Pyrolysis of 34. The adduct **34** (0.1 g) was heated at 200 °C for 2 h. Similar work-up gave **41** (0.058 g, 91%) and **42c** (0.015 g).

Hydrolysis of 55. To a solution of **55** (0.47 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h, and the reaction mixture was then diluted with water (30 ml). The diluted solution was neutralized with dilute hydrochloric acid and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel using benzene to give **64** (0.2 g, 50%) as colorless leaflets: mp 235–237 °C (dichloromethane–methanol); ir (KBr) 2210, 1605, 1505, 1455 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (m, 2 H, H_B), 4.90 (dd, 1 H, J = 6.0 and 3.5 Hz, H_A), 7.1–8.1 (m, 16 H, aromatic H), 8.70 (d, 2 H, J = 8.5 Hz, aromatic H).

Anal. Calcd for $C_{31}H_{21}N$: C, 91.35; H, 5.2; N, 3.45. Found: C, 91.1; H, 5.05; N, 3.55.

Hydrolysis of 56. To a solution of **56** (0.493 g) in Me_2SO (10 ml) was added a hot solution of KOH (0.17 g) in water (0.3 ml). The mixture was stirred at room temperature for 16 h. Similar work-up gave **64** (0.16 g, 40%).

Supplementary Material Available. Tables I, II, IV, and VI of NMR spectra (4 pages). Ordering information is given on any current masthead page.

Registry No.—**2,** 5660-91-3; **3,** 539-80-0; **4,** 57969-45-6; **6,** 57969-46-7; **7,** 941-69-5; **8,** 58002-01-0; **9,** 58002-02-1; **10,** 544-25-2; **11,** 57969-47-8; **13,** 57969-48-9; **14,** 57969-49-0; **15,** 57969-50-3; **16,** 57969-51-4; **17,** 57969-52-4; **18,** 2955-79-5; **19,** 57969-53-6; **22,** 57969-54-7; **23,** 57969-55-8; **24,** 57969-56-9; **26,** 573-57-9; **27,** 19019-88-6; **28,** 1829-60-3; **29,** 121-46-0; **30,** 208-96-8; **31,** 2175-91-9; **32,** 57969-57-0; **33,** 57969-58-1; **34,** 57969-59-2; **35,** 57969-60-5; **36,** 57969-61-6; **37,** 57969-62-7; **39,** 57969-63-8; **41,** 57969-64-9; **42c,** 4282-33-1; **45,** 670-54-2; **46,** 108-31-6; **47,** 106-51-4; **48,** 920-37-6; **49,** 3061-65-2; **50,** 762-42-5; **51,** 886-38-4; **52,** 36428-90-7; **53,** 57969-65-0; **54,** 57969-66-1; **55,** 57969-67-2; **56,** 57969-68-3; **57,** 57969-69-4; **58,** 57969-70-7; **59,** 57969-71-8; **64,** 57969-72-9.

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Synthesis of β-Lactams via Cycloaddition of Iminodithiocarbonate Esters with Azidoketene[1]

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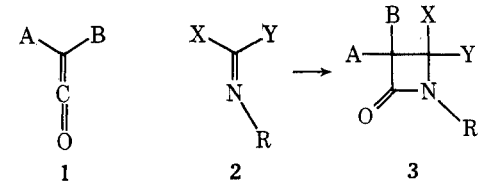
The reaction of iminodithiocarbonate esters with azidoketene afforded β-lactams containing an ortho ester functionality. The yield of cycloaddition is influenced by the steric and electronic nature of the imine substrate and by the order of addition of reagents. The 1,2-secopenam analogs **16b** and **25** were prepared through reaction of imines **15** and **22** with azidoacetyl chloride–triethylamine followed by transformation of the azide function to an acylamido function. Ring opening of the β-lactams was achieved under a variety of conditions: **7a** gave **11** with trifluoroacetic acid, **7b** gave **12** with hog pancreatic lipase, and **16b** and **25** were transformed to **17** and **26,** respectively, with silica gel.

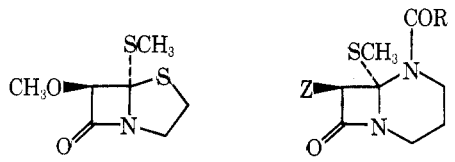
Spurred by the importance of penicillins and cephalosporins to antibiotic therapy, synthetic chemists have devised numerous methods for the preparation of the natural β-lactams and related analogues.[3] One such route, the reaction of ketenes with imines, has proven a versatile method for the synthesis of medicinally important compounds.[4a–e]

We became interested in the ortho ester functionality which would result from the cycloaddition of a ketene with a bishetero-substituted imine (1 + 2 → 3). The use of azidoketene in a cycloaddition reaction with a bishetero-substituted imine, besides incorporating the ortho ester functionality, would permit the subsequent introduction of the biologically important *N*-acylamido moiety onto the resultant β-lactams (1 + 2 → 3; A = N_3; B = H). Suitable choice of the imine can yield β-lactams containing other functionalities important for biological activity (i.e., R = $CHR'CO_2R''$).



1 2 3

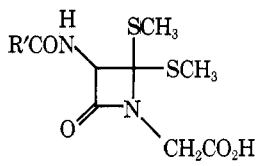
Several examples of β-lactams containing ortho ester functionality have been published. A Bayer group has described 41 β-lactams derived from the reaction of *N*-alkyliminodithiocarbonate dimethyl esters with various ketenes.[5] Bose has prepared the penicillin analogue **4** through the reaction of 2-methylthio-2-thiazoline with methoxyketene.[6] Bose has also described β-lactams of the general type **5** which were derived through the addition of various ketenes, including azidoketene, to N-acylated 2-methylthio-1,4,5,6-tetrahydropyrimidines.[7]



4 5

Results and Discussion

The initial target compound **6a** incorporated a glycine residue into the β-lactam. The plan was to prepare acid **6a**



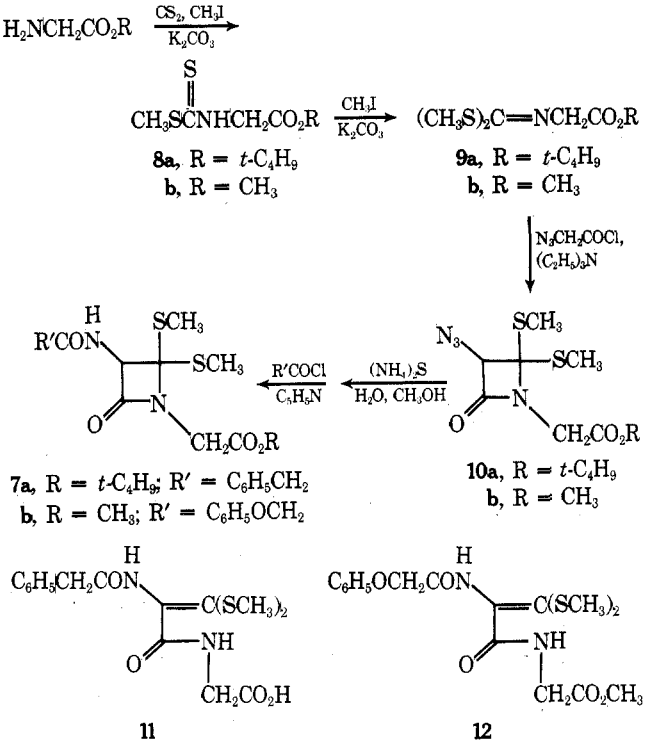
6a, R′ = $C_6H_5CH_2$
b, R′ = $C_6H_5OCH_2$

