(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.

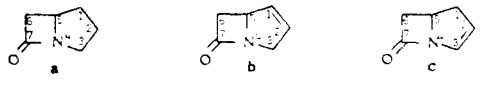
Thienamycin (**1**) is a broad-spectrum antibiotic[1] having a unique and synthetically challenging structure.[2] In part 1 of this series, the preparation of 4-(2-hydroxyethyl)-2-azetidinone (**2**) and its 3-substituted analogues **3a** and **3b**[3] was described. In part 2, we described model work 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

(1) 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 (1979), and references therein.

(2) 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).

(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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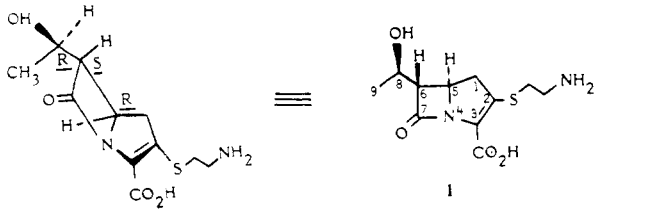

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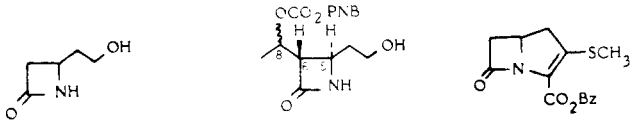
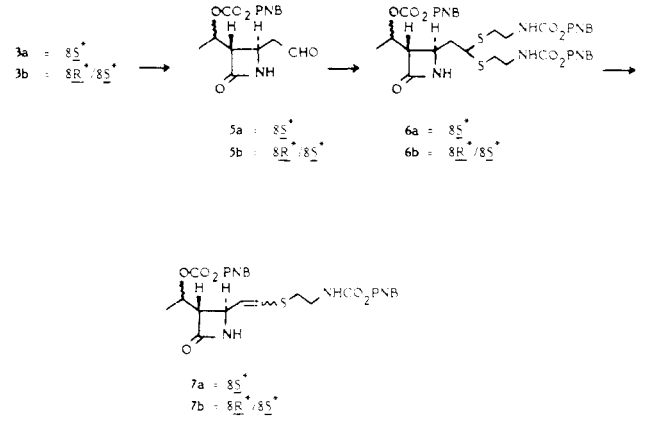


2 3a = 8S* 3b = 8R*/8S* 4

modifications to the total synthesis of (±)-8-epithienamycin[5] and (±)-thienamycin from *trans*-azetidinones **3a** and **3b**. Parts 1 and 2 immediately precede this paper.

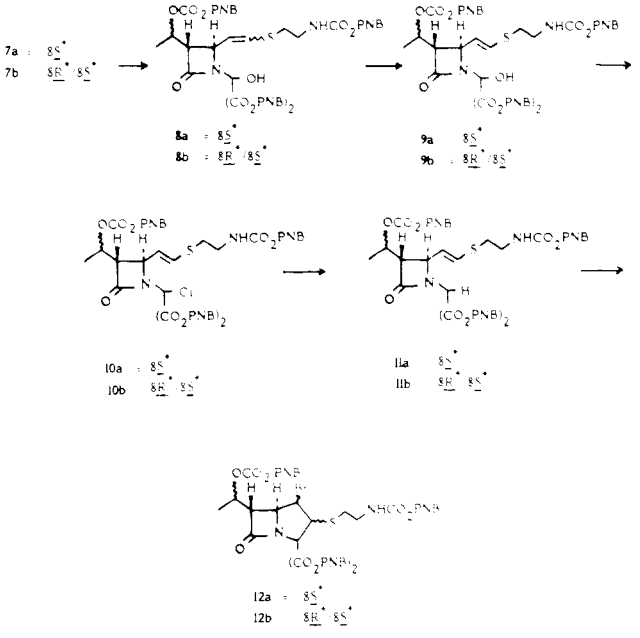
In part 1, the crystallization of *trans*-azetidinone **3a** which was assigned the 8S*[6] configuration left a mother liquor containing a mixture of the 8R* and 8S* diastereomers **3b** in a 3:2 ratio, respectively, The absolute stereochemistry of thienamycin is 5R,6S,8R.[2] Therefore, the following synthetic sequence when applied to pure 8S* alcohol **3a** resulted in the total synthesis of (±)-8-epithienamycin. Subsequent work with epimeric mixture **3b** then yielded (±)-thienamycin—a chromatographic separation of the pure 8R* diastereomer being achieved fairly late in the total synthesis.[7] In this paper, we wish to report the full details of the total synthesis of (±)-thienamycin[8] and (±)-8-epithienamycin.

Oxidation of alcohol **3a** with CrO_3·py in acetonitrile in the presence of Celite[9] gave a solution of aldehyde **5a** which was immediately treated with [[[(*p*-nitrobenzyl)oxy]-carbonyl]amino]ethanethiol[10] in the presence of BF_3·Et_2O to give thioacetal **6a**. Due to solubility problems encountered in attempting to condense **6a** with bis(*p*-nitrobenzyl) ketomalonate,[11] conversion to the thioenolether was carried out prior to the introduction of the malonate by successively treating **6a** with bromine in THF/Et_2O, cyclohexene, and then Et_3N in DMF. A mixture of *E* and *Z* thioenolethers **7a** in ca. a 5:2 ratio was produced. This suggested that the absence of a large group on nitrogen allowed the formation of a fair amount of the *Z* isomer in contrast to our experience in part 2 where conversion to the thioenolether subsequent to malonate introduction resulted in the production of little or none of the *Z* isomer.



3a = 8S* 3b = 8R*/8S* 5a = 8S* 5b = 8R*/8S* 6a = 8S* 6b = 8R*/8S* 7a = 8S* 7b = 8R*/8S*

The mixture of thioenolethers **7a**, dissolved in a THF/toluene solution, was successfully condensed[12] with bis(*p*-nitrobenzyl) ketomalonate in boiling toluene to give hydroxymalonate **8a**. Chromatographic separation of *E*



7a = 8S* 7b = 8R*/8S* 8a = 8S* 8b = 8R*/8S* 9a = 8S* 9b = 8R*/8S* 10a = 8S* 10b = 8R*/8S* 11a = 8S* 11b = 8R*/8S* 12a = 8S* 12b = 8R*/8S*

thioenolether **9a** was accomplished at this point in the synthesis.[13] Treatment with $SOCl_2$/pyridine in THF[12] converted **9a** to chloromalonate **10a**. Since the Zn/acetic acid reduction used in part 2 was incompatible with the nitro groups now present, reduction of **10a** by treatment with Bu_3P in aqueous DMF[14] in the presence of K_2HPO_4 gave the desired hydrogen malonate **11a**. Bromination of **11a** at 0 °C in a THF/Et_2O solution followed by stirring with Et_3N in DMF at room temperature afforded the desired bicyclic material **12a** as a mixture of two diastereomeric bromides.[15] The stereochemistry of these diastereomers will be discussed in a future publication dealing with the total synthesis of one of the cis stereoisomers of thienamycin since a complete stereochemical assignment became possible only upon comparison of the proton NMR data for **12a** with the spectra of analogous intermediates in the cis series.

The first major difficulty in adaptation of the chemistry of part 2 to the total synthesis occurred at this point. Attempted dehydrobromination of **12a** with DBU in Me_2SO resulted in an undesired elimination of the car-

(5) The *N*-acetyl derivative of 8-epithienamycin is a naturally occurring fermentation product: P. J. Cassidy, E. O. Stapley, R. T. Goegelman, T. W. Miller, B. H. Arison, G. Albers-Schönberg, S. B. Zimmerman, and J. Birnbaum, Abstracts, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1977, No. 81; E. O. Stapley, P. Cassidy, S. A. Currie, D. Daoust, R. Goegelman, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, R. L. Monaghan, J. B. Tunac, S. B. Zimmerman, and D. Hendlin, *ibid.*, No. 80.

(6) Numbering corresponds to the number the atom will eventually have in thienamycin. All totally synthetic materials are racemic.

