solution was heated at 85–90 °C for a period of 2.5 h and then lyophilized to give crystalline crude alcohol which was recrystallized from EtOAc or acetone. Yields were generally in the range of 70–80%.

Data for trans S^* alcohol **16a**: mp 104–106 °C; IR (CH_2Cl_2) 2.71 and 2.87 (OH and NH), 5.65 (β-lactam and carbonate) 6.22 and 6.56 (nitro) μm; NMR ($CDCl_3$) δ 1.47 (d, J = 6.5 Hz, CH_3), 1.9 (m, CH_2CH_2OH), 2.63 (br s, OH), 3.20 (dd, $J_{6,8}$ = 4 Hz, $J_{5,6}$ = 2 Hz, H_6), 3.7 (m, H_5 and CH_2CH_2OH), 5.20 (m, partially hidden, H_8), 5.30 (s, CH_2Ar), 6.70 (br s, NH), 7.60 (d, J = 8.5 Hz, two aromatic protons meta to nitro), 8.27 (d, J = 8.5 Hz, two aromatic protons ortho to nitro); mass spectrum (silylated), m/e 554 (M^+, trisilyl), 482 (M^+, disilyl), 467, 270, 136. Anal. ($C_{15}H_{18}N_2O_7$) C, H, N.

Data for trans R^* alcohol **16b**: IR (CH_2Cl_2) 2.70 and 2.87 (OH and NH), 5.65 (β-lactam and carbonate), 6.20 and 6.55 (nitro) μm; NMR ($CDCl_3$) δ 1.47 (d, J = 6.5 Hz, CH_3), 1.9 (m, CH_2CH_2OH), 2.23 (br s, OH), 3.10 (dd, $J_{6,8}$ = 7 Hz, $J_{5,6}$ = 2 Hz, H_6), 3.80 (m, H_5 and CH_2CH_2OH), 5.2 (m, partially hidden, H_8), 5.27 (s, CH_2Ar), 6.53 (br s, NH), 7.57 (d, J = 8.5 Hz, two aromatic protons meta to nitro), 8.27 (d, J = 8.5 Hz, two aromatic protons ortho to nitro); mass spectrum (silylated), m/e 555 [$(M + 1)^+$, trisilyl],[17] 483 [$(M + 1)^+$, disilyl], 467, 270, 136.

Data for cis R^* alcohol **16c**: mp 150–151 °C; IR (Nujol mull) 3.05, 5.69 (β-lactam), 5.74 (carbonate), 6.19 and 6.55 (nitro) μm; 300-MHz NMR (Me_2CO-d_6) δ 1.43 (d, J = 6 Hz, CH_3), 1.9 (m, CH_2CH_2OH), 3.42 (dd, $J_{6,8} = J_{5,6}$ = 4.5 Hz, H_6), 3.66 (dd, J = 10 and 6 Hz, CH_2CH_2OH), 3.89 (ddd, J = 10, 6, and 4.5 Hz, H_5), 5.16 (qd, J = 6 and 4.5 Hz), 5.38 (AB q, J = 13.5 Hz), 7.28 (br s, NH), 7.76 (d, J = 8 Hz, two aromatic protons meta to nitro), 8.32 (d, J = 8 Hz, two aromatic protons ortho to nitro); mass spectrum, m/e 339 [$(M + 1)^+$],[17] 265, 136. Anal. ($C_{15}H_{18}N_2O_7$) C, H, N.

Acknowledgment. We thank Mr. H. Flynn for recording the mass spectra and the 300-MHz NMR spectra and Dr. C. Shunk for synthetic support. F.A.B. thanks Drs. F. DiNinno and R. W. Ratcliffe for helpful discussions during the course of this work.

Registry No. 5, 1515-76-0; (*E*)-**7**, 67314-41-4; (*Z*)-**7**, 67314-40-3; **8**, 67245-83-4; **9**, 65750-47-2; **10**, 65750-48-3; **11a**, 72690-80-3; **11b**, 72690-81-4; **11c**, 65794-44-7; **11d**, 65794-45-8; **12a**, 65794-51-6; **12b**, 65750-51-8; **13**, 65750-49-4; **14**, 65750-50-7; **15a**, 65794-41-4; **15b**, 65794-46-9; **15c**, 72690-82-5; **15d**, 72690-83-6; **16a**, 65794-42-5; **16b**, 65794-47-0; **16c**, 72690-84-7.

Supplementary Material Available: Table containing the final fractional coordinates and thermal parameters for **15d** (2 pages). Ordering information is given on any current masthead page.

Thienamycin Total Synthesis. 2. Model Studies—Synthesis of a Simple 2-(Alkylthio)carbapen-2-em

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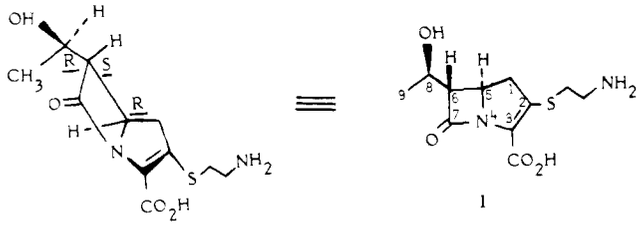
Received September 25, 1979

Model studies directed toward the total synthesis of (±)-thienamycin are described which have resulted in the preparation of the benzyl ester of (±)-2-(methylthio)carbapen-2-em-3-carboxylic acid (**2**). Azetidinone **3** was converted into thioenolether **24** via thioacetal **6**. Bromination of **24** followed by treatment with base afforded the key bicyclic intermediate **25**. Dehydrobromination, decarbalkoxylation, and isomerization of the double bond then yielded the desired model compound **2**. The synthesis of carbapenams **19a,b** (R = *t*-Bu and Bz) from azetidinone **11** is also described.

Thienamycin (**1**)[1] is a novel β-lactam antibiotic isolated from *Streptomyces cattleya*.[2] Its activity against *Pseudomonas* spp. and its resistance to bacterial β-lactamases are of particular interest.[2] Even more intriguing to an organic chemist is the challenge presented by the total synthesis of such a highly functionalized and unusual ring system.[3]



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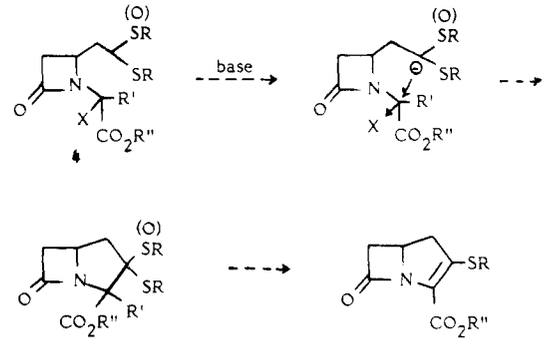
Scheme I

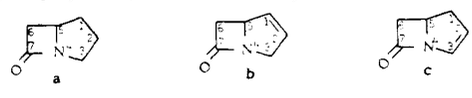


We felt that the total synthesis of (±)-thienamycin could conveniently be divided into three major synthetic objectives: (1) preparation of an azetidinone suitably sub-

(1) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).

(2) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, **32**, 1 (1978), and references therein.

(3) The numbering of the ring system adopted throughout this and the subsequent paper is based on assigning the terms carbapenam, carbapen-1-em, and carbapen-2-em to structures **a**, **b**, and **c**, respectively. This nomenclature is analogous to the penam and cepham nomenclature currently employed in β-lactam chemistry.



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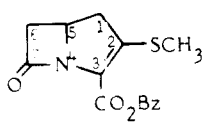
stituted at the C-4 position for subsequent elaboration of the second ring; (2) introduction of the hydroxyethyl side chain at the C-3 position; (3) elaboration of the resultant azetidinone to the properly functionalized carbapen-2-em.

The first two synthetic goals were accomplished as described in the preceding paper, part 1, of this series. While this chemistry was evolving, the methodology necessary to construct a 2-thioalkyl-substituted carbapen-2-em, a model system for thienamycin, was simultaneously developed. In this paper, we wish to describe the preparation of the benzyl ester of (±)-2-(methylthio)carbapen-2-em-3-carboxylic acid (**2**)[3]—a synthesis which, when coupled



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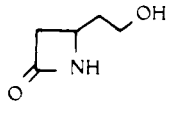
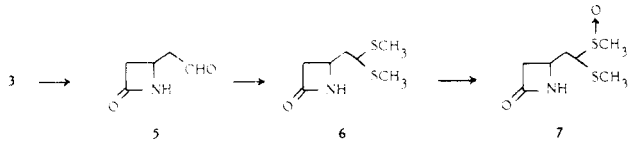


3

with the chemistry of part 1, led directly to the total synthesis of (±)-thienamycin and (±)-8-epithienamycin as described in the following paper, part 3, of this series.[4]

With 4-(2-hydroxyethyl)-2-azetidinone (**3**)[5] as a starting material, there are numerous conceivable methods to introduce the required functionalities and to ultimately construct the desired carbapenem. We chose to elaborate azetidinone **3** so that cyclization would entail C-2 to C-3 bond formation. That is, the original synthetic approach required the cyclization of a thioacetal or its monosulfoxide, **4** (X = Cl, R′ = H), as depicted in Scheme I.[6] If formation of the anion at the prospective C-2 position were followed by intramolecular alkylation, elimination of the alkylsulfenic acid would then give the desired carbapenem. Not unexpectedly, the incorporation of the necessary functionalities was an easy task in comparison to the difficulty encountered in closing to a bicyclic system.

