Orally Absorbable Cephalosporin Antibiotics. 1. Structure-Activity Relationships of Benzothienyl- and Naphthylglycine Derivatives of 7-Aminodeacetoxycephalosporanic Acid

Stjepan Kukolja,* Susan E. Draheim, Janice L. Pfeil, Robin D. G. Cooper, Bernard J. Graves, Richard E. Holmes, David A. Neel, George W. Huffman, J. Alan Webber, Michael D. Kinnick, Robert T. Vasileff, and Bennie J. Foster

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285. *Received December 17, 1984*

A structure-activity relationship study of a number of orally absorbed cephalosporins together with their syntheses is described. These new cephalosporins are benzothienyl- and naphthylglycine derivatives of 7-aminodeacetoxycephalosporanic acid. Several different synthetic methods for the glycine side chains, their protection, and the final acylations are reported. Several of these analogues were more active than cephalexin both in vitro and in vivo against commonly encountered Gram-positive bacteria. (*R*)-7-(3-Benzothienylglycylamido)-3-methyl-3-cephem-4-carboxylic acid (**1R**) has emerged as a potent antibacterial agent and is currently undergoing preclinical evaluation.

Three orally active cephalosporin antibiotics—cephaloglycine, cephalexin, and cefaclor—have been discovered in our laboratories.[1] These antibiotics are useful in treating a variety of bacterial infections. In spite of the fact that cephalexin and cefaclor are well accepted in clinical medicine, the search continues for new oral cephalosporins with improved spectra and pharmacokinetic properties. An attempt in this direction was reported recently by Böhme and co-workers.[2] They described [3,4-(methylenedioxy)phenyl]glycine and 2-(2,3-dihydroxy-5-benzofuranyl)glycine cephalosporins that are considerably more active than cephalexin against Gram-positive organisms.

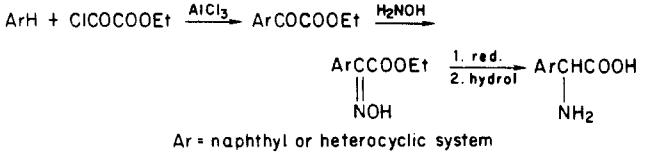
For good oral absorption the phenylglycine side chain is generally attached to a cephalosporin nucleus. As a departure from this we prepared new cephalosporins using bicyclic derivatives of aromatic and heteroaromatic glycines as side chains for coupling with 7-aminodeacetoxycephalosporanic acid (7-ADCA). These new cephalosporins were made by two different procedures which will be described in detail in the following paragraphs. First, we discuss the preparation of these compounds and later, their biological activities.

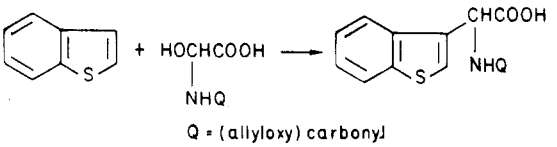
Chemistry

According to the first procedure, an amino acid was prepared, N-protected, and coupled with 7-ADCA (or a derivative). After deprotection, the desired cephalosporin was isolated and tested. The amino acids needed for acylation of the 7-ADCA nucleus were prepared by various methods and each will be described separately.

Procedure 1. Preparation of the Amino Acids and Their Coupling to 7-ADCA. 1A. Friedel–Crafts Acylation. A selected group of bicyclic compounds was acylated with ethoxalyl chloride with use of $AlCl_3$ as the catalyst. The resulting glyoxalates were isolated in good yields and subsequently treated with hydroxylamine to provide the corresponding oximes. After reduction with zinc and formic acid and hydrolysis, the desired amino acids were isolated as zwitterions or as amino protected derivatives.

1B. Amidoalkylation of Heterocyclic Compounds. Two amino acids were prepared by a method similar to that described by Ben-Ishai and co-workers.[3a] As an example, the alkylation of benzothiophene with *N*-[(allyloxy)carbonyl]-α-hydroxyglycine is illustrated:[3b]

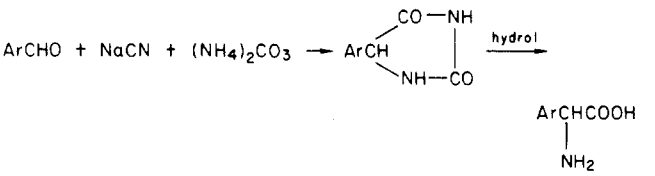




The reaction was carried out in trifluoroacetic acid at room temperature for 18 h and the protected 3-benzothiopheneglycine isolated in 88% yield. One advantage of this method is that the amino acid is isolated as the amino protected derivative which could be immediately used for acylation of 7-ADCA.