through acid-catalyzed hydrolysis of an ester such as **7a**. Accordingly, glycine *tert*-butyl ester was condensed with carbon disulfide, methyl iodide, and potassium carbonate to give dithiocarbonate **8a** (65%), which was further condensed with methyl iodide to give iminodithiocarbonate dimethyl ester **9a** (89%). Reaction of **9a** with azidoacetyl chloride in the presence of triethylamine (addition of the acid chloride to a solution of iminodithiocarbonate and triethylamine) afforded β-lactam **10a** in quantitative yield based on a 36% conversion of **9a**. The acylamido side chain was introduced by first reducing the azide to the amine with excess ammonium sulfide and then acylating with phenylacetyl chloride–pyridine to give **7a** (58%). Attempted hydrolysis of **7a** with trifluoracetic acid–anisole gave the ring-opened acid **11** instead of the desired acid **6a**.

In order to circumvent the difficulty posed by acid hydrolysis a methyl ester was substituted for the *tert*-butyl ester. Glycine methyl ester was transformed through **8b** (90%) to **9b** (50% from **8b**). Condensation of **9b** with azidoacetyl chloride–triethylamine afforded β-lactam **10b** in 80% yield based on 32% recovered **9b**. The azide **10b** was converted in two steps to the phenoxyacetamido compound **7b** (36%). The initial attempt at hydrolysis of ester **7b** using mild (pH 7) enzymatic conditions[8] gave the ester **12** in 70% yield. Having failed with enzymatic hydrolysis we opted for the more straightforward method of treating **7b** with 1.05 equiv of lithium hydroxide in water at room temperature. The desired acid **6b** was thereby obtained in 60% yield after acidification and work-up. These reactions are summarized in Scheme I.

Having achieved the overall transformation of an amino acid into a β-lactam consistent with the constraints which were originally imposed on functionality, an attempt was made to incorporate a carbon framework more in keeping with that of a penicillin. A molecule such as **13** could be thought of as an opened penicillin analogue (a 1, 2-secopenicillin). L-Valine methyl ester[9] was converted to the dithiocarbonate **14** (76%), which was smoothly transformed to the iminodithiocarbonate **15** (72%) with methyl iodide–sodium hydride in THF. The cycloaddition reaction of **15** with azidoketene was attempted with the usual conditions of addition of 1 equiv of azidoacetyl chloride to a methylene chloride solution of **15** and 1 equiv of triethylamine. This mode of addition gave rise to trace amounts of two new components by TLC analysis; moreover, the amount of these new components did not increase appreciably with the sequential addition of another equivalent of firstly triethylamine and then azidoacetyl chloride. The order of addition was inverted by adding 2 equiv of azidoacetyl chloride followed by 2 equiv of triethylamine. This inverted addition procedure resulted in substantially more of the two new components than did the normal addition procedure. A repeat reaction using the inverted addition procedure with the addition of 4 equiv of triethylamine to a methylene chloride solution of **15** and 4 equiv of azidoacetyl chloride afforded a diastereomeric mixture of β-lactams **16a** in 20% yield based on 34% recovered **15**. The mixture of azides **16a** was transformed into a mixture of phenacylamido β-lactams **16b** in 45% yield by ammonium sulfide reduction followed by acylation of the amine. The diastereomeric mixture **16b** (ca. 2:1 by NMR) could not be resolved into the individual diastereomers by silica gel chromatography. The chromatographic purification of **16b** was accompanied by some ring opening on the silica gel to give **17**.

Scheme I



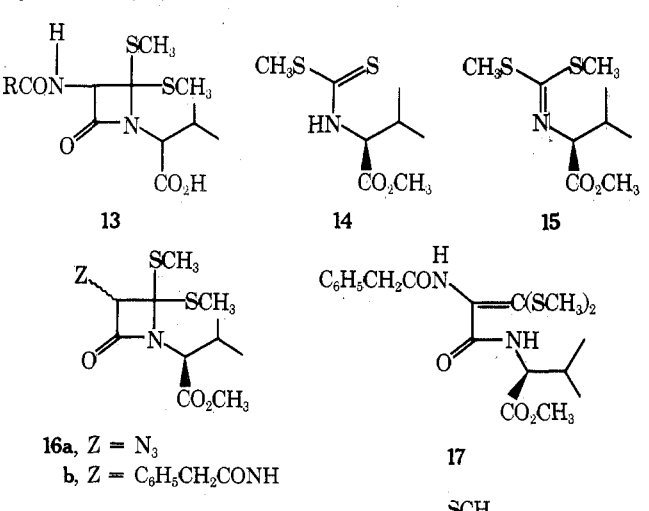
8a, R = *t*-C_4H_9
b, R = CH_3

9a, R = *t*-C_4H_9
b, R = CH_3

7a, R = *t*-C_4H_9; R′ = $C_6H_5CH_2$
b, R = CH_3; R′ = $C_6H_5OCH_2$

10a, R = *t*-C_4H_9
b, R = CH_3

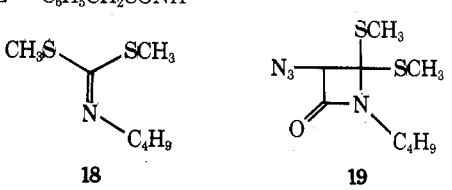
11 **12**



13 **14** **15**

16a, Z = N_3
b, Z = $C_6H_5CH_2CONH$

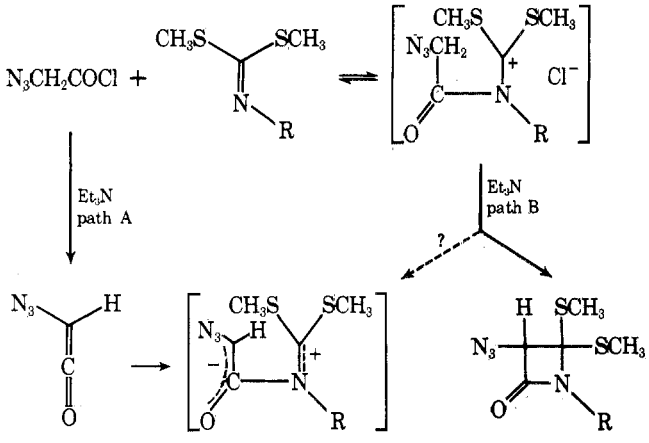
17



18 **19**

Attempting to explain the relative success of β-lactam formation with various substrates and the relative success