Oxidation of **3** with CrO_3·py in acetonitrile in the presence of Celite[7] gave a solution of aldehyde **5** which was immediately treated with MeSH in the presence of BF_3·Et_2O to give thioacetal **6**. Treatment of **6** with $NaIO_4$

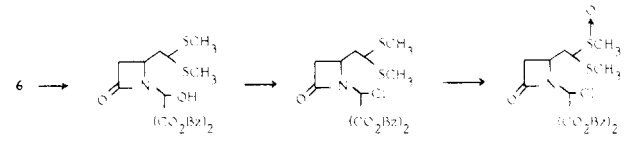


5 **6** **7**

in aqueous MeOH provided monosulfoxide **7** as a mixture of diastereomers. With the Woodward methodology,[8] such a thioacetal or its monosulfoxide could be condensed with a variety of glyoxylic esters to give hydroxyacetates **4** (X = OH, R′ = H) which upon treatment with $SOCl_2$/pyridine gave the desired chloroacetates **4** (X = Cl, R′ = H). All attempts to cyclize such chloroacetates gave discouragingly complex mixtures. These results were attributed at least in part to the presence of a number of other acidic protons in the molecule (namely, those α to the β-lactam carbonyl and geminal to the chlorine) which might have interfered with formation of the desired sulfur-stabilized anion. In addition, the chloroacetates were unstable to chromatography and therefore of questionable purity.

An attractive variant of Scheme I involved establishment of a chloromalonate rather than a chloroacetate substituent at nitrogen, thus effectively *blocking the proton* geminal to the chlorine by replacing it with a second carboalkoxy group, (Scheme I, **4**, X = Cl, R′ = CO_2R''). Subsequent to cyclization, a decarbalkoxylation followed by elimination of alkyl sulfide or sulfinate would then provide the desired carbapenem.

Thioacetal **6** could be condensed[8] with a variety of ketomalonates, in particular with dibenzyl ketomalonate, in boiling toluene to give hydroxymalonate **8**. Treatment

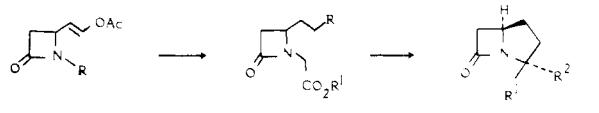


8 **9** **10**

with $SOCl_2$/pyridine in THF[8] gave chloromalonate **9**. Oxidation of **9** with *m*-chloroperbenzoic acid in Et_2O provided monosulfoxide **10**. Although chloromalonates **9** and **10** could be purified by thin-layer chromatography and structurally contained one less potentially interfering proton, cyclizations of such systems (Scheme I, X = Cl, R′ = CO_2R'') were also discouraging. Treatment with LDA or BuLi under a variety of reaction conditions generally resulted in the production of highly colored, complex mixtures yielding no isolable bicyclic materials.[9]

Reconsidering the proposed direction of cyclization, we investigated reversing the roles of the prospective C-2 and C-3 atoms by establishing a leaving group at the C-2 position and generating an anion at the C-3 position. The feasibility of such an approach was established by the preparation of carbapenams **19a,b** in the following manner.

Condensation[8] of enol acetate **11**[5] with *tert*-butyl glyoxylate[10] in boiling toluene gave the diastereomeric carbinols **12**. Treatment with $SOCl_2$/pyridine in THF[8] gave chloroacetate **13** which was immediately reduced with Zn in aqueous acetic acid[8] to yield **14**. Hydrogenation[11] of



11 R = H
12 R = CH(OH)CO_2*t*-Bu
13 R = CH(Cl)CO_2*t*-Bu
14 R = CH_2CO_2*t*-Bu

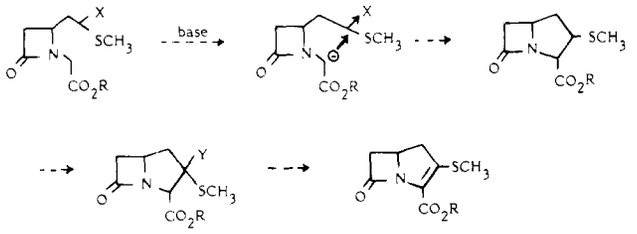
15 R = OAc; R^1 = *t*-Bu
16 R = OH; R^1 = *t*-Bu
17 R = OMs; R^1 = *t*-Bu
18 R = I; R^1 = *t*-Bu, H, or Bz

19a R^1 = H; R^2 = CO_2R; R = *t*-Bu or Bz
19b R^1 = CO_2R; R^2 = H; R = *t*-Bu or Bz

14 in the presence of 5% Pd/C in EtOAc gave saturated acetate **15**. Deacetylation[11] with NaOMe in MeOH provided alcohol **16**. Treatment with mesyl chloride and Et_3N in CH_2Cl_2 gave mesylate **17** which was converted to iodo compound **18** (R^1 = *t*-Bu) with NaI in acetone. Ring closure to carbapenams **19a,b** (R = *t*-Bu) was accomplished by treating **18** with NaH in DMF at room temperature for 5 h. The 300-MHz proton NMR spectrum of **19a,b** (R = *t*-Bu) indicated that the product was a mixture of diastereomers in approximately a 5:1 ratio.[12,13] The C-3

(4) The total synthesis of (±)-thienamycin has been briefly described by us in a communication: D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).
(5) Prepared in part 1 of this series.
(6) The synthetic utility of thioacetals and their monosulfoxides has been demonstrated by others: E. J. Corey and D. Seebach, *J. Org. Chem.*, 31, 4097 (1966); K. Ogura and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **45**, 2203 (1972); J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3267 (1973); K. Ogura, M. Yamashita, S. Furukawa, M. Suzuki, and G. Tsuchihashi, *ibid.*, 2767 (1975).
(7) Procedure developed by Dr. J. Fahey.
(8) R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972).
(9) The isolation of low yields of the corresponding hydrogen malonates indicated the occurrence of some halogen–metal interconversion during these attempted cyclizations.
(10) J. Blake, J. R. Tretter, G. J. Juhasz, W. Bonthrone, and H. Rapoport, *J. Am. Chem. Soc.*, **88**, 4061 (1966).
(11) Procedure developed in part 1 of this series.
(12) Minor peaks observable in the ^{13}C NMR of **19a,b** (R = *t*-Bu) also indicated the presence of the second diastereomer. See the Experimental Section.
(13) All compounds are racemic.

Scheme II

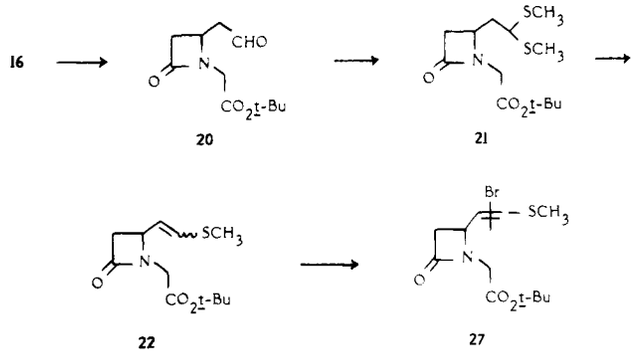


proton of the major diastereomer (**19a**, R = *t*-Bu) appeared as a triplet at δ 4.30 (J = 8 Hz) while the C-3 proton of the minor diastereomer (**19b**, R = *t*-Bu) appeared as a triplet at δ 3.78 (J = 5 Hz). By analogy to related systems, the major diastereomer has been assigned the thermodynamically more stable configuration[14] having the C-3 and C-5 protons trans to one another. The relative chemical shifts of the C-3 protons, as assigned above, are in accord with the trend previously observed by others for the C-3 protons of certain diastereomeric 1-oxapenams and penams.[14]

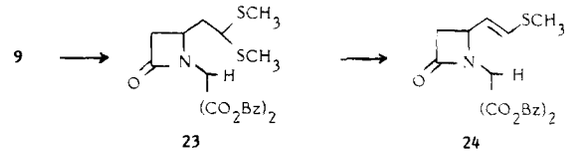
An attempt to deblock the **19a,b** (R = *t*-Bu) mixture by briefly treating it with trifluoroacetic acid resulted in destruction of the β-lactam. Similar treatment of iodo precursor **18** (R^1 = *t*-Bu), however, gave the expected free acid **18** (R^1 = H). Immediate reesterification with phenyldiazomethane provided **18** (R^1 = Bz). Cyclization as above gave carbapenams **19a,b** (R = Bz) as a mixture of diastereomers similar to the mixture produced when R = *t*-Bu. Although a nonacidic deblocking procedure now could be applied, the free acid remained elusive. Catalytic hydrogenolyses of **19a,b** (R = Bz) produced mixtures of decomposition products having little or no β-lactam-containing materials present although in one instance the crude product did exhibit some antibacterial activity. Probably the isolation of carbapenam-3-carboxylic acid (**19a,b**, R = H) is a difficult enterprise due to the compound's limited stability.

Returning to the primary synthetic objective, adaptation of the successful ring closure (**18** → **19a,b**) to a sulfur-substituted system required the cyclization of an α-halo sulfide as depicted in Scheme II. If anion generation were followed by intramolecular alkylation, a thioalkyl-substituted carbapenam would result. Conversion to the carbapen-2-em seemed possible since precedent exists for selective functionalization (e.g., chlorination,[15] Y = Cl) at the more highly substituted position α to sulfur. Elimination of the elements HY would then yield the desired carbapen-2-em.

