Found: C, 79.75; H, 10.30.

To an ethylamine (10 mL) solution of the (*E,Z,E*)-acetate IVb (R = Ac) (99 mg) was added Li (50 mg) at −78 °C under a nitrogen atmosphere. After 1 h, NH_4Cl (1 g) was added, ethylamine was evaporated, and the residue was taken into ether. From the ether solution was obtained (*E,Z,E*)-neocembrene (Vb) (35 mg, 43%) after passing through a SiO_2 column with *n*-hexane. (*E,Z,E*)-Neocembrene (Vb): mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46); NMR δ 1.58 (br s, 6 H, C_3- and C_{11}-Me), 1.67 (br s, 6 H, C_7- and C_{15}-Me), 4.67 (br s, C=CH_2), and 4.7-5.3 (3 C=CH); IR (film) 1660, 1642, and 890 cm^{-1}.

Similar treatment of (*E,E,Z*)-*cis*-isopropenyl alcohol IVc (R = H) (176 mg) with acetic anhydride (2 mL) and pyridine (4 mL) at room temperature overnight afforded the corresponding acetate IVc (R = Ac) (199 mg): mass spectrum, *m/e* 330 (M^+); NMR δ 1.62 (3 H), 1.68 (6 H), and 1.80 (3 H) (C=CMe), 1.93 (Ac), 4.76 and 4.92 (C=CH_2), 5.14 (br d, *J* = 8 Hz, C_2-H), 4.7-5.3 (m, 2 C=CH), and 5.57 (dd, *J* = 3 and 8 Hz, C_1-H); IR (film) 1740, 1667, 1645, and 895 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.68; H, 10.25.

To an ethylamine (15 mL) solution of the (*E,E,Z*)-*cis*-acetate IVc (R = Ac) (155 mg) was added Li (70 mg) at −78 °C under a nitrogen atmosphere. After stirring for 1.5 h at the same temperature, NH_4Cl (1.5 g) was added, ethylamine was evaporated, and the residue was extracted with *n*-hexane. The *n*-hexane soluble hydrocarbon was passed through a SiO_2 column with *n*-hexane to give (*E,E,Z*)-neocembrene (Vc): 45 mg, 35%; mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46); NMR δ 1.57 (6 H), 1.65 (3 H), and 1.67 (3 H) (C=CMe), 4.70 (br s, C=CH_2), and 5.03 (br m, 3 C=CH); IR (film) 1645, 890, and 832 cm^{-1}.

Preparation of *d*- and *l*-(*E,E,E*)-Neocembrenes. To an ice-cooled benzene (20 mL) solution of *dl*-(*E,E,E*)-*trans*-isopropenyl alcohol[13] XX (380 mg) and pyridine (1 mL) was added *l*-menthoxyacetic acid chloride (460 mg) and the mixture was stirred for 2 h with ice cooling and then overnight at room temperature, poured into ice water, and extracted with ether. After the solution was washed with aqueous HCl, $NaHCO_3$, and NaCl solutions, and then dried over $MgSO_4$, the ether was evaporated to obtain crude ester (590 mg), which was passed through a SiO_2 column with *n*-hexane–AcOEt (20:1) to give *l*-menthoxyacetate XXI: 568 mg; mp 68–71 °C; $[\alpha]_D$ −54.4°. Anal. Calcd for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.80; H, 11.09.

Repeated recrystallization of the ester with MeOH afforded needles, mp 82–83 °C, $[\alpha]_D$ −89.0°. The optically pure ester (73 mg) in ethylamine (15 mL) was cooled to −78 °C under a nitrogen atmosphere, Li (15 mg) was added with stirring, and the mixture was kept at the same temperature until the blue color disappeared. Water was added and the mixture was extracted with ether. Volatile materials were removed and the resultant residue was passed through a 10% $AgNO_3$–SiO_2 column with *n*-hexane–ether (10:1) to obtain *d*-neocembrene (23 mg), $[\alpha]_D$ +19.5°; mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46).

A benzene (5 mL) solution of *dl*-(*E,E,E*)-*trans*-isopropenyl alcohol XX (194 mg) and pyridine (0.5 mL) was similarly treated with *d*-methoxyacetic acid chloride (240 mg) to result in the isolation of the corresponding ester XXII (265 mg), mp 66–69 °C; $[\alpha]_D$ +53.5°. Anal. Calcd for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 81.75; H, 11.03.

The crude ester was repeatedly recrystallized from MeOH to get a pure specimen, needles, mp 82–83 °C; $[\alpha]_D$ +88.0°. To the pure ester (203 mg) in ethylamine (50 mL) was added Li (40 mg) under the same conditions as in the case of the *l*-ester and *l*-neocembrene (66 mg); $[\alpha]_D$ −19.0° was obtained after a pass through a 10% $AgNO_3$–SiO_2 column with *n*-hexane–ether (10:1): mass spectrum, *m/e* 272 ($C_{20}H_{32}$ requires *m/e* 272.46). *d*- and *l*-neocembrenes were superimposable with *dl*-neocembrene in their NMR and IR spectra.

Registry No. Ib, 72623-57-5; Ic, 72623-58-6; IIb, 72623-59-7; IIc, 72638-61-0; IIIb, 72623-60-0; IIIc, 72623-61-1; IVb (R = H), 72690-07-4; IVb (R = Ac), 72690-08-5; IVc (R = H), 72690-09-6; IVc (R = Ac), 72690-10-9; (+)-Va, 72691-72-6; (−)-Va, 31570-39-5; Vb, 72690-72-3; Vc, 72690-73-4; VIb, 3790-71-4; VIc, 3879-60-5; VIIc, 24163-94-8; VIIIc, 72638-62-1; IXb, 1117-51-7; IXc, 3953-35-3; Xb, 64759-50-8; Xc, 72638-63-2; XIb, 72638-64-3; XIc, 72638-65-4; XVIb, isomer 1, 72638-66-5; XVIb, isomer 2, 72638-67-6; XVIIb, 72690-74-5; XVIIc, 72690-75-6; (±)-XX, 59686-17-8; (−)-XXI, 72638-68-7; (+)-XXII, 72690-76-7; ethyl acetoacetate, 141-97-9; ethyl (*Z,E,Z*)-geranylgeranioate, 72638-69-8; (*E,E,Z*)-geranylgeranioic acid, 72638-70-1; ethyl (*Z,Z,E*)-geranylgeranioate, 64759-49-5; (*E,Z,E*)-geranylgeranioic acid, 72638-71-2.

