostannanes



Organostannane	Stille Adduct **74** (isolated % yield)
	 (**74a**, 80%)
	 (**74b**, 80%)
	 (**74c**, 74%)

the formation of furan adduct **74b** and indole[55] adduct **74c**. These examples demonstrate the compatibility of the reaction conditions with respect to the presence of the vinyl sulfide and β-lactam ring in **18** during the alkylation reaction and pointed to the likelihood that related palladium-promoted processes might also prove effective.

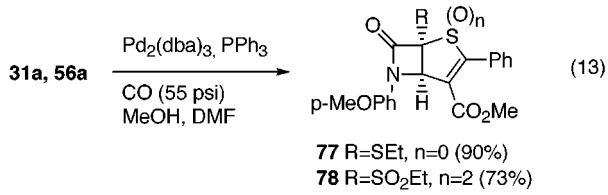
Upon additional investigation, we were pleased to find that palladium catalysis can be extended to CO insertion reactions of **18** for synthesizing carboxylic ester and acid derivatives. As shown in eq 12, iodo compound **18** provided good yields of the desired methyl and allyl esters **75** and **76** using 3−5 mol % of $Pd_2(dba)_3$ in a mixed alcohol−dimethylformamide solvent under an atmosphere of carbon monoxide.[56] Although these esterifications proceed well at room temperature, it was possible to run them at a slightly elevated temperature (55 °C) to increase the rate of conversion. Similarly, α-ethylthio β-lactam derivative **31a** and bis-sulfone **56a** underwent the CO insertion process to provide their corresponding methyl esters **77** and **78**, respectively (eq 13).



(12)

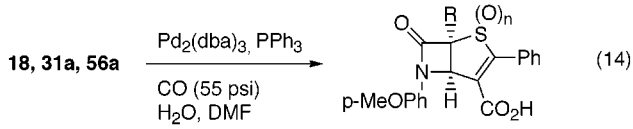
75 R = Me (75%)
76 R = $CH_2CH{=}CH_2$ (73%)

The efficiency of these esterifications encouraged us to consider carrying out CO insertion reactions in aqueous media as a means to prepare *carboxylic acid* derivatives directly from the vinyl iodides. Palladium-assisted carboxylations of this type are rare and rather limited in scope.[57] Moreover, we are unaware of any reports of palladium-catalyzed carboxylation reactions involving β-lactam ring systems. Despite our concern that the hydrolytic conditions of the reaction may cleave the β-lactam moiety, substrates **18**, **31a**, and **56a** were found to undergo the desired transformation to carboxylic acids **79**−**81**, respectively, in hydrous dimethylformamide solution (eq 14). Optimal conditions for this reaction require that only a minimal amount of water (<1%) be added to the solution and that the reactions be run at temperatures no higher than ambient. Despite the long reaction times required for completion (3−5 days), the β-lactam ring is not opened under these conditions, and the desired carboxylic acids can be obtained in 65−75% isolated yield after purification by flash chromatography. The structures of the acids were confirmed by ^1H NMR in two different deuterated solvents ($CDCl_3$ and DMSO-d_6), as well as through conversion to their methyl esters using ethereal diazomethane. Interestingly, in the carboxylation of β-lactam **31a**, a small amount (5−10%) of thioester **82** was also obtained through a yet unidentified pathway.



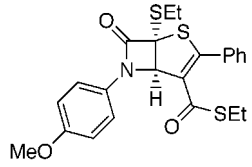
(13)

77 R=SEt, n=0 (90%)
78 R=SO_2Et, n=2 (73%)



(14)

79 R=H, n=0 (65%)
80 R=SEt, n=0 (75%)
81 R=SO_2Et, n=2 (72%)



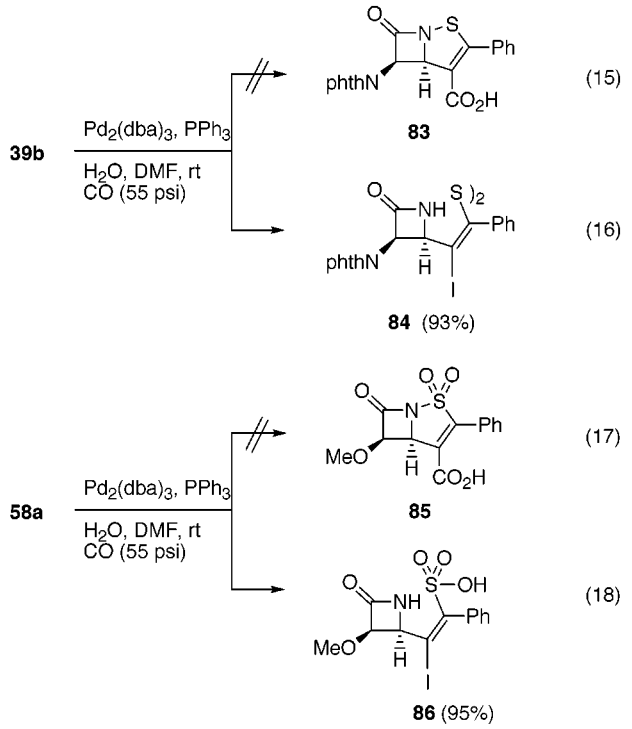
82

Disappointingly, application of the palladium-catalyzed CO insertion reactions using isopenem **39b** failed to deliver carboxylic acid derivative **83** (eq 15). Instead, a high yield of ring-opened disulfides **84** was obtained, which we later determined was the result of cleavage of the nitrogen−sulfur bond by PPh_3 in the reaction medium (eq 16). In an attempt to circumvent this problem, we examined the palladium-promoted carboxylation of sulfonamide derivative **58a**. Unfortunately, the reaction did not yield the carboxylic acid **85** (eq 17) but rather the ring-cleaved sulfinic acid **86** in 95% yield (eq 18).

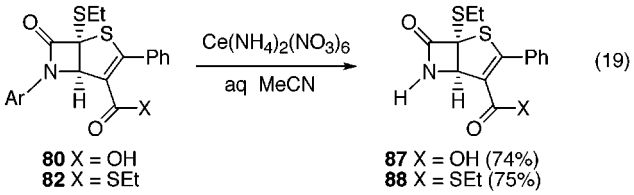
(55) For a related example of a Stille reaction involving an indole nucleus, see: Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1994**, *35*, 2405.

(56) (a) Grigg, R.; Sridharan, V.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1139. (b) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318.

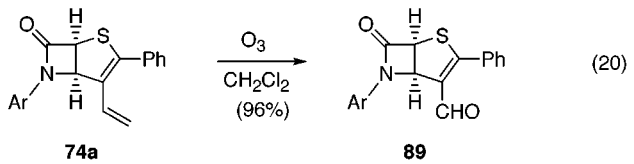
(57) (a) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849. (b) Fenton, D. M. *J. Org. Chem.* **1973**, *38*, 3192. (c) Larock, R. C. *J. Org. Chem.* **1975**, *40*, 3237. (d) Cassar, L.; Foa, M.; Gardano, A. *J. Organometallic Chem.* **1976**, *121*, C55. (e) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 220. (f) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775.



The *p*-methoxyphenyl N-protecting group of compounds **80** and **82** was oxidatively cleaved using ceric ammonium nitrate in aqueous acetonitrile to afford the free β-amino acid and thioester derivatives **87** and **88**, each in about 75% yield (eq 19).



One final transformation we would like to report is the ozonolysis of vinyl substrate **74a** to aldehyde **89** (eq 20). The cleavage reaction proceeds quickly upon bubbling a dilute stream of O_3 through a dichloromethane solution of **74a** at room temperature, to provide aldehyde **89**. The aldehyde can potentially open new avenues for introducing other types of functionality onto the core of these β-lactam ring systems.