1C. Metalation Method. Several bicyclic or heteroaromatic compounds were metalated with lithium. *n*-Butyllithium was used for the replacement of aromatic hydrogen or aromatic halo substituent in ether and THF at −100 °C. The lithio derivative was reacted with diethyl oxalate to yield an α-keto ester which was converted to an amino acid as described in method 1A.

1D. Strecker–Bücherer Synthesis. Some bicyclic glycines were made by the Bücherer modification of the Strecker procedure.[4] The reaction of the pertinent aromatic aldehyde with ammonium carbonate and sodium cyanide at 50 °C for 20 h gave a 5-substituted hydantoin, which upon an alkaline hydrolysis was converted to the corresponding amino acid.



(1) Spencer, J. L.; Flynn, E. H.; Roeske, R. W.; Siu, F. Y.; Chauvette, R. R. *J. Med. Chem.* **1966**, *9*, 746 (1966). Ryan, C. W.; Simon, R. L.; Van Heyningen, E. M. *Ibid.* **1969**, *12*, 310. Chauvette, R. R.; Pennington, P. A. *Ibid.* **1975**, *18*, 403.

(2) Böhme, E. H. W.; Bambury, R. E.; Baumann, R. J.; Erickson, R. C.; Harrison, B. L.; Hoffman, P. F.; McCarty, F. J.; Schnettler, R. A.; Vaal, M. J.; Wenstrup, D. L. *J. Med. Chem.* **1980**, *23*, 405.

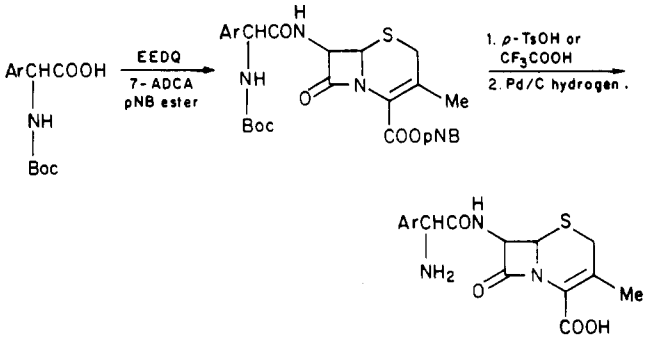
(3) (a) Ben-Ishai, D.; Berler, Z.; Altman, J. *J. Chem. Soc., Chem. Commun.* **1975**, *349*. (b) Huffman, G. W. U.S. Patent 4458085.

(4) Greenstein, J. P.; Winitz, M. "The Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. 1, p 698.

0022-2623/85/1828-1886$01.50/0

The majority of the amino acids prepared by methods 1A–D were protected with di-*tert*-butyl dicarbonate, yielding the Boc-protected amino acid. These derivatives were used in the next step to acylate 7-ADCA (or its ester) by means of *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline (EEDQ).[5] The Boc group was hydrolyzed with *p*-toluenesulfonic acid or trifluoroacetic acid. The ester was removed by catalytic hydrogenation. After removal of protecting groups, the desired cephalosporin was isolated as an epimer zwitterion. Separation of the diastereomers was accomplished by HPLC to furnish the *R* and *S* epimers.

A typical sequence of reactions involving procedure 1 is illustrated in the following example.

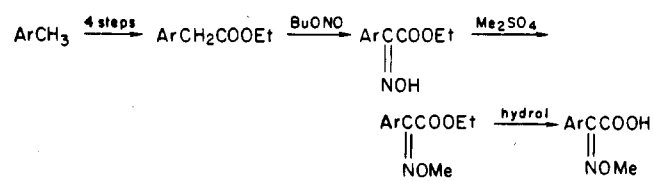


Procedure 2. Preparation of Bicyclic α-Methoximinoacetic Acids and Their Acylation on 7-ADCA. In the second procedure, a key intermediate was the bicyclic α-methoximinoacetic acid. This acid was converted to the corresponding acid chloride for acylation of 7-ADCA. The final step was reduction of the imino functionality to the amine and isolation of the desired cephalosporin. Procedure 2 thus avoids the need for protection of an amino group. In addition, the ease of acylation of 7-ADCA (not esters) simplifies the process.