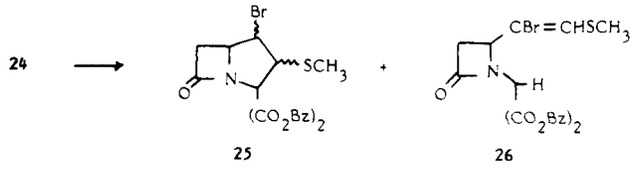
Since thioacetals have been cleaved with bromine to give α-bromo sulfides and the corresponding sulfenyl bromide,[16] α-halo sulfides were, in principle, readily available to us. Oxidation of alcohol **16** as described previously for **3**[7] gave aldehyde **20**. Treatment with MeSH in acetonitrile in the presence of $BF_3{\cdot}Et_2O$ gave thioacetal **21**. Addition of 1 equiv of bromine to an ether solution of **21** at 25 °C[16] quickly resulted, however, in complete destruction of the β-lactam. Since α-halo sulfides having β-hydrogens are known to eliminate hydrogen halide readily,[17] a situation which may have compromised the β-lactam, a one-pot procedure was developed for generation of the α-bromo sulfide and subsequent cyclization. Treatment of an ethereal solution of **21** with bromine at 0 °C was followed by addition of 1 equiv of cyclohexene to scavenge methanesulfenyl bromide. Addition of NaH and DMF to the resultant reaction mixture gave after 3 h at 0 °C an 89% yield of *E* and *Z* thioenolethers **22** rather than the desired carbapenam.



Expecting that the enhanced acidity of the malonate system might lead, under similar conditions, to cyclization rather than thioenolether formation, we reduced chloromalonate **9** with Zn in aqueous acetic acid[8] to give malonate **23**. However, even in the presence of the malonate system, bromination and base treatment in the above manner resulted in elimination rather than cyclization, thus producing the *E* thioenolether **24** in 87% yield.

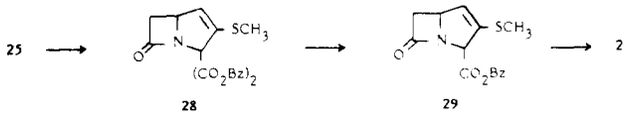


Only through further investigation into the synthetic possibilities presented by the availability of thioenolether **24** did a successful cyclization finally result. That is,



bromination of **24** in ether at 0 °C followed by exposure to NaH in DMF at room temperature gave bicyclic material **25** in 67% yield along with a 7% yield of elimination product **26**. Exposure of thioenolether **22** to the same conditions proved futile, however; cyclization did not compete successfully with elimination, and a 92% yield of a mixture of bromo olefins **27** was produced, thus suggesting that the presence of the malonate system was essential to ensure a successful ring closure.

The bromo substituent on **25** provided a useful handle for the introduction of the required unsaturation and completion of the model work. Dehydrobromination of **25** with DBU in Me_2SO[18] gave the unsaturated diester **28**.[19]

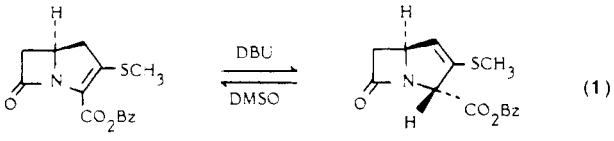


Decarbalkoxylation was achieved by heating **28** in collidine at 120 °C in the presence of LiI[20] for 30 min to give carbapen-1-em **29**. Failure to observe any conjugated ester

(14) A. G. Brown, D. F. Corbett, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 359 (1977), and references therein.
(15) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).
(16) M. L. Wolfrom, H. G. Garg, and D. Horton, *J. Org. Chem.*, **29**, 3280 (1964).
(17) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).
(18) H. Oediger and Fr. Möller, *Angew. Chem., Int. Ed. Engl.*, **6**, 76 (1967).
(19) Dehydrobromination of **25** with AgF in pyridine was later found to provide **28** in even better yield. See the Experimental Section.
(20) J. McMurry, *Org. React.*, **24**, 187 (1976).

2 as a product of this decarbalkoxylation was somewhat surprising and will be discussed later. Partial isomerization of the double bond was accomplished by brief treatment of **29** with a slight excess of DBU in Me_2SO. After 15 min, thin-layer chromatography indicated the presence of starting material and a slightly more polar material. Although the new, more polar material was destroyed if an aqueous workup was used, preparative thin-layer chromatography of the entire reaction mixture afforded a 25% isolated yield of the elusive carbapen-2-em **2** as well as a 25% recovery of the starting carbapen-1-em **29**.

As a result of the double-bond isomerization procedure developed above, determination of the stereochemistry at C-3 relative to C-5 in carbapen-1-em **29** became possible. The 60-MHz proton NMR of **29** suggested that only one pair of enantiomers was present since only one C-3 proton at δ 5.03 was observable, appearing as a doublet of doublets and exhibiting allylic ($J_{1,3}$ = 1.5 Hz) and homoallylic ($J_{3,5}$ = 3 Hz) coupling. When a chromatographically pure sample of carbapen-2-em **2** was reexposed to DBU in Me_2SO, the same mixture of Δ^1 and Δ^2 materials resulted as had been originally produced from carbapen-1-em **29**. This indicated that the double bond isomerization was an equilibrium process as represented by eq 1.[13] The car-

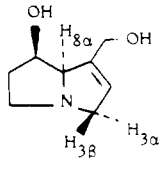


(1)

2 **29**

bapen-1-em produced in this manner was identical with **29** in all respects (IR, ^1H NMR, TLC). Since such equilibrium conditions should produce the thermodynamically more stable relative configuration at C-3,[14] **29** was assigned the relative stereochemisty depicted in eq 1. This is the C-3 configuration natural to the penicillins[21] and analogous to the C-4 configuration of Δ^2-cephalosporins.[22]

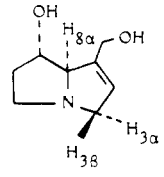
Additional evidence for the proposed stereochemical assignment was provided by comparison[23] of the homoallylic coupling constants observed in the pyrrolizidine alkaloids retronecine (**30**) and heliotridine (**31**)[24] with the



30

$J_{3\alpha,8\alpha}$ = 5.4 Hz

$J_{3\beta,8\alpha}$ = 3.5 Hz



31

$J_{3\alpha,8\alpha}$ = 4.6 Hz

$J_{3\beta,8\alpha}$ = 2.0 Hz

homoallylic coupling observed in **29**. The couplings between the 3α and 8α protons of **30** and **31**, 5.4 and 4.6 Hz, respectively, are much larger than the 3-Hz homoallylic coupling in **29**.[25] On the other hand, the comparable size of the coupling between the 3β and 8α protons of **30** and **31**, 3.5 and 2.0 Hz, respectively, suggests a similar stereochemical relationship exists between the C-3 and C-5 protons of **29**.

That none of carbapen-2-em **2** had been produced during the decarbalkoxylation of diester **28** remained puzzling especially in light of the isolation from the reaction of the carbapen-1-em having the thermodynamically more stable C-3 configuration. It was at first suspected that any **2** produced might have been destroyed during the subsequent aqueous workup. As noted previously, the instability of **2** to a similar workup had been observed during our first attempts at double-bond isomerization. Thin-layer chromatography of the crude decarbalkoxylation reaction directly after removal of the collidine in vacuo, however, showed the absence of any carbapen-2-em **2**. The carbapen-1-em **29** and starting diester **28** were, however, readily observable. It was subsequently discovered that **2** is unstable to the decarbalkoxylation conditions themselves, and complete destruction of the β-lactam results within the 30-min reaction time.

Although a one-step conversion of **28** to **2** was therefore not feasible under these conditions, with the development of the DBU-mediated double-bond isomerization of **29** to **2**, we had completed the synthesis of a simple 2-(alkylthio)carbapen-2-em. The application of this methodology to the total synthesis of (±)-thienamycin and (±)-8-epithienamycin is described in part 3 of this series.

Experimental Section

General Methods. Pyridine was distilled from powdered KOH and Et_3N from NaOH. Collidine (sym) was distilled in vacuo from powdered KOH. DBU was distilled in vacuo. $SOCl_2$ was distilled just prior to use. $BF_3{\cdot}Et_2O$ was purified according to Fieser and Fieser.[26] THF was freshly distilled from $LiAlH_4$. Me_2SO was distilled in vacuo from CaH_2. DMF was stirred overnight with anhydrous $CaSO_4$ and distilled in vacuo. In instances where anhydrous conditions were required, solvents not mentioned above were sieve dried. CrO_3 was dried in vacuo over P_2O_5. LiI was similarly dried at 60–100 °C.

For analytical purposes, compounds were visualized on thin-layer chromatography (TLC) under UV light, by staining with I_2, or by spraying with 1% ceric sulfate in 10% H_2SO_4 followed by charring using Analtech silica gel GF plates (10 × 2.5 cm). Preparative thin-layer chromatography (preparative TLC) was performed on 1000 μm Analtech silica gel GF plates. Products were visualized under UV light, and bands of interest were immediately scraped into the extracting solvent (EtOAc). Column chromatography was performed on Baker silica gel (60–200 mesh). Anhydrous $MgSO_4$ was used as a drying agent. Concentration, when indicated in the subsequent experiments, refers to concentration under a stream of N_2 followed by pumping under high vacuum without heating. As a general practice, β-lactams were refrigerated if stored for any length of time.