(7) Subsequent to the completion of the total synthesis, a much earlier separation of the C_8 diastereomers was achieved (see part 1).

(8) 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).

(9) Procedure developed by Dr. J. Fahey.

(10) Reagent prepared according to a procedure developed by Dr. D. G. Melillo of Developmental Research (see Experimental Section).

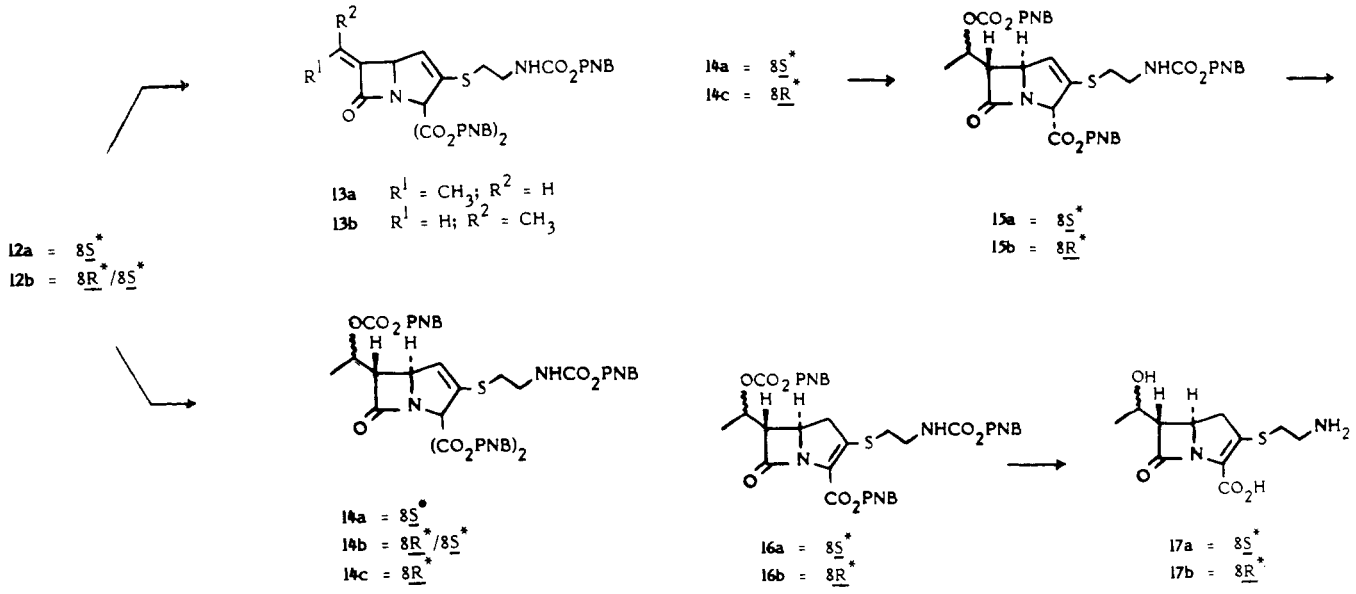
(11) Prepared by the SeO_2 oxidation of bis(*p*-nitrobenzyl) malonate (see Experimental Section).

(12) R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972).

(13) Subsequently, pure *Z* thioenolether and/or *E*/*Z* mixtures were carried through the synthesis to yield additional material.

(14) B. Jarvis and B. Marien, *J. Org. Chem.*, **41**, 2182 (1976).

(15) A less polar component of the reaction mixture having an R_f of ca. 0.7 (50% EtOAc/$CHCl_3$) contained a material which appeared by ^1H and ^{13}C NMR to be yet a third diastereomeric bromo compound.



bonate to give a mixture of ene lactams **13a** and **13b** in ca. a 7:3 ratio. An alternative dehydrobromination method was therefore required. Fortunately, treating **12a** with AgF in pyridine[16] gave a good yield of the desired unsaturated diester **14a** with only minor amounts of ene lactam formation.

Proceeding exactly as described above, a similar eight-step conversion of diastereomeric mixture **3b** to **14b** was possible. Thin-layer chromatography of **14b** on silica gel resulted in the desired separation of the less polar 8*R** diastereomer **14c** from 8*S** diastereomer **14a**. The 300-MHz proton NMR data for the individual diastereomers indicated a continuation of a trend observed throughout the synthesis and previously described in part 1. That is, the C_6 proton of 8*R** diastereomer **14c** appeared slightly upfield with respect to the C_6 proton of 8*S** diastereomer **14a**, while the C_5 proton of **14c** appeared slightly downfield with respect to the C_5 proton of **14a** (see Table I).

Decarbalkoxylation of **14a** with LiI in collidine[17] at 120–130 °C gave carbapen-1-em **15a** with a 23% recovery of starting material. Although the formation of some ene lactam materials as well as other impurities was noted during this reaction, chromatography afforded clean **15a** in 45% yield. A similar decarbalkoxylation of **14c** gave (8*R**)-carbapen-1-em **15b** in 45% yield.[18]

Utilization of DBU for isomerization of the double bond (as in part 2) was prohibited by the ene lactam formation previously encountered in its presence. A long search for alternative isomerization conditions resulted in the substitution of diisopropylamine for DBU. Treatment of **15a** with diisopropylamine in Me_2SO afforded a chromatographically separable mixture of starting material and (8*S**)-carbapen-2-em **16a**. Recycling the recovered **15a** two more times provided a 45% yield of **16a** based on recovered starting material. Similarly, isomerization of the double bond in **15b** gave (8*R**)-carbapen-2-em **16b** in 48% yield based on recovered starting material.

Additional verification of structures **15b** and **16b** was provided by the derivatization of naturally occurring thienamycin (1), according to Scheme I. Treatment with *p*-nitrobenzyl chloroformate in aqueous dioxane in the presence of $NaHCO_3$ provided upon workup the N-protected acid which was immediately converted to lithium salt **18**. Stirring the lyophilized salt with *p*-nitrobenzyl bromide in HMPA gave ester **19**.[19] Partial isomerization of the double bond with DBU in Me_2SO provided carbapen-1-em **20**.[19] Both **19** and **20** were reacted with *p*-nitrobenzyl chloroformate in CH_2Cl_2 in the presence of 4-(dimethylamino)pyridine[20] to give tris-derivatized species **21** and **22**, respectively. The 300-MHz proton NMR, IR, and TLC behavior of the totally synthetic materials **15b** and **16b** were identical with those of **22** and **21**, respectively.[21] The corresponding, totally synthetic 8*S** species **15a** and **16a**, in comparison to **22** and **21**, respectively, exhibited uniquely different C_6 protons in the NMR, once again reflecting the difference in side-chain stereochemistry (see Table I) and establishing the validity of the stereochemical assignments made in part 1.

Hydrogenolysis of 8*S** diastereomer **16a** with 10% Pd/C in a H_2O/dioxane/EtOH/K_2HPO_4 mixture followed by purification on an XAD-2 column, eluting with deionized water, afforded (±)-8-epithienamycin (**17a**), which showed reduced antibacterial potency in comparison to thienamycin (see Table II). Hydrogenolysis of 8*R** diastereomer **16b**, under similar conditions, provided (±)-thienamycin (**17b**), identical with the natural product by UV and 300-MHz proton NMR and having an antibacterial potency of approximately half that of thienamycin against a variety of microorganisms (see Table II).

Experimental Section

General Methods. See the Experimental Section of part 2 for a description of the purification and drying of solvents and reagents as well as for the chromatographic and experimental techniques used.

Upon purification by preparative TLC, extraction of desired products from the silica gel was accomplished with EtOAc or 1–2% MeOH/CH_2Cl_2. Reported R_f values refer to running rates as measured on Analtech silica gel GF plates (10 × 2.5 cm).

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 SC-300 spectrometer. ^{13}C NMR spectra were recorded on Varian CFT-20 and XL-100A spectrometers, and chemical shifts are reported in parts per million downfield from Me_4Si.

