5.2–5.53 (m, 2 H), 6.07 (ddt, 1 H, J = 17.7, 10.7, and 5.28 Hz), 6.80–7.73 (m, 4 H); UV (95% ethanol) 305 nm (ϵ 3620), 247 (8060); MS, m/e 176 (M^+), 161 (base), 133, 119, 105, 91, and 77. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.94; H, 6.92.

To a solution containing 0.5 g of this material in 10 mL of absolute alcohol was added a mixture containing 1.20 g of *N*-methylhydroxylamine hydrochloride and 2.84 g of a 20% aqueous sodium hydroxide solution in 10 mL of absolute alcohol. The mixture was heated at reflux and the condensate was passed through a column of 3-Å molecular sieves. After being heated for 36 h, the reaction mixture was cooled and worked up in the usual manner. Chromatography of the residue using an ethyl acetate–hexane mixture gave 0.45 g (78%) of 3a,4-dihydro-1-methyl-9b(1*H*)-methyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazole (**43**) as the exclusive product. This material was identical in every detail with the sample obtained from the reaction of [2-(2-propenyloxyl)phenyl]acetylene (**42**) with *N*-methylhydroxylamine.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health. Use of the high-field NMR spectrometer used in these studies was made possible through a NSF equipment grant.

Registry No. **6**, 29182-34-1; **7**, 29182-33-0; **12**, 102851-74-1; **13**, 66021-96-3; **14**, 102851-75-2; **15**, 102851-77-4; **16**, 102851-78-5; **17**, 102851-79-6; (*E*)-**18**, 102851-80-9; (*Z*)-**18**, 102851-81-0; **20**, 102869-63-6; **21**, 102851-82-1; **22**, 5828-16-0; **23**, 102851-83-2; **24**, 102851-84-3; **26**, 14447-00-8; **27**, 102851-86-5; **28**, 102851-87-6; **29**, 102869-64-7; **34**, 10557-03-6; **35**, 62772-79-6; **36**, 17165-01-4; **37**, 90766-20-4; **38**, 102851-88-7; **39**, 102851-89-8; **42**, 66021-96-3; **43**, 102869-65-8; **44**, 53327-14-3; *N*-methylhydroxylamine hydrochloride, 4229-44-1; methyl propiolate, 922-67-8; 2-(2-propenyloxy)benzaldehyde, 558-13-4; methyl chloroformate, 79-22-1; acetaldehyde, 75-07-0; 4-[2-(2-propenyloxy)phenyl]but-3-yn-2-ol, 102851-76-3; *N*-phenylhydroxylamine, 100-65-2; 1,7-octadiyne, 871-84-1; methyl 4b-[[[(4-methylphenyl)sulfonyl]hydrazonono]-methyl]-4b,5,6,7,8,9-hexahydrocarbazole-8a-acetate, 102851-85-4; phenylacetylene, 536-74-3; dimethyl acetylenedicarboxylate, 762-42-5; 1-[2-(2-propenyloxy)phenyl]ethanol, 28752-82-1; 2-(2-propenyloxy)acetophenone, 82315-95-5.

The Synthesis of Substituted [[3(*S*)-(Acylamino)-2-oxo-1-azetidinyl]thio]acetic Acids

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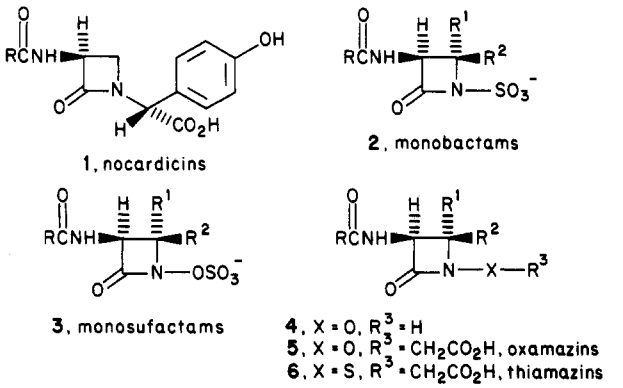
Received November 18, 1985

The synthesis of substituted [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]thio]acetic acids (**6**, thiamazins) is described. Various substituted 3(*S*)-(acylamino)-2-azetidinones were sulfenylated with *tert*-butyl (phthalimidothio)acetate. Deprotection of the *tert*-butyl ester with trifluoroacetic acid provided the title compounds. In sharp contrast to their oxygen analogues (oxamazins), the thiamazins were devoid of biological activity.

The recent discovery of the nocardicins **1**[1] and the monobactams **2**[2] (sulfazecins)[3] has generated considerable interest in the synthesis of novel monocyclic β-lactam antibiotics. In addition, the realization that the β-lactam ring could be activated toward nucleophilic attack by the presence of an electronegative atom on the azetidinyl nitrogen led to the development of the synthetic monosulfactams **3**[4,5] and oxamazins **5**.[6] The significant antibacterial properties inherent in these monocyclic β-lactams demonstrated that oxygen-induced chemical activation could be used to provide new biologically active compounds. As part of an effort examining the scope of heteroatom activation of β-lactam antibiotics, we have determined the effect that replacement of the oxygen with a sulfur atom has on chemical and biological activity. Herein, we report our attempts that ultimatley led to the synthesis of [[3(*S*)-(acylamino)-2-oxo-1-azetidinyl]thio]-acetic acids **6** (thiamazins).[7]

Since *N*-hydroxy-2-azetidinones **4** have proven to be useful intermediates in the synthesis of the oxamazins **5**[6] our first attempt to prepare the thiamazins centered on the synthesis of the unknown *N*-(thiohydroxy)-2-azetidinones **15**. Conceptually, these thiols were available by utilizing an approach analogous to the hydroxamate-mediated β-lactam synthesis developed in our laboratory[8] (Scheme I). However, attempts to separately couple both phenyloxomethane-[9] and triphenylmethanesulfenamides[10] **9a,b** with *N*-(carbobenzyloxy)-L-threonine (**7**) under



standard conditions (WSC; DCC; DCC/*N*-hydroxysuccinimide; EEDQ) failed. Alternatively, conversion of

† Fellow of the Alfred P. Sloan Foundation, 1981–1985. Recipient of a NIH Career Development Award, 1983–1988.

(1) Hashimoto, M.; Konori, T.; Kamiya, T. A. *J. Am. Chem. Soc.* **1976**, *98*, 3023. Kamiya, T. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Chemical Society: Cambridge, England, 1976; pp 287–294.

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(7) Woulfe, S. R.; Iwagami, H.; Miller, M. J. *Tetrahedron Lett.* **1985**, *3891*.

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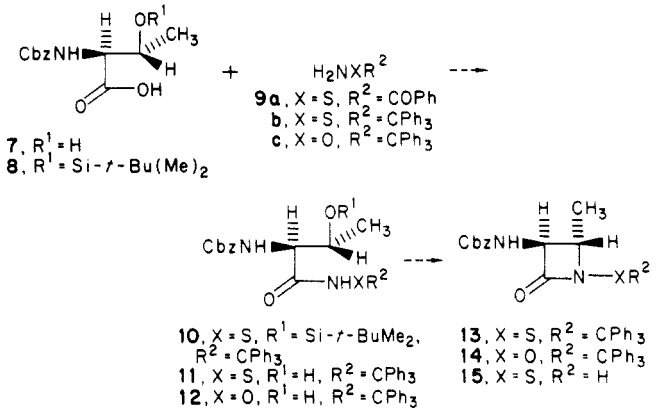
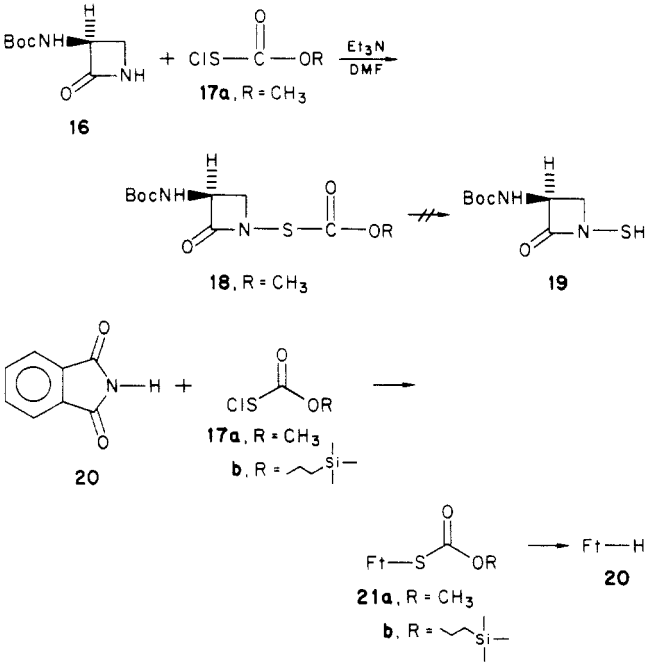
Scheme I