Each of the bicyclic β-lactams synthesized in our study was screened against a battery of common Gram-positive and Gram-negative microorganisms on tryptic soy agar using the disk diffusion method. Approximately 50 μg of each compound was deposited onto cellulose disks, and circular zones where bacterial growth was inhibited were measured. These preliminary tests indicate that compounds **58b**, **80**, **87**, and **89** have weak antibacterial activity against either *Staphylococcus aureus* or *Vibrio cholerae* but are ineffective against *E. cloacae*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. typhimurium*, and *S. marcesceus*. All other compounds were inactive against the strains tested. It would appear from these preliminary findings that the relocation of the lactam moiety within the classical bicyclic β-lactam framework has a detrimental effect on biological activity, reflecting the precision in which bioactive molecules must bind and interact with active site functionality. However, efforts are underway to prepare and study more highly functionalized β-lactam derivatives to address this issue more definitively.[58]

Experimental Section

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 generating unpleasant or noxious odors were carried out in an efficient fume hood. The imines used in this study were prepared by heating equimolar amounts of the appropriate aldehyde and amine in refluxing benzene solution in the presence of a small amount of *p*-toluenesulfonic acid under Dean−Stark conditions, followed by filtering the cooled solution through a 1-in. plug of silica gel to remove residual amine. The purity of the crude imine was checked by ^{1}H NMR prior to use. The acid chlorides were synthesized according to standard protocols by heating the corresponding carboxylic acid in thionyl chloride (removing residual volatiles by distillation) and used without further purification. 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. Reactions were followed by TLC using EM Reagents plates with fluorescence indicator (SiO_2-60, F-254) or 1% aqueous $KMnO_4$ stain. Flash chromatography was performed using J.T. Baker flash chromatography silica gel (40 μm). ^{1}H NMR spectra were recorded at 300, 360, 400, or 500 MHz, and ^{13}C NMR spectra were obtained at 75, 100, or 125 MHz, as indicated. IR spectra were obtained as a thin film smeared onto NaCl plates. Melting points are uncorrected. Mass spectra were run using electron impact or chemical ionization methods as noted. Elemental analyses were performed by Atlantic Microlab (Atlanta, GA).

Procedure for the Preparation of Monocyclic β-Lactams 17 and 20. To a stirred solution of Et_3N (1.25 mL, 8.97 mmol) and imine **16** (2.11 g, 8.92 mmol) in THF (60 mL) at −78 °C was added via cannula a solution of *S*-benzylthioacetyl chloride (**15**, 1.77 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 $MgSO_4$, filtered, and evaporated to give a dark brown oil. Flash chromatography (2:1 CH_2Cl_2:hexanes and then CH_2Cl_2) of the resulting material afforded 3.14 g (89%) of β-lactam **17** as a 10:1 mixture of trans:cis isomers.

To a stirred solution of the above crude 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 $MgSO_4$, filtered, and then evaporated. Flash chromatography of this material gave 3.12 g (88% overall, 2:1 mixture of cis:trans isomers) of **17** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.25 (m, 12H), 6.94 (d, J = 8.4 Hz, 2H, cis isomer), 6.91 (d, J = 8.4 Hz, 2H, trans isomer), 5.00 (d, J = 4.9 Hz, 1H, cis isomer), 4.39 (d, J = 4.9 Hz, 1H, cis isomer), 4.30 (AB m, 2H, trans isomer), 4.07 (AB m, 2H, cis isomer), 3.95 (s, 2H, trans isomer), 3.79 (2 overlapping s, total 3H, cis and trans 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,

(58) For a discussion on the bioactivation of β-lactam antibiotics having bicyclic frameworks, see: Rando, R. *Acc. Chem. Res.* **1975**, *8*, 281.

115.0, 88.4, 83.9, 58.0, 55.9, 51.0, 35.9; IR (thin film) 1750 cm^{-1} (β-lactam C=O); HRMS (CI, isobutane) calcd for $C_{25}H_{21}NO_2S$ (M + 1) 400.1366, obsd 400.1371. Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.16; H, 5.30. Found: C, 75.01; H, 5.35.

A similar procedure was used to prepare **20**.

20: 5.25 g (77%, 1:3 cis:trans mixture); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.21 (m, 7H), 6.82 (d, J = 8.8 Hz, 2 × 2H, cis and trans isomers), 5.30 (d, J = 9.6 Hz, 1H, cis isomer), 5.06 (d, J = 9.8 Hz, 1H, trans isomer), 4.75 (dd, J = 4.9, 9.6 Hz, 1H, cis isomer), 4.23 (dd, J = 2.0, 9.8 Hz, 1H, trans isomer), 3.85 (m, 2 × 2H, cis and trans isomers), 3.80 (s, 3H, cis isomer), 3.75 (s, 3H, trans isomer), 1.80 (s, 3H, cis isomer), 1.78 (s, 3H, cis isomer), 1.67 (s, 3H, trans isomer), 1.65 (s, 3H, trans isomer); ^{13}C NMR (75 MHz, $CDCl_3$) (trans 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} (β-lactam C=O); HRMS (CI, isobutane) calcd for $C_{21}H_{23}NO_2S$ (M + 1) 354.1522, obsd 354.1526. Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56. Found: C, 71.29; H, 6.65.

Procedure for the Preparation of *N*-Aryl-Protected β-Lactams. To a stirred solution of Et_3N (1.25 mL, 9.0 mmol) and imine **16** (1.88 g, 8.0 mmol) in CH_2Cl_2 (75 mL) at room temperature is added via cannula a solution of methoxyacetyl chloride (**35a**, 0.91 g, 10.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture is stirred at room temperature for 30 min, poured into 5% aqueous HCl (75 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers are dried over $MgSO_4$, filtered, and evaporated to give a brown oil that slowly crystallized upon standing. Flash chromatography (2:1 CH_2Cl_2:hexanes and then CH_2Cl_2) of the crude material afforded 2.20 g (89%) of β-lactam **36a**: white solid; 116−117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.35 (m, 7H), 6.90 (d, J = 7.8 Hz, 2H), 4.96 (d, J = 4.8 Hz, 1H), 4.81 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 157.4, 132.6, 129.3, 129.2, 129.1, 128.8, 119.1, 115.0, 84.8, 81.7, 59.1, 56.1, 56.0, 50.3; IR (thin film) 1752 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.10; H, 5.60; N, 4.57.

A similar procedure was used to make the following compounds.

30a: 1.39 g (88%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.27 (m, 7H), 6.89 (d, J = 8.8 Hz, 2H), 4.95 (s, 1H), 3.74 (s, 3H), 3.14−2.89 (m, 4H), 1.35−1.31 (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} (β-lactam C=O); HRMS (CI, isobutane) calcd for $C_{22}H_{23}NO_2S_2$ (M + 1) 398.1243, obsd 398.1255. Anal. Calcd for $C_{22}H_{23}NO_2S_2$: C, 66.47; H, 5.83. Found: C, 66.18; H, 5.60.

30b: 2.1 g (95%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.28 (m, 10H), 4.78 (d, J = 14.8 Hz, 1H), 4.42 (s, 1H), 4.23 (d, J = 14.8 Hz, 1H), 3.04−2.80 (m, 2H), 1.33−1.25 (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} (β-lactam C=O); HRMS (CI, isobutane) calcd for $C_{22}H_{23}NOS_2$ (M + 1) 382.1294, obsd 382.1301. Anal. Calcd for $C_{22}H_{23}NOS_2$: C, 69.25; H, 6.08. Found: C, 69.48; H, 6.10.