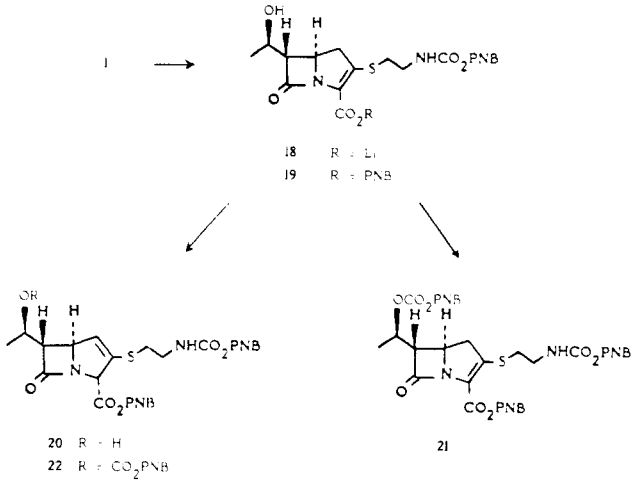
(16) L. Hough and B. Otter, *J. Chem. Soc., Chem. Commun.*, 173 (1966).
(17) J. McMurry, *Org. React.*, 24, 187 (1976).
(18) One recycling of recovered starting material was necessary to achieve this yield
(19) Procedures of Mr. W. J. Leanza and Dr. R. W. Ratcliffe.
(20) E. Guibé-Jampel and M. Wakselman, *J. Chem. Soc., Chem. Commun.*, 267 (1971).
(21) For reasons analogous to those fully detailed in part 2, the C_3 carboxylate has been assigned as α in **15a**, **15b**, **20**, and **22**.

Table I. Comparison of Proton NMR Data for 8R* and 8S* Diastereomers

compd	δ_{H_6} (dd)	$J_{6,8}$, Hz	$J_{5,6}$, Hz	δ_{H_5} (m)[a]
14a (8S*)[b]	~3.44[c]	*c*	*c*	4.55
14c (8R*)[b]	3.35	8	3	4.63
15a (8S*)[b]	3.36	5	3	4.53
15b (8R*)[b]	3.28	8	2.5	4.60
22 (8R)[b]	3.29	8	2.5	4.61
16a (8S*)[b]	3.51	5	3	4.18
16b (8R*)[b]	3.46	7	3	4.23
21 (8R)[b]	3.46	7	3	4.23
17a (8S*)[d]	3.49	4.9	2.5	4.15[a,e]
1 (8R)[d]	3.42	6.0	2.7	4.22[a,e]
17b (8R*)[f]	3.41	6.0	2.5	4.20[a,e]

[a] Represents the midpoint of the multiplet. [b] Spectra (300 MHz) were run in $CDCl_3$, and chemical shifts are reported in parts per million downfield from Me_4Si. [c] The C_6 proton is hidden under the SCH_2CH_2N multiplet centered at δ 3.44. [d] Spectra (100 MHz) were run in D_2O at ca. 5 °C with a trace of dioxane as an internal standard. [e] Multiplet contains H_8 and H_5. [f] Spectrum (300 MHz) run in D_2O.

Scheme I



[[[(*p*-Nitrobenzyl)oxy]carbonyl]amino]ethanethiol. A solution of $NaHCO_3$ (7.14 g, 85 mmol) in 75 mL of H_2O was added to a stirred mixture of cysteamine hydrochloride (3.2 g, 28.3 mmol) in 600 mL of Et_2O and 75 mL of H_2O under N_2 at 0 °C. The ice bath was removed, and a solution of *p*-nitrobenzyl chloroformate (6.75 g, 31.4 mmol) in 270 mL of Et_2O was added dropwise over a period of 1 h to the vigorously stirred reaction mixture. After 10 additional min, the layers were separated, and the organic layer was extracted with 150 mL of 0.25 N HCl followed by 200 mL of brine. Each aqueous layer was back-washed successively with 100 mL of Et_2O. The combined Et_2O layers were dried, filtered, and concentrated to a crystalline residue. Slurrying in a small volume of Et_2O, followed by filtration, afforded 4.7 g of [[[(*p*-nitrobenzyl)oxy]carbonyl]amino]ethanethiol (65%) as a pale yellow solid suitable for use in the preparation of thioacetals **6a** and **6b**: IR ($CHCl_3$) 5.79 μm; NMR (60 MHz, $CDCl_3$) δ 1.37 (t, *J* = 8 Hz, SH), 2.70 (m, SCH_2CH_2N), 3.42 (m, SCH_2CH_2N), 5.22 (s, CH_2Ar), 5.32 (br, NH), 7.50 (d, *J* = 8 Hz, aromatic protons meta to NO_2), 8.22 (d, *J* = 8 Hz, aromatic protons ortho to NO_2); mass spectrum *m/e* 256 (M^+), 209, 136, 120. Preparative TLC (30% EtOAc/$CHCl_3$) to remove a minor amount of *p*-nitrobenzyl alcohol followed by recrystallization from Et_2O–petroleum ether provided an analytical sample, mp 66.5–67.5 °C. Anal. ($C_{10}H_{12}N_2O_4S$) C, H, N, S.

Thioacetals 6a and 6b via Aldehydes 5a and 5b. Chromium trioxide (4.05 g, 40.5 mmol) was added with stirring to a solution of pyridine (6.75 mL, 83.9 mmol) in 350 mL of CH_3CN. The flask was stoppered with a drying tube containing Drierite, and stirring was continued for 30 min. Celite (9.6 g) was added to the stirred, orange-red solution, followed in a few minutes by a solution of **3a** (3.21 g, 9.5 mmol) in 40 mL of CH_3CN. After 1 h, $NaHSO_3$ (9.6 g, 92.3 mmol) was added, and stirring was continued for 5 min. Filtration of the reaction mixture through a bed of silica gel and anhydrous $MgSO_4$ (80 g, 1:1) was followed by thorough washing of the filter bed with CH_3CN until the volume of the filtrate was ca. 600–700 mL. The filtrate was concentrated under a stream of N_2 to a volume of ca. 130 mL. With stirring at 0 °C, the filtrate containing crude **5a** was treated with [[[(*p*-nitrobenzyl)oxy]carbonyl]amino]ethanethiol (9.64 g, 37.7 mmol) followed by BF_3·Et_2O (8.0 mL, 63.4 mmol). After stirring for 2–3 h at 0 °C under N_2, the reaction mixture was poured into a vigorously stirred, cold mixture of K_2HPO_4 (69 g), H_2O, and EtOAc. After phase separation, the aqueous layer was saturated with NaCl and then extracted with EtOAc. Each organic layer was washed with brine (2×). The combined organic layers were dried, filtered, and concentrated to give 14.5 g of crude **6a**. Chromatography on silica gel (450 g, eluting with 0–4% MeOH/$CHCl_3$) provided 5.09 g of **6a** (65%) as a white foam: IR ($CHCl_3$) 5.67, 5.80 μm; NMR (300 MHz, acetone-d_6)[6] δ 1.42 (d, *J* = 6 Hz, CH_3), 2.19 (m, side chain CH_2), 2.71–2.98 (m, SCH_2CH_2N), 3.19 (dd, $J_{5,6}$ = 2 Hz, $J_{6,8}$ = 4 Hz, H_6), 3.35–3.49 (m, SCH_2CH_2N), 3.80 (m, H_5), 4.14 (t, *J* = 7 Hz, SCHS), 5.18 (m, H_8), 5.24 (s, $NHCO_2CH_2Ar$), 5.34 (midpoint of 2 d, OCO_2CH_2Ar), 6.81 (br m, NH), 7.32 (br s, NH), 7.65–8.29 (aromatic protons).