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. With Me_4Si as an internal standard, ^1H NMR spectra were recorded on a Varian T-60 spectrometer unless otherwise noted, in which case a Varian SC-300 spectrometer was used. Mass spectra were obtained on an LKB Model 9000 spectrometer. ^{13}C NMR spectra were obtained on Varian CFT-20 and XL-100A spectrometers, and chemical shifts are reported in parts per million downfield from Me_4Si. All reported elemental analyses are within ±0.4% of the calculated values.

4-(2,2-Bis(methylthio)ethyl)-2-azetidinone (6) via 4-(2-Oxoethyl)-2-azetidinone (5). Chromium trioxide (2.77 g, 27.7 mmol) was added with stirring to a solution of pyridine (4.47 mL, 56 mmol) in 430 mL of CH_3CN. The flask was stoppered with a drying tube containing Drierite, and stirring was continued for 15 min. Celite (14 g) was added to the stirred orange-red solution,

(21) D. Crowfoot, C. W. Bunn, B. W. Rogers-Low, and A. Turner-Jones in "The Chemistry of Penicillin", H. T. Clarke, J. R. Johnston, and R. Robinson, Eds., Princeton University Press, Princeton, NJ, 1949, p 310.

(22) E. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, 11, 933 (1968).

(23) Comparison suggested by Dr. R. Ratcliffe.

(24) C. C. J. Culvenor, M. L. Heffernan, and W. G. Woods, *Aust. J. Chem.*, 18, 1605 (1965).

(25) The authors of ref 24 have attributed these unusually large homoallylic couplings to the additivity of the π-orbital, homoallylic interaction with a direct cross-ring interaction between the 3α and 8α protons. The additional effect of the long-range coupling is due to the particular arrangement in space of the 3α and 8α protons.

(26) M. Fieser and L. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 70.

followed in a few minutes by a solution of 4-(2-hydroxyethyl)-2-azetidinone (3; 2 g, 17.4 mmol) in 60 mL of CH_3CN. After 30 min, $NaHSO_3$ (6.9 g, 66.3 mmol) was added, and stirring was continued for an additional 5 min. Filtration of the reaction mixture through a bed of silica gel and anhydrous $MgSO_4$ (80 g, 1:1), followed by thorough washing of the filter bed with CH_3CN (6 × 50 mL), gave a dark filtrate which was concentrated under a stream of N_2 to a volume of ca. 120 mL. With stirring at 0 °C, the filtrate containing crude **5** was treated with MeSH (ca. 90 mL, 1.63 mmol, condensed in a dry ice/acetone chilled flask and decanted from precipitated impurities) followed by BF_3·Et_2O (5.9 mL, 46.7 mmol). After stirring for 2 h at 0 °C under N_2, the reaction mixture was poured into a vigorously stirred cold mixture of K_2HPO_4 (50.5 g, 290 mmol), H_2O, and Et_2O. After phase separation, the aqueous layer was reextracted with Et_2O (3×). The combined organic layers were washed with brine, dried, filtered, and concentrated to give 1.6 g of crude **6**. Chromatography on silica gel (50 g, eluting with 0–5% EtOAc/$CHCl_3$) gave 1.49 g of off-white crystals. Slurrying in a few milliliters of Et_2O, followed by filtration, gave 1.29 g of **6** (40%) as a white crystalline material. Recrystallization from Et_2O gave an analytical sample: mp 70–73 °C; IR ($CHCl_3$) 5.69 μm; NMR ($CDCl_3$) δ 2.12 (s and m, SCH_3's and side chain CH_2), 2.61 (ddd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, J_{NH} = 1 Hz, H_3), 3.17 (ddd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, J_{NH} = 2 Hz, H_3), 3.71 (t, J = 7 Hz, SCHS), 3.92 (m, H_4), 6.71 (br, NH). Anal. ($C_7H_{13}NOS_2$) C, H, N, S.

4-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-2-azetidinone (7). A solution of $NaIO_4$ (239 mg, 1.12 mmol) in 2 mL of H_2O was added dropwise to a stirred solution of **6** (200 mg, 1.05 mmol) in 8 mL of MeOH at 0 °C. After being stirred under N_2 for 4 h at room temperature, the reaction mixture was filtered. The solids were washed one time with MeOH (8 mL) and then repeatedly with CH_2Cl_2. The filtrate was concentrated to give 241 mg of crude **7**. Chromatography on silica gel (12 g, eluting with 0–4% MeOH/$CHCl_3$) provided 199 mg of **7** (92%) as a mixture of diastereomeric sulfoxides: IR ($CHCl_3$) 5.69 μm; NMR (300 MHz, $CDCl_3$) δ 1.76–2.64 (m, side chain methylenes), 2.20 and 2.21 (2 s, CH_3S of two major diastereomers), 2.32 and 2.33 (2 s, CH_3S of two minor diastereomers), 2.58 and 2.60 (2 s, CH_3S=O of two minor diastereomers), 2.72–2.82 (partially buried m, H_3's trans to H_4's), 2.77 and 2.78 (2 s, CH_3S=O of two major diastereomers), 3.16–3.27 (m, H_3's cis to H_4's), 3.48–3.70 (m, SCHS=O), 3.87–4.02 (m, H_4's), 6.28–6.70 (br, NH's); mass spectrum, m/e 143 (loss of methanesulfenic acid), 100.

Dibenzyl 2-[2,2-Bis(methylthio)ethyl]-α-hydroxy-4-oxo-1-azetidinemalonate (8). A freshly prepared solution of phenyldiazomethane (prepared from 6.5 g of azibenzil[27]) in 150 mL of Et_2O was added with stirring to a solution of oxomalonic acid monohydrate (1.0 g, 7.35 mmol) in 50 mL of EtOAc at 0 °C. After 2.5 h the yellow solution was concentrated with mild heating on a rotary evaporator to half the volume, dried over anhydrous Na_2SO_4, filtered, and concentrated as above to a yellow oil. To this crude dibenzyl ketomalonate in 50 mL of toluene was added **6** (1.29 g, 6.75 mmol). The solution was heated in an oil bath until a third of the toluene had boiled off. The toluene was replaced and the azeo drying process repeated three more times. The solution was then allowed to reflux under N_2 for 2 h. Concentration then provided 5 g of crude **8**. TLC (10% EtOAc/$CHCl_3$) indicated the presence of a less polar product (R_f ca. 0.54), starting material (R_f ca. 0.29), and materials derived from the excess crude dibenzyl ketomalonate. Column chromatography on silica gel (150 g, eluting with 0–1% EtOAc/$CHCl_3$) gave a waxy white solid. Slurrying in a few milliliters of Et_2O followed by filtration provided 1.32 g of **8** as a white crystalline material. Preparative TLC (10% EtOAc/$CHCl_3$) of the filtrate from above and column fractions still contaminated with impurities gave material which upon Et_2O treatment as above provided 0.24 g of additional **8** (47%). Recrystallization from Et_2O gave an analytical sample: mp 93–95 °C; IR (CCl_4) 5.70 μm; NMR ($CDCl_3$) δ 2.06 (2 s, SCH_3's), 2.18 (m, side chain CH_2), 2.65 (dd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, H_3), 3.16 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.62 (t, J = 8 Hz, SCHS), 4.44 (m, β-lactam methine proton), 4.97 (s, OH), 5.16 and 5.20 (2 s, CH_2Ph's), 7.28 (br s, Ph's); mass spectrum, m/e 489 (M^+), 442, 354. Anal. ($C_{24}H_{27}NO_6S_2$) C, H, N, S.

Dibenzyl 2-[2,2-Bis(methylthio)ethyl]-4-oxo-1-azetidinemalonate (23) via Chloromalonate 9. Thionyl chloride (438 mg, 3.68 mmol) in 1 mL of THF was added dropwise to a stirred solution of **8** (1.5 g, 3.07 mmol) and pyridine (0.3 mL, 3.73 mmol) in 35 mL of THF at −20 °C. The reaction mixture was stirred under N_2 for 5 min at −20 °C, 0.5 h at 0 °C, and finally 1 h at 25 °C. Under N_2, the pyridine hydrochloride was filtered off and washed twice with benzene. The combined filtrate and washings were concentrated to a yellow oil with a small amount of pyridine hydrochloride still present. The oil was dissolved in a small volume of benzene, dried, filtered under N_2, and concentrated to provide crude chloromalonate **9** as a clear yellow oil. The crude chloromalonate was placed in an ice bath, and 50 mL cold 9:1 HOAc/H_2O was added. With swirling, Zn powder (2.1 g, 32.1 mmol) was immediately added. The reaction mixture was stirred vigorously for 15 min at 0 °C, followed by 30 min at room temperature. The inorganics were filtered and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated to a yellow oil which was partitioned between CH_2Cl_2 and brine. After phase separation, the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to give 1.5 g of crude **23**. Chromatography on silica gel (75 g, 100% $CHCl_3$) gave 876 mg of **23** as an oil. Preparative TLC (10% EtOAc/$CHCl_3$) of column fractions which were still impure provided 295 mg of additional **23** (81%): IR (CCl_4) 5.69 μm (br); NMR ($CDCl_3$) δ 1.99 and 2.03 (2 s, SCH_3's), 2.07 (m, side chain CH_2), 2.68 (dd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, H_3), 3.17 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.52 (dd, J = 7.5 and 7 Hz, SCHS), 4.23 (m, β-lactam methine proton), 5.19 (br s, CH_2Ph's), 5.27 (s, $CH(CO_2CH_2Ph)_2$), 7.30 (br s, Ph's); mass spectrum, m/e 473 (M^+), 427, 382, 378.