30c: 0.183 g (94%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 4.65 (d, J = 15.6 Hz, 2H), 4.15 (s, 1H), 4.09 (d, J = 15.6 Hz, 2H), 2.90 (m, 1H), 2.84−2.72 (m, 3H), 1.28−1.19 (m, 6H), 0.99 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{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} (β-lactam C=O). HRMS (CI, isobutane) calcd for $C_{22}H_{33}NOS_2Si$ (M + 1) 420.1843, obsd 420.1833. Anal. Calcd for $C_{22}H_{33}NOS_2Si$: C, 62.96; H, 7.93. Found: C, 63.11; H, 7.62.

33: 0.261 g (58%) obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (m, 5H), 5.24 (d, J = 9.6 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 4.15 (d, J = 9.6 Hz, 1H), 3.93 (d, J = 14.8 Hz, 1H), 2.90−2.64 (m, 4H), 1.76 (s, 3H), 1.44 (s, 3H), 1.28−1.19 (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} (β-lactam C=O). HRMS (CI, isobutane) calcd for $C_{18}H_{25}NOS_2$ (M + 1) 336.1450, obsd 336.1452. Anal. Calcd for $C_{18}H_{25}NOS_2$: C, 64.43; H, 7.51. Found: C, 64.52; H, 7.29.

36b: 4.1 g (92%); colorless crystals (mp 172−173 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.75 (m, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.30−7.15 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 5.71 (d, J = 4.8 Hz, 1H), 5.18 (d, J = 4.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.4, 157.5, 135.2, 132.5, 132.4, 131.2, 129.7, 128.9, 124.5, 122.0, 119.4, 115.2, 90.5, 81.4, 58.5, 56.2, 50.3. Anal. Calcd for $C_{26}H_{18}N_2O_4$: C, 73.92; H, 4.30. Found: C, 73.72; H, 4.37.

48a: 4.7 g (89%); colorless crystals (mp 96−99 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.97 (dq, J = 7.0, 15.6 Hz, 1H), 5.52 (dd, J = 8.8, 15.6 Hz, 1H), 4.54 (d, J = 4.8 Hz, 1H), 4.50 (dd, J = 4.8, 8.8 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 1.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 156.9, 134.2, 131.8, 125.7, 119.2, 114.7, 84.8, 60.8, 59.0, 55.7, 18.3; IR (thin film) 1742 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.23; H, 6.99.

48b: 3.6 g (88%); colorless crystals (mp 161−162 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.95 (m, 1H), 5.55 (m, 2H), 4.82 (dd, J = 4.9, 7.8 Hz, 1H), 3.80 (s, 3H), 1.62 (d, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 161.3, 157.1, 135.7, 135.0, 132.3, 131.9, 125.1, 124.3, 119.3, 114.9, 61.0, 57.9, 55.8, 18.1. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01. Found: C, 69.78; H, 5.12.

Procedure for the Ozonolysis of Alkenyl β-Lactams. To a solution of olefinic β-lactam **48a** (3.72 g, 15.0 mmol) in CH_2Cl_2 (150 mL) at RT is bubbled a slow stream of ozone in air. The progress of the reaction is monitored by ^1H NMR until all of the starting olefin is consumed. The mixture is then poured into water and extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 3.35 g (95%) of aldehyde **49a** as a colorless oil, which was used immediately in the next step: ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, J = 4.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.86 (d, J = 6.0 Hz, 1H), 4.52 (dd, J = 4.0, 6.0 Hz, 1H), 3.86 (s, 3H), 3.58 (s, 3H).

A similar procedure was used to prepare aldehydes **49b** and **89**.

49b: 2.35 g (90%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, J = 3.2 Hz, 1H), 7.86−7.76 (m, 4H), 7.38 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.80 (d, J = 6.0 Hz, 1H), 4.78 (dd, J = 3.2, 6.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 167.5, 161.2, 157.8, 135.5, 134.9, 132.0, 131.1, 124.6, 124.2, 118.6, 115.4, 63.1, 55.9.

89: 0.15 g (96%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.75−6.85 (m, 9H), 5.88 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 133.0, 131.8, 131.7, 130.3, 130.2, 129.2, 129.1, 129.0, 128.4, 119.5, 119.4, 114.3, 114.2, 55.5. HRMS (CI, isobutane) calcd for $C_{19}H_{13}NO_3S$ (M + 1) 338.0847, obsd 338.0852. Anal. Calcd for $C_{19}H_{13}NO_3S$: C, 67.64; H, 4.48.

Procedure for the Grignard Reaction of Aldehydes 49. To a solution of phenylacetylene (1.56 g, 15.0 mmol) in THF (75 mL) at −78 °C under nitrogen is added n-BuLi (11.0 mL, 1.43 M in hexanes, 15.7 mmol), and the mixture is stirred for 30 min. To the above mixture is added anhydrous $MgBr_2$ (2.90 g, 15.5 mmol), and the mixture is stirred vigorously while warming to RT until the solid $MgBr_2$ completely dissolves.

To a solution of aldehyde **49a** (3.35 g, 14.2 mmol) in THF (50 mL) at −78 °C under N_2 is added slowly through cannula the above freshly prepared Grignard reagent. The reaction mixture is stirred for 30 min, warmed to RT, and then poured into 5% aqueous ammonium chloride solution (30 mL). The aqueous mixture is extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 4.02 g (69%, 5:1 mixture) of the hydroxy β-lactam as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.21 (m, 7H), 6.80 (d, J = 8.8 Hz, 2H), 5.06 (d, J = 9.0 Hz, 1H), 4.70 (d, J = 4.9 Hz, 1H), 4.39 (dd, J = 4.9, 9.0 Hz, 1H), 3.69 (s, 3H), 3.66

(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 157.4, 132.2, 130.5, 129.3, 129.0, 122.6, 120.0, 114.9, 87.5, 85.5, 84.3, 61.0, 60.8, 55.8; IR (thin film) 3500−3200 (OH), 1750 cm^{-1} (β-lactam C=O).

Azetidinyl Alcohol from 49b: 2.29 (80%, 2:1 mixture); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−6.82 (m, total 13H), 5.63 (m, total 1H), 5.10 (m, total 1H), 4.68 (m, total 1H), 3.75 (s, total 3H); IR (thin film) 3600−3200, 1780 (phthalimidyl C=O), 1750 cm^{-1} (β-lactam C=O).

Procedure for the Acylation of Alcohols. To a solution of the above hydroxy β-lactam (4.02 g, 9.6 mmol, prepared from **49a**) in DMSO (10 mL) and pyridine (4 mL) is added a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. To this mixture is added dropwise anhydrous acetic anhydride (5.0 mL, 50 mmol). The reaction mixture is stirred overnight and then poured into a 5% HCl solution (75 mL). The aqueous layer is extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 3.30 g (5:1 mixture, 80% from alcohol) of acetates **50a** as a colorless oil, with partial separation of the isomers. Data for major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 2H), 7.25−7.18 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 6.02 (d, J = 3.0 Hz, 1H), 4.68 (d, J = 3.0 Hz, 1H), 4.50 (dd, J = 3.0, 4.9 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 165.2, 157.3, 132.4, 131.2, 129.4, 129.0, 128.7, 120.1, 114.7, 89.3, 83.2, 83.0, 63.6, 60.4, 60.1, 55.7, 21.1; IR (thin film) 1750 (β-lactam C=O), 1735 cm^{-1} (acetate C=O). Data for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 2H), 7.25−7.18 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 6.02 (d, J = 3.0 Hz, 1H), 4.68 (d, J = 3.0 Hz, 1H), 4.66 (dd, J = 3.0, 4.9 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 165.2, 157.5, 132.5, 129.6, 128.9, 122.3, 120.7, 114.6, 111.3, 87.8, 84.3, 83.6, 63.6, 60.7, 60.1, 55.8, 20.8; IR (thin film) 1750 (β-lactam C=O), 1735 cm^{-1} (acetate C=O). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58. Found: C, 69.41; H, 5.31.