(13) Preparation of XX is described in ref 4.

Thienamycin Total Synthesis. 1. Synthesis of Azetidinone Precursors of (±)-Thienamycin and Its Stereoisomers

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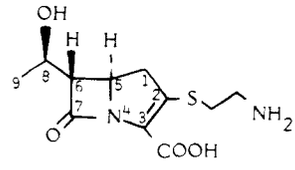
Received September 25, 1979

The synthesis of fully functionalized azetidinone precursors to (±)-thienamycin and its C(6)–C(8) stereoisomers is described. Cycloaddition of chlorosulfonyl isocyanate and 1-acetoxybutadiene afforded azetidinone 7 which, after appropriate modification, was hydroxyethylated via an aldol condensation, generating all four side-chain diastereomers, **11a-d**. Three of the four diastereomers were obtained in sufficient amounts for subsequent conversion to azetidinones **16a-c**, fully functionalized for elaboration to the bicyclic system.

Thienamycin (1) is an exceptionally potent, broad-spectrum β-lactam antibiotic particularly notable for its activity against *Pseudomonas* spp. and its resistance to bacterial β-lactamases. Its discovery, isolation, and structure elucidation have been the subject of previous communications from these laboratories.[1a,b] Recently we reported the total synthesis of (±)-thienamycin.[2] This and the following two papers are a full description of that work.

The absolute stereochemistry of thienamycin (1) is 5*R*,6*S*,8*R*.[1b] The novelty of the thienamycin structure can



I

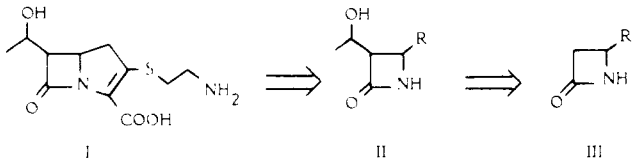
5R, 6S, 8R

(1) (a) 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 cited therein; (b) 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).

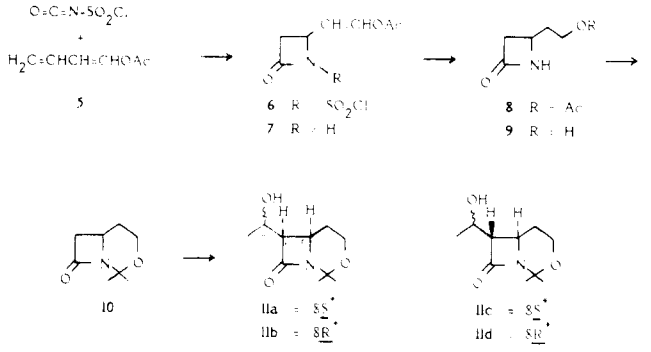
(2) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).

0022-3263/80/1945-1130$01.00/0

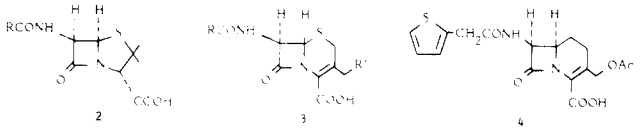
Scheme I



Scheme II



be recognized by comparing it to the penicillins **2** and the cephalosporins **3**. Replacement of the ring sulfur atom by carbon is unprecedented among the naturally occurring β-lactam antibiotics; however, (±)-1-carbacephalothin (**4**)



has been made by total synthesis.[3] More striking is the absence of the amide side chain and the trans relationship of the β-lactam protons rather than the heretofore always seen cis stereochemistry.[4]

Our synthetic strategy was influenced by the fact that our target compound is labile. To delay ring closure to the strained carbapenem system until as late as possible, the initial goal became the construction of the fully substituted azetidinone precursor II (see Scheme I) where R is a latent functionality suitable for elaboration of the second ring. The preparation of C(3)-unsubstituted azetidinone III followed by introduction of the hydroxyethyl side chain (III → II) and identification of the stereoisomers are the subjects of this paper.

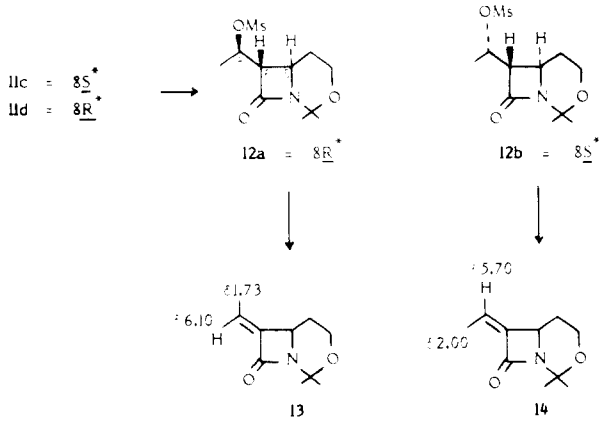
The [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) to olefins to produce β-lactams is a well-documented reaction,[5] but there are no known examples of CSI addition to heteroatom-substituted conjugated dienes. The reaction of CSI with 1-acetoxybutadiene **5**[6] gives the *N*-chlorosulfonyl β-lactam **6** as the major product (Scheme II). Reductive hydrolysis[7] provided N-unsubstituted β-lactam **7**, predominantly as the *E* isomer, in 41% overall yield based on CSI. Catalytic reduction of **7** gave acetate **8** which underwent base-catalyzed deacetylation to give alcohol **9**. Simultaneous blocking of the alcohol and lactam was accomplished by treating **9** with 2,2-dimethoxypropane in the presence of acid, providing acetonide **10** in 73% overall yield (three steps). Bicyclic acetonide **10** is an intermediate compatible with the carbanion chemistry planned for the introduction of the hydroxyethyl side chain.