Treatment of **3b** (3.54 g, 10.5 mmol) in the above manner gave 14.9 g of crude **6b**. Chromatography on silica gel (450 g, eluting with 0–3% MeOH/$CHCl_3$) provided 3.05 g of **6b** as a white foam. Preparative TLC (EtOAc) of impure column factions provided 0.72 g of additional **6b** (43% total yield): IR ($CHCl_3$) 5.68, 5.80 μm; NMR (300 MHz, acetone-d_6)[6,22] δ 1.40 (2 overlapping d, *J* = 6 Hz, CH_3 of *R** and *S**), 3.10 (dd, $J_{5,6}$ = 2 Hz, $J_{6,8}$ = 7.5 Hz, H_6), 3.89 (m, H_5), 4.12 (2 overlapping t, *J* = 7 Hz, SCHS of *R** and *S**), 5.06 (m, H_8).

Thioenolethers 7a and 7b. A freshly prepared solution of Br_2 in pentane[23] (10 mL of 0.66 M Br_2, 6.6 mmol) was added dropwise to a stirred solution of **6a** (5 g, 6.02 mmol) in 58 mL of THF and 65 mL of Et_2O at 0 °C under N_2. After the mixture was stirred for 10 min at 0 °C, cyclohexene (0.67 mL, 6.6 mmol) was added. After 5 min, Et_3N (1.7 mL, 12.3 mmol) was added followed immediately by 40 mL of cold DMF. The ice bath was removed, and stirring was continued for ca. 2 h at room temperature. The reaction mixture was poured into a stirred, cold mixture of 1 M KH_2PO_4 (12.6 mL), H_2O, and EtOAc. Continuing the workup as described in the preparation of **6a**, we obtained 7.25 g of crude **7a**. Chromatography on silica gel (250 g, eluting with 0–3% MeOH/$CHCl_3$) gave 2.0 g of **7a** as a mixture of *E* and *Z* isomers. Contaminated column fractions were rechromatographed on silica gel (eluting with 0–25% EtOAc/$CHCl_3$) to provide 0.65 g of additional **7a** (77% total yield): IR ($CHCl_3$) 5.68, 5.79 μm; NMR (300 MHz, $CDCl_3$)[6] δ 1.46 (2 overlapping d, CH_3 of *E* and *Z*), 2.83–2.91 (m, SCH_2CH_2N), 3.22 (m, H_6), 3.40–3.48 (m, SCH_2CH_2N), 4.05 (dd, *J* = 2 and 7.5 Hz, H_5 of *E*), 4.36 (dd, *J* = 2 and 9 Hz, H_5 of *Z*), 5.08–5.30 (m, CH_2Ar's and H_8), 5.65–5.75 (m, CH=CHS), 5.89 and 5.98 (2 br s, NH's), 6.20 (d, *J* = 9 Hz, CH=CHS of *Z*), 6.31 (d, *J* = 15 Hz, CH=CHS of *E*), 7.52–8.28 (aromatic protons).

Treatment of **6b** in the above manner provided 5.34 g of crude **7b**. Chromatography on silica gel (250 g, eluting with 0–3% MeOH/$CHCl_3$) gave 2.31 g of (*E*)- and (*Z*)-**7b** as a yellow foam which showed the presence of some residual DMF by NMR. The material was used as is in the following reaction. However, preparative TLC (80% EtOAc/$CHCl_3$) of 54 mg of this material provided 45 mg of **7b** free of DMF for complete characterization: IR ($CHCl_3$) 5.68, 5.79 μm; NMR (300 MHz, $CDCl_3$)[6,22] δ 1.42–1.50 (series of d, CH_3's), 3.11–3.16 (2 overlapping dd, H_6's of *E* and *Z*), 4.23 (dd, *J* = 2 and 8 Hz, H_5 of *E*), 4.49 (dd, *J* = 2.5 and 9 Hz, H_5 of *Z*).

Bis(*p*-nitrobenzyl) Ketomalonate. A mixture of *p*-nitrobenzyl bromide (100 g, 0.47 mol), malonic acid (28.6 g, 0.275 mol), and 750 mL of EtOH was stirred and warmed on a steam bath until solution was achieved. A solution of KOH (33 g, ca. 0.6 mol) in 200 mL of H_2O was carefully added with swirling. An additional

(22) Chemical shifts of some of the absorption peaks unique to the 8R* diastereomer.

(23) Bromine in CCl_4 can be used also.

Table II. Inhibitory Zone Diameters (Millimeters) vs. Penicillin-Sensitive and -Resistant Bacterial Strains

compd	disc content, μg (nmol)	*S. aureus*		*E. coli*		*Enterobacter cloacae*		*Pseudomonas aeruginosa*	
		MB2985	MB2314	MB2482	MB2964	MB2647	MB2646	MB2835	MB3350
thienamycin	9.64 (35.4)	37.2	40.5	27	27	22.7	23.7	23.5	22.5
17a	19.6 (72.1)	32	30.2	15.5	15.5	16.2	13.5	12.2	12.5
17b	19.4 (71.3)	38.5	40.5	28	26.5	23.7	24.7	23.2	22.5

200 mL of H_2O was added, and the two-phase system was refluxed for 1.8 h. During reflux the reaction mixture was slowly concentrated to ca. half the volume by allowing the refluxing solvent to distill off. After the mixture cooled in an ice bath, the precipitate was filtered, washed with a minimum of cold EtOH (2×), and dried by pulling dry N_2 through the cake to give 77 g of crude bis(*p*-nitrobenzyl) ester. Recrystallization from MeOH provided 43 g of bis(*p*-nitrobenzyl) malonate (50%), mp 87–88 °C.

A mixture of the above bis(*p*-nitrobenzyl) malonate (23.4 g, 62.6 mmol), SeO_2 (10 g, 90 mmol), and 30–40 mL of xylene was stirred in a flask immersed in an oil bath. The bath temperature was raised over 1 h to 130–135 °C. The reaction mixture gradually darkened, and after a total of 4 h at 130–135 °C, most of the insoluble residue was black, elemental Se. After the mixture cooled, $MgSO_4$ was added to remove the H_2O and Celite to aid in filtration. The mixture was filtered through Celite, and the cake was washed with xylene and a small portion of EtOAc, resulting in a total volume of ca. 60 mL. Chromatography of 10 mL of the filtrate on 100 g of silica gel packed in benzene [eluting with 2% (500 mL), 10% (3 × 500 mL), and finally 20% EtOAc/benzene] provided ca. 1.6 g of product in the third 10% and first 20% EtOAc/benzene fractions as judged by TLC (20% EtOAc/$CHCl_3$ or 40% acetone/hexane).[24] Recrystallization of 1 g of this material from benzene (50 mL concentrated to ca. 15 mL to which 1 mL of H_2O-saturated benzene was added) provided 0.24 g of bis(*p*-nitrobenzyl) ketomalonate as a partial hydrate (mp 121–122 °C with softening at 117 °C) which was suitable for condensation with **7a** and **7b**. Chromatography of the remaining 50 mL of filtrate, in an analogous manner, yielded additional ketomalonate reagent.

(*E*)-Hydroxymalonates 9a and 9b. A solution of **7a** (2.52 g, 4.39 mmol) in 20 mL of THF and 40 mL of toluene was added to a stirred, refluxing solution of bis(*p*-nitrobenzyl) ketomalonate (2.48 g, 6.39 mmol) in 400 mL of toluene. When ca. 25% of the original solvent had boiled off, the volume was brought to that originally present with fresh toluene. The azeo drying process was repeated three more times after which the solution was refluxed under N_2 for 30 min. Additional toluene was then allowed to boil off, but heating was discontinued before any oiling out or precipitation occurred. The total reaction time was ca. 2.5 h. The clear yellow reaction mixture was removed from the oil bath and concentrated under a N_2 stream to a yellow oil. The residue was dissolved in CH_2Cl_2, dried, filtered, and concentrated to give 5.1 g of crude **8a**. Chromatography on silica gel (250 g, 0–1% MeOH/$CHCl_3$) provided 1.22 g of *E* thioenolether **9a** which emerged just after the excess bis(*p*-nitrobenzyl) ketomalonate. Later column fractions provided 1.2 g of a mixture of *E* and *Z* thioenolethers **8a** as well as fractions containing starting material **7a**. Further chromatography of the *E*/*Z* mixture on silica gel (60 g, 0–0.5% MeOH/$CHCl_3$) provided 0.5 g of additional pure *E* thioenolether **9a** (41% total yield) and 0.6 g of material which was still a mixture of *E* and *Z* isomers:[13] IR ($CHCl_3$) 5.68, 5.79 μm (sh); NMR (300 MHz, acetone-d_6)[6] δ 1.42 (d, *J* = 6.5 Hz, CH_3), 2.88–2.93 (m, SCH_2CH_2N), 3.17–3.44 (m, SCH_2CH_2N and H_6), 4.68 (dd, *J* = 2.5 and 9 Hz, H_5), 5.18–5.49 (m, CH_2Ar's and H_8), 5.82 (dd, *J* = 9 and 15 Hz, CH=CHS), 6.49 (d, *J* = 15 Hz, CH=CHS), 6.80 (br m, NH), 7.60–8.27 (aromatic protons).