A similar procedure was used to prepare acetate **50b**.

50b: 2.13 g (2:1 mixture, 85% from alcohol); Data for major isomer: colorless crystals (mp 195−196 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−6.78 (m, 13H), 6.08 (d, J = 5.9 Hz, 1H), 5.56 (d, J = 6.8 Hz, 1H), 4.75 (dd, J = 5.9, 6.8 Hz, 1H), 3.65 (s, 3H), 1.81 (s, 3H). Anal. Calcd for $C_{29}H_{22}N_2O_6$: C, 70.44; H, 4.48. Found: C, 70.16; H, 4.32. Data for minor isomer: δ 7.76−6.78 (m, 13H), 5.98 (d, J = 9.0 Hz, 1H), 5.68 (d, J = 5.9 Hz, 1H), 4.84 (dd, J = 5.9, 9.0 Hz, 1H), 3.70 (s, 3H), 2.08 (s, 3H).

Procedure for the Dearylation of *N*-Aryl β-Lactams. To a solution of *N*-*p*-methoxyphenyl β-lactam **36a** (2.2 g, 7.2 mmol) in CH_3CN (100 mL) at 0 °C is added 100 mL of an aqueous solution of ammonium cerium(IV) nitrate (11.8 g, 21.6 mmol) over 5 min. The reaction mixture is stirred for 25 min and then poured into aqueous 5% $NaHSO_3$ (100 mL), and the aqueous mixture is extracted with Et_2O (3 × 50 mL). The combined organic layers are treated with 5% aqueous $NaHCO_3$ (100 mL), and the aqueous layer is back-washed with one portion of diethyl ether (50 mL). The combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 1.28 g (89%) of **37a**: white solid (mp 121−122 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 5H), 6.80 (broad s, 1H), 4.72 (d, J = 4.8 Hz, 1H), 4.60 (d, J = 4.8 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 132.4, 129.4, 128.9, 122.7, 87.9, 87.1, 83.7, 58.8, 46.6. HRMS (CI, isobutane) calcd for $C_{12}H_{11}NO_2$ (M + 1) 202.0865, obsd 202.0884. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.55; H, 5.53; N, 6.91.

37b: 0.46 g (92%); colorless crystals (mp 195−197 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.75 (m, 2H), 7.25−7.18 (m, 5H), 6.58 (broad s, 1H), 5.61 (d, J = 4.2 Hz, 1H), 4.90 (d, J = 4.2 Hz, 1H); IR (thin film) 3350−3200 (N−H), 1780 (phthalimidyl C=O), 1770 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82. Found: C, 72.01; H, 3.86.

45: 0.73 g (88%); white crystals (mp 135−137 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, H), 6.07 (br s, 1H), 4.22 (br d, J = 2.4 Hz, 1H), 4.16 (d, J = 2.4 Hz, 1H), 3.91 (app q, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 137.8, 132.4, 129.9, 129.7, 129.4, 129.1, 128.3, 122.5, 87.3, 85.5, 60.3, 48.1, 36.2; IR (thin film) 1770 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{18}H_{15}NOS$: C, 73.69; H, 5.15. Found: C, 73.84; H, 4.98.

51a: 0.34 g (5:1 mixture, 91%). Data for major isomer: colorless crystals (decomposed at 165−169 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.26 (m, 5H), 6.55 (s, 1H), 5.70 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 5.0 Hz, 1H), 4.01 (dd, J = 5.0, 6.8 Hz, 1H), 3.50 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.6, 132.6, 129.6, 128.9, 122.2, 88.0, 84.8, 83.7, 63.6, 59.8, 56.3, 21.0; IR (thin film) 3350−3200 (N−H), 1780 (β-lactam C=O), 1750 cm^{-1} (acetate C=O). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53. Found: C, 66.31; H, 5.29.

51b: 0.27 g (2:1 mixture, 87%); colorless oil. Data for major isomer: colorless crystals (decomposed at 170−172 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−6.98 (m, 9H), 6.42 (s, 1H), 5.90 (d, J = 9.0 Hz, 1H), 5.42 (d, J = 4.9 Hz, 1H), 4.30 (m, 1H), 2.02 (s, 3H). Anal. Calcd for $C_{22}H_{16}N_2O_5$: C, 68.04; H, 4.15. Found: C, 67.93; H, 4.05. Data for minor isomer: δ 7.82−6.98 (m, 9H), 6.60 (s, 1H), 5.75 (d, J = 9.0 Hz, 1H), 5.62 (d, J = 4.9 Hz, 1H), 4.30 (m, 1H), 2.12 (s, 3H).

87: 0.055 g (74%); colorless oil; ^{1}H NMR (360 MHz, DMSO-d_6) δ 9.03 (s, 1H), 7.04 (m, 5H), 4.66 (s, 1H), 2.51 (app q, J = 7.2 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 164.1, 163.2, 159.0, 132.4, 129.9, 129.4, 128.2, 121.3, 71.3, 31.6, 24.2, 14.8; IR (film) 1750 (β-lactam C=O), 1725 cm^{-1} (carboxylic acid C=O). Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26. Found: C, 54.68; H, 4.22.

88: 0.015 g (75%); white crystals (mp 116−118 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.40 (m, 5H), 6.50 (br s, 1H), 5.20 (s, 1H), 2.95 (AB m, 2H), 2.83 (q, J = 7.5 Hz, 2H), 1.38 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.5 Hz, 3H). HRMS (CI, isobutane) calcd for $C_{16}H_{17}NO_2S_3$ (M + 1) 352.0496, obsd 352.0492. Anal. Calcd for $C_{16}H_{17}NO_2S_3$: C, 54.67; H, 4.87. Found: C, 54.82; H, 4.92.

Procedure for the *N*-Methylthiolation of β-Lactams. To a solution of **37a** (1.28 g, 6.4 mmol) in THF at −78 °C is added *n*-butyllithium (5.0 mL, 1.38 M in hexanes, 6.9 mmol). After 30 min, methyl methanethiolsulfonate (0.85 g, 6.6 mmol) is added and the reaction mixture is stirred for 12 h with warming to RT. The mixture is poured into 5% aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 1.26 g (80%) of *N*-methylthio compound **38a**: colorless solid; mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.8 Hz, 2H), 7.30 (m, 3H), 4.72 (d, J = 4.8 Hz, 1H), 4.63 (d, J = 4.8 Hz, 1H), 3.56 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 132.4, 129.6, 129.0, 122.5, 89.3, 86.6, 82.5, 59.0, 55.1, 22.7; IR (thin film) 1772 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) calcd for $C_{13}H_{13}NO_2S$ (M + 1) 248.0742, obsd 248.0734. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.08; H, 5.33.

38b: 0.93 g (90%); colorless solid (mp 203−205 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 2.9, 4.9 Hz, 2H), 7.73 (dd, J = 2.9, 4.9 Hz, 2H), 7.26−7.12 (m, 5H), 5.63 (d, J = 4.8 Hz, 1H), 4.91 (d, J = 4.8 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 167.4, 135.2, 135.1, 132.2, 129.7, 128.9, 124.3, 121.9, 90.3, 82.0, 60.2, 54.5, 49.2, 22.5. HRMS (CI, isobutane) calcd for $C_{20}H_{14}N_2O_3S$ (M + 1) 363.0800, obsd 363.0780. Anal. Calcd for $C_{20}H_{14}N_2O_3S$: C, 66.28; H, 3.89. Found: C, 66.43; H, 3.92.