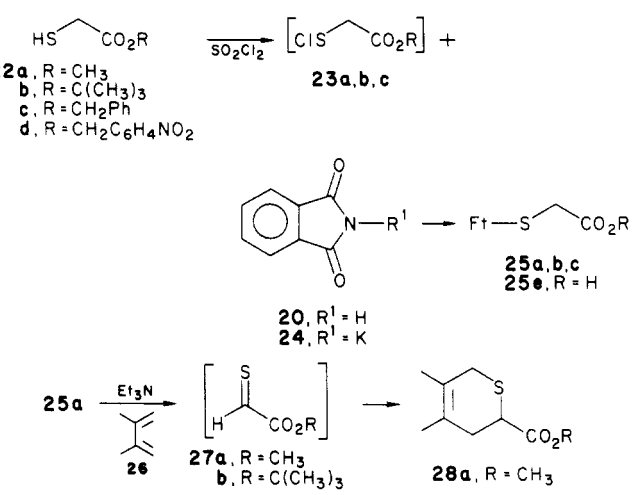


Scheme II



the *tert*-butyldimethylsilyl-protected[11] threonine **8** to the corresponding acid chloride (oxalyl chloride/DMF)[12] followed by reaction with triphenylmethanesufenamide **9b** provided the desired thiohydroxamate **10**. Unfortunately, removal of the silyl protecting group (n-Bu_4NF) to provide **11** followed by attempted cyclization under modified Mitsunobu conditions ($Ph_3P/CCl_4/Et_3N$) did not provide any of the desired β-lactam **13**.[13] In contrast, the *O*-tritylhydroxamate **12** cyclized cleanly under the same conditions to give the substituted *N*-hydroxy β-lactam **14**. We also envisioned that *N*-(thiohydroxy)-2-azetidinone **19** would be available by the deprotection of the thiocarbonate **18** (Scheme II). Crystalline thiocarbonate **18** was prepared by the sulfenylation of N-unsubstituted 2-azetidinone **16**[14]

Scheme III



with methoxyoxomethanesulfenyl chloride.[15] When **18** was treated with sodium carbonate in a methanol–water mixture, none of the desired *N*-(thiohydroxy)-2-azetidinone **19** was isolated. Instead, the original N-unsubstituted β-lactam **16** was recovered. This interesting reaction was examined further by using the phthalimido-substituted thiocarbonates **21** as models. As seen before, treatment of methyl ester **21a** with aqueous base or (trimethylsilyl)ethyl ester **21b** with n-Bu_4NF only gave back the original NH compound, in these cases, phthalimide. While it was possible that the desired R_2NSH compound was an unstable intermediate in these reactions, it was also possible that nucleophilic attack occurred at the sulfur atom rather than at the thiocarbonate carbonyl resulting in formation of the isolated R_2NH compound. This consideration suggested that the desired thiamazins **6** might be prepared by direct reaction of N-unsubstitued β-lactams at the sulfur of appropriately substituted *N*-sulfenylphthalimides **25a–c** (Schemes III and IV).

Interestingly, the first attempt to prepare the required *N*-sulfenylphthalimides by the reaction of phthalimide itself (**20**) with **23** (generated in situ from the corresponding mercaptoacetate **22**) in the presence of Et_3N resulted in the formation of a complex mixture and the recovery of phthalimide (**20**). Reportedly,[16] sulfenyl halides **23** and the corresponding phthalimides **25** can be converted to unstable thioaldehydes **27** under basic conditions. In fact, repetition of the reaction **25a** and Et_3N in the presence of dimethylbutadiene (**26**) provided the Diels–Alder product **28**, presumably by trapping the intermediate thioaldehyde **27**. This unwanted elimination reaction was avoided by reacting the sulfenyl chlorides **23**, as generated, with potassium phthalimide (**24**) to provide the (phthalimidothio)acetate esters **25a,c** directly. The direct reaction of 2-azetidinones **29** with thiophthalimides **25** (Scheme IV) was examined next. Treatment of **29a,b** separately with **25a,b** in benzene containing a catalytic amount of Et_3N cleanly gave the desired thiamazin nuclei in yields greater than 90%. Whether these reactions were proceeding by direct nucleophili attack of the 2-azetidinone on the thiophthalimide sulfur atom or by reaction of **29** with the thioaldehyde **27** generated from **25** was questionable. The latter route involving the thioaldehyde was considered less likely after the reaction was repeated in the presence of the diene **26** and none of the Diels–Alder adduct **28** was

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(9) Raasch, M. S. *J. Org. Chem.* **1972**, *37*, 3820.
(10) Vorlander, D.; Mittag, E. *Chem. Ber.* **1919**, *52*, 413.
(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(12) Stadler, P. A. *Helv. Chim. Acta.* **1978**, *61*, 1675.
(13) This result was somewhat surprising since the Squibb group had been able to cyclize serine derived *S*-aryl thiohydroxamates using mesylate chemistry: Cimarusti, C. M.; Denzel, T. H.; Fox, R.; Jacobs, G. A.; Kissick, T. P.; Koster, W. H.; Moniot, J. L.; Mueller, R. H. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: London, 1984; pp 293–304.
(14) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.
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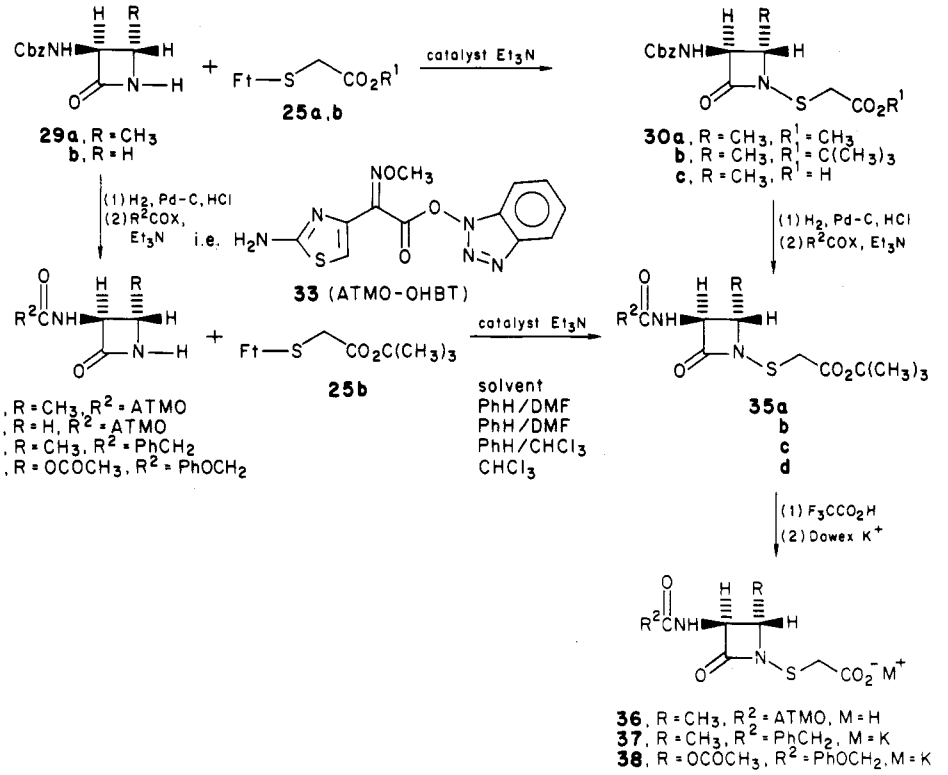
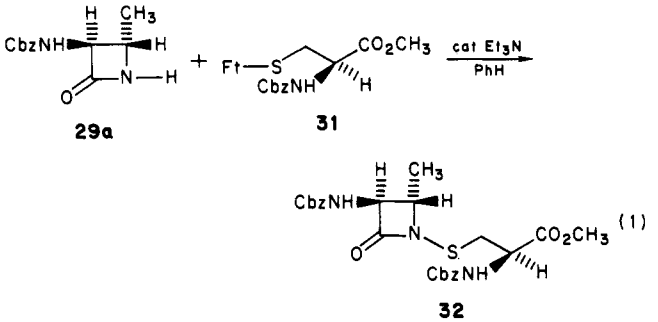
(16) Kirby, G. W.; Lochead, A. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1325.