Table I. 300-MHz ^{1}H NMR Data for Diastereomeric Carbinols 11a-d[a]

	solvent	11a (cis *S**)	11b (cis *R**)	11c (trans *S**)	11d (trans *R**)
shift (H_6, dd)	$CDCl_3$	3.18	3.14	2.85	2.83
	Me_2CO-d_6	3.08	3.08	2.85	2.69
$J_{5,6}$	$CDCl_3$	5	5	1.5	1.5
	Me_2CO-d_6	5	5	1.5	1.5
$J_{6,8}$	$CDCl_3$	10	9	6.5	6.5
	Me_2CO-d_6	10	7.5	4.5	7
yield		0.2	9	50	39

[a] Chemical shifts values are given in δ units, *J* values in hertz, and yields as percents.

Scheme III



Initially, a stereochemically indiscriminate introduction of the hydroxyethyl side chain via an aldol reaction was planned to provide all of the C(6)–C(8) thienamycin stereoisomers for structure–activity studies. The synthetic utility of simple, unactivated β-lactam enolates had been demonstrated.[8a-e] Analogously, treatment of **10** with lithium diisopropylamide at −78 °C followed by acetaldehyde gave hydroxyethylated products **11a–d**[9,10] in 98% yield after chromatography. Each of the four possible diastereomeric carbinols could be identified in the 300-MHz ^{1}H NMR spectrum of the product mixture[11] (see Table I). Four doublet of doublets assignable to H(6) are distinguishable in the δ 2.7–3.2 region. The two minor diastereomers **11a,b** were separated from the two major diastereomers **11c,d** by silica gel chromatography, with **11a,b** eluting off first. Assignment of relative stereochemistry at C(5)–C(6) was based on $J_{5,6}$ as cis β-lactam

(3) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).

(4) For a description of epithienamycin derivatives possessing the usual cis β-lactam stereochemistry see: (a) 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, Abstracts, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1977, No. 80; (b) P. J. Cassidy, E. O. Stapley, R. Goegelman, T. W. Miller, B. Arison, G. Albers-Schönberg, S. B. Zimmerman, and J. Birnbaum, *ibid.*, No. 81; (c) D. F. Corbett, A. J. Eglington, and T. T. Howarth, *Chem. Commun.*, 953 (1977), and references cited therein.

(5) For recent reviews see: (a) N. S. Isaacs, *Chem. Soc. Rev.*, **5**, 181 (1976); (b) J. K. Rasmussen and A. Hassner, *Chem. Rev.*, **76**, 389 (1976); (c) W. A. Szabo, *Aldrichimica Acta*, **10**, 23 (1977).

(6) H. C. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949). This diene is a mixture of *E*/*Z* isomers; however, this fact is of no consequence as the double bond is subsequently reduced.

(7) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).

(8) (a) T. Durst and M. J. LeBelle, *Can. J. Chem.*, **50**, 3196 (1972); (b) T. Durst, R. Van Den Elzin, and R. Legault, *ibid.*, **52**, 3206 (1974); (c) K. Kuhlein and H. Jensen, *Justus Liebigs Ann. Chem.*, **402**, 369 (1974); (d) F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.*, **42**, 2960 (1977); (e) S. Kano, T. Ebata, K. Funaki, and S. Shibuya, *Synthesis*, 746 (1978).

(9) Numbering corresponds to that of thienamycin.

(10) All compounds are racemic. All structural formulas and stereochemical designations refer to the enantiomer related to thienamycin.

(11) Diastereomer **11a**, formed in only 0.2% yield, was not detected until subsequent scale up of the initial aldol reaction.

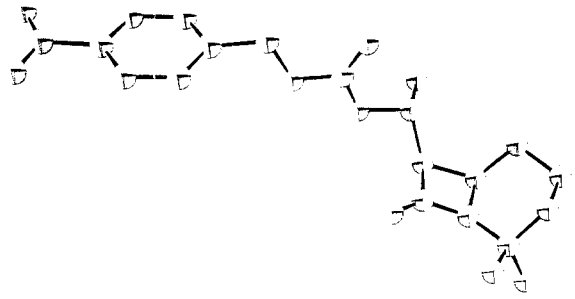


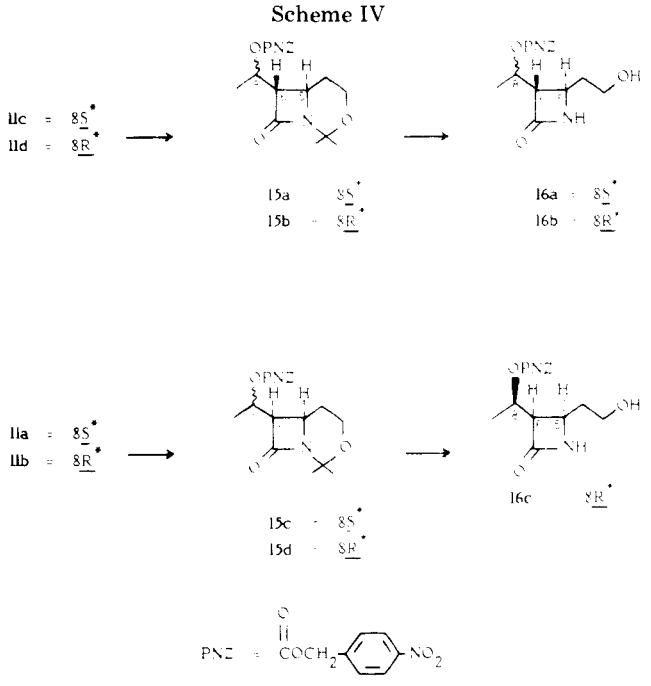
Figure 1. ORTEP drawing[15b] of **15d**.

coupling constants are larger than trans coupling constants.[12] Thus **11a,b** with $J_{5,6}$ = 5 Hz are the two cis diastereomers, and the more polar pair, **11c,d**, with $J_{5,6}$ = 1.5 Hz, are the two trans diastereomers. The two trans diastereomers, **11c,d**, account for 89% of the total hydroxyethylated product. As expected, electrophilic attack by the acetaldehyde occurred preferentially from the more accessible exo face of the β-lactam enolate.