Isolation of Dibenzyl 2-[2,2-Bis(methylthio)ethyl]-α-chloro-4-oxo-1-azetidinemalonate (9). The conversion of **8** (88 mg, 0.18 mmol) to **9** was performed as described above. Immediate preparative TLC (30% acetone/hexane) of the benzene solution containing the crude chloromalonate provided 52 mg of **9** (57%) as an oil: IR (CCl_4) 5.62, 5.69 μm; NMR ($CDCl_3$) δ 2.07 and 2.08 (2 s, SCH_3's), 1.90–2.67 (m, side chain CH_2), 2.70 (dd, J_{gem} = 14 Hz, J_{trans} = 3 Hz, H_3), 3.21 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.59 (dd, J = 8 and 6 Hz, SCHS), 4.56 (m, β-lactam methine proton), 5.17 (s, CH_2Ph's), 7.22 (br s, Ph's).

Dibenzyl α-Chloro-2-[2-(methylsulfinyl)-2-(methylthio)-ethyl]-4-oxo-1-azetidinemalonate (10). A solution of *m*-chloroperbenzoic acid (22.7 mg, 85% purity, 0.11 mmol) in 1.5 mL of Et_2O was added dropwise to a stirred solution of **9** (50 mg, 0.099 mmol) in 1.5 mL of Et_2O at −78 °C. Upon completion of the addition, the reaction mixture was stirred under N_2 at −78 °C for 5 min and then at room temperature for 2 h. The colorless solution was then cooled to 0 °C, and an excess of diazomethane in ether was added, thus facilitating the subsequent chromatographic purification by converting *m*-chlorobenzoic acid into its less polar methyl ester. After 5 min at 0 °C, the reaction mixture was concentrated. The residue was dissolved in $CHCl_3$, and preparative TLC (50% acetone/hexane) provided 33 mg of **10** (63%) as an oil: IR (CCl_4) 5.61, 5.69 μm; NMR ($CDCl_3$) δ 2.19 (s, SCH_3), 2.61 (m, side chain CH_2), 2.71 (s, CH_3S=O), 2.75 (dd, partially buried, J_{gem} = 14 Hz, J_{trans} = 3 Hz, H_3), 3.25 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.35 (t, J = 7 Hz, SCHS=O), 4.75 (m, β-lactam methine proton), 5.22 (s, CH_2Ph's), 7.28 (br s, Ph's).

***tert*-Butyl 2-(2-Acetoxyvinyl)-α-hydroxy-4-oxo-1-azetidineacetate (12).** A solution of crude *tert*-butyl glyoxylate[10] (2.0 g, 15.4 mmol) in 25 mL of toluene was dried by distilling off some of the toluene (ca. 5 mL). Additional toluene (5 mL) and 4-(2-acetoxyvinyl)-2-azetidinone (**11**,[5] 1.0 g, 6.45 mmol) were added. After the distillation of 5 mL of toluene, refluxing under N_2 was continued for 2 h. Concentration of the reaction mixture provided crude **12**. TLC (20% EtOAc/$CHCl_3$) indicated the presence of a new material with an R_f between those of **11** and *tert*-butyl glyoxylate. Dry column chromatography on silica gel H (according to Stahl, Type 60, EM Reagents) (300 g, eluting with 20% EtOAc/$CHCl_3$) provided 1.2 g of **12** (65%) as a mixture of diastereomeric carbinols: NMR ($CDCl_3$) δ 1.48 and 1.53 (2 s, *tert*-butyls), 2.10 and 2.15 (2 s, OAc's), 2.70 and 2.73 (2 dd, both having J_{gem} = 15 Hz, J_{trans} = 2 Hz, H_3's), 3.25 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3's), 4.27 (m, β-lactam methine proton and OH's), 5.07 and 5.28

(27) P. Yates and B. L. Shapiro, *J. Org. Chem.*, **23**, 759 (1958).

(2 br d partially buried, CHOH's), 5.33 and 5.55 (2 dd, J = 10 and 8 Hz, J = 10 and 7 Hz, CH=CHOAc's), 7.38 and 7.40 (2 d, both having J = 10 Hz, CH=CHOAc's).

***tert*-Butyl 2-(2-Acetoxyvinyl)-4-oxo-1-azetidineacetate (14) via *tert*-Butyl 2-(2-Acetoxyvinyl)-α-chloro-4-oxo-1-azetidineacetate (13).** A toluene solution of crude carbinol **12** [prepared as above from 11 (5 g, 32.3 mmol) and *tert*-butyl glyoxylate (7.42 g, 57.1 mmol)] was dried, filtered, and concentrated under a stream of N_2. The residue was dissolved in 150 mL of THF and cooled to −20 °C under N_2. With stirring, pyridine (2.9 mL, 36 mmol) was added followed by the dropwise addition of $SOCl_2$ (2.58 mL, 35.5 mmol) in 3 mL of THF. The reaction mixture was stirred for 5 min at −20 °C, for 0.5 h at 0 °C, and finally for 1 h at room temperature. After workup (as in the preparation of crude **9**), crude chloroacetate **13** was dissolved in 15 mL of THF. The solution was added to a stirred mixture of Zn powder (101 g, 1.55 mmol) in 150 mL of cold 9:1 HOAc/H_2O. The reaction mixture was vigorously stirred for 15 min at 0 °C followed by 45 min at room temperature. Workup (as in the preparation of crude **23**) gave 8.6 g of crude **14**. Chromatography on silica gel (270 g, eluting with $CHCl_3$) provided 6.64 g of **14** (76%) as a white solid. Recrystallization from Et_2O gave an analytical sample: mp 82–85 °C; IR (CCl_4) 5.67, 5.75 μm; NMR ($CDCl_3$) δ 1.48 (s, *tert*-butyl), 2.13 (s, OAc), 2.72 (dd, J_{gem} = 15 Hz, J_{trans} = 2 Hz, H_3), 3.28 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.77 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu), 4.25 (m, β-lactam methine proton), 5.40 (dd, J = 12 and 10 Hz, CH=CHOAc), 7.37 (d, J = 12 Hz, CH=CHOAc). Anal. ($C_{13}H_{19}NO_5$) C, H, N.

***tert*-Butyl 2-(2-Acetoxyethyl)-4-oxo-1-azetidineacetate (15).** A solution of **14** (6.02 g, 22.4 mmol) in 120 mL of EtOAc was hydrogenated in the presence of 5% Pd/C (750 mg) on a Parr shaker for 1.5 h under 45 psi of H_2. The reaction mixture was filtered through Celite which was washed well with additional EtOAc. Concentration of the filtrate provided 5.96 g of **15** (98%) as a white crystalline solid. Recrystallization from Et_2O/petroleum ether gave an analytical sample: mp 39–40 °C; IR (CCl_4) 5.66, 5.73 μm; NMR ($CDCl_3$) δ 1.48 (s, *tert*-butyl), 2.05 (s, OAc), 1.70–2.37 (m, CH_2CH_2OAc), 2.68 (dd, J_{gem} = 15 Hz, J_{trans} = 2.5 Hz, H_3), 3.18 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.87 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu), 3.93 (partially buried m, β-lactam methine proton), 4.13 (t, J = 6 Hz, CH_2OAc); mass spectrum, m/e 271 (M^+), 243, 215, 198. Anal. ($C_{13}H_{21}NO_5$) C, H, N.

***tert*-Butyl 2-(2-Hydroxyethyl)-4-oxo-1-azetidineacetate (16).** To a solution of **15** (5.59 g, 20.6 mmol) in 50 mL of MeOH at 0 °C under N_2 with stirring was added NaOMe in MeOH (6.1 mL of 0.92 M NaOMe, 5.6 mmol). After being stirred for 1 h at 0 °C, the reaction was quenced with glacial CH_3CO_2H (1 mL) and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O. After phase separation, the aqueous layer was reextracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried, filtered, and concentrated to give 4.5 g of crude **16**. Chromatography on silica gel (130 g, eluting with 0–2.5% MeOH/$CHCl_3$) provided 3.64 g of **16** (76%) as an oil: IR (CCl_4) 5.70, 5.77 μm; NMR ($CDCl_3$) δ 1.40 (s, *tert*-butyl), 1.68–2.10 (m, CH_2CH_2OH), 2.13 (br t, J = 4 Hz, OH), 2.65 (dd, J_{gem} = 15 Hz, J_{trans} = 2.5 Hz, H_3), 3.13 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.75 (br m, CH_2CH_2OH), 3.88 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu) [β-lactam methine proton buried in CH_2OH/CH_2CO_2-*t*-Bu area; addition of D_2O causes the following changes: disappearance of br t at 2.13 (OH), 3.65 (sharp t, J = 6 Hz, CH_2OH), 3.82 (partially buried m, β-lactam methine proton)]; mass spectrum, m/e 229 (M^+), 201, 173, 128.