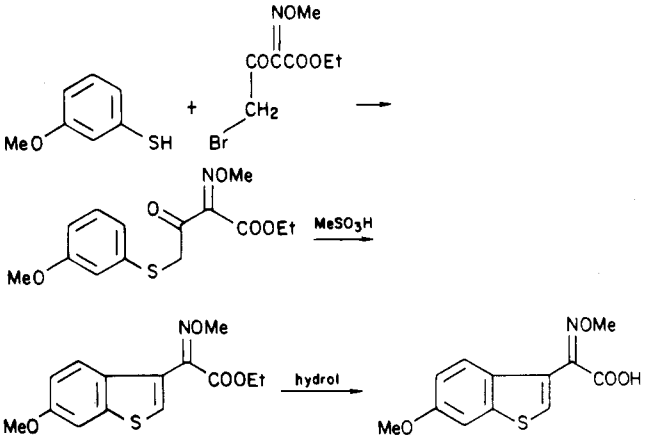
2A. Preparation of α-Methoximino Derivatives via Glyoxalate. Some glyoxalates, prepared as previously illustrated by methods 1A–C, were treated with methoxylamine, and the expected methoximes were isolated as esters.

The resulting esters were hydrolyzed and the bicyclic α-methoximinoacetic acids isolated in good yields.

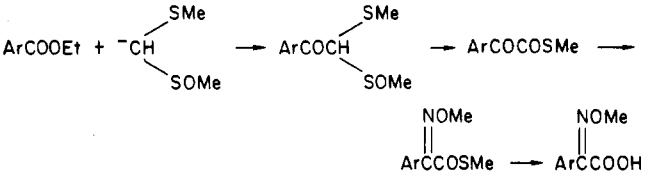
2B. Preparation of α-Methoximino Derivatives by Nitrosation of Corresponding Acetates. Most of the bicyclic acetates needed for nitrosation were prepared by elaboration of the methyl group in the corresponding bicyclic compounds by standard methods (see Experimental Section). Nitrosation was carried out by treatment with butyl nitrite to give oximes which, upon alkylation with dimethyl sulfate, afforded α-methoximino compounds. After hydrolysis of the esters, the α-methoximinoacetic acids were isolated as stable compounds and subsequently used for acylation.



2C. Cyclization of an Aromatic β-Keto Ester. Some substituted benzothiophene derivatives were prepared by cyclization of an aromatic β-keto ester. For example, ethyl α-(6-methoxy-3α-benzothienyl)-α-methoximinoacetate was made by alkylation of 3-methoxythiophenol with ethyl 2-methoximino-3-oxo-4-bromobutyrate and subsequently cyclized to the benzothiophene ring. After hydrolysis of the ester, the desired acid was isolated.

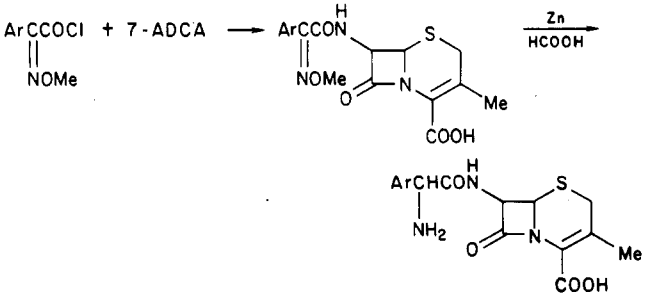


2D. Homologation of an Ester to an α-Keto Thio Ester. A procedure for homologation of an aromatic ester to an α-keto thio ester was reported recently by Ogura and co-workers.[6] Following their method, the addition of the carbanion of methyl (methylthio)methyl sulfoxide to an ester afforded a β-keto sulfoxide which was not isolated but treated directly with formic acid and acetic anhydride at 65 °C for 30 min followed by addition of sodium periodate and stirring for an additional 15 min. After workup a methylthio α-keto ester was isolated. This thio ester was then treated with methoxyamine for 16 h at 25 °C to give the α-methoximino thio ester which was immediately hydrolyzed at pH 2 to the corresponding α-methoximinoacetic acid. This acid was later used for acylation of 7-ADCA.