Data for *E* and *Z* mixture **8a**: NMR (60 MHz, acetone-d_6,[6] only absorption peaks unique to *Z* isomer listed): δ 5.02 (dd, *J* = 2.5 and 8.5 Hz, H_5), 5.93 (overlapping dd appearing as a t, *J* = 8.5 and 8.5 Hz, CH=CHS), 6.40 (d, *J* = 8.5 Hz, CH=CHS).

Treatment of **7b** (2.26 g, 3.94 mmol) in the above manner gave 4.7 g of crude **8b**. Chromatography on silica gel (250 g, 0–1% MeOH/$CHCl_3$) provided 0.98 g of pure *E* thioenolether **9b** (26%), emerging just after the excess reagent. Material from later column fractions was rechromatographed as above followed by final preparative TLC (40% acetone/hexane) to remove *p*-nitrobenzyl alcohol to give 0.69 g of a mixture of *E* and *Z* thioenolethers **8b** (18%)[13] and 0.70 g of starting material (31%).

Data for *E* thioenolether **9b**: IR ($CHCl_3$) 5.68, 5.79 μm (sh); NMR (300 MHz, $CDCl_3$)[6] δ 1.43 (2 overlapping d, *J* = 6 Hz, CH_3 of *R** and *S**), 2.79–2.88 (m, SCH_2CH_2N), 3.17 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 8 Hz, H_6 of *R**), 3.24 (br dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 5 Hz, H_6 of *S**), 3.30–3.54 (m, SCH_2CH_2N), 4.58 (dd, *J* = 2.5 and 9 Hz, H_5 of *S**), 4.64 (dd, *J* = 2.5 and 9 Hz, H_5 of *R**), 5.12–5.50 (m, CH_2Ar's and H_8), 5.66 (dd, *J* = 9 and 15 Hz, CH=CHS), 6.19 (d, *J* = 15 Hz, CH=CHS of *R**), 6.30 (d, *J* = 15 Hz, CH=CHS of *S**), 7.43–8.29 (aromatic protons).

Data for *E* and *Z* mixture **8b**: NMR (300 MHz, $CDCl_3$,[6] only absorption peaks unique to *Z* isomers listed): δ 4.96 (m, H_5 of *R** and *S**), 5.78 (2 overlapping dd, CH=CHS of *R** and *S**), 6.16 and 6.19 (2 d, *J* = 9 Hz for both, CH=CHS of *R** and *S**).

Hydrogen Malonates 11a and 11b via Chloromalonates 10a and 10b. A solution of $SOCl_2$ (294 mg, 2.47 mmol) in 5 mL of THF was added dropwise to a stirred solution of **9a** (1.47 g, 1.53 mmol) and pyridine (0.21 mL, 2.56 mmol) in 25 mL of THF at −20 °C under N_2. 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 with 10 mL of THF (2×). The combined filtrate and washings were concentrated to a yellow foam. The foam was redissolved in 25 mL of THF, and a small amount of insoluble material was filtered off under N_2. The filtrate was concentrated to provide chloromalonate **10a** as a yellow foam. A suspension of Bu_3P (678 mg, 3.36 mmol) in 37 mL of 9:1 DMF/H_2O was added to **10a** followed immediately by K_2HPO_4 (294 mg, 1.69 mmol). The reaction mixture was stirred under N_2 for 35 min and then added to a mixture of EtOAc and brine. After phase separation, the aqueous layer was reextracted with EtOAc. The combined organic layers were washed with brine, dried, filtered, and concentrated to give 2 g of a reddish orange oil. The oil was slurried with a small volume of petroleum ether. The supernatant, containing some of the excess Bu_3P and $Bu_3P(O)$, was removed, and the process was repeated a number of times. The resultant residue was chromatographed on silica gel (100 g, eluting with 0–0.5% MeOH/$CHCl_3$) to give 786 mg of **11a** as a white foam. Preparative TLC (50% acetone/hexane) of impure column fractions provided 203 mg of additional **11a** (69% total yield): IR ($CHCl_3$) 5.60 (sh), 5.70, 5.80 μm (sh); NMR (300 MHz, $CDCl_3$)[6] δ 1.45 (d, *J* = 6 Hz, CH_3), 2.81–2.86 (m, SCH_2CH_2N), 3.32 (dd, $J_{5,6}$ = 2 Hz, $J_{6,8}$ = 5 Hz, H_6), 3.34–3.47 (m, SCH_2CH_2N), 4.44 (dd, *J* = 2 and 9 Hz, H_5), 5.15–5.40 (m, CH_2Ar's, H_8, and $CH(CO_2PNB)_2$), 5.49 (dd, *J* = 9 and 15 Hz, CH=CHS), 6.34 (d, *J* = 15 Hz, CH=CHS), 7.48–8.28 (aromatic protons).

Treatment of **9b** (980 mg, 1.02 mmol) in the above manner gave 1.49 g of crude **11b**. Chromatography on silica gel (100 g, eluting with 0–0.5% MeOH/$CHCl_3$) gave 678 mg of slightly impure **11b**. Preparative TLC (40% acetone/hexane) provided 554 mg of **11b** (57%) as a white foam: IR ($CHCl_3$) 5.61 (sh), 5.70, 5.79 μm (sh); NMR (300 MHz, $CDCl_3$)[6,22] δ 1.44 (2 overlapping d, CH_3 of *R** and *S**), 3.24 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 7 Hz, H_6), 4.52 (dd, *J* = 2.5 and 10 Hz, H_5), 6.24 (d, *J* = 15 Hz, CH=CHS).

Bromo Bicyclic Compounds 12a and 12b. A freshly prepared solution of Br_2 in pentane[23] (1.8 mL, 0.45 M Br_2, 0.81 mmol) was added dropwise to a stirred solution of **11a** (706 mg, 0.75 mmol) in 18 mL of THF and 5.7 mL of Et_2O at 0 °C under N_2. After 15 min at 0 °C, Et_3N (0.42 mL, 3.0 mmol) was added followed immediately by 10.5 mL of cold DMF. The reaction mixture was stirred for 2 h at room temperature and then poured into a stirred,

(24) Subsequently, 1:2 acetone/hexane was found to be a superior column eluant.