41: 0.35 g (87%); colorless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.95 (dq, J = 7.0, 15.6 Hz, 1H), 5.54 (dd, J = 8.8, 15.6 Hz, 1H), 4.61 (d, J = 4.8 Hz, 1H), 4.18 (dd, J = 4.8, 8.8 Hz, 1H), 3.47 (s, 3H), 2.43 (s, 3H), 1.82 (d, J = 7.0 Hz, 3H);^{13}C NMR (90 MHz, $CDCl_3$) δ 170.4, 134.8, 124.5, 85.8, 65.3, 58.7, 22.7, 18.2. Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00. Found: C, 51.67; H, 6.75.

46: 0.15 g (85%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.25 (m, 10H), 4.20 (d, J = 2.4 Hz, 1H), 4.14 (d, J = 2.4 Hz, 1H), 3.90 (app q, J = 13.2 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 137.6, 132.4, 129.8, 129.5, 129.2, 128.4, 122.3, 88.7, 84.7, 59.2, 56.2, 36.3, 23.3. Anal. Calcd for $C_{19}H_{17}NOS_2$: C, 67.22; H, 5.05. Found: C, 67.20; H, 5.13.

52a (one isomer, 81%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.26 (m, 5H), 5.80 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 5.0 Hz, 1H), 4.02 (dd, J = 5.0, 6.8 Hz, 1H), 3.48 (s, 3H), 2.48 (s, 3H), 2.08 (s, 3H). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37. Found: C, 60.28; H, 5.33.

52b (5:1 mixture, 92%): colorless oil. Data for major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.24 (m, 9H), 5.88 (d, J = 8.0 Hz, 1H), 5.47 (d, J = 6.0 Hz, 1H), 4.30 (dd, J = 6.0, 8.0 Hz, 1H), 2.57 (s, 3H), 1.80 (s, 3H). Data for minor isomer: δ 7.80−7.24 (m, 9H), 5.90 (d, J = 9.8 Hz, 1H), 5.64 (d, J = 6.0 Hz, 1H), 4.36 (dd, J = 6.0, 9.8 Hz, 1H), 2.52 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (5:1 mixture) δ 170.0, 167.8, 167.7, 135.1, 132.3, 132.0, 129.6, 128.6, 124.3, 88.4, 82.0, 64.9, 63.1, 56.6, 22.7, 21.1. Anal. Calcd for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18. Found: C, 63.43; H, 4.21.

Procedure for Halocyclization Reactions. To a solution of β-lactam **38a** (1.25 g, 5.1 mmol) in CH_2Cl_2 (50 mL) is added I_2 (1.28 g, 5.1 mmol). The mixture is stirred while heating at reflux for 4 h. After cooling to RT, the reaction mixture is poured into 5% aqueous $Na_2S_2O_3$ (25 mL) and stirred until the purple coloration of iodine has dissipated. The aqueous mixture is extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude mixture affords 1.28 g (72%) of **39a** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.37 (m, 5H), 5.17 (overlapping signal, 2H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 148.2, 131.5, 130.5, 129.5, 129.4, 90.0, 78.0, 69.7, 60.8; IR (thin film) 1790 cm^{-1} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{12}H_{10}NO_2SI$ (M + 1) 359.9553, obsd 359.9578. Anal. Calcd for $C_{12}H_{10}NO_2SI$: C, 40.13; H, 2.81. Found: C, 40.51; H, 2.98.

An analogous procedure was used to prepare the following bicyclic β-lactams.

39b: 0.054 g (84%); colorless solid (mp 217−218 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 2.9, 4.9 Hz, 2H), 7.75 (dd, J = 2.9, 4.9 Hz, 2H), 7.47−7.38 (m, 5H), 6.10 (d, J = 4.8 Hz, 2H), 5.30 (d, J = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 166.9, 147.7, 135.4, 132.0, 131.5, 130.6, 129.5, 129.0, 124.9, 76.2, 69.6, 62.9; IR (thin film) 1790 cm^{-1} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{19}H_{11}N_2O_3SI$ (M + 1) 474.9611, obsd 474.9595. Anal. Calcd for $C_{19}H_{11}N_2O_3SI$: C, 48.12; H, 2.34. Found: C, 48.28; H, 2.18.

47: 0.111 g (95% yield based on the estimated amount of **45** in a 1:10 mixture of **43**:**45**); colorless solid (mp 124−126 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.24 (m, 10H), 4.85 (d, J = 2.3 Hz, 1H), 4.29 (d, J = 2.3 Hz, 1H), 3.98 (AB m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 146.9, 137.1, 131.1, 131.0, 130.0, 129.6, 129.5, 129.5, 128.4, 82.4, 73.0, 62.1, 36.8; IR (thin film) 1780 cm^{-1} (β-lactam C═O); Anal. Calcd for $C_{18}H_{14}NOS_2I$: C, 47.90; H, 3.13. Found: C, 47.66; H, 3.30.

The following compounds were prepared in a similar manner, except that the halogenation reactions were conducted at room temperature.

18: 0.066 g (approximately 95% based on the cis:trans ratio of β-lactams **17**); colorless crystals (mp 150−151 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.39 (m, 7H), 6.90 (d, J = 8.8 Hz, 2H), 5.59 (d, J = 4.8 Hz, 1H), 5.02 (d, J = 4.8 Hz, 1H), 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} (β-lactam C═O). Anal. Calcd for $C_{18}H_{14}NO_2SI$: C, 49.67; H, 3.24. Found: 49.77; H, 3.33.

21: 0.057 g (approximately 90% based on the cis:trans ratio of β-lactams **20**); colorless oil. Data for major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.02 (dd, J = 4.0, 4.8 Hz, 1H), 4.73 (d, J = 4.8 Hz, 1H), 4.37 (d, J = 4.0 Hz, 1H), 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} (β-lactam C═O); MS (relative intensity) 342 (M + 1, 94), 264 (33), 232 (32), 190 (52), 167 (14), 149 (52), 129 (33), 113 (52). HRMS (CI, isobutane) calcd for $C_{14}H_{16}NO_2SBr$ (M + 1) 342.0159, obsd 342.0151. Anal. Calcd for $C_{14}H_{16}NO_2SBr$: C, 49.13; H, 4.71. Found: 49.50; H, 4.38. Data for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.15 (dd, J = 4.8, 5.2 Hz, 1H), 4.52 (d, J = 5.2 Hz, 1H), 4.13 (d, J = 4.8 Hz, 1H), 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} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{14}H_{16}NO_2SBr$ (M + 1) 342.0159, obsd 342.0078.

31a: 0.121 g (98%); colorless crystals (mp 99−100 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2H), 7.50−7.36 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 5.32 (s, 1H), 3.80 (s, 3H), 2.93 (q, J = 5.8 Hz, 2H), 1.38 (t, J = 5.8 Hz, 3H); ^{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} (β-lactam C═O). Anal. Calcd for $C_{20}H_{18}NO_2S_2I$: C, 48.49; H, 3.66. Found: C, 48.24; H, 3.33.

31b: 0.098 g (73%); colorless crystalline solid (mp 105−108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.30 (m, 10H), 4.80 (d, J = 15.6 Hz, 1H), 4.71 (s, 1H), 4.60 (d, J = 15.6 Hz, 1H), 2.85−2.80 (m, 2H), 1.28 (t, J = 6.8 Hz, 3H); ^{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} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{20}H_{18}NOS_2I$ (M + 1) 479.9949, obsd 479.9940. Anal. Calcd for $C_{20}H_{18}NOS_2I$: C, 50.11; H, 3.78. Found: C, 49.87; H, 3.95.