Evidence for the assignment of side chain configuration for the pair of trans diastereomers, **11c,d**, was obtained via a two-step mesylation–elimination sequence[1b] to ene lactams **13** and **14** as outlined in Scheme III. Mesylation[13] of mixture **11c,d** gave mesylates **12a** and **12b** in a ratio reflecting that of the starting material. The mesylates, which were separable by silica gel chromatography, underwent elimination upon treatment with $NaHCO_3$ in refluxing MeOH, each giving a single, different ene lactam. Structural assignments by NMR for the pair of ene lactams were based on the anisotropic deshielding effect of the β-lactam carbonyl on the vinyl methyl group and the vinyl proton. The vinyl methyl group of ene lactam **14** derived from the major mesylate, **12b**, appeared at δ 2.00, downfield of the vinyl methyl group of ene lactam **13** derived from the minor mesylate, **12a**, which appeared at δ 1.73. The converse is true for the vinyl protons. Presuming a trans coplanar elimination of CH_3SO_3H, it follows that the side-chain configuration of the major mesylate, **12b**, is *S** and that of the minor mesylate, **12a**, is *R**. Since the conversion of **11c,d** to **12a,b** is high (68%) and the mesylation was actually performed on a chromatography fraction considerably enriched in **11c** (2:1 **11c/11d**), it seems reasonable to conclude that **11c**, leading to the major mesylate, **12b**, also has the *S** side-chain configuration, and **11d**, leading to the minor mesylate, **12a**, the *R** side-chain configuration.[14]

The major cis aldol product, **11b**, was initially assigned the *R** side-chain configuration by analogy to related work in which 6(7)-hydroxyethyl-substituted penicillins and cephalosporins were prepared.[8d] DiNinno et al. observed the formation of only a single 6β-hydroxyethyl penicillanate whose carbinol configuration was *R*. This high specificity of attack on the endo face of the β-lactam enolate was explained in terms of steric approach control of the acetaldehyde concomitantly coordinated to the metal enolate. Confirmation of the structural assignment of **11b** was obtained in a single-crystal X-ray analysis of its (*p*-nitrobenzyloxy)carbonyl derivative, **15d** (see Figure 1).[15a]

Scheme IV



Having introduced the hydroxyethyl side chain and identified the diastereomers, we next found it necessary to protect the carbinol. A protecting group removable under mild, neutral conditions was required. We knew from an ongoing thienamycin derivative program in these laboratories that the *p*-nitrobenzyl group, removable by hydrogenolysis, was our best choice. Analogous derivatization of the amine and carboxyl functionalities as they were subsequently introduced would allow for the simultaneous deblocking of all three groups as the final step of the synthesis.

Acylation of trans carbinol mixture **11c,d** with *p*-nitrobenzyl chloroformate with *n*-butyllithium or 4-(dimethylamino)pyridine[16] as base gave *p*-nitrobenzyl carbonates **15a,b** (Scheme IV). Initially, treatment of a mixture of **15a,b** with aqueous acetic acid to reverse the acetonide provided azetidinones **16a,b** from which pure trans *S** diastereomer **16a** was obtained crystalline, leaving a mother liquor mixture containing **16a/16b** in an ~2:3 ratio, respectively. Subsequently, separation of **15a,b** was achieved on silica gel, and the two trans diastereomers could be carried on independently from this point. In an analogous manner, **15c,d** was prepared from **11a,b**, and **15d** was converted to **16c**.

Azetidinones **16a** and **16b** are fully functionalized for elaboration to (±)-thienamycin and its C(8) epimer (work described in the following papers). Azetidinone **16c** is particularly interesting as it is a precursor for a thienamycin isomer whose natural counterpart has not yet been described.

Finally, it seems worthwhile to note an NMR correlation that has proven useful as an indication of side-chain stereochemistry for a given pair of trans *R,S* diastereomers as represented in Table II. Referring to H(6) (or to that β-lactam proton corresponding to H(6) of thienamycin), one observes that δ H(6) is upfield for that diastereomer

(12) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, p 330.

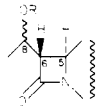
(13) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(14) A similar mesylation–elimination sequence performed on cis carbinol **11b** gave ene lactams **13** and **14** in a ratio of 2:1, respectively. Since steric crowding on the endo face of the cis mesylate prevents the mesyloxy group and H(6) from readily achieving the anti relationship necessary for facile E2 elimination, it is not surprising that, in this case, other pathways are found, and a mixture of ene lactams results.

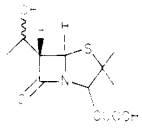
(15) (a) We thank Dr. J. Springer of these laboratories for this analysis. Details have been submitted as supplementary material. (b) C. A. Johnson, "ORTEP-II: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations", Report ORNL-3794 (2nd revision, with supplemental instructions), U.S. Atomic Energy Commission, Oak Ridge National Laboratory, Oak Ridge, TN, 1970.

(16) E. Guibe-Jampel and M. Wakselman, *Chem. Commun.*, 267 (1971).

Table II. Correlation of δ_{H_6} with Side-Chain Configuration



$\delta_{H_6}(8R)$ upfield of $\delta_{H_6}(8S)$

diastereomer pair	structure	side-chain config	δ_{H_6}	solvent
1[8d]		*R*	3.26	$CDCl_3$
		S	3.38	
2	11a	*R**	2.69	Me_2CO-d_6
	11b	*S**	2.85	
3	12a	*R**	2.61	C_6D_6
	12b	*S**	2.67	
4	15a	*R**	3.02	$CDCl_3$
	15b	*S**	3.12	
5	16a	*R**	3.07	$CDCl_3$
	16b	*S**	3.19	

whose side-chain configuration at C(8) is *R*. This generality held throughout the synthesis of thienamycin and 8-epithienamycin (see part 3 of this series) as well as in the earlier related work on the 6α-hydroxyethyl penicillanates.[8d] However, in subsequent and as yet unpublished work, exceptions have been found. Thus the correlation must be used with discretion and cannot by itself rigorously establish side-chain stereochemistry.