cold mixture of 1 M KH_2PO_4 (3.1 mL), H_2O, and EtOAc. Continuing the workup as described in the preparation of **6a**, we obtained 823 mg of crude **12a**. Isolation of the major reaction product which had an R_f of ca. 0.54 (50% EtOAc/$CHCl_3$) was achieved by chromatography on silica gel (60 g, 0–5% EtOAc/$CHCl_3$) to provide 385 mg of a white foam containing a mixture of two diastereomeric bromo compounds, **12a** (50%), in a 7:3 ratio:[15] IR ($CHCl_3$) 5.62, 5.74, 5.82 μm (sh); NMR (300 MHz, acetone-d_6) major diastereomer δ 1.46 (d, J = 6 Hz, CH_3), 2.80–3.10 (m, SCH_2CH_2N), 3.35–3.53 (m, SCH_2CH_2N), 3.90 (dd appearing as a t, $J_{5,6} = J_{6,8}$ = 3 Hz, H_6), 4.32 (dd, $J_{5,6}$ = 3 Hz, $J_{1,5}$ = 5 Hz, H_5), 4.54 (d, $J_{1,2}$ = 6 Hz, H_2), 5.12 (dd, $J_{1,5}$ = 5 Hz, $J_{1,2}$ = 6 Hz, H_1), 5.24–5.59 (m, CH_2Ar's and H_8), 6.70 (br m, NH), 7.65–8.29 (aromatic protons); absorption peaks unique to minor diastereomer δ 1.53 (d, J = 6 Hz, CH_3), 2.58–2.72 (m, SCH_2CH_2N), 3.53–3.70 (m, SCH_2CH_2N), 4.03 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 4 Hz, H_6), 4.19 (dd, $J_{5,6}$ = 2.5 Hz, $J_{1,5}$ = 5 Hz, H_5), 4.98 (d, $J_{1,2}$ = 5 Hz, H_2), 5.03 (dd appearing as a t, $J_{1,5} = J_{1,2}$ = 5 Hz, H_1); ^{13}C NMR ($CDCl_3$)[6] 17.8 (C_9), 34.7 (SCH_2), 40.0 (CH_2N), 51.9 (C_1), 60.4 (C_6), 61.0 (C_2), 62.6 (C_5), 65.3–68.2 (4 CH_2Ar), 7.12 (C_8), 123.7–147.9 (Ar's), 154.1 (OCO_2), 155.9 (NCO_2), 165.2 and 170.0 ppm (C_7 and ester C=O's).

Treatment of **11b** (200 mg, 0.211 mmol) in the above manner gave 232 mg of crude **12b**. Isolation of the major reaction product which had an R_f of ca. 0.5 was achieved by preparative TLC (50% EtOAc/$CHCl_3$) followed by column chromatography to remove residual, minor impurities (0–3% EtOAc/$CHCl_3$) to provide 102 mg of **12b** (47%) as a white foam: IR ($CHCl_3$) 5.61, 5.74, 5.81 μm (sh); NMR (300 MHz, acetone-d_6)[22] δ 1.45 (2 overlapping d, CH_3 of R^* and S^*), 3.83 (dd, $J_{5,6}$ = 2 Hz, $J_{6,8}$ = 5 Hz, H_6), 4.37 (dd, $J_{5,6}$ = 2 Hz, $J_{1,5}$ = 6 Hz, H_5), 4.54 (br d, $J_{1,2}$ = 6 Hz, H_2 of R^* and S^*), 5.12 (2 overlapping dd, H_1 of R^* and S^*).

Ene Lactams 13a and 13b. With stirring, DBU (11 μL, 0.072 mmol) was added to a solution of **12a** (67 mg, 0.065 mmol) in 0.7 mL of Me_2SO. The resultant, dark blue solution was stoppered and stirred for 2 h at 25 °C. The reaction mixture was then added to a mixture of 1 M KH_2PO_4 (290 μL), H_2O, and EtOAc. After phase separation, the organic layer was washed with brine (2×), dried, filtered, and concentrated to give 56 mg of crude **13a** and **13b**. Preparative TLC (50% acetone/hexane) gave 26 mg of slightly impure material. A second preparative TLC (50% EtOAc/$CHCl_3$) provided 20 mg of **13a** and **13b** (41%) as a white foam: IR ($CHCl_3$) 5.70, 5.80 μm (sh); NMR (300 MHz, $CDCl_3$) δ 1.88 (d, J = 7.5 Hz, CH_3 of **13b**), 2.04 (d, J = 7.5 Hz, CH_3 of **13a**), 2.98–3.02 (m, SCH_2CH_2N), 3.35–3.49 (m, SCH_2CH_2N), 5.02 (br s, H_5 of **13a**), 5.14 (br s, H_5 of **13b**), 5.18–5.43 (m, CH_2Ar's), 5.95 (q, J = 7.5 Hz, H_8 of **13a**), 6.11 (br s, H_1 of **13a**), 6.17 (br s, H_1 of **13b**), 6.36 (m, H_8 of **13b**), 7.50–8.26 (aromatic protons).

Diesters 14a and 14c. Silver fluoride (29 mg, 0.23 mmol) was added to a stirred solution of **12a** (146 mg, 0.143 mmol) in 3.5 mL of pyridine. The reaction mixture was stirred under N_2 in the dark for 1 h and then poured into a mixture of EtOAc–H_2O. After phase separation, the aqueous layer was reextracted with EtOAc (2×) and then with $CHCl_3$. Each organic layer was washed with H_2O and then brine. The combined organic layers were dried, filtered, and concentrated to give 143 mg of crude **14a**. Preparative TLC (40% acetone/hexane) yielded **14a** which was still slightly impure. Chromatography on silica gel (eluting with 0–2% EtOAc/$CHCl_3$) provided 95 mg of **14a** (70%) as a white foam: IR ($CHCl_3$) 5.61, 5.72, 5.80 μm (sh); NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J = 6.5 Hz, CH_3), 2.98–3.04 (m, SCH_2CH_2N), 3.40–3.47 (m, SCH_2CH_2N and H_6), 4.55 (m, H_5), 5.18 (midpoint of m, H_8), 5.20–5.38 (CH_2Ar's), 6.16 (br s, H_1), 7.50–8.28 (aromatic protons); the 60-MHz NMR spectrum showed additional splitting not clearly observable in the 300-MHz spectrum (dd, $J_{5,6}$ = 3 Hz, $J_{1,5}$ = 1.5 Hz, H_5) and (d, $J_{1,5}$ = 1.5 Hz, H_1); ^{13}C NMR ($CDCl_3$)[6] 17.8 (C_9), 33.8 (SCH_2), 39.4 (CH_2N), 62.2 (C_5), 63.0 (C_6), 65.4–68.2 (4 CH_2Ar), 71.4 (C_8), 81.2 (C_3), 123.8–147.9 (Ar's), 154.2 (OCO_2), 155.9 (NCO_2), 163.9 and 165.3 (ester C=O's), 172.8 ppm (C_7).

Treatment of **12b** (72 mg, 0.07 mmol) in the above manner gave 67 mg of crude **14b**. Preparative TLC (40% acetone/hexane) provided 52 mg of **14b** (79%) as a white foam. Separation of 8R^* diastereomer **14c** from 8S^* diastereomer **14a** was achieved by preparative TLC (50% EtOAc/$CHCl_3$). The more polar half of the UV band gave 19 mg of **14a**. The forward half provided 30 mg of **14c** slightly contaminated with **14a**. A second preparative TLC (50% EtOAc/$CHCl_3$) provided 21 mg of pure **14c** as a white foam: IR ($CHCl_3$) 5.61, 5.72, 5.81 μm (sh); NMR (300 MHz, $CDCl_3$) δ 1.44 (d, J = 6 Hz, CH_3), 2.97–3.03 (m, SCH_2CH_2N), 3.35 (dd, $J_{5,6}$ = 3 Hz, $J_{6,8}$ = 8 Hz, H_6), 3.39–3.47 (m, SCH_2CH_2N), 4.63 (m, H_5), 5.17–5.34 (CH_2Ar's and H_8), 6.12 (br s, H_1), 7.48–8.25 (aromatic protons); the 60-MHz NMR spectrum showed additional splitting not clearly observable in the 300-MHz spectrum (dd, $J_{5,6}$ = 3 Hz, $J_{1,5}$ = 1.5 Hz, H_5) and (d, $J_{1,5}$ = 1.5 Hz, H_1).