The bicyclic α-methoximinoacetic acids (prepared by methods (2A–D) were treated with oxalyl chloride to yield the pertinent acid chlorides which were then utilized for acylation of 7-ADCA. Finally, the oximino functions were reduced with zinc and formic acid and the expected epimeric cephalosporins isolated. Separation of isomers by HPLC afforded *R* and *S* epimers.

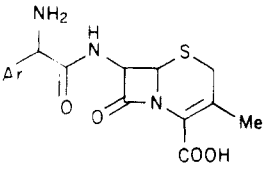
To illustrate the sequence of reactions involving procedure 2, the following example is given:

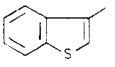
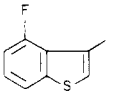
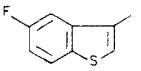
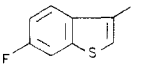
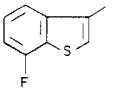
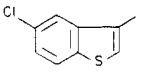
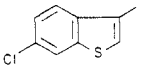
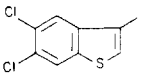
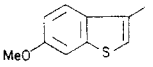
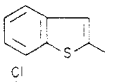
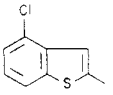
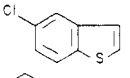
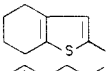
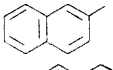
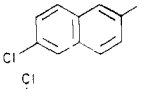
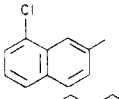
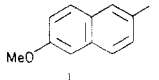
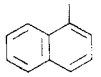
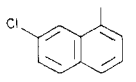


(5) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651.

(6) Ogura, K.; Yamashita, M.; Tsuchihasi, G. *Tetrahedron Lett.* **1978**, 1303. Ogura, K.; Katoh, N.; Yoshimura, I.; Tsuchihashi, G. *Ibid.* **1978**, 375. Ogura, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 1960.

Table I



compd no. and config[a,b]	Ar	prep of side chain	coupling method[d]	formula	anal.
1R		1A, 1B	E	$C_{18}H_{17}N_3O_4S_2$	C, H, N
1S				$C_{18}H_{17}N_3O_4S_2$	C, H, N
2R		2B	AC	$C_{18}H_{16}FN_3O_4S_2$	C, H, N, F
3R		2B	AC	$C_{18}H_{16}FN_3O_4S_2$	C, H, N, F
3S		2B	AC	$C_{18}H_{16}FN_3O_4S_2$	C, H, N, F
4R		2B	AC	$C_{18}H_{16}FN_3O_4S_2$	C, H, N, F
5R		2B	AC	$C_{18}H_{16}FN_3O_4S_2$	C, H, N, F
6R		2B	E		*c, e*
7R		2B	AC		*c, e*
8R		2B	AC	$C_{18}H_{15}Cl_2N_3O_4S_2$	C, H, N, Cl
8S				$C_{18}H_{15}Cl_2N_3O_4S_2$	C, H, N, Cl
9R		2C	AC		*c, e*
10R		1C	E		*c, e*
11R		1D	AC		*c, e*
12R		2D	AC		*c, e*
13R		1A	E		*c, e*
14R		2D	E	$C_{20}H_{27}N_3O_8S$	C, H, N, S
15R		1A	E		*c, e*
16R		2D, 2A	AC		*c, e*
17R		1C	E		*c, e*
18R		2D	E		*c, e*
19R		1A	E		*c, e*

[a] *R* and *S* epimers were isolated by preparative HPLC. [b] Configuration at the chiral carbon in the side chain. [c] Not analyzed. Estimation of purity of analogues without elemental analyses was greater than 95% by analytical HPLC. In most cases the identity of the other components was determined to be unreacted side chain and/or cephem nucleus. [d] E = EEDQ, AC = acetyl chloride. [e] Characterized by NMR spectrum.

Table I indicates the procedure utilized for preparation of each side chain as well as the coupling method employed. When the synthesis of a side chain is not fully described in literature, its preparation is described in detail in the Experimental Section.