Scheme IV



detected by HPLC. The lack of thioaldehyde involvment was further supported by the fact that reaction of the cysteine derived thiophthalimide **31**, which has much less acidic protons α to the sulfur atom, with **29a** provided the sulfenylation product **32** cleanly (eq 1).



With the fully protected thiamazin nucleus in hand, we concentrated on preparing a compound suitable for biological testing. Although the *tert*-butyl groups of **25b** and **30b** were easily cleaved with trifluoroacetic acid to give free acids **25e** and **30c**, respectively, we were unable to replace the Cbz group of protected nucleus **30b** with amide side chains. For example, catalytic hydrogenation of **30b** followed by treatment with the active ester **33** did not give any of the 2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)-acetamido (ATMO) derivative **35a**, presumably because the sulfur in **30b** poisoned the catalyst. Therefore, this transacylation reaction was performed one step earlier. Catalytic hydrogenation of the N-unsubstituted 2-azetidinones **29a,b** followed by reacylation with the appropriate side chain active ester provided the 3-(acylamino)-2-azetidinones **34a,c**. Compound **34d**, with the phenoxyacetyl side chain and the 4-acetoxy group, is a degradation product of penicillin V and was supplied by Eli Lilly and Co. The sulfenylation of these N-unsubstituted β-lactams **34** with the thiophthalimide **25b** was not as straightforward as it had been previously with **29a,b**. In the case of the ATMO derivatives **34a,b**, the polar nature of these compounds required the use of DMF as a cosolvent for solubilization. Under these conditions decomposition of the thiophthalimide **25b** to the unstable thioaldehyde **27b** apparently occurred to a considerable extent and accounted for the low (36%) yield of **35a**. In the case of **34b** even lower yields of **35b** were isolated along with an unidentified, inseparable impurity. Again, as a result of solubility problems, the sulfenylation of **34c,d** required the use of chloroform as a cosolvent. No appreciable decomposition of **25b** was detected and sulfenylation products **35c** and **35d** were isolated in yields of 43% and 79%, respectively. *tert*-Butyl esters **35a,c,d** were cleanly deprotected with trifluoroacetic acid without incident. Ion-exchange chromatography provided the thiamazins **37** and **38**.

Thiamazins **36**, **37**, and **38** were evaluated as antibacterial agents. Somewhat to our surprise, all three compounds were devoid of biological activity. We are currently examining factors which may account for the large discrepancy in activity between the structurally similar thiamazins and oxamazins.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727b spectrometer. ^{1}H NMR spectra were obtained in chloroform-*d* with tetramethylsilane as a reference, unless otherwise stated, on a Varian EM 390 or XL-100, Magnachem A200 or Nicolet NB 300 spectrometer. Field desorption and fast atom bombardment mass spectra were recorded by John Occolowitz at Eli Lilly and Co. Electron impact mass spectra were recorded on a AEI Scientific Apparatus MS 902. Elemental analyses were determined by Midwest Microlabs, Indianapolis, IN, or M-H-W Laboratories, Phoenix, AZ. High-pressure liquid chromatography was carried out with a Beckman/Altex model 332 chromatograph. Radial chromatography was performed with a Chromatotron Model 7924 purchased from Harrison Research Inc., Palo Alto, CA. TLC was carried out with aluminum-backed silica gel 60 F-254, 0.2-mm plates purchased from MCB Reagents, NJ. Opti-up C_{12} glass-backed plates, purchased from Fluka Chemical Corp., were used for reversed-

phase TLC. Whatman No. 1 filter paper was used for paper chromatography. Biological testing was done at Eli Lilly and Co. by standard methods. Solvents used were dried and purified by standard methods.

***N*-(Carbobenzyloxy)-*O*-(*tert*-butyldimethylsilyl)-L-threonine (8).** *N*-Carbobenzyloxy-L-threonine (7), (1.0 g, 4.0 mmol), imidazole (806 mg, 12 mmol), *N,N*-(dimethylamino)-pyridine (48 mg, 0.4 mmol), and *tert*-butyldimethylsilyl chloride (1.5 g, 10 mmol) were stirred together in 50 mL of *N,N*-dimethylformamide at room temperature. After 8 h the mixture was taken up into ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue consisted mainly of the bis-O-silylated product, which was unstable on silica gel. Chromatography (silica, 7:3 hexanes–ethyl acetate) gave 1.1 g (2.9 mmol, 73%) of 8 as a white solid that was recrystallized from ethyl acetate–hexanes: mp 157.5–158.5 °C; ^{1}H NMR (90 MHz) δ 0.00 (s, 6 H), 0.80 (s, 9 H), 1.18 4.2–4.7 (m, 2 H), 5.25 (s, 2 H), 5.5–5.7 (br d, 1 H), 7.53 (s, 5 H), 10.5 (br s, 1 H); IR (in $CDCl_3$) 1720 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.86; H, 7.90; N, 3.81. Found: C, 59.04; H, 8.02; N, 3.82.

Phenyloxomethanesulfenamide (9a) was prepared by the procedure of Raasch.[9] Hydrogen sulfide gas was bubbled through a solution of potassium hydroxide (50 g, 893 mmol) in 200 mL of 90% ethanol for 1 h. This solution was cooled to 0 °C, and benzoyl chloride (50 g, 356 mmol) was added dropwise. After 1 h the precipitated potassium chloride was filtered, and the filtrate was evaporated. The residue was dissolved in 175 mL of cold water and washed with ethyl acetate. The aqueous layer was acidified to pH 3 with 6 N HCl and extracted with ether. The ether layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was distilled through a fractionating column under a reduced nitrogen atmosphere (10 torr). Pure thiobenzoic acid (37.6 g, 77%) was collected from 95 to 100 °C [lit. bp[17] 85–87 °C (10 torr)]: ^{1}H NMR (90 MHz) γ 4.60 (br s, 1 H), 7.30–7.75 (m, 3 H), 7.85–8.10 (m, 2 H); IR (in $CDCl_3$) 1665, 1200 cm^{-1}. This thioacid (4.7 g, 34 mmol) and sodium hydroxide (1.4 g, 34 mmol) were dissolved in 30 mL of water at 0 °C. A solution of hydroxylamine-*O*-sulfonic acid (3.9 g, 34 mmol) and sodium hydroxide (1.4 g, 34 mmol) in 15 mL of water was added dropwise. The precipitate was filtered and recrystallized twice from ether to give 4.3 g (28 mmol, 82%) of **9a** as white needles: mp 87–89 °C (lit. mp[9] 88.5–90 °C); ^{1}H NMR (90 MHz) δ 2.65–2.95 (br s, 2 H), 7.30–7.70 (m, 3 H), 7.80–8.00 (m, 2 H); IR (in $CHCl_3$) 1660 cm^{-1}. Anal. Calcd for C_7H_7NSO: C, 54.90;, H, 4.58; N, 9.15. Found: C, 54.90; H, 4.67; N, 8.93.

Triphenylmethanesulfenamide (9b) was prepared by the method of Vorlander.[10] Triphenylmethyl mercaptan (5.0 g, 18 mmol) was stirred in 50 mL of ether and 5 mL of benzene at 0 °C. Sulfuryl chloride (1.8 mL, 22 mmol) was added dropwise. After 30 min the precipitated triphenylmethanesulfenyl chloride was filtered off. The filtrate was evaporated and the residue crystallized from chloroform–ethanol to give a combined total of 4.2 g (13.5 mmol, 75%) of the sulfenyl chloride: mp 133–136 °C (lit. mp[10] 137 °C); ^{1}H NMR (90 MHz) δ 7.4 (s); IR (in $CDCl_3$) 1490, 1420 cm^{-1}. A volume of 25 mL of ether was saturated with ammonia gas at 0 °C. Without interrupting the flow of ammonia, the sulfenyl chloride (2.0 g, 6.4 mmol), dissolved in 5 mL of ether, was added dropwise. After the yellow color of the sulfenyl chloride had vanished, the mixture was added to a separatory funnel, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to leave 1.0 g (3.5 mmol, 55%) of **9b** as a yellow solid: mp 115–120 °C (lit. mp[10] 126 °C); ^{1}H NMR (90 MHz) δ 2.15–2.45 (br s, 2 H), 7.10–7.55 (m, 15 H); IR (in $CDCl_3$) 1485, 1440 cm^{-1}.