Carbapen-1-ems 15a and 15b. A solution of **14a** (77 mg, 0.082 mmol) in 0.9 mL of collidine (sym) was added to LiI (13.4 mg, 0.1 mmol). The reaction mixture was stirred under N_2 at 120–130 °C for 30 min. It was then cooled, diluted with CH_2Cl_2, and transferred to a wide-necked flask for concentration. The orange-red residue was partitioned between 1 M KH_2PO_4 (1 mL), H_2O and EtOAc. After phase separation, the aqueous layer was extracted with EtOAc (2×) and with $CHCl_3$ (1×). Each organic layer was washed with brine. The combined organic layers were dried, filtered, and concentrated to give 76 mg of crude **15a**. Preparative TLC (double development with 40% acetone/hexane) provided 28 mg of **15a** (45%) as a white foam, traveling just ahead of starting material (18 mg, 23%): IR ($CHCl_3$) 5.63, 5.71, 5.79 μm; NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 6 Hz, CH_3), 2.90–3.10 (m, SCH_2CH_2N), 3.36 (dd, $J_{5,6}$ = 3 Hz, $J_{6,8}$ = 5 Hz, H_6), 3.38–3.52 (m, SCH_2CH_2N), 4.53 (m, H_5), 5.15–5.36 (CH_2Ar's, H_3 and H_8), 6.00 (br s, H_1), 7.52–8.28 (aromatic protons); ^{13}C NMR ($CDCl_3$)[6] 17.9 (C_9), 32.6 (SCH_2), 39.7 (CH_2N), 62.5 (C_5), 62.6 (C_6), 65.4, 65.9 and 68.1 (3 CH_2Ar), 68.0 (C_3), 71.7 (C_8), 123.4 (C_1), 139.5 (C_2), 123.8–150 (Ar's), 155–176 ppm (4 C=O's); R_f ca. 0.48 (50% EtOAc/$CHCl_3$).

Treatment of **14c** (152 mg, 0.16 mmol) in the above manner provided 172 mg of crude **15b**. Preparative TLC (40% acetone/hexane) provided 61 mg of slightly impure **15b** traveling just ahead of 48 mg of slightly impure starting material, **14c**. Preparative TLC (50% EtOAc/$CHCl_3$) of recovered **14c** to remove polar impurities provided 39 mg of **14c** which was resubmitted to the decarbalkoxylation procedure and initial chromatography to give 12 mg of additional product. Extensive preparative TLC of the combined product (double development in 40% acetone/hexane, isolation, and then double development in 25% EtOAc/$CHCl_3$) was necessary to provide 55 mg of pure **15b** (45%) as a white foam: IR ($CHCl_3$) 5.63, 5.71, 5.80 μm (sh); NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 6.5 Hz, CH_3), 2.90–3.10 (m, SCH_2CH_2N), 3.28 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 8 Hz, H_6), 3.36–3.52 (m, SCH_2CH_2N), 4.60 (m, H_5), 5.13–5.39 (CH_2Ar's, H_3 and H_8), 5.98 (br s, H_1), 7.52–8.29 (aromatic protons); R_f ca. 0.54 (50% EtOAc/$CHCl_3$).

Carbapen-2-ems 16a and 16b. Diisopropylamine (100 μL, 0.71 mmol) was added to a stirred solution of **15a** (49 mg, 0.064 mmol) in 0.7 mL of Me_2SO. The stoppered reaction mixture was allowed to stand for 2 h. The red solution was then concentrated under reduced pressure. The residue was dissolved in EtOAc and reconcentrated. The process was repeated a few times, thus removing most of the Me_2SO. Preparative TLC (50% EtOAc/$CHCl_3$) of the resultant foam provided 6 mg of **16a** as a pale yellow foam. Approximately 35 mg of starting material was recovered from the less polar, major UV band. Recovered **15a** was recycled (2×) to provide 11 mg of additional **16a** (35% total yield) with a final recovery of 11 mg of **15a** (22%).

Data for **16a**: IR ($CHCl_3$) 5.61, 5.74 (sh), 5.80 μm; NMR (300 MHz, $CDCl_3$) δ 1.50 (d, J = 6 Hz, CH_3), 2.90–3.11 (m, SCH_2CH_2N), 3.13 (dd, $J_{1,5}$ = 8 Hz, $J_{1,1}$ = 18 Hz, H_1), 3.39 (partially buried dd, $J_{1,5}$ = 10 Hz, $J_{1,1}$ = 18 Hz, H_1), 3.40–3.48 (m, SCH_2CH_2N), 3.51 (dd, $J_{5,6}$ = 3 Hz, $J_{6,8}$ = 5 Hz, H_6), 4.18 (m, H_5), 5.18 (partially buried m, H_8), 5.20 (s, $NHCO_2CH_2Ar$), 5.27 (s, OCO_2CH_2Ar), 5.40 (midpoint of 2 d, J = 14 Hz, nonequivalent CO_2CH_2Ar protons), 7.51–8.26 (aromatic protons); R_f ca. 0.32 (50% EtOAc/$CHCl_3$).

Treatment of **15b** (55 mg, 0.072 mmol) in the above manner provided, after preparative TLC (50% EtOAc/$CHCl_3$), 10 mg of **16b** and from the less polar, major UV band, 40 mg of recovered **15b**. Starting material was recycled (3×) to provide 15 mg of additional **16b** with a final recovery of 13 mg of starting material (24%). A final preparative TLC (40% acetone/hexane) of the combined product afforded 20 mg of pure **16b** (36%) as a pale yellow foam: IR ($CHCl_3$) 5.61, 5.74 (sh), 5.80 μm; NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 6 Hz, CH_3), 2.92–3.17 (m, SCH_2CH_2N and H_1), 3.33–3.50 (m, SCH_2CH_2N and H_1), 3.46 (dd, $J_{5,6}$ = 3 Hz, $J_{6,8}$ = 7 Hz, H_6), 4.20–4.26 (m, H_5), 5.18 (partially buried m, H_8), 5.20

(s, $NHCO_2CH_2Ar$), 5.26 (s, OCO_2CH_2Ar), 5.38 (midpoint of 2 d, J = 14 Hz, nonequivalent CO_2CH_2Ar protons), 7.51–8.28 (aromatic protons); R_f ca. 0.44 (50% EtOAc/$CHCl_3$).

***N*-[[(*p*-Nitrobenzyl)oxy]carbonyl]thienamycin *p*-Nitrobenzyl Ester (19).** With stirring in an ice/NaCl bath, $NaHCO_3$ (1.27 g, 15.1 mmol) in 20 mL of H_2O was added to a solution of thienamycin (412 mg, 1.51 mmol) in 100 mL of H_2O and 100 mL of dioxane. After briefly stirring, *p*-nitrobenzyl chloroformate (494 mg, 2.30 mmol) in 5 mL of dioxane was added dropwise over 1.5–2 min. After being stirred in the cold for an additional 10 min, the reaction mixture was extracted with 50 mL of cold Et_2O (5×). The aqueous layer was stirred with continued cooling in the ice/NaCl bath, layered with 50 mL of cold EtOAc, and carefully acidified to ca. pH 2 with 2 M H_3PO_4. The phases were separated, and the aqueous layer was extracted with 50 mL of cold EtOAc (2×). The combined EtOAc layers were washed with brine and then with cooling and shaking were treated with 0.05 M LiOH. The pH of the aqueous layer remained near 7 up to the addition of 30 mL of base (1.5 mmol). After phase separation, the aqueous layer was washed with EtOAc. After careful evacuation to remove residual EtOAc, the aqueous layer was lyophilized to give 636 mg of lithium salt **18** as a yellow solid.

Lithium salt **18** was stirred with *p*-nitrobenzyl bromide (972 mg, 4.52 mmol) in 10 mL of HMPA for 3 h at room temperature under N_2, poured into 100 mL of H_2O, and extracted repeatedly with EtOAc. The combined EtOAc layers were washed with H_2O and brine, dried, filtered, and concentrated. The residue was slurried with ether, filtered, and washed with additional ether to provide 410 mg of **19** (46% yield) as a pale yellow powder: IR (Nujol) 5.66, 5.79 (sh), 5.91 μm; NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6 Hz, CH_3), 1.68 (d, J = 6 Hz, OH), 2.94–3.14 (m, SCH_2CH_2N), 3.14 (dd, $J_{1,5}$ = 8 Hz, $J_{1,1}$ = 18 Hz, H_1), 3.23 (dd, $J_{5,6}$ = 2 Hz, $J_{6,8}$ = 6 Hz, H_6), 3.40 (partially buried dd, $J_{1,5}$ = 10 Hz, $J_{1,1}$ = 18 Hz, H_1), 3.41–3.51 (m, SCH_2CH_2N), 4.23–4.32 (m, H_5 and H_8), 5.21 (s, $NHCO_2CH_2Ar$), 5.40 (midpoint of 2 d, J = 14 Hz, nonequivalent CO_2CH_2Ar protons), 7.53–8.30 (m, aromatic protons).