Biological Results and Discussion

The cephalosporins described in this paper were pre-

Table II. Minimum Inhibitory Concentrations (MIC) Values (μg/mL) of Cephalosporins Having Benzothienyl- and Naphthylglycine Side Chains[a]

	Staphylococcus aureus				*Staph. epidermis*	*Streptococcus*			*Haemophilus influenzae*	
	penicillin G		methicillin resistant							
no.	sens, X1.1	res, V41	S13E	X400	EPI 1	*Pyogenes* C203	*Pneumoniae* Park	group D, X66	sens, C.L.	res, 76
1R	1	8	8	64	8	0.5	0.5	128	2	0.5
2R	4	32	32		32	1	4		16	4
3R	1	8	8	64	8	0.25	1	128	4	4
4R	1	8	8	64	4	0.125	0.5	128	2	0.5
5R	0.5	16	8	128	4	0.125	0.5		4	0.5
6R	0.5	4	2	16	4	0.125	0.25	64	8	0.5
7R	1	8	8	16	4	0.5	1	128	8	1
8R	1	8	4	64	4	0.25	0.5		4	1
9R	1	8	4	16	4	0.125	0.125		32	4
10R	0.5	16	16		2	0.5	2		32	1
11R	0.5	4	4	16	2	0.125	0.5	64	32	1
12R	0.25	8	16		2	0.125	0.25		64	4
13R	0.25	16	8		2	0.06	0.25	64	16	4
14R	0.5	8	8	64	4	0.125	0.5	64	8	2
15R	0.25	8	8	64	4	0.06	0.25	64	32	2
16R	0.5	1	1	4	1	0.25	0.25	16	8	0.5
17R	0.25	16	16	64	4	0.125	0.125		16	4
18R	4	32	32	64	8	2	2	128	8	2
19R	1	4	4	16	2	0.25			16	4
keflex	4	128	128	128	32	0.5	1	128	8	8

[a] Determined by agar dilution method of Kirst et al: Kirst, H. A.; Wild, G. M.; Baltz, R. H.; Hamill, R. L.; Ott, J. L.; Counter, F. T.; Ose, E. E. *J. Antibiot.* **1982**, *35*, 1675. Blank spaces indicate an MIC > 128.

Table III. Efficacy of Selected Derivatives of 7-ADCA against Lethal Mouse Infections: ED_{50} Values (mg/kg × 2)[a]

	Streptococcus pyogenes C203			*Staphylococcus aureus* 3055			*Streptococcus pneumonia* Park I		
cephalosporin side chain no.	po	sc	MIC	po	sc	MIC	po	sc	MIC
3-benzthienylglycine (**1R**)	1.7	2.3	0.5	0.6	0.4	1	16.0	18.0	1
2-benzthienylglycine (**10R**)	2.3	2.6	0.25	0.13	0.13	0.25	31	15	1
2-naphthylglycine (**14R**)	3.4	2.0	0.125	0.41	0.07	0.5	>25	17.6	1
cefaclor	0.8	1.4	0.25	0.13	0.03	1	10.7	11.5	2
cephalexin	3.3	2.9	0.5	0.34	0.2	1	51	23	4

[a] Compounds administered either subcutaneously (sc) or orally (po) to 20-g mice at 1- and 5-h intervals after intraperitoneal bacterial challenge.

pared as epimeric mixtures. The epimers were separated by chromatography. Since the side chains with the *S* configuration are less active,[7] the in vitro and in vivo studies were performed with side chains of the *R* configuration.

Microbiological evaluation of the described cephalosporins shows that replacement of the phenyl moiety of cephalexin with benzothiophene, naphthyl, or their substituted derivatives improves the MIC values against Gram-positive organisms. From Table II it can be seen that, in general, MIC values are lower than those of cephalexin against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., and *Haemophilus influenzae*. In some cases, halogen substitution on the bicyclic ring lowers the MIC values. In particular, compounds **3R**, **4R**, **6R**, **8R**, **9R**, **11R**, **12R**, **18R**, and **19R** are superior to cephalexin against *Staphylococcal* and *Streptococcal* bacteria. The best in vitro activity against *Haemophilus influenzae* is displayed by compounds **1R**, **3R**, **4R**, **5R**, and **8R**.