Attempts To Couple Phenyloxomethanesulfenamide (9a) to *N*-(Carbobenzyloxy)-L-threonine (7). Compounds **9a** (2.3 g, 15 mmol) and **7** (3.8 g, 15 mmol) were stirred in 100 mL of ethyl acetate at room temperature. A solution of dicyclohexylcarbodiimide (3.1 g, 15 mmol) in 10 mL of ethyl acetate was added dropwise. After 2 h, precipitated dicyclohexylurea (2.9 g, 87%) was filtered, and the filtrate was evaporated. The residue was chromatographed (silica, 1:1 etyl acetate–hexanes) to give two crude fractions. Unreacted **9c** (700 mg, 4.6 mmol, 31%) was crystallized from the first fraction. The second fraction consisted predominantly of what apparently was polymeric **7**. None of the desired coupled product was isolated. Similar results were observed when water-soluble carbodiimide, dicyclohexylcarbodiimide/*N*-hydroxysuccinimide, or 1-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline was used as the coupling reagent.

***S*-Triphenylmethyl *N*-(Carbobenzyloxy)-*O*-(*tert*-butyldimethylsilyl)-L-threoninethiohydroxamate (10).** *N,N*-Dimethylformamide (152 μL, 2.0 mmol) was stirred in 10 mL of acetonitrile at −20 °C under a $CaCl_2$ drying tube. Oxalyl chloride (57 μL, 0.65 mmol) was added slowly. After 15 min compound 8 (240 mg, 0.65 mmol) was added. After an additional 15 min compound **9b** (190 mg, 0.65 mmol) and pyridine (132 μL, 1.64 mmol) were added. After 1 h at room temperature the reaction was taken up into ethyl acetate, washed with water, 5% $NaHCO_3$, 1.2 N HCl, and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica, 9:1 hexanes–ethyl acetate) to give 260 mg (0.4 mmol, 63%) of thiohydroxamate **10** as a clear oil: ^{1}H NMR (300 MHz) δ 0.00 (d, 6 H), 0.83 (s, 9 H), 0.95 (d, 3 H), 2.85–2.95 (br, 1 H), 3.83–3.95 (m, 1 H), 4.20–4.30 (m, 1 H), 5.05 (s, 2 H), 5.50 (br d, 1 H), 7.18–7.45 (m, 20 H); IR (in $CDCl_3$) 1720, 1700 cm^{-1}.

***S*-Triphenylmethyl *N*-(Carbobenzyloxy)-L-threoninethiohydroxamate (11).** The silyl ether **10** (161 mg, 0.24 mmol) was stirred in 15 mL of tetrahydrofuran and tetra-*n*-butylammonium fluoride (0.71 mL of a 1.0 N solution in THF, 0.71 mmol) was added. The reaction was followed by TLC (silica, 7:3 hexanes–ethyl acetate). After 1 h the mixture was taken up in ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica, 7:3 hexanes–ethyl acetate) to give 114 mg (0.22 mmol, 91%) of thiohydroxamate **11** as a clear oil: ^{1}H NMR (90 MHz) δ 0.90 (d, 3 H), 2.50–2.80 (br s, 1 H), 3.80–4.0 (m, 1 H), 4.0–4.3 (m, 1 H), 5.02 (s, 2 H), 5.38–5.62 (br d, 1 H), 7.10–7.80 (m, 20 H); IR (in $CDCl_3$) 3400, 1720, 1700 cm^{-1}.

***O*-Triphenylmethyl *N*-(Carbobenzyloxy)-L-threoninehydroxamate (12).** *N*-(Carbobenzyloxy)-L-threonine (**7**, 2.0 g, 7.91 mmol) and *O*-tritylhydroxylamine (**9c**, Fluka, 2.17 g, 7.91 mmol) were dissolved in 100 mL of ethyl acetate and stirred at room temperature while 1.63 g (7.91 mmol) of DCC in ethyl acetate was added dropwise. After 2.5 h the solution was cooled to 0 °C, and the precipitated DCU was removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel by using a hexanes–ethyl acetate gradient (70:30–30:70) to give 3.84 g (95%) of **12** as a glassy solid: ^{1}H NMR (100 MHz) δ 1.00 (d, 2 H), 2.95–3.2 (br, 1 H), 2.65–3.3 (m, 3 H), 5.95 (s, 2 H), 6.05 (m, 1 H), 6.58 (br d, NH), 7.2–7.6 (m, 20 H). IR ($CDCl_3$) 1680, 1700–1720 cm^{-1}.

4(*S*)-Methyl-3(*S*)-[(benzyloxy)formamido]-*N*-(trityloxy)-2-azetidinone (14). The *O*-trityl hydroxamate **12** (1.5 g, 2.94 mmol) was dissolved in 50 mL of acetonitrile containing 2 mL of carbon tetrachloride by stirring at room temperature for a few minutes. Triethylamine (3.23 mmol) and triphenylphosphine (0.771 g, 3.23 mmol) were added, and the solution was stirred for another 2 h at room temperature. The solvents were then evaporated, and the residue was taken up into ethyl acetate. This solution was washed with water, 1.2 N HCl, and then brine. Drying over magnesium sulfate followed by filtration, concentration, and chromatography on silica gel with hexanes–ethyl acetate (70:30) gave 847 mg (59%) of **14** as a glassy solid: ^{1}H NMR (100 MHz) δ 1.10 (d, 3 H), 2.55 (m, 1 H), 4.0 (d, 1 H), 4.98 (s, 2 H), 5.3 (br, NH), 7.1–7.8 (m, 20 H).

3(*S*)-(*tert*-Butoxyformamido)-2-azetidinone (16) was prepared as reported earlier.[14]

Methoxyoxomethanesulfenyl chloride (17a) was prepared by the method of Field.[15] Methanol (1.22 g, 38 mmol) in 3 mL of ether was added dropwise to a solution of chlorooxomethanesulfenyl chloride (5.0 g, 38 mmol) in 15 mL of ether at room temperature. The mixture was stirred for 24 h. The ether was evaporated and the residue vacuum distilled to give 2.6 g (21 mmol, 54%) of **17a** as a light yellow oil: bp 67–68 °C (74 torr) [lit. bp[15] 67–68 °C (74 torr)]; ^{1}H NMR (90 MHz) δ 4.0 (s); IR (neat 2990, 1750, 1710, 1420, 1130 cm^{-1}.

[2-(Trimethylsilyl)ethoxy]oxomethanesulfenyl chloride (17b) was prepared in the same manner from 2-(trimethylsilyl)ethanol and chlorooxomethanesulfenyl chloride as a yellow oil: bp 35 °C (4 torr) (foamed over); ^{1}H NMR (90 MHz) δ 0.0

(17) Noble, P.; Tarbell, D. S. *Organic Syntheses*; Wiley: New York 1963; Collect. Vol. IV, p 924.

(s, 9 H), 1.10 (t, 2 H), 4.55 (t, 2 H); IR (neat) 1760, 1710 cm^{-1}.

S-3(S)-(tert-Butoxyformamido)-2-oxo-1-azetidinyl O-Methyl Thiocarbonate (18). 2-Azetidinone **16** (100 mg, 0.54 mmol) and sulfenyl chloride **17a** (68 mg, 0.54 mmol) were stirred in 7 mL of *N,N*-dimethylformamide at 0 °C. Triethylamine (75 μL, 0.54 mmol) was added, and the reaction was followed by TLC (silica, 1:1 ethyl acetate–hexanes). After 15 min the reaction mixture was taken up into ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica, 6:4 hexanes–ethyl acetate) to give 102 mg (0.37 mmol, 69%) of **18** as a white solid. Recrystallization from ethyl acetate provided an analytically pure sample: mp 115–116 °C; ^1H NMR (90 MHz) δ 1.45 (s, 9 H), 3.60 (dd, 1 H), 3.88 (t, 1 H), 3.93 (s, 3 H), 4.90–5.25 (m, 1 H), 5.33–5.60 (br d, 1 H); IR (in $CDCl_3$) 3400, 1800, 1730, 1680 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_5S$: C, 43.48; H, 5.80; N, 10.14. Found: C, 43.14; H, 5.87; N, 10.13.

S-Phthalimido O-methyl thiocarbonate (21a) was prepared in a similar manner from phthalimide and methoxyoxomethanesulfenyl chloride (**17a**) in 80% yield as a white solid: mp 138.5–143.5 °C; ^1H NMR (90 MHz) δ 3.92 (s, 3 H), 7.80–8.18 (m, 4 H); IR (in $CDCl_3$) 1760, 1730 cm^{-1}; EI mass spectrum, *m/e* 237 (M^+), 206 (M – OMe), 178 (M – CO_2Me).