31c: 0.132 g (92%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 4.78 (d, J = 15.6 Hz, 2H), 4.56 (s, 1H), 4.40 (d, J = 15.6 Hz, 2H), 2.82−2.70 (m, 2H), 1.25 (t, J = 6.8 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.85 (q, J = 8.0 Hz, 6H); ^{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} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{20}H_{28}NOS_2SiI$ (M + 1) 518.0498, obsd 518.0517. Anal. Calcd for $C_{20}H_{28}NOS_2SiI$: C, 46.41; H, 5.45. Found: 46.50; H, 5.38.

34: 0.098 g (4:1 mixture, 100%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.34 (m, 5H, both isomers), 4.90 (d, J = 15.6 Hz, 1H, α-isomer), 4.75 (d, J = 15.6 Hz, 1H, β-isomer), 4.31 (d, J = 15.6 Hz, 1H, α-isomer), 4.29 (d, J = 4.8 Hz, 1H, β-isomer), 4.18 (d, J = 15.6 Hz, 1H, β-isomer), 4.16 (d, J = 4.8 Hz, 1H, β-isomer), 4.15 (partially obscured d, J = 4.8 Hz,1H, α-isomer), 4.08 (d, J = 4.8 Hz, 1H, α-isomer), 2.71 (q, J = 5.9 Hz, 2H, both isomers), 1.64 (s, 3H, both isomers), 1.39 (s, 3H, both isomers), 1.24 (t, J = 5.9 Hz, 3H, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$) (β-isomer only) 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; IR (thin film) 1755 cm^{-1} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{16}H_{20}NOS_2Br$ (M + 1) 386.0243, obsd 386.0237. Anal. Calcd for $C_{16}H_{20}NOS_2Br$: C, 49.74; H, 5.22. Found, C, 49.77; H, 5.50.

53a (one isomer, 54%): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 5.88 (d, J = 4.9 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.10 (dd, J = 4.9, 3.6 Hz, 1H), 3.57 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 168.8, 141.7, 138.6, 130.6, 130.0, 129.4, 86.7, 86.4, 67.9, 60.1, 58.1, 21.6; IR (thin film) 1780 (β-lactam C═O), 1750 cm^{-1} (acetate C═O). HRMS (CI, isobutane) calcd for $C_{15}H_{14}NO_4SI$ (M + 1) 431.9763, obsd 431.9778. Anal. Calcd for $C_{15}H_{14}NO_4SI$: C, 41.78; H, 3.27. Found: C, 41.99; H, 3.11.

53b: (major isomer, 61%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 2.9, 4.9 Hz, 2H), 7.78 (dd, J = 2.9, 4.9 Hz, 2H), 7.45−7.38 (m, 5H), 5.76 (d, J = 4.9 Hz, 1H), 5.60 (d, J = 6.8 Hz, 1H), 4.15 (dd, J = 4.9, 6.8 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 168.0, 163.7, 139.5, 138.2, 135.1, 132.2, 130.7, 130.1, 129.4, 124.4, 85.2, 67.2, 59.7, 57.3, 20.9; IR (thin film) 1780 cm^{-1} (β-lactam C═O). HRMS (CI, isobutane) calcd for $C_{22}H_{17}N_2O_5SI$ (M + 1) 546.9825, obsd 546.9791. Anal. Calcd for $C_{22}H_{17}N_2O_5SI$: C, 48.37; H, 2.77. Found: 48.11; H, 3.02.

Procedure for the Sulfonylation of β-Lactams. To a stirred suspension of **39a** (335 mg, 0.675 mmol) and KH_2PO_4−Na_2HPO_4 (pH 7.8, 20 mL) in CH_2Cl_2 (50 mL) at room temperature is added in one portion *m*-chloroperoxybenzoic acid (1.50 g, 50−60%, ∼4.2 mmol). The mixture is stirred for 12 h and poured into a 5% aqueous $NaHSO_3$ solution (60 mL). The mixture is stirred for 8 h until the layers become separated, and the organic layer is washed with a 5% aqueous $NaHCO_3$ solution (50 mL). The aqueous layer is extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers

are dried over anhydrous $MgSO_4$ and evaporated. Flash chromatography of the crude mixture affords 326 mg (82%) of sulfone **58a** as a white solid (decomposed upon heating): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.48 (m, 5H), 5.61 (d, J = 5.0 Hz, 2H), 5.23 (d, J = 5.0 Hz, 1H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.4, 131.9, 129.9, 129.8, 126.8, 101.4, 96.0, 67.9, 57.8; IR (thin film) 1801 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) calcd for $C_{12}H_{10}NO_4SI$ (M + 1) 391.9451, obsd 391.9460. Anal. Calcd for $C_{12}H_{10}NO_4SI$: C, 36.84; H, 2.58. Found, C, 33.70; H, 2.68.

56a: 0.028 g (86%); colorless solid (95−96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.48 (m, 7H), 6.95 (d, J = 8.8 Hz, 2H), 5.81 (s, 1H), 3.82 (s, 3H), 3.75−3.62 (m, 2H), 1.62 (t, J = 6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.2, 153.4, 152.3, 132.1, 129.9, 129.7, 127.9, 127.0, 123.1, 114.9, 100.0, 87.7, 63.0, 55.8, 49.8, 5.0; IR (thin film) 1780 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) calcd for $C_{20}H_{18}NO_6S_2I$ (M + 1) 559.9694, obsd 559.9708. Anal. Calcd for $C_{20}H_{18}NO_6S_2I$: C, 42.94; H, 3.24. Found, C, 42.66; H, 3.47.

56b: 0.012 g (45%); colorless crystals (mp 192−194 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.30 (m, 10H), 5.19 (s, 1H), 5.04 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 3.60 (q, J = 6.8 Hz, 2H), 1.62 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 154.2, 134.0, 131.8, 131.5, 129.9, 129.8, 128.6, 128.5, 99.9, 92.0, 68.2, 48.4, 48.3, 47.1, 5.5; IR (thin film) 1785 cm^{-1} (β-lactam C=O); CIMS (relative intensity) 544 (M + 1, 8), 420 (70), 395 (100), 379 (98), 294 (69), 262 (45), 253 (68), 220 (69), 133 (21). Anal. Calcd for $C_{20}H_{18}NO_5S_2I$: C, 44.21; H, 3.34. Found, C, 44.46; H, 3.37.

56c: 0.053 g (72%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 5.15 (s, 1H), 4.91 (d, J = 15.0 Hz, 1H), 4.58 (d, J = 15.0 Hz, 1H), 3.66 (td, J = 6.8, 10.8 Hz, 1H), 3.53 (td, J = 6.8, 10.8 Hz, 1H), 1.58 (t, J = 6.8 Hz, 3H), 0.08 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 141.5, 131.1, 127.8, 127.6, 127.1, 100.5, 87.4, 62.2, 47.8, 44.9, 4.7, 3.9, 3.0; IR (thin film) 1785 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{20}H_{28}NO_5S_2SiI$: C, 41.31; H, 4.85. Found: C, 41.27; H, 4.51.