The bacteriological evaluation of compounds **1R**, **10R**, and **14R** shown in Table III demonstrates both parenteral and oral activity in mice infected with *S. aureus*, *S. pyogenes*, and *S. pneumonia*. ED_{50} values for these new cephalosporins indicate efficient absorption after oral administration and are quite comparable to the values for cefaclor and cephalexin.

Compound **1R** has emerged as a potent antibacterial agent against the commonly encountered Gram-positive bacteria and is currently undergoing preclinical evaluation. The microbiological, pharmacokinetic, and bacteriological studies concerning **1R** and its analogues were reported elsewhere.[8]

Experimental Section

Melting points are uncorrected. IR spectra were recorded on Beckman IR-7 or Perkin-Elmer Model 21 or Infracord instru-

(7) Doyle, F. P.; Foster, G. R.; Nayler, J. H. C.; Smith, H. *J. Chem. Soc.* **1962**, 1440. Long, A. A. W.; Nayler, J. H. C.; Smith, H. Taylor, T.; Ward, N. *Ibid.* **1971**, 1920.

(8) (a) Ott, J. L.; Blaszczak, L. C.; Copper, R. D. G.; Daugherty, B. W.; Draheim, S. E.; Foster, B. J.; Graves, B. J.; Holmes, R. E.; Hunden, D. C.; Kinnick, M. D.; Kukolja, S.; Neel, D. A.; Pfeil, J. L.; Vasileff, R. T.; Webber, J. A.; Wheeler, W. E.; Wishka, D. G. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 8–10, 1984, Washington, DC, Abstract 227. (b) Wright, W. E.; Eudaly, J. A.; Johnson, R. J. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 8–10, 1984, Washington, DC, Abstract 228. (c) Preston, D. A.; Counter, F. T.; Ensminger, P. W.; Ott, J. L.; Turner, J. L. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 8–10, 1984, Washington, DC, Abstract 229. (d) Turner, J. C.; Kau, D. L.; Pasini, C. E.; Quay, J. F.; Stucky, J. F., II; Sullivan, H. R. 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 8–10, 1984, Washington, DC, Abstract 231.

Table IV. NMR Spectral Data of Cephalosporins Having Benzothienyl- and Naphthylglycine Side Chains[a]

no.	3-CH_3, s	SCH_2, q	6-H, d	7-H, d	Ar CH, s	arom, m	solvent
1R	2.01	3.09, 3.33, AB q, J = 18	5.01, J = 4.6	5.64, J = 4.6	5.75	7.5–8.0, m, SH	D_2O DCl
2R	1.99	3.3; 3.55, AB q, J = 18	5.02, J = 4.6	5.61, J = 4.6	5.01	7.05–7.90, m, 4 H	Me_2SO
3R	2.01	3.23, 3.52, AB q, J = 18	4.97, J = 4.5	5.63, J = 4.5	4.98	7.23–7.9, m, 4 H	Me_2SO
4R	1.97	3.21, 3.46, AB q, J = 18	4.98, J = 4.6	5.62, J = 4.6	5.07	7.23–8.15, m, 4 H	Me_2SO
5R	1.99	3.3, 3.50, AB q, J = 18	5.00, J = 4.5	5.61, J = 4.5	4.99	7.21–7.95, m, 4 H	Me_2SO
6R	1.92	3.18, 3.42, AB q, J = 18	4.95, J = 4.5	5.57, J = 4.5	4.90	7.2–8.1, m, 4 H	Me_2SO
7R	1.95	3.20, 3.51, AB q, J = 20	4.98, J = 4.5	5.6, J = 4.5	5.00	7.38–8.16, m, 4 H	Me_2SO
8R	2.04	3.20, 3.50, AB q, J = 18	5.05, J = 4.6	5.63, J = 4.6	4.98	8.08–8.42, m, 3 H	Me_2SO
9R	1.82	2.94, 3.40, AB q, J = 18	5.00, J = 4.3	5.70, J = 4.3	5.62	7.16–7.84, m, 4 H	D_2O
10R	2.30	3.3, 3.5, AB q, J = 18	5.10, J = 5.4	5.78, J = 5.4	6.0	7.4–7.9, m, 5 H	TFA-d
11R	2.10	3.3, 3.60, AB q, J = 18	5.1, J = 4.6	5.6, J = 4.6	4.97	7.2–7.97, m, 4 H	Me_2SO-d_6
12R	2.32	4.10 s, 2 H	5.22, J = 4.5	5.81, J = 4.5	6.00	7.50–7.88, m, 4 H	TFA-*d*
13R	2.00	3.3, 3.5, AB q, J = 18	5.03, J = 4.6	5.63, J = 4.6	4.7	6.67, s, 1 H	Me_2SO-d_6
14R	2.53	3.42, 3.7, AB q, J = 18	5.43, J = 5.4	6.0, J = 5.4	5.99	7.8–8.4, m, 7 H	TFA-*d*
16R	1.96	3.3, 3.46, AB q, J = 17	5.03, J = 4.5	5.58, J = 4.5	4.96	7.4–8.2, m, 6 H	Me_2SO-d_6
17R	2.42	3.4, 3.7, AB q, J = 18	5.4, J = 4.6	5.98, J = 4.6	5.85	7.4–8.3, m, 6 H	TFA-*d*
18R	1.98	3.50, 3.77, AB q, J = 20	5.5, J = 4.5	6.0, J = 4.5	6.57	7.8–8.44, m, 7 H	TFA-*d*
19R	2.34	3.24, 3.53	5.23	5.79	6.23	7.6–8.17, m, 6 H	TFA-*d*