S-Phthalimido O-2-(trimethylsilyl)ethyl thiocarbonate (21b) was prepared in a similar manner from phthalimide and [2-(trimethylsilyl)ethoxy]oxomethanesulfenyl chloride (**17b**) in 42% yield as a yellow oil: ^1H NMR (90 MHz) δ 0.00 (s, 9 H), 1.10 (t, 2 H), 4.52 (t, 2 H), 8.00–8.33 (m, 4 H); IR (neat) 3000, 1750, 1730 cm^{-1}.

Treatment of S-Phthalimido O-Methyl Thiocarbonate (21a) with Aqueous Base. Compound **21a** (100 mg, 0.42 mmol) was stirred in 9 mL of methanol–water (1:1) and 2 mL of tetrahydrofuran at 0 °C. Potassium carbonate (58 mg, 0.42 mmol) was added, and the reaction was followed by TLC (silica, 1:1 ethyl acetate–hexanes). After 35 min the mixture was taken up into ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to leave a white solid. Recrystallization from ethyl acetate–hexanes gave 39 mg (0.27 mmol, 63%) of phthalimide. Evaporation of the mother liquor gave 44 mg of yellow solid that was a mixture of phthalimide and a complex mixture of other unidentified products. When compound **18** was subjected to these conditions the *N*-unsubstituted β-lactam **16** was the only identified product.

Treatment of S-Phthalimido O-2-(Trimethylsilyl)ethyl Thiocarbonate (21b) with Tetra-n-butylammonium Fluoride. Compound **21b** (112 mg, 0.35 mmol) was stirred in 20 mL of tetrahydrofuran at 25 °C under a nitrogen atmosphere. Tetra-*n*-butylammonium fluoride (0.4 mL of a 1.0 N tetrahydrofuran solution, 0.40 mmol) was added. The solution immediately turned from clear to yellow to purple then became and remained dark green. The solution was taken up into ethyl acetate, washed with 1.2 N HCl and brine, dried over $MgSO_4$, filtered, and evaporated to give 79 mg of residue that consisted mainly of phthalimide.

***tert*-Butyl mercaptoacetate (22b)** was prepared by the procedure of Honkanen[18] using a modification described by Kricheldorf.[19] Potassium ethylxanthate (29.0 g, 182 mmol) was suspended in 100 mL of dry acetone at room temperature. *tert*-Butyl chloroacetate (25 g, 166 mmol) was added dropwise with stirring. After 18 h potassium chloride was removed by filtration, and the solvent was evaporated. The residue was taken up into ether, washed with 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and evaporated to leave 38 g (161 mmol, 97%) of *O*-ethyl *S*-(*tert*-butoxycarbonyl)methyl dithiocarbonate as a thick oil: ^1H NMR (90 MHz) δ 1.43 (t, 3 H), 1.50 (s, 9 H), 3.97 (s, 2 H), 4.80 (q, 2 H); IR (neat) 3000, 2950, 1740 cm^{-1}. This oil was stirred with ethanolamine (161 mmol) for 2 h at room temperature. The reaction mixture was taken up into ethyl acetate, washed with 1.2 N HCl, water, and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was vacuum distilled to give 16.3 g (110 mmol, 68%) of mercaptan **22b** as a clear oil: bp 62–65 °C (6.25 torr) [lit. bp[18,19] 44 °C (6 torr); 59–60 °C (12 torr)]; ^1H NMR (90 MHz) δ 1.42 (s, 9 H), 1.90 (t, 1 H), 3.16 (d, 2 H); IR (neat) 3000, 2950, 1730 cm^{-1}.

Phenylmethyl Mercaptoacetate (22c). Mercaptoacetic acid (5.3 g, 58 mmol), benzyl alcohol (6.0 mL, 58 mmol), and 2 drops of concentrated sulfuric acid and were added to 200 mL of toluene. The flask was fitted with a Dean–Stark trap and refluxed for 2 h. The toluene was evaporated, and the residue was vacuum distilled through a fractionating column to give 6.2 g (34 mmol, 59%) of **22c** as a clear oil: bp 118.5 °C (1.5 torr); ^1H (90 MHz) NMR δ 2.00 (t, 1 H), 3.29 (d, 2 H), 5.20 (s, 2 H), 7.43 (s, 5 H); IR (in $CDCl_3$) 1750 cm^{-1}; EI mass spectrum, *m/e* 182 (M^+).

(4-Nitrophenyl)methyl mercaptoacetate (22d) was prepared in the same manner from 4-nitrobenzyl alcohol and mercaptoacetic acid in 64% yield as a yellow solid: mp near room temperature; ^1H NMR (90 MHz) δ 2.04 (t, 1 H), 3.35 (d, 2 H), 5.30 (s, 2 H), 7.60 (d 2 H), 8.26 (d, 2 H); IR (neat) 1730 cm^{-1}; EI mass spectrum, exact mass calcd for $C_9H_9NO_4S$ 227.025, found 227.026.

Methyl (Phthalimidothio)acetate (25a). Methyl mercaptoacetate (2.4 g, 22 mmol) and pyridine (1.7 mL, 22 mmol) in 5 mL of carbon tetrachloride were added dropwise to a stirred 0 °C solution of sulfuryl chloride (1.8 mL, 22 mmol) in 25 mL of carbon tetrachloride under a nitrogen atmosphere. After 20 min the precipitated pyridine hydrochloride was filtered off and 50 mL of 1,2-dichloroethane was added to the filtrate. This solution was cooled to 0 °C, and solid potassium phthalimide (3.2 g, 22 mmol) was added with stirring. After the yellow color had vanished (10 min), potassium chloride and unreacted potassium phthalimide were filtered off. The filtrate was evaporated, and 50 mL of toluene was added to the residue. This solution was cooled to 0 °C, and the precipitated phthalimide was removed by filtration. Evaporation of the filtrate and recrystallization of the residue from ethyl acetate–hexanes gave 3.3 g (11 mmol, 51%) of analytically pure **25a** as a white solid: mp 124–127 °C (lit. mp[16] 125–130 °C); ^1H NMR (90 MHz) δ 3.55 (s, 2 H), 3.68 (s, 3 H), 7.7–8.1 (m, 4 H); IR (KBr) 1780, 1710 cm^{-1}; EI mass spectrum, *m/e* 251 (M^+). Anal. Calcd for $C_{11}H_9NO_4S$: C, 52.59; H, 3.59; N, 5.58. Found: C, 52.34; H, 3.89; N, 5.58.

***tert*-Butyl (phthalimidothio)acetate (25b)** was prepared in a similar manner from *tert*-butyl mercaptoacetate (**22b**) in 57% yield as a white crystalline solid: mp 93–96 °C; ^1H NMR (90 MHz) δ 1.37 (s, 9 H), 3.48 (s, 2 H), 7.35–8.10 (m, 4 H); IR (in $CDCl_3$) 1790, 1740, 1710 cm^{-1}; EI mass spectrum, *m/e* 293 (M^+).

Phenylmethyl (phthalimidothio)acetate (25c) was prepared from phenylmethyl mercaptoacetate (**22c**) in 56% yield as a white crystalline solid: mp 88–90 °C; ^1H NMR (90 MHz) δ 3.55 (s, 2 H), 5.10 (s, 2 H), 7.31 (s, 5 H), 7.7–8.00 (m, 4 H), IR (in $CDCl_3$) 1790, 1750, 1720 cm^{-1}: EI mass spectrum, exact mass calcd for $C_{17}H_{13}NO_4S$ 327.056, found 327.059. Anal. Calcd for $C_{17}H_{13}NO_4S$: C, 62.39; H, 3.98. Found: C, 62.24; H, 4.06.

(4-Nitrophenyl)methyl mercaptoacetate disulfide was the predominant product when (4-nitrophenyl)methyl mercaptoacetate (**22d**) was subjected to these reaction conditions: mp 93–95 °C, yellow crystals; ^1H NMR (90 MHz) δ 3.63 (s, 4 H), 5.28 (s, 4 H), 7.60 (d, 4 H), 8.30 (d, 4 H); IR (in $CDCl_3$) 1740 cm^{-1}; EI mass spectrum, exact mass calcd for $C_{18}H_{16}N_2O_8S_2$ 452.035, found 452.035.

Diels–Alder adduct 28a was prepared by the method reported by Kirby.[16] Thiophthalimide **25a** (500 mg, 2.0 mmol), 2,3-dimethyl-1,3-butadiene (225 μL, 2.0 mmol), and triethylamine (277 μL, 2.0 mmol) were stirred together in 50 mL of benzene at room temperature under a $CaCl_2$ drying tube. After 3 h the precipitated phthalimide was filtered off and the filtrate evaporated. The residue was chromatographed (silica, 1:1 ethyl acetate–hexanes) to give 154 mg (0.83 mmol, 42%) of **28a** as a clear oil: ^1H NMR (300 MHz) δ 1.66 (s, 3 H), 1.68 (s, 3 H) 2.427 (br d, 2 H), 3.06 (dd, 2 H), 3.60 (t, 1 H), 3.70 (s, 3 H); IR (in $CDCl_3$) 1740 cm^{-1}.