57: 0.053 g (1:4 mixture of α:β isomers, 73%). Data for major isomer: white crystals (mp 145−148 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 5H), 4.78 (d, J = 15.6 Hz, 1H), 4.67 (d, J = 5.9 Hz, 1H), 4.33 (d, J = 15.6 Hz, 1H), 4.15 (d, J = 5.9 Hz, 1H), 3.62 (q, J = 4.9 Hz, 2H), 1.55 (s, 3H), 1.50 (t, J = 4.9 Hz, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 132.6, 129.9, 129.8, 129.6, 91.6, 75.8, 61.4, 51.4, 48.0, 46.5, 19.4, 18.4, 4.4; IR (thin film) 1775 cm^{-1} (β-lactam C=O). Data for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 5H), 5.04 (d, J = 15.0 Hz, 1H), 4.73 (d, J = 3.9 Hz, 1H), 4.38 (d, J = 15.0 Hz, 1H), 4.30 (d, J = 3.9 Hz, 1H), 3.59 (td, J = 6.8, 10.8 Hz, 1H), 3.44 (td, J = 6.8, 10.8 Hz, 1H), 1.76 (s, 3H), 1.58 (t, J = 6.8 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 132.8, 129.9, 129.8, 129.7, 89.0, 67.5, 57.0, 50.9, 50.0, 47.9, 22.3, 21.8, 5.2; IR (thin film) 1775 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{16}H_{20}NO_5S_2Br$: C, 42.67; H, 4.48. Found: C, 42.77; H, 4.61.

58b: 0.051 g (87%); colorless crystals (decomposed upon heating); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.78 (m, 4H), 7.53−7.46 (m, 5H), 5.89 (d, J = 6.1 Hz, 1H), 5.62 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 167.6, 166.5, 158.6, 135.7, 131.1, 129.8, 129.4, 125.1, 124.9, 99.5, 75.6, 57.4; IR (thin film) 1795 cm^{-1} (β-lactam C=O). Anal. Calcd for $C_{19}H_{11}N_2O_5SI$: C, 45.08; H, 2.19. Found: C, 45.37. H, 2.43.

Stille Cross-Coupling Reactions of Organostannanes with β-Lactam 18. To a stirred solution of β-lactam **18** (0.120 g, 0.28 mmol) in anhydrous DMF (10 mL) at RT were added Pd_2dba_3 (0.010 g, 0.011 mmol) and PPh_3 (0.005 g, 0.02 mmol). Tributylvinyltin (0.100 g, 0.31 mmol) was added, and the mixture was stirred under N_2 for 12 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The crude oil was purified by flash chromatography on silica gel to provide 0.085 g (80%) of **74a** as a transparent oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41−7.38 (overlapping m, 7H), 6.86 (d, J = 8.9 Hz, 2H), 6.52 (dd, J = 11.1, 17.6 Hz, 1H), 5.76 (d, J = 5.3 Hz, 1H), 5.15 (d, J = 17.6 Hz, 1H), 5.06 (d, J = 11.1 Hz, 1H), 4.97 (dd, J = 1.4, 5.3 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.0, 157.7, 147.4, 133.1, 130.5, 129.6, 129.4, 129.0, 128.9, 128.6, 126.3, 123.6, 114.2, 68.7, 55.4, 54.0; IR (film) 1750 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) m/z calcd for $C_{20}H_{17}NO_2S$ (M + 1) 336.1054, found 336.1061. Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11. Found: C, 71.45; H, 4.87.

A similar procedure was used to prepare β-lactam derivatives **74b** and **74c**.

74b: 0.075 g (80%); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (app s, 4H), 7.30−7.26 (m, 3H), 6.77 (d, J = 9.0 Hz, 2H), 6.20 (dd, J = 1.5, 3.5 Hz, 1H), 6.01 (d, J = 5.5 Hz, 1H), 5.70 (d, J = 3.5 Hz, 1H), 5.03 (d, J = 5.5 Hz, 1H), 3.82 (d, J = 1.5 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz) δ 164.8, 157.5, 149.7, 141.2, 134.3, 130.8, 130.0, 129.4, 129.1, 121.3, 118.5, 114.9, 114.7, 112.5, 108.9, 70.4, 56.1, 55.0; IR (film) 1750 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) m/z calcd for $C_{22}H_{17}NO_3S$ (M + 1) 376.1003, found 376.0993. Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56. Found: C, 70.65; H, 4.83.

74c: 0.120 g (74%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.18 (m, 13H), 6.61 (s, 1H), 5.81 (d, J = 5.6 Hz, 1H), 5.09 (d, J = 5.6 Hz, 1H), 3.60 (s, 3H), 2.76 (s, 3H); IR (film) 1750 cm^{-1} (β-lactam C=O). HRMS (CI, isobutane) m/z calcd for $C_{27}H_{22}N_2O_2S$ (M + 1) 439.1475, found 439.1480. Anal. Calcd for $C_{27}H_{22}N_2O_2S$: C, 73.95; H, 5.06. Found: C, 73.65; H, 4.83.

Palladium-Catalyzed Esterification of β-Lactam Iodides 18, 31a, and 56a. To a stirred solution of **18** (0.260 g, 0.62 mmol) in a mixture of anhydrous DMF (10 mL) and anhydrous methanol (5 mL) in a heavy-walled pressure bottle were added Pd_2dba_3 (0.026 g, 0.028 mmol) and PPh_3 (0.013 g, 0.05 mmol). The mixture was stirred for 5 min. A flow of carbon monoxide was passed through the pressure bottle for 5 min, the valve was closed, and the bottle was pressurized with CO to 55 psi. The reaction mixture was stirred for 4 d at RT (or for 24 h at 50−56 °C). Water (75 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography of the crude product afforded 0.169 g (75%) of **75** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 2H), 7.40−7.37 (m, 5H), 6.87 (d, J = 8.8 Hz, 2H), 6.00 (d, J = 5.9 Hz, 1H), 4.98 (d, J = 5.9 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 164.2, 163.8, 157.5, 133.6, 130.7, 128.8, 128.7, 120.9, 118.8, 114.9, 69.5, 66.6, 56.2, 55.2, 52.1, 34.8, 23.1, 16.0, 14.8; IR (film) 1750 (β-lactam C=O), 1730 cm^{-1} (ester C=O). HRMS (CI, isobutane) m/z calcd for $C_{20}H_{17}NO_4S$ (M + 1) 368.0952, found 368.0954. Anal. Calcd for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66. Found: C, 65.31; H, 4.83.

A similar procedure was used to prepare compounds **76**−**78**.

76: 0.150 g (73%); colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59−7.24 (m, 7H), 6.86 (d, J = 8.8 Hz, 2H), 6.01 (d, J = 5.5 Hz, 1H), 5.82 (ddd, J = 5.5, 11.1, 22.7 Hz, 1H), 5.61 (ddd, J = 5.5, 10.8, 22.7 Hz, 1 H), 4.94−5.20 (AB m, 2H), 4.67 (d, J = 5.5 Hz, 1H), 4.43 (d, J = 5.6 Hz, 1H), 3.80 (s, 3H); IR (film) 1750 (β-lactam C=O), 1730 cm^{-1} (ester C=O). HRMS (CI, isobutane) m/z calcd for $C_{22}H_{19}O_4NS$ (M^+) 393.1030, found 393.1040. Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87. Found: C, 67.50; H, 4.65.

77: 0.093 g (90%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 9.0 Hz, 2H), 7.37−7.35 (m, 5H), 6.87 (d, J = 9.0 Hz, 2H), 5.73 (s, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 2.96 (AB m, 2H), 1.37 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.0, 162.8, 157.7, 133.2, 130.9, 130.3, 129.0, 128.7, 121.1, 118.0, 115.0, 71.6, 56.2, 54.2, 52.3, 25.8, 15.6; IR (film) 1755 (β-lactam C=O), 1730 cm^{-1} (ester C=O). HRMS (CI, isobutane) m/z calcd for $C_{22}H_{21}NO_4S_2$ (M + 1) 428.0985, found 428.0990. Anal. Calcd for $C_{22}H_{21}NO_4S_2$: C, 61.80; H, 4.95. Found: C, 62.11; H, 5.13.