***tert*-Butyl 2-[2-[(Methanesulfonyl)oxy]ethyl]-4-oxo-1-azetidineacetate (17).** To **16** (210 mg, 0.92 mmol) in 3 mL of CH_2Cl_2 with stirring at 0 °C under N_2 was added Et_3N (0.14 mL, 1 mmol) followed by a solution of MsCl (114 mg, 1 mmol) in 1.1 mL of CH_2Cl_2. The reaction mixture was stirred at 0 °C for 1 h and then poured into a mixture of 1 M K_2HPO_4 (1 mL), H_2O, and CH_2Cl_2. After phase separation, the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried, filtered, and concentrated to give 278 mg of crude **17**. Column chromatography on silica gel (10 g, eluting with $CHCl_3$) provided 264 mg of **17** (94%) as an oil: IR (CCl_4) 5.64, 5.73 μm; NMR ($CDCl_3$) δ 1.48 (s, *tert*-butyl), 2.17 (m, CH_2CH_2OMs), 2.72 (dd, J_{gem} = 14 Hz, J_{trans} = 3 Hz, H_3), 3.03 (s, SO_2CH_3), 3.25 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.90 (midpoint of 2 d, J = 18 Hz, CH_2CO-*t*-Bu), 3.83–4.08 (m, β-lactam methine proton), 4.32 (t, J = 6 Hz, CH_2OMs); mass spectrum, m/e 307 (M^+), 251, 206.

***tert*-Butyl 2-(2-Iodoethyl)-4-oxo-1-azetidineacetate (18).** A mixture of **17** (75 mg, 0.244 mmol) and NaI (85 mg, 0.57 mmol) in 2 mL of acetone was stirred under N_2 at room temperature for 15 h. The reaction was filtered, and the insoluble materials were washed well with CH_2Cl_2. The combined filtrate and washings were concentrated, and the residue was partitioned between CH_2Cl_2 and H_2O. After phase separation, the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were washed with 5% $Na_2S_2O_3$ and then with brine. The organic layer was dried, filtered, and concentrated to give 78 mg of crude **18**. Preparative TLC (15% EtOAc/$CHCl_3$) provided 71 mg of *tert*-butyl ester **18** (86%) as a white crystalline solid. Recrystallization from hexane gave an analytical sample: mp 67–68 °C; IR (CCl_4) 5.65, 5.73 μm; NMR ($CDCl_3$) δ 1.50 (s, *tert*-butyl), 1.88–2.60 (m, CH_2CH_2I), 2.68 (dd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, H_3), 3.17 (t, J = 7 Hz, CH_2I), 3.22 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.88 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu), 3.77–4.10 (m, β-lactam methine proton); mass spectrum, m/e 339 (M^+), 283, 238. Anal. ($C_{11}H_{18}NIO_3$) C, H, N.

***tert*-Butyl Carbapenam-3-carboxylate (19a,b).** Sodium hydride (57% in mineral oil, 10.6 mg, 0.25 mmol) was slurried in 1 mL of petroleum ether and centrifuged, and the supernatant was pipetted off. A solution of *tert*-butyl ester **18** (66 mg, 0.19 mmol) in 0.5 mL of DMF was added to the above oil-free NaH. With stirring under N_2 at room temperature, a gentle gas evolution was initially observed. After 15–20 min, gas evolution had ceased. The reaction mixture was diluted with 1.5 mL of additional DMF and allowed to stir under N_2 for a total of 5 h. The reaction mixture was then added with stirring to a mixture of 1 M KH_2PO_4 (0.3 mL), CH_2Cl_2, and H_2O. After phase separation, the aqueous layer was extracted repeatedly with CH_2Cl_2. The combined organic layers were washed with brine, dried, filtered, and concentrated to give 34 mg of crude **19a,b**. Preparative TLC (20% EtOAc/$CHCl_3$) yielded, upon extraction of a band traveling just ahead of the starting iodide, 21 mg of *tert*-butyl ester **19a,b** (53%) as an oil: IR (CCl_4) 5.65, 5.77 μm; NMR (300 MHz, $CDCl_3$) δ 1.44 (s, *tert*-butyl), 2.04–2.36 and 2.48–2.58 (m, protons at C_1 and C_2), 2.62 (dd, J_{gem} = 16 Hz, J_{trans} = 2 Hz, H_6), 3.28 (dd, J_{gem} = 16 Hz, J_{cis} = 5 Hz, H_6), 3.84–3.91 (m, H_5), 4.30 (t, J = 8 Hz, H_3); peaks unique to minor diastereomer δ 1.48 (s, *tert*-butyl), 2.76 (dd, J_{gem} = 16 Hz, J_{trans} = 2 Hz, H_6), 3.10 (ddd, J_{gem} = 16 Hz, J_{cis} = 4.5 Hz, $J_{1,6}$ = 1 Hz, H_6), 3.64–3.72 (m, H_5), 3.78 (t, J = 5 Hz, H_3); ^{13}C NMR ($CDCl_3$) 27.9 (q, $C(CH_3)_3$), 31.1 (t, C_2), 35.8 (t, C_1), 42.5 (t, C_6), 53.1 (d, C_5), 59.7 (d, C_3), 81.7 ($C(CH_3)_3$), 170.8 and 176.5 ppm (β-lactam and ester C=O's); peaks attributable to minor diastereomer at 29.5 (C_2), 37.0 (C_1), 41.3 (C_6), 60.7 (C_3); mass spectrum, m/e 211 (M^+), 155, 110.

Benzyl Ester 18. Freshly distilled CF_3CO_2H (0.54 mL) was added to *tert*-butyl ester **18** (76 mg, 0.224 mmol). The reaction was stoppered and stirred at room temperature. After 7 min, the solution was quickly concentrated to a colorless oil which was repeatedly dissolved in a small amount of CH_3CN and reconcentrated in order to remove any residual CF_3CO_2H. The residue was then dissolved in 0.5 mL of CH_3CN. With stirring, an Et_2O solution of phenyldiazomethane[27] (ca. 0.84 mmol) was added, causing an immediate, vigorous gas evolution. After stirring under N_2 for 20 min, the orange solution was concentrated to give 108 mg of crude benzyl ester **18**. Preparative TLC (15% EtOAc/$CHCl_3$) provided 66 mg of benzyl ester **18** (79%) as an oil: IR (CCl_4) 5.66, 5.73 (sh) μm; NMR ($CDCl_3$) δ 1.93–2.38 (m, CH_2CH_2I), 2.63 (dd, J_{gem} = 14 Hz, J_{trans} = 3 Hz, H_3), 3.10 (t, J = 7 Hz, CH_2I), 3.17 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.83 (m, β-lactam methine proton), 4.02 (midpoint of 2 d, J = 18 Hz, $CH_2CO_2CH_2Ph$), 5.17 (s, CH_2Ph), 7.33 (s, Ph); mass spectrum, m/e 373 (M^+), 331, 282, 238.

Benzyl Ester 19a,b. Sodium hydride (57% in mineral oil, 12.8 mg, 0.304 mmol) was slurried in 1 mL of petroleum ether and centrifuged, and the supernatant was pipetted off. A solution of benzyl ester **18** (75 mg, 0.201 mmol) in 2 mL of DMF was added to the above oil-free NaH. The reaction mixture was stirred at room temperature under N_2 for 5 h and then added to a stirred mixture of 1 M KH_2PO_4 (0.36 mL), CH_2Cl_2, and H_2O. After phase separation, the aqueous layer was extracted with EtOAc (2×).

Each organic layer was washed with brine. The combined organic layers were dried, filtered, and concentrated to give 44 mg of crude **19a,b**. Preparative TLC (15% EtOAc/$CHCl_3$) yielded, upon extraction of a band which was faintly observable under UV light and traveled just ahead of the starting iodide, 31 mg of benzyl ester **19a,b** (63%) as an oil: IR (CCl_4) 5.64, 5.74 μm; NMR (300 MHz, $CDCl_3$) δ 2.08–2.38 and 2.52–2.64 (m, protons at C_1 and C_2), 2.64 (dd, J_{gem} = 16 Hz, J_{trans} = 2 Hz, H_6), 3.30 (dd, J_{gem} = 16 Hz, J_{cis} = 5 Hz, H_6), 3.85–3.92 (m, H_5), 4.46 (t, J = 7 Hz, H_3), 5.16 (s, CH_2Ph), 7.36 (s, Ph); peaks unique to minor diastereomer δ 2.77 (dd, J_{gem} = 16 Hz, J_{trans} = 2 Hz, H_6), 3.13 (dd, J_{gem} = 16 Hz, J_{cis} = 5 Hz, $J_{1,6}$ = 1 Hz, H_6), 3.67–3.76 (m, H_5), 3.94 (t, J = 5 Hz, H_3), 5.19 (s, CH_2Ph), 7.38 (s, Ph); mass spectrum, m/e 245 (M^+), 217, 203, 110.

***tert*-Butyl 2-Oxo-4-(2-oxoethyl)-1-azetidineacetate (20).** Alcohol **16** (950 mg, 4.15 mmol) was oxidized by the same procedure used to oxidize alcohol **3** above. The dark brown oxidation mixture was filtered through a bed of Celite and silica gel (20 g, 1:1) followed by thorough washing of the filter bed with CH_3CN (5 × 50 mL). The dark brown filtrate was concentrated to a brown oil. Chromatography on silica gel (30 g, eluting with 0–5% MeOH/$CHCl_3$) gave 515 mg of **20** (55%) as a white solid. Approximately 400 mg of starting material was subsequently eluted from the column. Recrystallization of **20** from Et_2O gave an analytical sample: mp 47–50 °C; IR (CCl_4) 5.68, 5.77 μm; NMR ($CDCl_3$) δ 1.45 (s, *tert*-butyl), 2.62 (dd, J_{gem} = 15 Hz, J_{trans} = 2 Hz, H_3), 2.95 (m, side chain CH_2), 3.20 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 3.87 (s, CH_2CO_2-*t*-Bu), 4.14 (m, H_4), 9.79 (s, CHO). Anal. ($C_{11}H_{17}NO_4$) C, H, N.