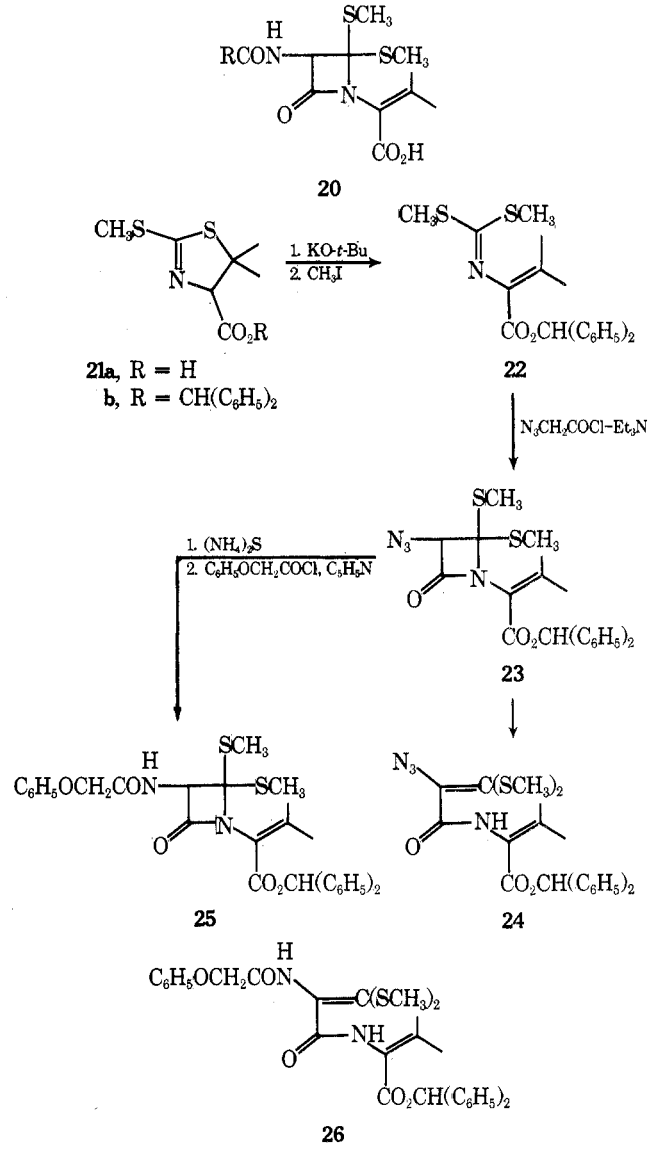
Scheme II



of the normal vs. the inverse addition mode brings up some of the complexities inherent in the mechanism(s) of the cycloaddition reaction (Scheme II). Bose has coined the term "the acid chloride reaction" for a reaction in which the imine and acid chloride are mixed and then triethylamine is added to that mixture to give a β-lactam.[10] In the case studied by Bose it was felt from NMR evidence that a covalently bonded intermediate was formed in a reversible reaction of the acid chloride with the imine, and that β-lactam formation "may entirely by-pass the ketene pathway—at least in those instances where *cis* β-lactams are formed". On the other hand, Ghosez[11] interpreted the normal addition mode (acid chloride added to a solution of imine plus triethylamine) as proceeding primarily through the intermediacy of a ketene which then reacted with an imine to form a heterodiene dipolar intermediate.[12] In Ghosez's case the use of the inverse addition mode by the prior formation of an adduct of benzalaniline with dichloroacetyl chloride and subsequent reaction with triethylamine afforded the β-lactam in much lower yield than that which accompanied the normal addition mode. Such a result may indeed mean that a covalently bonded intermediate may proceed to β-lactam without going through a dipolar intermediate.[13] In our examples we find that if the imine is deactivated by steric or electronic factors, then the inverse addition mode is indicated for a successful reaction. Consistent with this notion of substrate dependence we find that the omission of the carboxylate functionality, which is presumably deactivating through its inductive effect, was beneficial in terms of giving a high yield for β-lactam formation: the iminodithiocarbonate **18** reacted with azidoacetyl chloride by the normal addition procedure to give **19** in 92% yield. One unresolved question which is posed by a successful result obtained through the normal addition mode is whether the product was formed through a ketene pathway (A), or through a prior acylation step followed by proton abstraction and ring closure (B). In the case of a reactive (undeactivated) imine, there is the possibility of exclusive reaction by path B if the imine acylation step could compete in rate with the alternative of ketene formation by proton abstraction from azidoacetyl chloride.

The investigation of systems resembling an open penicillin was extended to the β-lactam **20.** Methylthiothiazoline **21a**[14] was converted to the benzhydryl ester **21b,** which upon treatment with potassium *tert*-butoxide in THF at −65 °C followed by trapping with methyl iodide afforded iminodithiocarbonate **22** (88%). The course of the reaction of **22** with azidoacetyl chloride–triethylamine paralleled that of **15.** Again the inverse addition mode seemed crucial to the success of the cycloaddition. The resulting β-lactam proved to be very unstable to normal silica gel or alumina

Scheme III

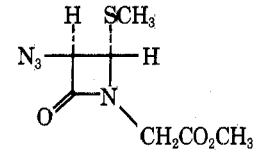


chromatography so recourse was taken to purification through the use of countercurrent distribution,[15] whereby we were able to obtain reasonably pure β-lactam **23** in 61% yield. The decomposition of **23** on silica gel gave the ring-opened material **24.** The purified azide **23** was transformed into the phenoxyacetamido derivative **25** by the normal route. Compound **25** was very difficult to purify and it was obtained in ca. 85% purity with the major impurity being **26.** These reactions are summarized in Scheme III.

A chord struck throughout this study is that of the ring cleavage of these ortho ester type β-lactams. Bose has observed this type of cleavage in the presence of trifluoroacetic acid and suggested that protonation of the amide nitrogen initiated ring opening.[6] Ring opening can then lead to a carbonium ion stabilized by two sulfur substituents. Loss of a proton from this intermediate gives the ring-opened product. In some of our cases a strong acid such as trifluoroacetic acid was not needed, and indeed, silica gel was sufficiently acidic to cleave **16b, 23,** and **25.**

On a final note we became interested in what effect, if any, the ortho ester functionality exerted on the β-lactam carbonyl infrared stretching frequency. Carbonyl stretching frequencies of β-lactams have been taken as a measure of relative acylating power and have been successfully correlated with biological activity.[16] Comparison of β-lactam carbonyl stretching frequencies for pairs **10b** and **27**[17]

(1785 vs. 1785 cm^{-1}: $CHCl_3$) and **25** and **28**[18] (1775 vs. 1765 cm^{-1}: $CHCl_3$) showed that the ortho ester functionality imparted no consistent effect to the carbonyl stretching frequency. The results of biological testing of compound **29**[17] paralleled the experience of a Beecham group with 1,2-secopenicillin **30**;[19] with both compounds there was no significant antibacterial activity.