78: 0.121 g (73%); white crystals (mp 154−157 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37−7.35 (m, 7H), 6.87 (d, J = 9.2 Hz, 2H), 6.03 (s, 1H), 3.81 (s, 3H), 3.78 (overlapping m, 2H), 3.65 (s, 3H), 1.64 (t, J = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.0, 162.6, 158.0, 151.0, 133.8, 131.2, 130.2, 129.8, 129.3, 128.7, 128.3, 121.2, 114.4, 62.7, 55.5, 52.9, 48.2, 14.2; IR (film)

1780 (β-lactam C═O), 1730 cm^{-1} (ester C═O). Anal. Calcd for $C_{22}H_{21}NO_8S_2$: C, 53.76; H, 4.31. Found: C, 53.65; H, 4.33.

Palladium-Catalyzed Carboxylation of β-Lactam Acids 18, 31a, and 56a. To a stirred solution of **18** (0.120 g, 0.28 mmol) in a mixture of DMF (10 mL) and H_2O (0.1 mL) in a heavy glass pressure bottle were added Pd_2dba_3 (0.014 g, 0.015 mmol) and PPh_3 (0.005 g, 0.02 mmol). The mixture was stirred for 10 min and purged with CO for 5 min. The valve was closed, and the bottle was pressurized with CO (55 psi). The reaction mixture was stirred for 5 days at RT. Water (50 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography afforded 0.065 g (65%) of **79** as a colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6) 12.6 (br s, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.38 (s, 5H), 6.95 (d, J = 7.5 Hz, 2H), 6.00 (d, J = 3.5 Hz, 1H), 5.31 (d, J = 3.5 Hz, 1H), 3.74 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 7H), 6.82 (d, J = 9.5 Hz, 2H), 5.99 (d, J = 5.5 Hz, 1H), 5.10 (d, J = 5.5 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.1, 163.3, 161.7, 156.1, 133.0, 130.0, 129.7, 128.1, 128.0, 119.8, 119.4, 114.2, 69.1, 55.3, 54.0; IR (film) 1750 (β-lactam C═O), 1725 cm^{-1} (carboxylic acid C═O). Anal. Calcd for $C_{19}H_{15}NO_4S$: C, 64.58; H, 4.28. Found: C, 64.48; H, 4.38.

A similar procedure was used to prepare compounds **80** and **81**.

80: 0.068 g (75%); colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.9 Hz, 2H), 7.39−7.37 (m, 5H), 6.84 (d, J = 9.1 Hz, 2H), 5.69 (s, 1H), 3.80 (s, 3H), 2.94 (AB m, 2H), 1.38 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 167.7, 162.6, 157.7, 132.8, 131.2, 130.3, 129.2, 128.9, 121.0, 116.9, 115.0, 76.7, 71.4, 56.2, 25.9, 15.6; IR (film) 1755 (β-lactam C═O), 1725 cm^{-1} (carboxylic acid C═O). Anal. Calcd for $C_{21}H_{19}NO_4S_2$: C, 61.00; H, 4.63. Found: C, 61.16; H, 4.58.

In addition to compound **80**, thioester **82** was also obtained: 0.013 g (10%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 9.6 Hz, 2H), 7.39−7.37 (m, 5H), 6.85 (d, J = 8.4 Hz, 2H), 5.77 (s, 1H), 3.78 (s, 3H), 2.93 (AB m, 2H), 2.75 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz) δ 188.1, 162.8, 162.6, 157.7, 132.5, 131.2, 130.4, 129.4, 129.3, 127.8, 121.1, 114.9, 56.2, 54.2, 25.8, 24.6, 15.6, 15.2; IR (film) 1758 cm^{-1} (β-lactam C═O). HRMS (CI, isobutane) m/z calcd for $C_{23}H_{23}NO_3S_3$ (M + 1) 458.0913, found 458.1065. Anal. Calcd for $C_{23}H_{23}NO_3S_3$: C, 60.36; H, 5.07. Found: C, 60.35; H, 5.30.

81: 0.099 g (72%); colorless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.66−7.30 (m, 7H), 1H), 6.89 (d, J = 8.8 Hz, 2H), 5.88 (s, 1H), 3.79 (s, 3H), 3.75 (overlapping m, 1H), 3.60 (m, 1H), 1.61 (t, J = 7.6 Hz, 3H); IR (film) 1785 (β-lactam C═O), 1725 cm^{-1} (carboxylic acid C═O). Anal. Calcd for $C_{21}H_{19}NO_8S_2$: C, 52.82; H, 4.01. Found: C, 52.59; H, 3.84.

Attempted carboxylation of **39b** and **58a** under similar conditions led to the formation of **84** and **86**, respectively.

84: 0.099 g (1:1 mixture of diastereomers, 93%) from **39b** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.78 (m, 2H), 7.30 (m, 3H), 6.95 and 6.89 (d, J = 3.6 Hz, 2H each), 6.06 and 5.85 (br s, 1H each), 5.51 (d, J = 5.6 Hz, 1H) and 5.34 (d, J = 4.4 Hz, 1H), 4.45 (d, J = 5.6 Hz, 1H) and 4.26 (d, J = 5.6 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 8.4 Hz, 2H), 7.97−7.83 (m, 3H), 7.18−7.08 (m, 2H), 6.63 and 6.40 (br s, 1H each), 5.60 and 5.28 (d, J = 5.6 Hz, 1H each), 4.59 and 4.15 (d, J = 5.2 Hz, 1H each). Anal. Calcd for $C_{38}H_{24}N_4O_6S_2I_2$: C, 48.02; H, 2.54. Found: C, 47.67; H, 2.82.

86: 0.063 g (95%) from **58a** as a colorless solid (mp 150−153 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69−7.41 (m, 5H), 5.46 (br H, 1H), 5.19 (d, J = 3.9 Hz, 1H), 4.39 (d, J = 3.9 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (125 MHz) δ 171.7, 163.3, 151.7, 132.4, 132.2, 130.5, 129.7, 128.7, 104.4, 59.1. HRMS (CI, isobutane) m/z calcd for $C_{12}H_{12}NO_5SI$ (M + 1) 409.9556, found 409.9573. Anal. Calcd for $C_{12}H_{12}NO_5SI$: C, 35.22; H, 2.96. Found: C, 35.60; H, 3.21.

Testing for Antimicrobial Susceptibilities. The following strains of bacteria were used to test our β-lactam compounds for antimicrobial susceptibilities: *Enterobacter cloacae* USF510 (environmental isolate), *Escherichia coli* USF503 (ATCC 23590), *Klebsiella pneumoniae* USF512, *Pseudomonas aeruginosa* USF620 (ATCC 15442), *Salmonella typhimurium* USF515 (obtained from University of South Florida Medical Clinic), *Serratia marcescens* USF519 (ATCC 29634), *Staphylococcus aureus* USF525 (ATCC 25923), *Vibrio cholerae* USF1018 (biotype El Tor Inaba, cholera toxin positive, CDC E5906), and *Vibrio cholerae* USF1019 (biotype El Tor Ogawa, cholera toxin negative, CDC 1074-78). Bacteria were streaked for isolation onto tryptic soy agar (TSA) plates (REMEL, Lenexa, KS). An isolated colony from each plate was removed with a sterile swab and streaked onto a TSA plate. Sterile $^1/_4$-in.-diameter Bacto concentration disks (Difco Laboratories, Detroit, MI) were impregnated with 20 μL of the test compound dissolved in DMSO (or DMSO, as a control), dried for 3 h in a biohazard safety cabinet, and placed onto the inoculated TSA plates.[59] The inoculated TSA plates with the compound-impregnated disks were incubated for 24 h at 37 °C, and antimicrobial susceptibilities were determined by measuring the zone of growth inhibition around each disk.[60]

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