Experimental Section

General Methods. Methylene chloride was dried over 4A molecular sieves. Tetrahydrofuran was distilled from sodium–benzophenone ketyl. Commercial CH_3CHO and CH_3SO_2Cl were distilled prior to use. Diisopropylamine was distilled from CaH_2. Boron trifluoride etherate was purified according to the method of Fieser and Fieser.[20] Routine workup of reaction mixtures is represented as follows: extraction solvent, washing solutions (saturated unless otherwise specified), drying agent. Filtration and concentration of the organic phase on a rotary evaporator are implied. Plate layer chromatography (PLC) was performed on Analtech silica gel GF plates, and EtOAc was routinely used as the eluting solvent. Column chromatography was done by using Baker silica gel (60–200 mesh). High-pressure liquid chromatography (LC) was done on a Waters Associates Prep LC/System 500 instrument using PrepPAK-500/Silica cartridges which contain 325 g of packing per cartridge.

Melting points are uncorrected. NMR spectra were recorded on a 60-MHz spectrometer unless otherwise noted, using tetramethylsilane as internal standard. All reported elemental analyses are within ±0.4% of the calculated value.

4-(2-Acetoxyvinyl)-2-azetidinone (7). Maintaining the temperature at −23 °C, we added a solution of chlorosulfonyl isocyanate (75 mL, 0.87 mol) in 150 mL of Et_2O, over a period of 75 min, to a stirred solution of freshly distilled 1-acetoxybutadiene **5** (124 g, 1.1 mol) in 225 mL of Et_2O. The resulting solution was stirred for an additional 45 min at −23 °C, and then it was cautiously poured into an efficiently stirred solution of Na_2SO_3 (150 g, 1.19 mol) and K_2HPO_4 (375 g, 2.16 mol) in 1.5 L of water to which 1.5 kg of ice and 1.5 L of Et_2O had been added, keeping the temperature ≤5 °C. After the addition was completed, the temperature was allowed to rise to 15 °C over a period of ~5 min. Workup [Et_2O (5 × 500 mL), $MgSO_4$] gave an Et_2O solution which was concentrated to a volume of ~500 mL, resulting in the bulk of the product crystallizing out to give 52.1 g of [acetoxy-(*E*)-vinyl]azetidinone **7**, mp 90–91 °C. Treatment of the mother liquors with charcoal and concentration of the filtrate afforded a second crop of (*E*)-**7**, giving a total of 55.6 g (41%). Recrystallization from Et_2O gave analytically pure material: mp 91–92 °C; NMR ($CDCl_3$) δ 2.15 (s, $COCH_3$), 2.72 (ddd, J_{gem} = 15 Hz, J_{trans} = 3 Hz, J_{NH} = 1.5 Hz, H_3), 3.30 (ddd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, J_{NH} = 2 Hz, H_3), 4.20 (ddd, J = 8 Hz, J_{cis} = 5 Hz, J_{trans} = 3 Hz, H_4), 5.53 (dd, J_{vinyl} = 13 Hz, J = 8 Hz, CHC**H**=CHOAc), 6.3 (br s, NH), 7.35 (d, J = 13 Hz, CHOAc). Anal. ($C_7H_9NO_3$) C, H, N.

Further treatment of the mother liquors afforded a small third crop of material which was a mixture of *E*/*Z* isomers. Recrystallization from Et_2O gave pure (*Z*)-**7**: mp 105–107 °C; NMR ($CDCl_3$) δ 2.20 (s, $COCH_3$), 2.77 (ddd, J_{gem} = 15 Hz, J_{trans} = 2.5 Hz, J_{NH} = 1.5 Hz, H_3), 3.33 (ddd, J_{gem} = 15 Hz, J_{cis} = 5 Hz, J_{NH} = 2 Hz, H_3), 4.65 (ddd, J = 9 Hz, J_{cis} = 5 Hz, J_{trans} = 2.5 Hz, H_4), 5.05 (dd, J_{vinyl} = 6 Hz, J = 9 Hz, CHC**H**=CHOAc), 6.2 (br s, NH), 7.18 (d, J = 6 Hz, CHOAc). Anal. ($C_7H_9NO_3$) C, H, N.

4-(2-Acetoxyethyl)-2-azetidinone (8). A solution of **7** (10.0 g, 0.065 mol) in 200 mL of EtOAc containing 100 mg of 10% Pd/C was hydrogenated on a Parr shaker at 25 °C under 40 psi of H_2 for a period of 15 min. The reaction mixture was filtered through a packed bed of Supercel which was washed with additional EtOAc. Evaporation of the filtrate in vacuo gave 10.0 g (99% yield) of **8** as a white crystalline solid. Recrystallization from Et_2O afforded an analytical sample: mp 44–47 °C; IR ($CHCl_3$) 5.66, 5.74 μm; NMR ($CDCl_3$) δ 1.98 (m, CH_2CH_2OAc), 2.07 (s, $COCH_3$), 2.62 (ddd, J_{gem} = 13 Hz, J_{trans} = 2.3 Hz, J_{NH} = 1.0 Hz, H_3), 3.13 (ddd, J_{gem} = 13 Hz, J_{cis} = 4.5 Hz, J_{NH} = 1.9 Hz, H_3), 3.71 (m, H_4), 4.18 (m, CH_2OAc), 6.56 (br s, NH); mass spectrum, *m*/*e* 114, 84, 73, 43. Anal. ($C_7H_{11}NO_3$) C, H, N.

4-(2-Hydroxyethyl)-2-azetidinone (9). Under nitrogen at 0 °C, a solution of NaOMe (77 mg, 1.4 mmol) in 5 mL of anhydrous MeOH was added to a solution of **8** (2.24 g, 0.014 mol) in 25 mL of anhydrous MeOH, and the resulting solution was stirred for a period of 2 h. The solution was then neutralized with glacial HOAc, and the MeOH was removed under reduced pressure to give an oil. The product was purified by column chromatography on silica gel (80 g, 10% MeOH/$CHCl_3$ elution) to give 1.55 g (96% yield) of **9** as a hygroscopic, crystalline solid: mp 50 °C; IR ($CHCl_3$) 5.67 μm; NMR ($CDCl_3$) δ 1.84 (m, CH_2CH_2OH), 2.58 (ddd, J_{gem} = 13 Hz, J_{trans} = 2.2 Hz, J_{NH} = 1.1 Hz, H_3), 3.1 (br s, OH), 3.10 (ddd, J_{gem} = 13 Hz, J_{cis} = 4.2 Hz, J_{NH} = 1.6 Hz, H_3), 3.72 (t, J = 6 Hz, CH_2OH), 3.76 (m, H_4), 6.80 (br s, NH); mass spectrum (silylated), *m*/*e* 332 [(M + 1)$^+$, trisilyl],[17] 260 [(M + 1)$^+$, disilyl], 259 (M$^+$, disilyl), 244, 188 [(M + 1)$^+$, monosilyl], 174.