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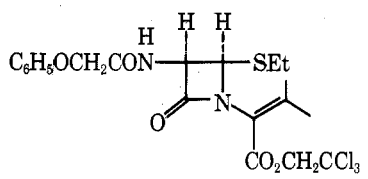

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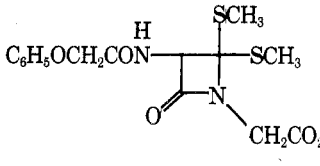

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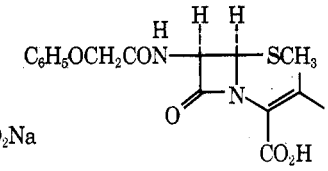

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Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B grating spectrometer. NMR spectra, unless noted otherwise, were obtained in deuteriochloroform (ca. 10% w/v) with Me_4Si internal standard using a Varian A-60 or HA-100. Combustion analyses were performed by A. Bernhardt, Mulheim (Ruhr), West Germany, and by our microanalytical laboratory. The mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We gratefully acknowledge Mr. V. Hayashida, Dr. M. Maddox, Mrs. J. Nelson, Mrs. L. Kurz, Dr. L. Tökès, and Mr. J. Smith for their assistance with analytical measurements.

***tert*-Butyl 2-(*S*-Methyldithiocarbamoyl)acetate (8a).** A 500-ml Erlenmeyer flask equipped with a magnetic stirrer was charged with 250 ml of methanol and 7.85 g (50 mmol) of *tert*-butyl azidoacetate. The flask was cooled in a water bath and 80 ml of a 22% ammonium sulfide solution was added in one portion. After 0.5 h, the solution was saturated with sodium chloride and was thoroughly extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and the chloroform was evaporated to give 7.25 g of an oil. The oil was taken up into 75 ml of THF and 7 ml of water and this mixture was added to a 250-ml Erlenmeyer along with 3.33 ml (4.21 g, 55.3 mmol) of carbon disulfide. After 10 min, 3.82 g (27.6 mmol) of potassium carbonate and 8.25 g (3.62 ml, 58 mmol) of methyl iodide were added. After an additional 15 min, the solution was diluted with ca. 150 ml of diethyl ether and was washed with water. The organic layer was collected, dried (Na_2SO_4), and evaporated to give 8 g of crude acetate **8a** (72% from the azide). Recrystallization from acetone–hexane afforded 7.5 g of white crystals: mp 108–112 °C; NMR δ 1.49 [s, 9 H, $C(CH_3)_3$], 2.63 (s, 3 H, SCH_3), 4.35 (d, 2 H, J = 4.5 Hz, $HNCH_2$), 7.25 (broad, 1 H, NH); ir ($CHCl_3$) 3290, 1725, 1520 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.45; H, 6.83; N, 6.33. Found: C, 43.28; H, 6.83; N, 6.25. MS *m/e* 221 (M^+).

Methyl 2-(*S*-Methyldithiocarbamoyl)acetate (8b). Carbon disulfide (4.8 ml, 79.6 mmol) and 75 ml of THF were placed in a 250-ml Erlenmeyer flask equipped with a magnetic stirrer. To this solution were added 10 g (79.6 mmol) of methyl glycinate hydrochloride, 7 ml of water, and 10.9 g (78.9 mmol) of potassium carbonate. After 15 min, 4.95 ml (11.28 g, 79.5 mmol) of methyl iodide was added. The solution was stirred for 0.5 h and was worked up in the same manner as **8a** to give 11.5 g (81%) of an oil which crystallized on standing to give a solid: mp 44–46 °C; NMR δ 2.63 (s, 3 H, SCH_3), 3.79 (s, 3 H, OCH_3), 4.49 (d, 2 H, J = 5 Hz, $HNCH_2$), 7.83 (broad, 1 H, NH); ir (film) 3345, 1745 cm^{-1}. Anal. Calcd for $C_5H_9NO_2S_2$: C, 33.50; H, 5.06; N, 7.81. Found: C, 33.24; H, 5.17; N, 7.73. MS *m/e* 179 (M^+).

Methylation of 2-(*S*-Methyldithiocarbamoyl)acetates. The methyl ester **8b** (10 g, 55.8 mmol) was dissolved in a solution of 75 ml of THF and 7 ml of water, and 3.85 g (27.8 mmol) of potassium carbonate was added to the solution. Methyl iodide (17.5 ml, 280 mmol) was added and the solution was heated at reflux for ca. 15 h. Water (ca. 100 ml) was added and the mixture was extracted with diethyl ether. The ether was dried (Na_2SO_4) and evaporated to an oil. The oil was chromatographed from ca. 200 g of silica gel (3.5:1 hexane–diethyl ether) to give 5.4 g (50%) of the bismethylthioimino acetate **9b** as an oil: NMR δ 2.38 (s, 3 H, SCH_3), 2.53 (s, 3 H, SCH_3), 3.68 (s, 3 H, OCH_3), 4.12 (s, 2 H, NCH_2); ir (film) 1755, 1580 cm^{-1}; *m/e* 193 (M^+). The *tert*-butyl imino acetate **9a** was prepared using 2 equiv of potassium carbonate. The yield of **9a** (oil) was 89% following chromatography from silica gel (6:1 hexane–diethyl ether): NMR δ 1.48 [s, 9 H, $C(CH_3)_3$], 2.43 (s, 3 H, SCH_3), 2.55 (s, 3 H, SCH_3), 4.15 (s, 2 H, NCH_2); ir (film) 1750, 1585 cm^{-1}; *m/e* 235 (M^+). Calcd for $C_9H_{17}NO_2S_2$: C, 45.92; H, 7.28; N, 5.95. Found: C, 45.57; H, 7.31; N, 5.91.

***tert*-Butyl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-acetate (10a).** A 50-ml round-bottom three-necked flask equipped with an addition funnel, magnetic stirrer, and gas inlet tube was dried and flushed with nitrogen. A solution of **9a** (2.35 g, 10 mmol) in 5 ml of methylene chloride was added to the flask along with 1.39 ml (1.01 g, 10 mmol) of triethylamine. The flask was immersed in a water bath at ca. 30 °C and a solution of 0.89 ml of azidoacetyl chloride in 5 ml of methylene chloride was added dropwise over 1–1.5 h. After the addition was completed, 0.42 ml of triethylamine was added, and then 0.27 ml of azidoacetyl chloride in 2 ml of methylene chloride was added over ca. 1 h. The solvent was evaporated under vacuum, and the residue was chromatographed from ca. 100 g of silica gel with 3:1 hexane–diethyl ether to give 1.13 g (36%) of the oily β-lactam **10a** along with 1.5 g of the imine **9a**: NMR δ 1.49 [s, 9 H, $C(CH_3)_3$], 2.23 (s, 6 H, SCH_3), 3.87 (apparent doublet 2 H, NCH_2), 4.80 (s, 1 H, N_3CH); ir (film) 2120, 1785, 1740 cm^{-1}.