***tert*-Butyl 2-[2,2-Bis(methylthio)ethyl]-4-oxo-1-azetidineacetate (21).** To **20** (150 mg, 0.66 mmol) in 6 mL of CH_3CN with stirring at 0 °C under N_2 was added MeSH (ca. 3 mL, 54.3 mmol) followed immediately by BF_3·Et_2O (200 μL, 1.58 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was poured into a stirred cold mixture of 1 M K_2HPO_4 (10.5 mL), Et_2O, and H_2O. After phase separation, the aqueous layer was reextracted with Et_2O (2×). The combined organic layers were washed with brine, dried, filtered, and concentrated to give 185 mg of crude **21**. Preparative TLC (20% EtOAc/$CHCl_3$) provided 174 mg of **21** (86%) as an oil: IR (CCl_4) 5.67, 5.76 μm; NMR ($CDCl_3$) δ 1.49 (s, *tert*-butyl), 2.09 (s, SCH_3's), 2.15 (m, side chain CH_2), 2.63 (dd, J_{gem} = 14 Hz, J_{trans} = 2 Hz, H_3), 3.17 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.63 (t, J = 7 Hz, SCHS), 3.83 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu), 4.00 (m, β-lactam methine proton); mass spectrum, m/e 305 (M^+), 249, 154.

***tert*-Butyl 2-[2-(Methylthio)vinyl]-4-oxo-1-azetidineacetate (22).** A freshly prepared 0.52 M solution of Br_2 in pentane (1 mL, 0.52 mmol) was added dropwise to a stirred solution of **21** (150 mg, 0.49 mmol) in 7 mL of Et_2O at 0 °C under N_2. After stirring for 10 min at 0 °C, cyclohexene (53 μL, 0.52 mmol) was added. After 5 min, NaH (57% in oil dispersion, 24 mg, 0.57 mmol) was added followed immediately by 6.5 mL of cold DMF. Stirring was continued for 3 h at 0 °C. The reaction mixture was poured into a stirred cold mixture of 1 M KH_2PO_4 (1.2 mL), Et_2O, and H_2O. After phase separation, the aqueous layer was saturated with NaCl and reextracted with ether. The combined organic layers were washed with brine, dried, filtered, and concentrated to provide 151 mg of crude **22**. Preparative TLC (50% EtOAc/hexane) provided 97 mg of the *E* thioenolether **22** (77%) as an oil. A slightly less polar band yielded 15 mg of the *Z* thioenolether **22** (12%).

Data for (*E*)-**22**: IR (CCl_4) 5.68, 5.75 μm; NMR ($CDCl_3$) δ 1.49 (s, *tert*-butyl), 2.06 (s, SCH_3), 2.74 (dd, J_{gem} = 15 Hz, J_{trans} = 2 Hz, H_3), 3.30 (dd, J_{gem} = 15 Hz, J_{cis} = 4.5 Hz, H_3), 3.80 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-Bu), 4.36 (m, β-lactam methine proton), 5.32 (dd, J = 14 and 8 Hz, C**H**=CHS), 6.43 (d, J = 14 Hz, CH=C**H**S); mass spectrum, m/e 257 (M^+), 201, 184, 158.

Data for (*Z*)-**22**: IR (CCl_4) 5.68, 5.75 μm; NMR ($CDCl_3$) δ 1.48 (s, *tert*-butyl), 2.31 (s, SCH_3), 2.74 (dd, J_{gem} = 14 Hz, J_{trans} = 2 Hz, H_3), 3.33 (dd, J_{gem} = 14 Hz, J_{cis} = 5 Hz, H_3), 3.80 (midpoint of 2 d, J = 18 Hz, CH_2CO_2-*t*-butyl), 4.64 (m, β-lactam methine proton), 5.57 (dd appearing as a t, J = 9 Hz, C**H**=CHS), 6.29 (d, J = 9 Hz, CH=C**H**S); mass spectrum, m/e 257 (M^+), 201, 184, 158.

Dibenzyl (*E*)-2-[2-(Methylthio)vinyl]-4-oxo-1-azetidinemalonate (24). Treatment of **23** (0.5 g, 1.06 mmol) in the exact manner previously described for the conversion of **21** to **22** provided upon workup (EtOAc being used rather than Et_2O as the extracting solvent) 0.5 g of crude **24**. Preparative TLC (30% acetone/hexane) provided 0.39 g of **24** (86%) as an oil: IR (CCl_4) 5.60, 5.71 μm; NMR ($CDCl_3$) δ 2.13 (s, SCH_3), 2.75 (dd, J_{gem} = 15 Hz, J_{trans} = 2.5 Hz, H_3), 3.27 (dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3), 4.50 (m, β-lactam methine proton), 5.13 and 5.17 (2 s, CH_2Ph's), 5.20 (s, C**H**(CO_2CH_2Ph)$_2$), 5.28 (partially buried dd, J = 14 and 10 Hz, C**H**=CHS), 6.26 (d, J = 14 Hz, CH=C**H**S), 7.28 (br s, Ph); mass spectrum, m/e 425 (M^+), 397, 378, 334.

Dibenzyl 1-Bromo-2-(methylthio)carbapenam-3,3-dicarboxylate (25) and Dibenzyl 2-[1-Bromo-2-(methylthio)vinyl]-4-oxo-1-azetidinemalonate (26). A freshly prepared 0.81 M solution of Br_2 in pentane (1 mL, 0.81 mmol) was added dropwise to a stirred solution of **24** (325 mg, 0.765 mmol) in 17 mL of Et_2O at 0 °C under N_2. After 15 min at 0 °C, NaH (57% in oil dispersion, 44 mg, 1.05 mmol) was added, followed immediately by 8.2 mL of cold DMF. The reaction mixture was stirred for 1.5 h at room temperature and then poured into a stirred cold mixture of 1 M KH_2PO_4 (2.2 mL), EtOAc, and H_2O. Workup, as in the preparation of **24**, provided 408 mg of crude material. Preparative TLC (30% acetone/hexane) revealed two major bands. Extraction of the less polar band (faintly observable under UV light) provided 258 mg of the desired bicyclic compound **25** (67%): IR (CCl_4) 5.59, 5.75 μm; NMR ($CDCl_3$) δ 2.16 (s, SCH_3), 2.78 (dd, J_{gem} = 14.5 Hz, J_{trans} = 2 Hz, H_6), 3.33 (dd, J_{gem} = 14.5 Hz, J_{cis} = 4.5 Hz, H_6), 3.95 (d, J = 5.5 Hz, H_2), 4.11 (m, H_5), 4.63 (dd, J = 6.5 and 5.5 Hz, H_1), 5.16 (s, CH_2Ph), 5.22 (midpoint of 2 d, J = 12 Hz, CH_2Ph), 7.27 (m, Ph's); ^{13}C NMR ($CDCl_3$) 18.6 (SCH_3), 41.8 (C_6), 52.7 (C_1), 59.3 (C_5), 63.9 (C_2), 68.1 and 68.8 (CO_2CH_2Ph's), 77.7 (C_3), 128.5, 128.7, 134.4, and 134.6 (aromatics), 165.6 and 165.9 (ester C=O's), 171.6 ppm (β-lactam C=O); mass spectrum, m/e 505 and 503 (M^+), 424, 382.

Extraction of the second more polar band (intensely observable under UV light) provided 74 mg of a mixture of vinyl bromide **26** and a diastereomer of the bicyclic material **25**. Treatment of the mixture with AgF in pyridine (in the manner subsequently described for the dehydrobromination of **25** to **28**) provided a mixture of unchanged vinyl bromide **26** and the dehydrobrominated bicyclic material **28** now separable by preparative TLC (30% acetone/hexane). The more polar band provided 27 mg of **28** (identical with that prepared from the major diastereomer of **25** and described subsequently). The less polar band provided 28 mg of vinyl bromide **26** (7%) as an oil: IR (CCl_4) 5.61, 5.71 μm; NMR (300 MHz, $CDCl_3$) δ 2.28 (s, SCH_3), 3.09 (dd, J_{gem} = 14.5 Hz, J_{trans} = 3 Hz, H_3), 3.21 (dd, J_{gem} = 14.5 Hz, J_{cis} = 5 Hz, H_3), 4.77 (dd, J_{trans} = 3 Hz, J_{cis} = 5 Hz, β-lactam methine proton), 5.17 (m, CH_2Ph's and C**H**(CO_2CH_2Ph)$_2$), 6.70 (s, CBr=CHS), 7.31 (m, Ph's); mass spectrum, m/e 505 and 503 (M^+), 414, 412.

Mixture of Bromo Olefins 27. Treatment of **22** (90 mg, 0.35 mmol) in the exact manner previously described for the conversion of **24** to **25** provided upon workup 120 mg of crude **27**. Preparative TLC (30% acetone/hexane) provided 108 mg of **27** (92%) as a mixture of three of the four possible bromo olefins: IR (CCl_4) 5.67, 5.77 μm; NMR (300 MHz, $CDCl_3$) δ 1.47 (*tert*-butyl), 2.38, 2.39, and 2.40 (SCH_3's), 2.81, 2.82, and 2.99 (3 dd, for all J_{gem} = 15 Hz, J_{trans} = 2 Hz, H_3's), 3.19, 3.32, and 3.36 (3 dd, for all J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_3's), 3.82, 3.83, and 3.83 (midpoints of three widely spaced pairs of d, for all J = 18 Hz, nonequivalent methylene protons of CH_2CO_2-*t*-butyl's), 4.57, 4.71, and 4.82 (3 m, β-lactam methine protons), 6.03 (d, J = 8 Hz, C**H**=CBrSCH$_3$), 6.29 (d, J = 9 Hz, C**H**=CBrSCH$_3$), 6.82 (s, CBr=C**H**SCH$_3$); mass spectrum m/e 337 and 335 (M^+), 281, 279.