8-Oxo-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octane (10). Boron trifluoride etherate (0.642 mL, 0.005 mol) was added to a solution of **9** (6.0 g, 0.052 mol) and 2,2-dimethoxypropane (6.5 g, 0.063 mol) in 60 mL of anhydrous CH_2Cl_2 at ambient temperature. The resulting solution was stirred for 90 min. Workup [1 M pH 7 phosphate buffer (60 mL), H_2O (2×), NaCl] gave 5.3 g of crystalline product which was recrystallized from petroleum ether/Et_2O to give 4.1 g (77% yield) of analytically pure **10**: mp 61–62 °C; IR ($CHCl_3$) 5.73 μm; NMR ($CDCl_3$) δ 1.43 and 1.77 (2 s, *gem*-dimethyls), 1.75 (m, $CHCH_2CH_2$), 2.53 (dd, $J_{7,7}$ = 14 Hz, J_{trans} = 2 Hz, H_7), 3.10 (dd, $J_{7,7}$ = 14 Hz, J_{cis} = 4.5 Hz, H_7), 3.58 (m, H_6), 3.85 (m, CH_2O); mass spectrum, *m*/*e* 140, 98. Anal. ($C_8H_{13}NO_2$) C, H, N.

Diastereomeric Carbinols 11a–d. A solution of **10** (20.0 g, 0.129 mol) in 250 mL of anhydrous THF was cooled under a nitrogen atmosphere to −78 °C. Using a Flex-needle, we transferred this solution under positive nitrogen pressure over a 3-min period to a freshly prepared solution of lithium diisopropylamide under nitrogen at −78 °C made from *n*-BuLi (54.6 mL of a 2.6 M solution in *n*-hexane, 0.142 mol) and diisopropylamine (19.8 mL, 0.142 mol) in 500 mL of anhydrous THF. The resulting enolate solution was aged at −78 °C for a period of 10 min and then treated with neat CH_3CHO (10.8 mL, 0.194 mol). The reaction was quenched in 30 s by the addition of 150 mL of saturated NH_4Cl solution. The cooling bath was removed, and the mixture was allowed to warm to ~0 °C. Workup [EtOAc (250 mL, 2 × 150 mL), NaCl (500 mL)] gave 25.6 g of an oil. This

(17) This intermediate (**9**) and the related intermediates **16b,c** showed an unusually high tendency toward undergoing molecule-ion reactions in the mass spectrometer, producing intense (M + 1)$^+$ peaks. That they are indeed (M + 1)$^+$ peaks was confirmed by high-resolution and d_9-silylation studies for which we thank Mr. J. L. Smith and Dr. G. Albers-Schönberg.

material was redissolved in 1:4 EtOAc/CH_2Cl_2 and filtered through a wet bed of silica gel (125 g, 1:4 EtOAc/CH_2Cl elution) prior to purification by high-pressure LC. High-pressure LC was done in 5-g batches by using two silica cartridges (3:2 EtOAc/CH_2Cl_2 elution) to provide, overall, 2.2 g (9%) of diastereomeric cis carbinols **11a,b** and 23.0 g (89%) of diastereomeric trans carbinols **11c,d** as pale yellow oils.

Data for **11b** which eluted off first: IR (CH_2Cl_2) 5.72 μm; NMR ($CDCl_3$) δ 1.22 (d, J = 6.5 Hz, C**H**$_3$CH), 1.40 and 1.73 (2 s, *gem*-dimethyls), 1.7 (m, C**H**$_2$CH$_2$O), 3.1 (br s, OH), 3.14 (dd, $J_{6,8}$ = 9 Hz, $J_{5,6}$ = 5 Hz, H_6), 4.0 (m, CH_2O, H_5, and H_8); mass spectrum (silylated), m/e 271 (M^+), 256.

Data for **11c,d**: IR (CH_2Cl_2) 5.73 μm; NMR (Me_2CO-d_6) δ 1.23 (d, J = 6.5 Hz, C**H**$_3$CH), 1.40 and 1.63 (2 s, *gem*-dimethyls), 1.8 (m, C**H**$_2$CH$_2$O), 2.69 (dd, $J_{6,8}$ = 7 Hz, $J_{5,6}$ = 1.5 Hz, H_6 of **11d**), 2.85 (dd, $J_{6,8}$ = 4.5 Hz, $J_{5,6}$ = 1.5 Hz, H_6 of **11c**), 3.3 (br s, OH), 3.8 (m, CH_2O, H_5, and H_8); mass spectrum (silylated), m/e 271 (M^+), 256.

The high-pressure LC cut providing **11b** also contained **11a** but in an amount observable only by FT NMR. See Table I for the 300-MHz ^{1}H NMR data of **11a** and the other diastereomers.

Mesylates 12a,b. Under a nitrogen atmosphere, methanesulfonyl chloride (55 μL, 0.71 mmol) was added to a solution of **11c,d** (~2:1 **11c**/**11d**) and NEt_3 (134 μL, 0.97 mmol) in 5 mL of CH_2Cl_2 cooled to 0 °C. The resulting solution was stirred for 30 min. Workup (H_2O, 1 M pH 3 phosphate buffer, 5% $NaHCO_3$, H_2O, NaCl) gave 156 mg of a pale yellow oil. The crude mesylate mixture was purified by PLC. Multiple development [1:9 Me_2CO/hexane (4×)] was necessary to separate the diastereomers.