3(S)-[(Benzyloxy)formamido]-2-azetidinone (29b) was prepared from (carbobenzyloxy)-L-serine methyl ester as reported earlier.[5]

4(S)-Methyl-3(S)-[(benzyloxy)formamido]-2-azetidinone (29a) was prepared in an identical manner from (carbobenzyloxy)-L-threonine methyl ester. Thus, (carbobenzyloxy)-L-threonine methyl ester (5.0 g, 18.7 mmol) was stirred in 75 mL of anhydrous methanol at 0 °C. A freshly prepared methanolic solution of hydroxylamine [potassium hydroxide (78.5 mmol) and hydroxylamine hydrochloride (37.4 mmol) in methanol] was added. The reaction was followed by TLC (silica, ethyl acetate). After 45 min,

(18) Honkanen, E. *Acta Chem. Scand.* **1970**, *24*, 1120.
(19) Kricheldorf, H. R.; Kaschig, J. *Liebigs Ann. Chem.* **1976**, *68*, 882.

acetic anhydride (37.4 mmol) was added, and after another 5 min the reaction mixture was poured into a separatory funnel containing 5% $NaHCO_3$ and ethyl acetate. The layers were separated, and the organic layer was washed with more 5% $NaHCO_3$. The aqueous layers were combined, acidified to pH 4 by the addition of 6 N HCl, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated. The solid residue was recrystallized from ethyl acetate–hexanes to give 4.1 g (13.2 mmol, 71%) of *O*-acetyl *N*-(benzyloxycarbonyl)-L-threoninehydroxamates as a white crystalline solid: mp 111–113 °C; ^1H NMR (90 MHz) δ 1.17 (d, 3 H), 2.16 (s, 3 H), 3.1–3.6 (br s, 1 H), 4.25 (br d, 2 H), 5.13 (s, 2 H), 5.9 (br d, 1 H), 7.33 (s, 5 H), 10.3 (br s, 1 H); IR (KBr) 3250 br, 1800, 1660 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.81. Found: C, 54.25; H, 5.90. EI mass spectrum, exact mass calcd for $C_{14}H_{18}N_2O_6$ 310.117, found 310.119.

O-Acetyl *N*-(carbobenzyloxy)-L-threoninehydroxamate (2.10 g, 6.76 mmol) was dissolved in 50 mL of tetrahydrofuran. Triphenylphosphine (1.77 g, 6.76 mmol) and diisopropyl azodicarboxylate (or diethyl azodicarboxylate, 6.76 mmol) were added in that order. The mixture was stirred at room temperature under a $CaCl_2$ drying tube. The reaction was followed by TLC (silica, ethyl acetate). After 3 h the solvent was evaporated, and the residue was stirred in 45 mL of methanol–water (2:1) at 0 °C. Solid sodium carbonate (1.79 g, 16.9 mmol) was added, and the mixture was vigorously stirred for 35 min. The reaction mixture was taken up in 5% $NaHCO_3$ and washed with ethyl acetate. The aqueous layer was acidified to pH 3 with 6 N HCl and extracted with ethyl acetate. The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to leave 1.25 g (5.00 mmol, 74%) of *N*-hydroxy-4(*S*)-methyl-3(*S*)-[(benzyloxy)formamido]-2-azetidinone: mp 108–112 °C; ^1H NMR (90 MHz) δ 1.37 (d, 3 H), 3.6–3.95 (m, 1 H), 4.1 (dd, 1 H), 5.02 (s, 2 H), 6.25 (br d, 1 H), 7.3 (s, 5 H); IR ($CDCl_3$) 3350, 1760, 1690 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60. Found: C, 57.56; H, 5.73.

This *N*-hydroxy-2-azetidinone (1.0 g, 4.2 mmol) was stirred in 26 mL of anhydrous methanol and 17 mL of 4.5 M ammonium acetate under a nitrogen atmosphere. A 20% solution of aqueous titanium trichloride (9.9 mL, 13 mmol) was added. After 2 h tartaric acid (13 mmol) was added (to avoid formation of a suspension of Ti^{4+} salts), and the pH was adjusted to 10 by the addition of 2 N NaOH. This suspension was extracted four times with 25 mL of ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica, ethyl acetate–hexanes) to give 720 mg (3.2 mmol, 75%) of **29a** as a very thick oil that was crystallized from ethyl acetate–hexanes: mp 96–98 °C; ^1H NMR (90 MHz) δ 1.3 (d, 3 H), 3.6 (dq, 1 H), 4.3 (dd, 1 H), 5.1 (s, 2 H), 6.4 (br d, 1 H), 6.9 (br s, 1 H), 7.3 (s, 5 H); IR (in $CDCl_3$) 1760 cm^{-1}; TLC (silica, 7:3 ethyl acetate–hexanes) R_f 0.30. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.97. Found: C, 61.43; H, 6.00; N, 12.07. EI mass spectrum, exact mass calcd for $C_{12}H_{14}N_2O_3$ 234.100, found 234.100.

N-Sulfenylation of 2-Azetidinones Using S-Substituted Thiophthalimides 25. In a typical reaction, 1 mmol of the 2-azetidinone, 1 mmol of the substituted thiophthalimide, and 2 μL of triethylamine were added to 20 mL of dry benzene and stirred under nitrogen at 25 °C. The reaction was monitored by TLC. Upon completion of the reaction, the solution was cooled in an ice bath, and the precipitated phthalimide was removed by filtration. The filtrate was evaporated and the residue chromatographed on silica gel to provide the product.

Methyl [[4(*S*)-methyl-3(*S*)-((benzyloxy)formamido)-2-oxo-1-azetidinyl]thio]acetate (30a) was prepared from **29a** and **25a** in this manner in 90% yield as a clear oil. Benzene was used as the solvent, and the reaction was complete in 45 min: ^1H NMR ($CDCl_3$, 30 °C, 300 MHz) δ 1.45 (d, 3 H), 3.5 (dd, 2 H), 3.75 (s, 3 H), 3.85 (dq, 1 H), 4.4 (dd, 1 H), 5.1 (s, 2 H), 5.6 (br d, 1 H), 7.4 (s, 5 H). At lower temperatures (–20 °C) a 9:1 mixture of configurational isomers about the N–S linkage was discernable in the NMR spectrum. The coalescence temperature was near room temperature: IR (in $CDCl_3$) 1775 cm^{-1}; EI mass spectrum, *m/e* 338 (M^+), 307 (M – OMe); TLC (silica, 1:1 ethyl acetate–hexanes) R_f 0.30. When this reaction was performed in the presence of 1 equiv of 2,3-dimethyl-1,3-butadiene (**26**) none of the Diels–Alder adduct **28a** was detected in the reaction mixture by HPLC analysis.

***tert*-Butyl [[4(*S*)-methyl-3(*S*)-((benzyloxy)formamido)-2-oxo-1-azetidinyl]thio]acetate (30b)** was prepared from **29a** and **25b** in 96% yield as a colorless oil. Benzene was used as the solvent, and the reaction was complete in 30 min: ^1H NMR (90 MHz) δ 1.35 (d, 3 H), 1.45 (s, 9 H), 3.4 (dd, 2 H), 3.85 (dq, 1 H), 4.35 (dd, 1 H), 5.12 (s, 2 H), 6.10 (br d, 1 H), 7.38 (s, 5 H); IR (in $CDCl_3$) 1775 cm^{-1}; EI mass spectrum, *m/e* 380 (M^+).