Dibenzyl 2-(Methylthio)carbapen-1-em-3,3-dicarboxylate (28). DBU Method. A solution of DBU (40 mg, 0.263 mmol) in 0.7 mL of Me_2SO was added to **25** (121 mg, 0.241 mmol) in 0.25 mL of Me_2SO at room temperature. The reaction mixture was stirred for 4 h under N_2 and then added to a cold mixture of 1 M KH_2PO_4 (0.48 mL), EtOAc, and H_2O. After phase separation, the aqueous layer was reextracted with EtOAc. The combined organic layers were washed with brine, dried, filtered, and concentrated to give 118 mg of crude **28**. Preparative TLC (30% acetone/hexane) yielded 56 mg of **28** (55%) as an oil. Extraction of the less polar starting material band provided 20 mg of recovered **25**. Data for **28**: IR (CCl_4) 5.58, 5.70 μm; NMR ($CDCl_3$) δ 2.29 (s, SCH_3), 2.83 (dd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, H_6), 3.34

(dd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, H_6), 4.56 (m, H_5), 5.14 and 5.20 (2 s, CH_2Ph's), 5.71 (d, J = 1.5 Hz, H_1), 7.25 (br s, Ph's); mass spectrum, m/e 423 (M^+), 395, 288, 246.

AgF/Pyridine Method. Silver fluoride (86 mg, 0.68 mmol) was added to a solution of **25** (256 mg, 0.509 mmol) in 20 mL of pyridine. After being stirred in the dark under N_2 for 1 h, the reaction mixture was partitioned between EtOAc and H_2O. After phase separation, the aqueous layer was reextracted with EtOAc (2×) followed by $CHCl_3$. Each organic layer was washed with brine. The combined organic layers were dried, filtered, and concentrated to give 220 mg of crude **28**. Preparative TLC (30% acetone/hexane) provided 180 mg of **28** (84%) identical with the material prepared by the DBU-mediated dehydrobromination.

Benzyl 2-(Methylthio)carbapen-1-em-3-carboxylate (29). A solution of **28** (100 mg, 0.236 mmol) in 2.5 mL of collidine (sym) was added to LiI (45 mg, 0.336 mmol). The reaction mixture was stirred under N_2 for 30 min in an oil bath at 120–130 °C. After cooling to room temperature, the reaction mixture was transferred to a wide-mouth round-bottom flask with CH_2Cl_2 for concentration to 211 mg of an orange oil which smelled strongly of collidine. The oil was partitioned between 1 M KH_2PO_4 (1.8 mL), EtOAc, and H_2O. After phase separation, the aqueous layer was reextracted with EtOAc (2×). The combined organic layers were washed with brine, dried, filtered, and concentrated to give 72 mg of crude **29**. Preparative TLC (30% acetone/hexane) provided 36 mg of **29** (53%) as an oil. Extraction of the more polar starting material band gave 20 mg of recovered **28**. Data for **29**: IR (CCl_4) 5.61, 5.72 μm; IR ($CHCl_3$) 5.65, 5.74 μm; NMR (CCl_4) δ 2.32 (s, SCH_3), 2.76 (dd, J_{gem} = 14 Hz, J_{trans} = 2.5 Hz, H_6), 3.37 (dd, J_{gem} = 14 Hz, J_{cis} = 4.5 Hz, H_6), 5.03 (dd, $J_{1,3}$ = 1.5 Hz, $J_{3,5}$ = 3 Hz, H_3), 5.14 (s, CH_2Ph), 5.66 (overlapping dd appearing as a t, $J_{1,3}$ = $J_{1,5}$ = 1.5 Hz, H_1), 7.33 (s, Ph); mass spectrum, m/e 289 (M^+), 261, 154, 112; UV max (Diox) 245 nm.

Benzyl (±)-2-(Methylthio)carbapen-2-em-3-carboxylate (2). With stirring, DBU (9.5 μL, 0.063 mmol) was added to a solution of **29** (16 mg, 0.055 mmol) in 0.2 mL of Me_2SO. The solution was stirred for 15 min at room temperature under N_2. After dilution with $CHCl_3$ to a total volume of 1 mL, the solution was chromatographed on two 1000 μm silica gel GF plates (30% acetone/hexane). Two bands were faintly observable under UV light. The less polar band provided 4 mg of recovered starting material **29** (25%). The more polar product band gave 5 mg of oily **2**. Slurrying with CCl_4 caused solidification. The solid was slurried in Et_2O (ca. 0.5 mL). The pale yellow supernatant was removed, and a second Et_2O wash was performed, thus providing 4 mg of **2** (25%) as a white solid: mp 137 °C dec; IR ($CHCl_3$) 5.62, 5.90 μm; NMR (300 MHz, $CDCl_3$) δ 2.36 (s, SCH_3), 2.94 (dd, J_{gem} = 16.5 Hz, J_{trans} = 3 Hz, H_6), 3.03 (dd, $J_{1,1}$ = 18 Hz, $J_{1,5}$ = 8.5 Hz, H_1), 3.25 (dd, $J_{1,1}$ = 18 Hz, $J_{1,5}$ = 9.5 Hz, H_1), 3.49 (dd, J_{gem} = 16.5 Hz, J_{cis} = 5 Hz, H_6), 4.22 (m, H_5), 5.30 (midpoint of 2 d, J = 12 Hz, nonequivalent methylene protons of CH_2Ph), 7.30–7.50 (m, Ph); mass spectrum, m/e 289 (M^+), 247, 141; UV max (Diox) 316 nm (ε 11 100).

Acknowledgment. We wish to thank Mr. H. Flynn for obtaining the 300-MHz ^1H NMR spectra, Dr. A. W. Douglas and Mr. R. A. Reamer for recording and interpreting the ^{13}C NMR spectra, Mr. H. Flynn and Mr. Jack Smith for obtaining the mass spectral data, Mr. J. P. Gilbert and his associates for elemental analyses, and Dr. C. H. Shunk for help in the preparation of intermediates.

Registry No. (±)-**2**, 72658-57-2; (±)-**3**, 65750-47-2; (±)-**5**, 72658-58-3; (±)-**6**, 72658-59-4; **7**, 72672-36-7; (±)-**8**, 72672-37-8; (±)-**9**, 72672-38-9; **10**, 72658-60-7; (±)-(*E*)-**11**, 67314-41-4; **12**, 72658-61-8; **13**, 72658-62-9; (±)-(*E*)-**14**, 72658-63-0; (±)-**15**, 72658-64-1; (±)-**16**, 72658-65-2; (±)-**17**, 72658-66-3; (±)-**18** (R = *t*-Bu), 72658-67-4; (±)-**18** (R = Bz), 72658-68-5; (±)-**19a** (R = *t*-Bu), 72658-69-6; (±)-**19a** (R = Bz), 72658-70-9; (±)-**19b** (R = *t*-Bu), 72658-71-0; (±)-**19b** (R = Bz), 72658-72-1; (±)-**20**, 72658-73-2; (±)-**21**, 72658-74-3; (±)-(*E*)-**22**, 72658-75-4; (±)-(*Z*)-**22**, 72658-76-5; (±)-**23**, 72658-77-6; (±)-(*E*)-**24**, 72658-78-7; **25**, 72658-79-8; (±)-**26**, 72658-80-1; **27**, isomer 1, 72658-81-2; **27**, isomer 2, 72658-82-3; **27**, isomer 3, 72658-83-4; (±)-**28**, 72658-84-5; **29**, 72658-85-6; *tert*-butyl glyoxylate, 7633-32-1.

Thienamycin Total Synthesis. 3. Total Synthesis of (±)-Thienamycin and (±)-8-Epithienamycin

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Received September 25, 1979

The completion of the total synthesis of (±)-8-epithienamycin and (±)-thienamycin from azetidinones **3a** and **3b** using the methodology developed for the synthesis of model compound **4** (see part 2) is described.

Thienamycin (**1**) is a broad-spectrum antibiotic[1] having a unique and synthetically challenging structure.[2] In part 1 of this series, the preparation of 4-(2-hydroxyethyl)-2-azetidinone (**2**) and its 3-substituted analogues **3a** and **3b**[3] was described. In part 2, we described model work which resulted in the preparation of the benzyl ester of (±)-2-(methylthio)carbapen-2-em-3-carboxylic acid (**4**) from **2**.[4] The chemistry of part 2 has now been adapted with minor

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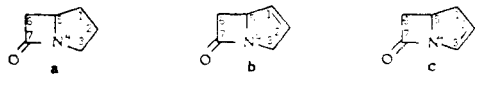
(3) PNB is equivalent to *p*-nitrobenzyl.

(4) The numbering of the ring system adopted throughout this and the previous paper is based on assignment of the terms carbapenam, carbapen-1-em, and carbapen-2-em to structures a, b, and c, respectively. This nomenclature is analogous to the penam and cepham nomenclature currently employed in β-lactam chemistry.



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