Data for **12a** (44 mg, 25%): R_f 0.13; mp 89–90 °C; IR (CH_2Cl_2) 5.73 μm; NMR (C_6D_6) δ 1.30 (d, J = 6.5 Hz, C**H**$_3$CH), 1.3 (m, C**H**$_2$CH$_2$O), 1.09 and 1.83 (2 s, *gem*-dimethyls), 2.40 (s, CH_3SO_2), 2.61 (dd, $J_{6,8}$ = 7.5 Hz, $J_{5,6}$ = 1.8 Hz, H_6), 3.4 (m, CH_2O and H_5), 4.82 (qq, $J_{6,8}$ = 7.5 Hz, $J_{8,9}$ = 6.5 Hz, H_8); mass spectrum, m/e 277 (M^+), 262, 182, 124. Anal. ($C_{11}H_{19}NO_5S$) C, H, N, S.

Data for **12b** (77 mg, 43%): R_f 0.08; mp 103 °C; IR (CH_2Cl_2) 5.71 μm; NMR (C_6D_6) 1.2 (m, C**H**$_2$CH$_2$O), 1.16 and 1.81 (2 s, *gem*-dimethyls), 1.34 (d, J = 6.5 Hz, C**H**$_3$CH), 2.46 (s, CH_3SO_2), 2.67 (dd, J = 4.5 Hz, J = 1.8 Hz, H_6), 3.4 (m, CH_2O and H_5), 4.83 (qq, $J_{6,8}$ = 7.5 Hz, $J_{8,9}$ = 6.5 Hz, H_8); mass spectrum, m/e 277 (M^+), 262, 182, 124.

Ene Lactam 13. A mixture of **12a** (44 mg, 0.16 mmol) and $NaHCO_3$ (27 mg, 0.32 mmol) in 2.5 mL of MeOH was refluxed for a period of 30 min. The reaction mixture was allowed to reach ambient temperature, diluted with $CHCl_3$, and filtered. Evaporation of the filtrate in vacuo gave 29 mg of crude product which was purified by PLC (1:4 Me_2CO/hexane) to give 21 mg (42%) of crystalline ene lactam **13**. Recrystallization from Et_2O/petroleum ether provided an analytical sample: mp 98 °C; IR (CH_2Cl_2) 5.74 μm; UV (MeOH) 208 nm; NMR ($CDCl_3$) δ 1.47 and 1.77 (2 s, *gem*-dimethyls), 1.73 (d, J = 7 Hz, C**H**$_3$CH), 1.8 (m, C**H**$_2$CH$_2$O), 4.0 (m, CH_2O and H_5), 6.10 (qd, $J_{8,9}$ = 7 Hz, $J_{5,8}$ = 1 Hz, H_8); mass spectrum, m/e 166, 125. Anal. ($C_{10}H_{15}NO_2$) C, H, N.

Ene Lactam 14. Following the procedure described above for the preparation of ene lactam **13**, we prepared **14** from **12b** in 50% yield: IR (CH_2Cl_2) 5.78 μm; UV (MeOH) 209 nm; NMR ($CDCl_3$) δ 1.45 and 1.83 (2 s, *gem*-dimethyls), 1.8 (m, C**H**$_2$CH$_2$O), 2.00 (d, J = 7.5 Hz, C**H**$_3$CH), 3.7–4.1 (m, CH_2O and H_5), 5.70 (q, J = 7.5 Hz, H_8); mass spectrum, m/e 166, 125.

General Procedures for the Preparation of Carbonates 15a–d. (A) *n*-Butyllithium Method. Under a nitrogen atmosphere, a solution of the carbinol in THF (0.14 M) was cooled to −78 °C and treated with *n*-BuLi (1.1 equiv) in *n*-hexane. After being stirred for 5 min, a solution of *p*-nitrobenzyl chloroformate in THF (1.1 equiv, 0.92 M) was added, and stirring, at −78 °C, was continued for a period of 45 min. The reaction mixture was then poured into ice–water, and the aqueous phase was saturated with NaCl. Workup (EtOAc (2×), NaCl) gave an oil which was purified by silica gel chromatogtaphy (see below) to provide carbonate in yields of up to 85%.

(B) 4-(Dimethylamino)pyridine[16] (DMAP) Method. DMAP (2 equiv) was added to a solution of the carbinol (0.23 M) and *p*-nitrobenzyl chloroformate (2 equiv) in CH_2Cl_2 cooled to 0 °C under a nitrogen atmosphere. A heavy white precipitate appeared immediately. The cooling bath was removed, and stirring was continued for a period of 2.5 h. The reaction mixture became homogeneous within about 45 min. Prior to workup the reaction mixture was doubled in volume by adding CH_2Cl_2. Workup (0.25 N HCl, H_2O (3×), NaCl) gave the crude product as an oil which was purified by silica gel chromatography (see below) to provide carbonate in yields of up to 71%.

(C) Isolation. The crude carbonate prepared by method A or B was purified by PLC on silica gel (1:2 EtOAc/C_6H_{12}). In an instance in which a mixture of **15a–c** was chromatographed, multiple development (2×) was necessary to efficiently separate the three diastereomers. Conventional column chromatography of a mixture of **15a–d** using the same solvent system provided the following elution profile which was consistent with that observed by PLC: (1) **15d**, (2) **15a**, (3) **15b**, (4) **15c**. Recrystallization of **15c** and **15d** from EtOAc/C_6H_{12} afforded analytical samples.

Data for trans S^* carbonate **15a**: IR (CH_2Cl_2) 5.70 (β-lactam and carbonate), 6.20 and 6.56 (nitro) μm; NMR ($CDCl_3$) δ 1.40 and 1.75 (2 s, *gem*-dimethyls), 1.43 (d, J = 6 Hz, C**H**$_3$CH), 1.8 (m, C**H**$_2$CH$_2$O), 3.11 (dd, $J_{6,8}$ = 5.5 Hz, $J_{5,6}$ = 2 Hz, H_6), 3.5 (m, H_5), 3.85 (m, CH_2O), 5.1 (m, H_8), 5.28 (s, C**H**$_2$Ar), 7.58 (d, J = 8 Hz, two aromatic protons meta to nitro group), 8.25 (d, J = 8 Hz, two aromatic protons ortho to nitro group); mass spectrum, m/e 378 (M^+), 363, 319.