***S*-Phthalimido-*N*-(carbobenzyloxy)-L-cysteine methyl ester (31)** was prepared in the same manner reported by Harpp[20] for the trifluoroacetyl derivative. L-Cystine dimethyl ester dihydrochloride (3.4 g, 10 mmol) was stirred in 30 mL of saturated $NaHCO_3$ and 30 mL of chloroform at 0 °C. Benzyl chloroformate (4 mL 28 mmol) was added. After 30 min the aqueous layer was separated, and 1 mL of pyridine was added to the organic layer. This solution was washed with 1.2 N HCl, water, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and evaporated to leave 4.6 g (8.6 mmol, 86%) of *N,N*-bis(carbobenzyloxy)-L-cystine dimethyl ester[21] as a thick oil that solidified in the refrigerator (4 °C) after 3 days: ^1H NMR δ 3.1 (d, 4 H), 3.7 (s, 6 H), 4.7 (m, 2 H), 5.15 (s, 4 H), 5.8 (br d, 2 H), 7.4 (s, 10 H); IR (in $CDCl_3$) 1720 cm^{-1}. This disulfide (2.7 g, 5.0 mmol) was suspended in 15 mL of 1,2-dichloroethane at 0 °C under a nitrogen atmosphere. Bromine (2.4 g, 15 mmol) in 7.5 mL of 1,2-dichloroethane was added dropwise. After being stirred for 2 min, this mixture was transferred to a suspension of potassium phthalimide (1.85 g, 10 mmol) in 20 mL of 1,2-dichloroethane at 0 °C. After 10 min at 0 °C and 90 min at room temperature, the precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed (silica, ethyl acetate–hexanes) to give 1.0 g (2.4 mmol, 24%) of **31** as a very thick oil: ^1H NMR (90 MHz) δ 3.0–3.25 (m, 2 H), 3.58 (s, 3 H), 4.6–4.85 (m, 1 H), 5.10 (s, 2 H), 6.2 (br d, 1 H), 7.40 (s, 5 H), 7.7–8.05 (m, 4 H); IR (in $CDCl_3$) 1780, 1720 br cm^{-1}.

***S*-[4(*S*)-Methyl-3(*S*)-((benzyloxy)formamido)-2-oxo-1-azetidinyl]-*N*-(carbobenzyloxy)-L-cysteine methyl ester (32)** was prepared from **29a** and **31** in 66% yield as a clear oil. Benzene was the reaction solvent, and the reaction was complete in 2.5 h: ^1H NMR (90 MHz) δ 1.36 (d, 3 H), 3.15 (dq, 2 H), 3.7 (m, 1 H), 3.75 (s, 3 H), 4.4 (dd, 1 H), 4.7 (m, 1 H), 5.15 (pair of s, 4 H total), 6.0 (br d, 1 H), 6.2 (br d, 1 H), 7.3 (s, 10 H); IR (in $CDCl_3$) 1770, 1700–1735 cm^{-1}.

4(*S*)-Methyl-3(*S*)-[2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetamido]-2-azetidinone (34a). 2-Azetidinone **29a** (115 mg, 0.49 mmol) and 0.41 mL of 1.2 N HCl (0.49 mmol) were stirred in 10 mL of absolute alcohol at room temperature. Pd–C (10 mg of 5%) was added, and hydrogen was bubbled through this suspension. The reaction was followed by TLC (silica, ethyl acetate). After 30 min the catalyst was removed by filtration, and 10 mL of tetrahydrofuran was added to the filtrate. This solution was cooled to 0 °C and triethylamine (137 μL, 0.98 mmol) and the ATMO active ester **33** (158 mg, 0.54 mmol, obtained from the Eli Lilly and Co.) were added. This mixture was stirred at room temperature, and the reaction was followed by TLC (silica, 15:3:1 ethyl acetate–acetic acid–water). After 4 h the solvent was evaporated and the residue chromatographed (silica, ethyl acetate) to give 119 mg (0.42 mmol, 86%) of **34a** as a white solid: mp >85 °C dec; ^1H NMR (acetone-d_6, 300 MHz) δ 1.24 (d, 3 H), 3.53 (dq, 1 H), 3.79 (s, 3 H), 4.37 (dd, 1 H), 6.68 (s, 1 H), 7.17 (br s, 2 H), 8.16 (br s, 1 H), 9.12 (d, 1 H); IR (KBr) 3600–2800, 1760–1720 cm^{-1}; FD mass spectrum, *m/e* 284 (M + 1), 283 (M^+).

3(*S*)-[2-(2-Amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetamido]-2-azetidinone (34b) was prepared in the same manner from 2-azetidinone **29b** in a 76% yield as a white solid: ^1H NMR (Me_2SO-d_6, 300 MHz) δ 3.15 (dd, 1 H), 3.45 (t, 1 H), 3.8 (s, 3 H), 4.95 (m, 1 H), 6.67 (s, 1 H), 7.18 (s, 2 H), 8.05 (s, 1 H), 9.2 (d, 1 H): IR (KBr) 3500–2800, 1730 br, 1650 cm^{-1}; FD mass spectrum, *m/e* 270 (M + 1), 269 (M^+).

4(*S*)-Methyl-3(*S*)-(phenylacetamido)-2-azetidinone (34c) was prepared in the same manner from 2-azetidinone **29a** and the *N*-hydroxysuccinimide active ester[22] of phenylacetic acid [(mp

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(21) Zervas, L.; Photaki, I. *J. Am. Chem. Soc.* **1962**, *84*, 3887.

114–117 °C; ^{1}H NMR (90 MHz) δ 2.75 (s, 4 H), 3.92 (s, 2 H), 7.38 (s, 5 H); IR (in $CDCl_3$) 1820, 1780, 1730 cm^{-1}] in 61% yield as a white solid: mp 159–162 °C (lit. mp[23] 138–140 °C); ^{1}H NMR (acetone-d_6, 90 MHz) δ 1.30 (d, 3 H), 2.88 (s, 1 H), 3.58 (s, 2 H), 3.7 (dq, 1 H), 4.50 (dd, 1 H), 7.3–7.65 (s, 5 H), 7.9–8.20 (br s, 1 H); IR (KBr) 1760 cm^{-1}.

***tert*-Butyl [[4(*S*)-methyl-3(*S*)-[2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetamido]-2-oxo-1-azetidinyl]thio]acetate (35a)** was prepared from **34a** and **25b** in 36% yield, after chromatography, as a pinkish oil. *N,N*-Dimethylformamide–benzene (1:20) was used as the solvent. The starting materials were consumed after 2.5 h: ^{1}H NMR (90 MHz) δ 1.4 (s, 9 H), 1.5 (s, 3 H), 3.5 (dd, 2 H), 3.95 (s, 3 H), 4.05 (dq, 1 H), 4.80 (dd, 1 H), 5.7 (br s, 2 H), 6.78 (s, 1 H), 8.2 (d, 1 H); IR (in $CDCl_3$) 1770, 1730 cm^{-1}; FD mass spectrum, *m/e* 430 (M + 1); TLC (silica, ethyl acetate) R_f 0.18.

***tert*-Butyl [[4(*S*)-methyl-3(*S*)-(phenylacetamido)-2-oxo-1-azetidinyl]thioacetate (35c)** was prepared from **34c** and **25b** in 43% yield as a clear oil. Chloroform–benzene (1:1) was used as the solvent, and the reaction was worked up after 24 h: ^{1}H NMR (200 MHz) δ 1.45 (d, 3 H), 1.50 (s, 9 H), 3.40 (dd, 2 H, *J* = 15 Hz), 3.57 (s, 2 H), 3.76 (dq, 1 H), 4.46 (dd, 1 H), 6.64 (br d, 1 H), 7.28 (m, 5 H); IR (in $CDCl_3$) 1780, 1760, 1720 cm^{-1}: EI mass spectrum, exact mass calcd for $C_{18}H_{24}N_2O_4S$ 364.146, found 364.145. Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.34; H, 6.59. Found: C, 59.17: H, 6.62. TLC (silica, 1:1 ethyl acetate–hexanes) R_f 0.30.

***tert*-Butyl [[4(*S*)-acetoxy-3(*S*)-(phenoxyacetamido)-2-oxo-1-azetidinyl]thio]acetate (35d)** was prepared from **34d** and **25b** to give a clear oil in 79% yield that was crystallized from chloroform–hexanes. Chloroform was used as the reaction solvent, and the reaction was worked up after 24 h: mp 95–99 °C; ^{1}H NMR (200 MHz) δ 1.40 (s, 9 H), 2.18 (s, 3 H), 3.55 (dd 2 H, *J* = 12 Hz), 4.53 (s, 2 H), 4.98 (dd, 1 H), 6.18 (d, 1 H), 6.8–7.6 (m, 6 H total); IR (in $CDCl_3$) 1800, 1720, 1680 cm^{-1}; EI mass spectrum, exact mass calcd for $C_{19}H_{24}N_2O_7S$: 424.130. Found: 424.130. Anal. Calcd for $C_{19}H_{24}N_2O_7S$: C, 53.77; H, 5.66. Found: C, 53.89; H, 5.77. TLC (silica, 1:1 ethyl acetate–hexanes) R_f 0.45.