Methyl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)acetate (10b). The method of preparation was similar to that used to prepare **10a**. Here, however, 2 equiv of triethylamine was present initially in solution with the imide **9b**. Upon complete addition of 1 equiv of azidoacetyl chloride, an additional 1 equiv of triethylamine was added to the reaction mixture and a further 1 equiv of azidoacetyl chloride in methylene chloride was added dropwise. Direct chromatography of the mixture afforded 32% recovered **9b** and 55% of the oily β-lactam **10b**: NMR δ 2.23 (s, 6 H, SCH_3), 3.78 (s, 3 H, OCH_3), 3.98 (apparent doublet, 2 H, NCH_2), 4.85 (s, 1 H, N_3CH); ir ($CHCl_3$) 2130, 1785, 1755 cm^{-1}.

Methyl 2-*S*-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-3-methylbutyrate (16a). L-Valine hydrochloride methyl ester[20] (76 g, 454 mmol) was condensed with carbon disulfide (27.3 ml, 453 mmol) and methyl iodide (28.3 ml, 454 mmol) in THF–water as described for **8b**. The yield of the oily butyrate **14** was 76%: NMR δ 1.00 [two doublets, 6 H, J = 6 Hz, $HC(CH_3)_2$], 2.37 [m, 1 H, $HC(CH_3)_2$], 2.63 (s, 3 H, SCH_3), 3.78 (s, 3 H, OCH_3), 5.27 (dd, 1 H, J = 6, J' = 5 Hz, HNCHCH), 7.63 (broad, 1 H, HN); ir (film) 1740 cm^{-1}; *m/e* 221 (M^+). Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.41; H, 6.83; N, 6.32. Found: C, 43.17; H, 6.88; N, 6.24.

The ester **14** (5.3 g, 24 mmol) along with 2.97 ml of methyl iodide were dissolved in 20 ml of THF under a nitrogen atmosphere in a three-necked, 250-ml flask. Sodium hydride (1.01 g of a 51% mineral oil suspension, 24 mmol) was added in small portions. Vigorous stirring of the mixture, coupled with slow addition of the sodium hydride, was necessary to control the foaming. After 5 min the solution was diluted with 100 ml of diethyl ether and the resulting mixture was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to an oil, which was distilled under vacuum (bp 94 °C, 0.5 mm) to give 4.06 g (72%) of the oily bismethylthioimine **15**: NMR δ 0.92 [two doublets, 6 H, J = 7 Hz, $HC(CH_3)_2$], 2.23 [m, 1 H, $HC(CH_3)_2$], 2.40 (s, 3 H, SCH_3), 2.52 (s, 3 H, SCH_3), 3.68 (s, 3 H, OCH_3), 4.15 (d, 1 H, J = 5.5 Hz, NCHCH); ir (film) 1745, 1582 cm^{-1}; *m/e* 192 ($M^+ - C_3H_7$), 188 ($M^+ - SCH_3$). Anal. Calcd for $C_9H_{17}NO_2S_2$: C, 45.92; H, 7.28; N, 5.95. Found: C, 46.01; H, 7.08; N, 5.73.

The imino ester **15** when treated with triethylamine–azidoacetyl chloride as in the preparations of β-lactams **10a** and **10b** gave only minor amounts of product. Reversal of the order of addition by first mixing **15** with azidoacetyl chloride in methylene chloride, followed by dropwise addition over ca. 1 h of a methylene chloride solution of triethylamine (1 equiv), produced the β-lactam **16a** in ca. 30% yield. The azide **16a** was sensitive to silica gel chromatography, but rapid chromatography using 2.5:1 hexane–diethyl ether gave an oily product with satisfactory spectral properties: NMR δ 0.95, 1.07 [two doublets, 6 H, J = 6.5 Hz, $HC(CH_3)_2$], 2.16, 2.19, 2.23, 2.25 (four singlets, 6 H, SCH_3), 2.69 [m, 1 H, $HC(CH_3)_2$], 3.45

(d, 1 H, J = 9.5 Hz, NCHCH), 3.76 (s, 3 H, OCH_3), 4.54, 4.65 [two singlets, 1 H (relative ratio ca. 2:1), N_3CH]; ir ($CHCl_3$) 2100, 1775, 1740 cm^{-1}.

Reduction and Acylation of 3-Azido-2-azetidones. The β-lactam **10a** (1 g, 3.15 mmol) was dissolved in 15 ml of methanol. Approximately 5 ml of a 22% ammonium sulfide solution was added. After 0.5 h 30 ml of a saturated solution of sodium chloride in water was added, and the resulting mixture was extracted with methylene chloride. After drying over Na_2SO_4, the methylene chloride solution was concentrated to ca. 10 ml. To this solution cooled to 0 °C were added 0.98 g (6.35 mmol) of phenylacetyl chloride and 0.5 g (6.35 mmol) of pyridine. The cooling bath was removed after 15 min and the solution was stirred at room temperature for 45 min. After washing with water, the methylene chloride layer was dried (Na_2SO_4) and evaporated to a residue which was crystallized from acetone–hexane to give 0.76 g (59%) of **7a**: mp 116–117 °C; NMR δ 1.46 [s, 9 H, $C(CH_3)_3$], 1.86 (s, 3 H, SCH_3), 2.63 (s, 3 H, SCH_3), 3.67 (s, 2 H, $C_6H_5CH_2$), 3.82 (s, 2 H, NCH_2), 5.61 (d, 1 H, J = 9.5 Hz, HNCH), 6.62 (broad doublet, 1 H, J = 9.5 Hz, HNCH), 7.33 (s, 5 H, C_6H_5); ir (KBr) 1790, 1735, 1670 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_4S_2$: C, 55.58; H, 6.38; N, 6.82. Found: C, 55.55; H, 6.25; N, 6.65. MS m/e 410 (M^+).

The β-lactams **7b** and **16b** were prepared in identical fashion, with the exception that phenoxyacetyl chloride was substituted for phenylacetyl chloride in the case of **7b**. The yield of the 3-phenoxyacetamidoazetidinone **7b** (mp 89.5–90 °C) was 35%: NMR δ 2.03 (s, 3 H, SCH_3), 2.28 (s, 3 H, SCH_3), 3.79 (s, 3 H, OCH_3), 4.00 (s, 2 H, NCH_2), 4.59 (s, 2 H, OCH_2), 5.70 (d, 1 H, J = 9.5 Hz, HNCH), 7.2 (m, 5 H, C_6H_5), 7.78 (broad doublet, 1 H, J = 9.5 Hz, HNCH); ir (KBr) 3350, 1775, 1750, 1685 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_5S_2$: C, 49.98; H, 5.24; N, 7.28. Found: C, 49.86; H, 5.12; N, 7.19. MS m/e 384 (M^+).