[a] Chemical sifts are in δ values and coupling constants (J) in hertz.

ments. NMR spectra were determined on Varian HA-60 and T-60, JEOL FX-90Q, and Brucher WM270 instruments with Me_4Si as the internal reference. TLC was done with Merck silica gel plates. Preparative HPLC was carried out on a Waters Associates Prep LC System 500A fitted with an ISCO Model UA-5 280-nm UV detector. Elution was performed at flow rate 200 mL/min with 8-L gradient, starting with H_2O–MeCN–AcOH (95:5:2) with an increase to the ratio 80:20:2. The progress of separation (R and

S epimers) and the check of purity was monitored on an analytical Waters μ-Bondapak C_{18} column with 20% MeCN, 79% water, and 1% acetic acid as the mobile phase. All temperatures are reported in degrees centigrade. Estimation of purity of analogues without elemental analyses was greater than 95% by analytical HPLC. In most cases the identity of the other components was determined to be unreacted side chain and/or cephem nucleus.

A. Preparation of Protected Amino Acids. (*RS*)-Ethyl α-Amino-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate (Method 1A). 4-(2-Thienyl)butyric acid was reacted with thionyl chloride and stannic chloride to provide 5-oxo-4,5,6,7-tetrahydrobenzothiophene, which upon reaction with hydrazine and NaOH gave 4,5,6,7-tetrahydrobenzothiophene. A solution of 13.3 g of 4,5,6,7-tetrahydrobenzothiophene in 150 mL of CH_2Cl_2 was added dropwise to a stirred suspension of 13.1 g of ethoxalyl chloride and 14.0 g of $AlCl_3$ in 200 mL of CH_2Cl_2. The reaction mixture was stirred for 12 h at 25 °C following the addition. The reaction mixture was poured into 500 g of ice and then the organic layer was separated and dried, and the solvent was removed by evaporation to give 19.2 g of ethyl α-oxo-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate: NMR ($CDCl_3$) δ 1.44 (3 H), 1.88 (m, 4 H), 2.76 (m, 4 H), 4.40 (q, 2 H), 7.75 (s, 1 H).

A solution of 14.0 g of ethyl α-oxo-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate in 300 mL of EtOH containing 5.31 g of sodium acetate and 6.50 g of hydroxylamine hydrochloride was heated at reflux for 3 h. The reaction mixture was cooled and the solvent was evaporated under reduced pressure to provide 14.7 g of ethyl α-(hydroxyimino)-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate.

To a cold (5 °C) stirred solution of the oxime from above in 120 mL of MeOH containing 75 mL of 90% HCO_2H and 60 mL of water was added portionwise over 40 min 7.58 g of zinc metal dust. Following complete addition, the reaction mixture was stirred at 0 °C for 12 h. After warming of the mixture to about 25 °C, it was filtered and the filtrate was concentrated to dryness to give an oil. The oil was dissolved in 100 mL of 1 N HCl and the solution was washed with 50 mL of EtOAc. The aqueous layer was made alkaline to pH 8 by addition of 1 N NaOH and the product was extracted into EtOAc which was dried and concentrated to afford 12.74 g of (*RS*)-ethyl α-amino-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate as an oil: NMR ($CDCl_3$) δ 1.27 (3 H), 2.79 (m, 4 H), 2.50 (m, 6 H), 4.20 (q, 2 H), 4.75 (s, 1 H), 6.64 (s, 1 H).