Carboxylic Acid Deprotections: (Phthalimidothio)acetic Acid (25e). *tert*-Butyl ester **25b** (77 mg, 0.26 mmol) was stirred in 5 mL of trifluoroacetic acid for 30 min at 0 °C. The solvent was evaporated and the residue was recrystallized from ethyl acetate–hexanes to give 44 mg (0.19 mmol, 71%) of free acid **25e** as white needles: mp 175–177 °C; ^{1}H NMR (90 MHz, $CDCl_3$, acetone-d_6 1:1) δ 3.80 (s, 2 H), 4.3–5.3 (br s, 1 H), 8.25 (s, 4 H); IR (KBr) 1740, 1700 cm^{-1}; EI mass spectrum, exact mass calcd for $C_{10}H_7NO_4S$ 237.010, found 237.010.

[[4(*S*)-Methyl-3(*S*)-((benzyloxy)formamido)-2-oxo-1-azetidinyl]thio]acetic Acid (30c). *tert*-Butyl ester **30b** (88 mg, 0.23 mmol) was stirred in 6 mL of trifluoroacetic acid at room temperature for 30 min. The solvent was evaporated, and the residue was taken up into 5% $NaHCO_3$, washed with ethyl acetate, acidified to pH 3 with 6 N HCl, and extracted into ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to leave 57 mg (0.18 mmol, 76%) of **30c** as a colorless oil: ^{1}H NMR (90 MHz, acetone-d_6) δ 1.35 (d, 3 H), 3.60 (dd, 2 H), 3.9 (dq, 1 H), 4.4 (dd, 1 H), 5.15 (s, 2 H), 5.6–6.4 (br s, 1 H), 7.1 (br d, 1 H), 7.3 (s, 5 H); IR (in $CDCl_3$) 1800, 1740 cm^{-1}.

[[4(*S*)-Methyl-3(*S*)-[2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetamido]-2-oxo-1-azetidinyl]thio]acetic Acid (36). *tert*-Butyl ester **35a** (26 mg, 0.06 mmol) was stirred in 5 mL of trifluoroacetic acid for 30 min at room temperature. The solvent was evaporated and the residue was taken up into water, washed with ethyl acetate, and freeze-dried to leave 22 mg (0.059 mmol, 97%) of **36** as a fluffy white solid: ^{1}H NMR (90 MHz, acetone-d_6) δ 1.38 (d, 3 H), 3.7 (dd, 2 H, *J* = 15 Hz), 4.0 (s, 3 H), 4.1 (dq, 1 H), 4.7 (dd, 1 H), 6.0–6.8 (br s, 3 H total), 7.2 (s, 1 H), 8.7 (d, 1 H); IR (KBr) 3600–2800, 1760, 1660 cm^{-1}; FD mass spectrum, *m/e* 374 (M + 1).

Potassium [[4(*S*)-Methyl-3(*S*)-(phenylacetamido)-2-oxo-1-azetidinyl]thio]acetate (37). *tert*-Butyl ester **35c** (47 mg, 0.13 mmol) was stirred in 1 mL of trifluoroacetic acid for 30 min at room temperature. The solvent was evaporated, and the residue was passed through an ion-exchange column (1 × 20 cm, Dowex 50W-8X, K^+ form, 25 mL of tetrahydrofuran–water (1:1) as eluant). The solvents were evaporated and freeze-dried to leave the potassium salt **37** (27 mg, 60%) as an off-white film: ^{1}H NMR (300 MHz, D_2O) δ 1.45 (d, 3 H), 3.7 (dd, 2 H), 3.75 (s, 2 H), 4.05 (dq, 1 H), 4.55 (d, 1 H), 7.35–7.55 (m, 5 H); IR (KBr) 1750 cm^{-1}; reversed-phase TLC (1:1 2-propanol–water) R_f 0.56; paper chromatography (9:1 2-propanol–water) R_f 0.27.

Potassium [[4(*S*)-Acetoxy-3(*S*)-(phenoxyacetamido)-2-oxo-1-azetidinyl]thio]acetate (38). *tert*-Butyl ester **35d** (34 mg, 0.08 mmol) was stirred in 1 mL of trifluoroacetic acid for 30 min at room temperature. The solvent was evaporated to leave a clear oil: ^{1}H NMR (90 MHz) δ 2.1 (s, 3 H), 3.6 (dd, 2 H), 4.5 (s, 2 H), 4.8 (dd, 1 H), 6.3 (d, 1 H), 6.8–7.4 (m, 5 H), 7.8 (br d, 1 H), 9.5 (br s, 1 H); IR (in $CDCl_3$) 1780–1720 cm^{-1}. The free acid was passed through an ion-exchange column (1 × 20 cm, Dowex 50W-8X, K^+ form, 25 mL of tetrahydrofuran–water (2:3 as eluant). The solvents were evaporated and freeze-dried to leave potassium salt **38** (32 mg, 100%) as a fluffy white solid: ^{1}H NMR (300 MHz, D_2O) δ 2.27 (s, 3 H), 3.73 (dd, 2 H), 4.78 (s, 2 H), 5.0 (d, 1 H), 6.25 (d, 1 H), 7.1–7.5 (m, 5 H); IR (KBr) 1780, 1760, 1670 cm^{-1}; reversed-phase TLC (1:1 2-propanol–water) R_f 0.63; paper chromatography (7.5:2.5 2-propanol–water) R_f 0.62.

Acknowledgment. We gratefully acknowledge the support from the National Institutes of Health (NIH), Eli Lilly and Co., and a Reilly Fellowship (1983–1985) for S.R.W. We are grateful to the Lilly group, especially Dr. Robin D. G. Cooper, Bryon Daugherty, and Dr. John L. Ott for gifts of **33** and **34d** and for the biological tests. Kathleen Peterson obtained the 300-MHz NMR spectra, using an NMR spectrometer made available by grants from the NIH and the University of Notre Dame.

Registry No. **7**, 19728-63-3; **8**, 94820-26-5; **9a**, 25740-80-1; **9b**, 38499-08-0; **9c**, 31938-11-1; **10**, 102652-68-6; **11**, 102652-69-7; **12**, 102652-70-0; **14**, 102745-10-8; **16**, 72229-74-4; **17a** (R = CH_3), 26555-40-8; **17b** (R = $Me_3Si(CH_2)_2$), 102652-71-1; **18**, 102652-72-2; **21a**, 102652-73-3; **21b**, 102652-74-4; **22b**, 20291-99-0; **22c**, 7383-63-3; **22d**, 64832-05-9; **25a**, 42300-49-2; **25b**, 100239-01-8; **25c**, 102652-75-5; **25e**, 70216-77-2; **28a**, 89141-10-6; **29a**, 80582-04-3; **29b**, 80082-81-1; **30a**, 100239-03-0; **30b**, 100239-04-1; **30c**, 102652-82-4; **31**, 100239-02-9; **32**, 100239-05-2; **33**, 82423-07-2; **34a**, 102734-23-6; **34b**, 102652-78-8; **34c**, 87791-64-8; **35a**, 102652-79-9; **35c**, 102652-80-2; **35d**, 102652-81-3; **36**, 102652-83-5; **37**, 102652-84-6; **38**, 102652-85-7; Ph_3CSCl, 24165-03-5; ClC(O)SCl, 2757-23-5; $Me_3Si(CH_2)_2OH$, 2916-68-9; $ClCH_2C(O)O$-*t*-Bu, 107-59-5; EtOC(S)$SCH_2C(O)O$-*t*-Bu, 27240-57-9; $HSCH_2CO_2H$, 68-11-1; *p*-$NO_2C_6H_4CH_2OH$, 619-73-8; $HSCH_2C(O)OMe$, 2365-48-2; CH_2=$C(CH_3)C(CH_3)$=CH_2, 513-81-5; thiobenzoic acid, 98-91-9; triphenylmethyl mercaptan, 3695-77-0; potassium ethylxanthate, 140-89-6; potassium phthalimide, 1074-82-4; (4-nitrophenyl)methyl mercaptoacetate disulfide, 102652-76-6; *N*-[(benzyloxy)carbonyl]-L-threonine methyl ester, 57224-63-2; *O*-acetyl-*N*-[(benzyloxy)carbonyl]-L-threonine hydroxamate, 102652-77-7; *N*-hydroxy-4(*S*)-methyl-3(*S*)-[(benzyloxy)formamido]-2-azetidinone, 93589-31-2; L-cystine dimethyl ester dihydrochloride, 32854-09-4; *N,N*-bis[(benzyloxy)carbonyl]-L-cystine dimethyl ester, 3693-95-6; *N*-[(benzylcarbonyl)oxy]succinimide, 23776-85-4.

(22) For a general reference on the preparation of active esters, see: Klausner, Y. S.; Bodansky, M. *Synthesis* **1972**, 453.

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