Bis-Derivatized Carbapen-1-em 20. A mixture of **19** (150 mg, 0.26 mmol) and DBU (4 μL, 0.027 mmol) in 1.5 mL of Me_2SO was stirred for 0.5 h and then added to 10 mL of 1 M KH_2PO_4 and 3 mL of EtOAc. After the phases were shaken and separated, the aqueous phase was extracted with 1 mL of EtOAc (5×). The combined extracts were washed with 1 M KH_2PO_4, dried, and concentrated to give 144 mg of a mixture of **19** and the desired product which traveled slightly faster on silica gel (7% MeOH/$CHCl_3$). The residue was slurried with $CHCl_3$ and filtered to give 75 mg of recovered starting material **19** (50%). Preparative TLC (7% MeOH/$CHCl_3$) of the filtrate provided 32 mg of **20** as a foam (21%): IR ($CHCl_3$) 5.66 (br), 6.81 μm; NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J = 6 Hz, CH_3), 1.75 (d, J = 4 Hz, OH), 2.90–3.10 (m, SCH_2CH_2N), 3.11 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 7 Hz, H_6), 3.38–3.52 (m, SCH_2CH_2N), 4.22–4.32 (m, H_8), 4.63 (m, H_5), 5.17 (m, H_3), 5.21 (s, $NHCO_2CH_2Ar$), 5.28 (s, CO_2CH_2Ar), 6.02 (br s, H_1), 7.52–8.27 (aromatic protons).

***N*-[[(*p*-Nitrobenzyl)oxy]carbonyl]-*O*-[[(*p*-nitrobenzyl)oxy]carbonyl]thienamycin *p*-Nitrobenzyl Ester (21).** A solution of *p*-nitrobenzyl chloroformate (30 mg, 0.14 mmol) in 1 mL of CH_2Cl_2 was added to a stirred mixture of **19** (41 mg, 0.07 mmol) and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol) in 1 mL of CH_2Cl_2 at 0 °C. After stirring under N_2 for 2.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O containing 0.3 mL of 1 M K_2HPO_4, followed by H_2O containing 0.3 mL of 1 M KH_2PO_4 and brine. The organic layer was then dried, filtered, and concentrated to give 56 mg of crude **21**. Preparative TLC (50% EtOAc/$CHCl_3$) provided 31 mg of **21** (58%) as a yellow foam having an IR, 300-MHz proton NMR (see Table I for absorption peaks of particular interest), and R_f identical with those of the totally synthetic material **16b**.

Tris-Derivatized Carbapen-1-em 22. Treatment of **20** (11 mg, 0.019 mmol) in the manner described for the conversion of **19** to **21** provided 12 mg of crude **22**. Preparative TLC (40% acetone/hexane) gave 7 mg of **22** (49%) as a white foam having an IR, 300-MHz proton NMR (see Table I for absorption peaks of particular interest), and R_f identical with those of the totally synthetic material **15b**.

(±)-8-Epithienamycin (17a) and (±)-Thienamycin (17b). To a solution of **16a** (5.2 mg, 0.0068 mmol) in 0.60 mL of dioxane, 50 μL of EtOH, 0.35 mL of deionized water (DI H_2O), and 10 μL of 1.0 M K_2HPO_4 was added 5 mg of 10% Pd/C. The suspension was alternately flushed with N_2 and evacuated (3×) and then alternately flushed with 50 psi of H_2 and evacuated (3×). It was then shaken for 30–40 min under 50 psi of H_2. After the mixture cooled in an ice bath and was centrifuged, the supernatant was removed from the catalyst and stored at 0 °C. The Pd/C was washed and centrifuged as above with 0.5 mL of DI H_2O (3×). The combined supernatants were extracted with 1–2 mL of Et_2O (5×) in the cold after which the aqueous layer was pumped briefly on a water aspirator to remove any residual organic solvents. The aqueous solution was then applied to a XAD-2 column (20 × 140 mm) which was eluted with DI H_2O. The fractions (100 drops = 6–7 mL each) were collected with continuous UV monitoring. Emergence of strongly UV absorbing material began at fractions 3–5 and was complete by fractions 25–30. Early fractions were examined by UV to exclude those few which absorbed too strongly in the 270–280-nm region. The remaining fractions (λ_{max} 298 nm) were combined and lyophilized to give (±)-8-epithienamycin (**17a**, 23% yield based on hydroxylamine-extinguishable UV absorption[1] at 298 nm): NMR (100 MHz measured at 5 °C, D_2O with dioxane as an internal standard) δ 1.31 (d, J = 6.4 Hz, CH_3), 3.14 and 3.20 (prominent peaks of m, SCH_2CH_2N and H_1's), 3.49 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 4.9 Hz, H_6), 4.15 (midpoint of m, H_5 and H_8). See Table II for antibacterial potency.

Treatment of **16b** in the above manner provided (±)-thienamycin (**17b**, 20–25% yield based on hydroxylamine-extinguishable UV absorption[1] at 298 nm): NMR (300 MHz, D_2O with no internal standard) δ 1.24 (d, J = 6.0 Hz, CH_3), 3.07, 3.13, and 3.21 (prominent peaks of m, SCH_2CH_2N and H_1's), 3.41 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6,8}$ = 6.0 Hz, H_6), 4.20 (midpoint of m, H_5 and H_8), 4.80 (HDO). The spectrum was superimposable on a 300-MHz proton NMR spectrum of an authentic sample of thienamycin. See Table II for antibacterial potency.

Acknowledgment. We wish to thank Dr. B. H. Arison and Mr. H. Flynn for obtaining the 300-MHz ^1H NMR spectra, Dr. A. W. Douglas for the 100-MHz ^1H NMR spectra, Dr. A. W. Douglas and Mr. R. A. Reamer for recording and interpreting the ^{13}C NMR spectra, Dr. C. H. Shunk for help in the preparation of intermediates, and Ms. J. S. Kahan for the antibacterial assays.

Registry No. 1, 59995-64-1; **3a**, 65794-42-5; **3b**, 65794-47-0; **5a**, 67314-42-5; **5b**, 72778-03-1; **6a**, 65750-52-9; **6b**, 65794-48-1; **7a** (*E* isomer), 67336-39-4; **7a** (*Z* isomer), 67314-47-0; **7b** (*E* isomer), 72778-04-2; **7b** (*Z* isomer), 72778-05-3; **8a** (*Z* isomer), 72843-06-2; **8b** (*Z* isomer), 72843-07-3; **9a**, 6581-09-6; **9b**, 65750-61-0; **10a**, 65750-60-9; **10b**, 65794-50-5; **11a**, 65750-53-0; **11b**, 65794-49-2; **12**, 65750-54-1; **13a**, 72749-11-2; **13b**, 72765-22-1; **14a**, 65750-55-2; **14c**, 65794-43-6; **15a**, 72778-06-4; **15b**, 72778-07-5; **16a**, 67576-51-6; **16b**, 65991-26-6; **17a**, 67314-45-8; **17b**, 65750-57-4; **18**, 64066-86-0; **19**, 64067-13-6; **20**, 72778-08-6; **21**, 72778-09-7; **22**, 72843-08-4; [[(*p*-nitrobenzyl)carbonyl]amino]ethanethiol, 65750-59-6; bis(*p*-nitrobenzyl) ketomalonate, 65750-58-5; cysteamine hydrochloride, 156-57-0; *p*-nitrobenzyl chloroformate, 4457-32-3; *p*-nitrobenzyl bromide, 100-11-8; malonic acid, 141-82-2; bis(*p*-nitrobenzyl) malonate, 67245-85-6.