The yield of methyl 2-(3-phenylacetamido-4,4-dimethylthio-3-azetidinon-2-yl)-3-methylbutyrate (**16b**) from the azide **16a** was 45%, as a 2:1 mixture of diastereomers: NMR δ 1.15 [apparent triplet, 6 H, $CH(CH_3)_2$], 1.78, 1.90, 2.17, 2.2 (four singlets, 6 H, SCH_3), 2.62 [m, 1 H, $CH(CH_3)_2$], 3.43, 3.47 (two doublets, 1 H, J = 9 Hz, NCHCH), 3.63 (s, 2 H, $C_6H_5CH_2$), 3.68, 3.73 (two singlets, 3 H, OCH_3), 5.47 (d, 1 H, J = 9 Hz, HNCH), 6.77 (broad, 1 H, HNCH), 7.3 (s, 5 H, C_6H_5); ir ($CHCl_3$) 1775, 1745, 1685 cm^{-1}. MS m/e 363 ($M^+ - SCH_3$).

The purification of **16b** was complicated by its sensitivity to silica gel chromatography. A rearranged product **17** was obtained: NMR δ 1.02 [two doublets, 6 H, J = 6.5 Hz, $CH(CH_3)_2$], 2.14 (s, 3 H, SCH_3), ca. 2.2 [m, 1 H, $HC(CH_3)_2$], 2.25 (s, 3 H, SCH_3), 3.67 (s, 2 H, $C_6H_5CH_2$), 3.75 (s, 3 H, OCH_3), 4.66 (dd, 1 H, J_1 = 8, J_2 = 4 Hz, HNCHCH), 6.72 (broad, 1 H, HN), 7.33 (s, 5 H, C_6H_5), 7.62 (broad, 1 H, HN); ir ($CHCl_3$) 1725, 1655 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_4S_2$: C, 55.58; H, 6.38; N, 6.82. Found: C, 55.32; H, 6.46; N, 6.87.

Methyl 2-(3-Azido-4-methylthio-2-azetidinon-1-yl)acetate (27). Glycine (10 g, 133 mmol) was added to 37 ml of formic–acetic anhydride at 0 °C. After 1 min a precipitate formed. This was collected by filtration and was recrystallized from methanol to give 12.87 g (94%) of N-formylglycine, mp 140–150 °C dec. An ethereal solution of excess diazomethane at 0 °C was added to 7.5 g (72.8 mmol) of the N-formylglycine. Upon dissolution of the acid, the solution remained at 0 °C for 1 h. The solution was allowed to warm to room temperature and set aside until the yellow color of diazomethane had disappeared. The ether was decanted from an oily residue and was evaporated to give a crude product. This product was distilled under vacuum to give 6.1 g (72%) of methyl N-formylglycinate (bp 100 °C, 1 mm): NMR ($CDCl_3$) δ 3.75 (s, 3 H, OCH_3), 4.08 (d, 2 H, J = 5.5 Hz, $HNCH_2$), 7.08 (broad, 1 H, HN), 8.25 (s, 1 H, HCO); ir (film) 1750, 1675 cm^{-1}.

The methyl N-formylglycinate (2.5 g, 21.4 mmol) was dissolved in 25 ml of dry THF and to this solution was added 7 g (31.5 mmol) of phosphorus pentasulfide. After 0.5 h, the mixture was filtered and the yellow solid was washed with ethyl acetate. The combined filtrate and washings was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give an oil. This crude product was chromatographed from ca. 200 g of silica gel with chloroform. Methyl N-thioformylglycinate, mp 45–48 °C, was obtained in 54% yield (1.53 g): NMR δ 3.80 (s, 3 H, OCH_3), 4.45 (d, 2 H, J = 5 Hz); ir (KBr) 1730 cm^{-1}. Anal. Calcd for $C_4H_7NO_2S$: C, 36.07; H, 5.30; N, 10.52. Found: C, 35.86; H, 5.39; N, 10.22.

Methyl N-thioformylglycinate (5 g, 37.6 mmol), potassium carbonate (5.71 g, 41.4 mmol), and methyl iodide (2.8 ml, 45 mmol) were mixed with 10 ml of acetone under nitrogen and stirred at room temperature for 24 h. Water (50 ml) was added, and the mixture was extracted with diethyl ether. The ether extracts were combined and dried (Na_2SO_4). Evaporation of the ether and distillation afforded 2.1 g (38%) of an oil (bp 72 °C, 1.5 mm) whose spectral data were consistent with a mixture of *syn*- and *anti*-methyl 2-(methylthioimino)acetate diastereomers: NMR δ 2.40, 2.53 (two singlets, 3 H, SCH_3) 3.73, 3.78 (two singlets 3 H, OCH_3), 4.08, 4.27 (doublet and singlet, 2 H, J = 2 Hz, $SCH{=}NCH_2$), 8.30 (m, 1 H, HC=N); ir (film) 1755, 1605 cm^{-1}. MS m/e 147 (M^+).

The usual procedure of adding azidoacetyl chloride to the methylene chloride solution of imine and triethylamine was used, incorporating 2 equiv of the acid chloride and amine. Starting with 0.5 g of the methylthioimine, a 70% yield of the trans β-lactam **27** was realized: NMR δ 2.01 (s, 3 H, SCH_3), 3.72, 4.30 two doublets, 2 H, J = 18 Hz, NCH_2), 3.78 (s, 3 H, OCH_3), 4.57 (d, 1 H, J = 2 Hz, SCH), 4.78 (d, 1 H, J = 2 Hz, N_3CH); ir ($CHCl_3$) 1785, 1755 cm^{-1}. MS m/e 231 ($M^+ + 1$), 229 ($M^+ - 1$). The azide failed to give a satisfactory combustion analysis. The corresponding 3-phenylacetamido-2-azetidinone was prepared via reduction of the azide **27** with ammonium sulfide, followed by acetylation with phenylacetyl chloride, as in the preparation of **7a**. The methyl 2-(*trans*-3′-phenylacetamide-4′-methylthio-2′-azetidinon-1′-yl)acetate was purified using column and thin layer chromatography, and crystallized after prolonged standing at room temperature: mp 87.5–88.5 °C; NMR δ 2.08 (s, 3 H, $-SCH_3$), 3.58 (s, 2 H, $PhCH_2CONH$), 3.70 (s, 3 H, $-CO_2CH_3$), 3.71 (d, 1 H, J = 18 Hz, $-NCH_2CO_2CH_3$), 4.20 (d, 1 H, J = 18 Hz, $NCH_2CO_2CH_3$), 4.71 (d, 1 H, J = 2 Hz, $-CHSCH_3$), 4.92 (d of d, 1 H, J = 2, 8 Hz, O=CNHCH), 6.58 (broad signal, 1 H, $-CONH-$), 7.27 (s, 5 H, $-C_6H_5$); ir ($CHCl_3$) 1775, 1745, 1680 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.62; N, 8.68. Found: C, 55.76; H, 5.81; N, 8.28.