Data for trans R^* carbonate **15b**: IR (CH_2Cl_2) 5.71 (β-lactam and carbonate), 6.20 and 6.56 (nitro) μm; NMR ($CDCl_3$) δ 1.42 and 1.75 (2 s, *gem*-dimethyls), 1.47 (d, J = 6 Hz, C**H**$_3$CH), 1.6 (m, C**H**$_2$CH$_2$O), 3.02 (dd, $J_{6,8}$ = 8 Hz, $J_{5,6}$ = 1.9 Hz, H_6), 3.7 (m, H_5 and CH_2O), 5.1 (m, H_8), 5.30 (s, CH_2Ar), 7.58 (d, J = 8 Hz, two aromatic protons meta to nitro), 8.30 (d, J = 8 Hz, two aromatic protons ortho to nitro); mass spectrum, m/e 378 (M^+), 363, 319.

Data for cis S^* carbonate **15c**: mp 136 °C; IR (CH_2Cl_2) 5.71 (β-lactam and carbonate), 6.22 and 6.56 (nitro) μm; NMR ($CDCl_3$) δ 1.43 and 1.77 (2 s, *gem*-dimethyls), 1.53 (d, J = 6 Hz, C**H**$_3$CH), 1.8 (m, C**H**$_2$CH$_2$O), 3.40 (dd, $J_{6,8}$ = 9.5 Hz, $J_{5,6}$ = 4.5 Hz, H_6), 3.63–3.93 (m, CH_2O and H_5), 4.97–5.47 (m, H_8), 5.25 (s, CH_2Ar), 7.55 (d, J = 8 Hz, two aromatic protons meta to nitro), 8.25 (d, J = 8 Hz, two aromatic protons ortho to nitro); mass spectrum, m/e 378 (M^+), 363, 319. Anal. ($C_{18}H_{22}N_2O_7$) C, H, N.

Data for cis R^* carbonate **15d**: mp 101 °C; IR (CH_2Cl_2) 5.71 (β-lactam and carbonate), 6.20 and 6.56 (nitro) μm; NMR ($CDCl_3$) δ 1.37 (d, J = 6 Hz, C**H**$_3$CH), 1.40 and 1.72 (2 s, *gem*-dimethyls), 1.8 (m, C**H**$_2$CH$_2$O), 3.33 (dd, $J_{6,8}$ = 7.5 Hz, $J_{5,6}$ = 4.5 Hz, H_6), 3.8 (m, CH_2O and H_5), 5.2 (m, H_8), 5.28 (s, CH_2Ar), 7.57 (d, J = 8 Hz, two aromatic protons meta to nitro), 8.20 (d, J = 8 Hz, two aromatic protons ortho to nitro group); mass spectrum, m/e 378 (M^+), 363, 319. Anal. ($C_{18}H_{22}N_2O_7$) C, H, N.

(D) X-ray Diffraction Analysis of 15d. Preliminary X-ray diffraction experiments indicated that the symmetry of the crystals of **15d** was $P2_1/c$ with a = 12.100 (4), b = 7.758 (2), and c = 20.113 (3) Å and β = 97.24 (2)° for a calculated density of 1.34 g/cm^3 with Z = 4. Of the 2538 unique reflections measured by using Cu Kα radiation (λ = 1.5418 Å) with $2\theta \leq 114°$, 1970 (78%) were considered observed [$I \geq 3\sigma(I)$]. Data were corrected for Lorentz, polarization, and background effects but not for absorption. Positions for 25 of the 27 nonhydrogen atoms were found by using a multisolution tangent formula approach.[18] Positions for the remaining nonhydrogen atoms and the hydrogen atoms were found by using Fourier analyses and least-squares refinements and minimizing $\sum w(|F_o| - |F_c|)^2$ with $w = (1/\sigma F_o)^2$.[19] The final unweighted residual after full-matrix least-squares refinements employing anisotropic temperature parameters for the nonhydrogen atoms and fixed isotropic temperature parameters for the hydrogens was 0.060.

General Procedure for the Preparation of Alcohols 16a–c. Aqueous acetic acid (1:2 H_2O/HOAc) was added to a solution of the acetonide (**15a**, **15b**, or **15d**, 0.5 M) in *p*-dioxane. The volume of H_2O/HOAc used was equal to twice that of *p*-dioxane. This

(18) P. Main, L. Lessinger, M. M. Woolfson, G. Germain, and J. P. Declercq, "MULTAN 74. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", University of York, England, and University of Louvain, Belgium, 1974.

(19) J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, "The X-ray System, Version of June 1972: TR-192", Computer Science Center, University of Maryland, College Park, MD, 1972.

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

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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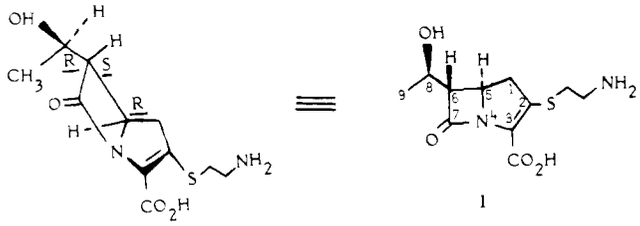
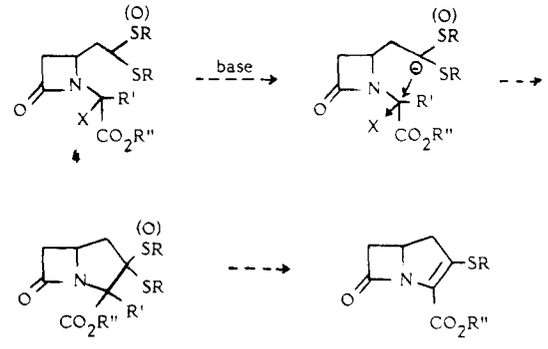
Model studies directed toward the total synthesis of (±)-thienamycin are described which have resulted in the preparation of the benzyl ester of (±)-2-(methylthio)carbapen-2-em-3-carboxylic acid (**2**). Azetidinone **3** was converted into thioenolether **24** via thioacetal **6**. Bromination of **24** 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]



1

Scheme I

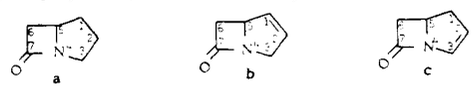


We felt that the total synthesis of (±)-thienamycin could conveniently be divided into three major synthetic objectives: (1) preparation of an azetidinone suitably sub-

(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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