Rearrangement of *tert*-Butyl 2-(4,4-Dimethylthio-3-phenylacetamido-2-azetidinone-1-yl)acetate with Trifluoroacetic Acid. The β-lactam **7a** (0.25 g, 0.61 mmol) was stirred with 1 ml of anisole at 0 °C under nitrogen. Trifluoroacetic acid (6 ml) was added to this suspension. After 10 min the TFA–anisole solution was evaporated under vacuum. Sodium bicarbonate (0.25 g in 5 ml of water) and ethyl acetate (5 ml) were added to the residue. The ethyl acetate layer was discarded and the aqueous layer was washed with another 5-ml portion of ethyl acetate. The separated aqueous layer was acidified to ca. pH 4 with 3 N HCl. The precipitate which formed was collected and dried to give 0.14 g of **11**: mp 148–153 °C dec; NMR (acetone-d_6) δ 2.23 (s, 3 H, SCH_3), 2.30 (s, 3 H, SCH_3), 3.73 (s, 2 H, $C_6H_5CH_2$), ca. 4 (broad, 1 H, HN), 4.06 (d, 2 H, J = 5.5 Hz, $HNCH_2$), 7.37 (s, 5 H, C_6H_5), ca. 7.7 (broad, 2 H, HN and CO_2H); ir (KBr) 1735, 1635 cm^{-1}; MS m/e 336 ($M^+ - H_2O$). Anal. Calcd for $C_{15}H_{18}N_2O_4S_2$: C, 50.83; H, 5.11; H, 7.90. Found: C, 50.86; H, 5.05; N, 7.90.

Rearrangement of Methyl 2-(3-Phenoxyaceamido-4,4-dimethylthio-2-azetidinon-1-yl)acetate (7b) with Hog Pancreas Esterase. Five grams of pancreatin (grade II, Sigma) was stirred for 0.5 h at 0 °C in 25 ml of a 0.1 M NaCl–0.05 M $CaCl_2$ solution. The mixture was centrifuged 10 000g and the supernatant liquid was collected. The pH of the supernatant was adjusted to 7.0 using 0.1 N NaOH. To this solution was added 100 mg of **7b**. The mixture was sonicated to ensure complete dispersion. After stirring for 0.5 h at 0 °C, with periodic addition of 0.1 N NaOH to maintain pH at 7.0, the mixture was poured into 300 ml of acetone. The mixture was filtered through Celite and the filter cake was washed thoroughly with acetone. The filtrate was evaporated and the resulting solid was recrystallized from acetone–hexane to afford 70 mg of **12**: mp 135–138 °C; NMR δ 2.33 (s, 6 H, SCH_3), 3.78 (s, 3 H, OCH_3), 4.23 (d, 2 H, J = 5 Hz, $HNCH_2$), 4.58 (s, 2 H, OCH_2), 7.17 (m, 5 H, C_6H_5), 8.48 (broad singlet, 1 H, NH); ir 1740, 1700, 1665 cm^{-1}; MS m/e 384 (M^+). Calcd for $C_{16}H_{20}N_2O_5S_2$: C, 49.98; H, 5.24; N, 7.29. Found: C, 49.53; H, 5.09; N, 7.05.

***N*-Butyldimethylthioimine (18).** A mixture of n-butylamine (3.65 g, 50 mmol), carbon disulfide (3.8 g, 50 mmol), and potassium carbonate (6.9 g, 50 mmol) was stirred in 60 ml of water for 1 h. Methyl iodide (14.2 g, 100 mmol) was added and the mixture was stirred for an additional 3 h, at which time the mixture was extracted with diethyl ether. After drying (Na_2SO_4) and removal of the ether, there was obtained a crude oil. Chromatography of this crude product from ca. 150 g of silica gel with hexane afforded 3.2 g (32%) of the oily dimethylthiomine **18**: NMR δ ca. 1.34 (m, 7 H, $CH_2CH_2CH_3$), 2.35 (s, 3 H, SCH_3), 2.53 (s, 3 H, SCH_3), 3.40 (t, 2 H, J = 6 Hz, NCH_2CH_2); ir (film) 1579 cm^{-1}.

1-Butyl-3-azido-4,4-dimethylthio-2-azetidinone (19). The procedure was similar to that used in the preparation of β-lactams **10a** and **10b**. Using 0.354 g (2 mmol) of the imine **18** and ca. 2 equiv each of triethylamine and azidoacetyl chloride, a 92% yield

of β-lactam **19** was obtained as an oil after silica gel chromatography with hexene–diethyl ether (5:1): NMR δ 0.95 (t, 3 H, J = 6 Hz, CH_2CH_3), 1.52 (m, 4 H, CH_2CH_2), 2.20 (s, 3 H, SCH_3), 2.24 (s, 3 H, SCH_3), 3.21, (t, 2 H, J = 6 Hz, NCH_2CH_2), 4.69 (s, 1 H, N_3CH); ir ($CHCl_3$) 2117, 1763 cm^{-1}; MS m/e 213 ($M^+ - SCH_3$). Anal. Calcd for $C_9H_{16}N_4OS_2$: C, 41.51; H, 6.19; N, 21.52. Found: C, 41.22; H, 6.25; N, 21.22.

Benzhydryl 2-(Dimethylthioimino)-3-methyl-2-butenoate (22). Diphenyldiazomethane (0.5 g, 2.58 mmol) was added to a solution of 0.4 g (1.95 mmol) of acid **21a**[14] in 25 ml of benzene. The solution was heated at reflux for 80 min. Removal of the benzene and chromatography from ca. 40 g of silica gel with hexane–diethyl ether (8:1) afforded 0.623 g (86%) of the ester **21b.** Recrystallization from hexane afforded a solid: mp 99–102 °C; NMR δ 1.16 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.51 (s, 3 H, SCH_3), 4.70 (s, 1 H, NCH), 6.96 [s, 1 H, $(C_6H_5)_2CH$], 7.31 (broad singlet, 10 H, C_6H_5); ir ($CHCl_3$) 1745, 1540 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_2S_2$: C, 64.66; H, 5.70; N, 3.77. Found: C, 64.85; H, 5.58; N, 3.42.

The ester **21b** (0.464 g, 1.25 mmol) was dissolved in 5 ml of dry THF. This solution was added dropwise to a THF solution (10 ml) of potassium *tert*-butoxide (0.21 g, 1.88 mmol) at −65 °C. After 30 min, methyl iodide (0.205 g, 1.44 mmol) was added and the solution was warmed to room temperature. Water (ca. 40 ml) was added and the mixture was extracted with diethyl ether. After drying (Na_2SO_4) and removal of ether, 0.425 g (88%) of the oily dimethylthioimine **22** was obtained. A sample crystallized on standing to give a white solid: mp 34–35 °C; NMR δ 1.66 (s, 3 H, SCH_3), 2.11 (s, 3 H, SCH_3), 2.41 (s, 6 H, $=C-CH_3$), 6.87 [s, 1 H, $CH(C_6H_5)_2$], 7.29 (broad singlet, 10 H, C_6H_5); ir ($CHCl_3$) 1708, 1558 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_2S_2$: C, 65.42; H, 6.01; N, 3.63. Found: C, 65.20; H, 6.21; N, 3.56.

Benzhydryl 2-(3-Azido-4,4-dimethylthio-2-azetidinon-1-yl)-3-methyl-2-butenoate (23). To the imine **22** (0.423 g, 1.1 mmol) in 20 ml of methylene chloride was added 0.132 g of azidoacetyl chloride (1.1 mmol) over ca. 2 min at 5 °C under nitrogen. Triethylamine (0.111 g, 1.1 mmol) was added over 20 min. This order of addition was repeated until a total of 4 equiv of the acid chloride and amine had been added. The mixture was washed with water and dried over Na_2SO_4. The solution was concentrated to a small volume and some polar material was precipitated by the addition of diethyl ether. Filtration and removal of ether afforded a brown gum. This material was dissolved in acetonitrile and applied to a countercurrent distribution device[15] with heptane as the moving phase. In this manner 0.313 g (61%) of β-lactam **23** was obtained as an oil: NMR (C_6D_6) δ 1.60 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 1.78 (s, 3 H), 4.17 (s, 1 H, N_3CH), 7.07 (m, 11 H); ir ($CHCl_3$) 2117, 1771, 1716 cm^{-1}.

Reduction and Acylation of 23. The azide **23** (0.106 g, 0.23 mmol) in 8 ml of methanol was treated with 0.6 ml of a 22% ammonium sulfide solution at room temperature for 5 min. The reaction mixture was diluted with 20 ml of water and extracted with methylene chloride. The methylene chloride solution was dried over Na_2SO_4. The solvent was removed under vacuum and the residue was taken up in 10 ml of methylene chloride. To this solution was added 0.6 ml of triethylamine and 0.11 g (0.64 mmol) of phenoxyacetyl chloride at ca. 0 °C. After 20 min the mixture was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was dissolved in diethyl ether. Addition of hexane resulted in the precipitation of polar impurities. Removal of solvent under vacuum gave **25** as an oil (ca. 85% purity): NMR δ 1.79 (s, 3 H), 2.01 (s, 3 H), 2.06 (s, 3 H, 2.09 (s, 3 H), 4.56 (s, 2 H, OCH_2), 5.48 (d, 1 H, J = 9 Hz, HNCH), ca. 7.2 (m, 11 H); ir ($CHCl_3$) 1775, 1695 cm^{-1}.

Rearrangement of 25. A small sample (ca. 15 mg) of **25** was stirred with ca. 0.2 g of silica gel in 5 ml of diethyl ether for 3 h. The mixture was filtered and washed with ether. Removal of the ether and chromatography of the residue on a 20 × 20 cm, 0.5 mm silica gel GF plate afforded 7.5 mg of an oil whose spectral properties were consistent with **26.** Crystallization from acetone–hexane afforded a white solid: mp 174–176 °C; NMR δ 2.02 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 2.28 (s, 3 H), 4.48 (s, 2 H, OCH_2), ca. 7.3 (m, 11 H), 7.78 (broad singlet, 1 H, HN), 8.55 (broad singlet, 1 H, HN); ir 1705, 1685 cm^{-1}; MS m/e 409 [$M^+ - (C_6H_5)_2CH$]. Anal. Calcd for $C_{31}H_{32}N_2O_5S_2$: C, 64.56; H, 5.59; N, 4.86. Found: C, 64.43; H, 5.72; N, 4.64.

Hydrolysis of 7b. The lactam **7b** (35 mg, 0.091 mmol) was dissolved in 1 ml of methanol. To this solution was added 0.96 ml of 0.1 M aqueous lithium hydroxide and the mixture was stirred at room temperature until TLC analysis indicated virtually complete disappearance of **7b.** Water (5 ml) was added and the mixture was acidified with HCl. The mixture was extracted thoroughly with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and concentrated to a foam. Treatment of this solid with acetone–hexane gave 15 mg of **6b** as a white solid, mp 121–123 °C. A total of 9 mg of the starting ester **7b** was recovered from the acetone–hexane solution: NMR δ 2.03 (s, 3 H, SCH_3), 2.15 (s, 3 H, SCH_3), 4.01 (s, 2 H, NCH_2), 4.6 (s, 2 H, OCH_2), 5.69 (d, 1 H, J = 10 Hz, HNCH), 6.6 (s, 1 H, CO_2H), 6.9–7.5 (m, 5 H, C_6H_5), 7.74 (d, 1 H, J = 10 Hz, NH); ir ($CHCl_3$) 1765, 1720 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_5S_2$: C, 48.63; H, 4.90; N, 7.56. Found: C, 48.87; H, 5.12; N, 7.30.

The hydrolysis of **7b** was repeated using 391 mg of **7b.** The resulting acid was taken up in ca. 1 ml of ethyl acetate and this solution was added to ca. 3 ml of a saturated solution of sodium 2-ethylhexanoate in isopropyl alcohol. Addition of ca. 3 ml of diethyl ether gave a precipitate which was collected by filtration and was washed with additional diethyl ether. In this manner 60 mg of **29** was obtained as a light yellow, hydroscopic solid. NMR analysis indicated a purity of ca. 90%.

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Registry No.—**6b,** 58091-02-4; **7a,** 58091-03-5; **7b,** 58091-04-6; **8a,** 58091-05-7; **8b,** 58091-06-8; **9a,** 58091-07-9; **9b,** 58091-08-0; **10a,** 58091-09-1; **10b,** 58091-10-4; **11,** 58091-11-5; **12,** 58091-12-6; **14,** 58091-13-7; **15,** 58091-14-8; **16a** isomer 1, 58091-15-9; **16a** isomer 2, 58091-16-0; **16b** isomer 1, 58091-17-1; **16b** isomer 2, 58091-18-2; **17,** 58091-19-3; **18,** 54208-96-7; **19,** 58091-20-6; **21a,** 58091-21-7; **21b,** 58091-22-8; **22,** 58091-23-9; **23,** 58091-24-0; **25,** 58091-25-1; **26,** 58091-26-2; **27,** 58091-27-3; *tert*-butyl aminoacetate, 6456-74-2; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methyl glycinate hydrochloride, 5680-79-5; azidoacetyl chloride, 30426-58-5; L-valine hydrochloride methyl ester, 6306-52-1; phenylacetyl chloride, 103-80-0; phenoxyacetyl chloride, 701-99-5; glycine, 56-40-6; formic–acetic anhydride, 2258-42-6; *N*-formylglycine, 2491-15-8; methyl *N*-formylglycinate, 3152-54-9; phosphorus pentasulfide, 1314-80-3; methyl *N*-thioformylglycinate, 58091-28-4; *syn*-methyl 2-(methylthioimino)acetate, 58091-29-5; *anti*-methyl 2-(methylthioimino)acetate, 58091-30-8; methyl 2-(*trans*-3′-phenylacetamido-4′-methylthio-2′-azetidinon-1′-yl)acetate, 58091-31-9; trifluoroacetic acid, 76-05-1; hog pancreas esterase, 9001-08-5; *n*-butylamine, 109-73-9; diphenyldiazomethane, 883-40-9.

References and Notes

(1) Contribution No. 462 from the Syntex Institute of Organic Chemistry and No. 2 in the series Studies in β-Lactams.
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