(*RS*)-*N*-(*tert*-Butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycine. A solution of 2.6 g of (*RS*)-ethyl α-amino-α-(4,5,6,7-tetrahydro-2-benzothienyl)acetate in 30 mL of EtOH and 100 mL of 1 N NaOH was stirred at 25 °C for 2 h. The reaction mixture was diluted by addition of 50 mL of THF and then 4.5 mL of di-*tert*-butyl dicarbonate was added and stirring was continued for an additional 12 h. The organic solvents were next removed by evaporation, and the aqueous mixture was washed with 100 mL of 1:1 ethyl acetate–diethyl ether. The aqueous layer was separated and acidified to pH 2.3 by addition of 1N HCl. The aqueous acid solution was extracted with EtOAc and the organic layer was washed with water, dried, and concentrated to dryness to afford 2.50 g (73% yield) of (*RS*)-*N*-(*tert*-butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycine as an oil: NMR ($CDCl_3$) δ 1.42 (s, 9 H)8 1.75 (m, 4 H), 5.46 (br, 2 H), 6.74 (s, 1 H).

***N*-[(Allyloxy)carbonyl]-3-benzothienylglycine (Method 1B).** A solution of 5.15 g (29.4 mmol) of (*RS*)-*N*-[(allyloxy)-carbonyl]-α-hydroxyglycine and 3.95 g (29.4 mmol) of benzo[*b*]thiophene in 40 mL of TFA was stirred at 22.5 °C for 18 h. The reaction mixture was then concentrated by evaporation under reduced pressure to give an oil, and the oil was dissolved in a mixture of 100 mL of EtOAc and 100 mL of water. The organic layer was separated, and the aqueous layer was extracted twice more with 50-mL portions of fresh EtOAc. The organic extracts were combined, washed with water, and then extracted twice with 100-mL portions of 10% aqueous $NaHCO_3$. The aqueous extracts were combined, added to 100 mL of fresh EtOAc, and acidified to pH 2.0 by the addition of concentrated HCl. The organic layer was separated and the aqueous acid layer was extracted with two 50-mL portions of fresh EtOAc. The organic portions were combined and dried, and the solvent was removed by evaporation to provide 7.55 g (88% yield) of colorless crystals of *N*[(allyloxy)carbonyl]-3-benzothienylglycine. Anal. ($C_{14}H_{13}NO_4S$) C, H, N, O, S [MS, *m/e* 291 (M^+)].

(*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-benzothienylglycine (Method 1C). Benzothiophene (13.4 g, 0.1 mol) was dissolved in 1 L of a 4:1:1 THF–pentane–ether solution and cooled to −100 °C and 62.5 mL of a 1.6 M solution of *n*-butyllithium was added. This solution was transferred, via canula, to another liter of the 4:1:1 solution containing 27 mL (2 equiv) of diethyl oxalate, also at −100 °C. After 60 min the solution was allowed to warm to 0 °C and was quenched with saturated aqueous NH_4Cl. The organic solvents were evaporated, and the aqueous residue was extracted four times with CH_2Cl_2. The combined extracts were washed with dilute HCl, then dried over $MgSO_4$, and evaporated to afford crude material containing the desired product and diethyl oxalate. Prep 500 chromatography gave 16.24 g (69%) of 2-(ethylglyoxyl)benzothiophene: NMR ($CDCl_3$) δ 1.5 (t, 3 H, CH_3), 4.5 (q, 2 H, CH_2), 7.4–8.4 (m, 5 H, arom).

By following the procedure of method 1A, 7.5 g of the amino ester was isolated: NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_3), 2.1 (s, 2 H, NH_2), 4.2 (q, 2 H, CH_2), 4.9 (d, 1 H, α-H), 7.2–7.8 (m, 5 H, arom).

The amino ester (3.49 g, 0.015 mol) was dissolved in 300 mL of 1 N NaOH and 150 mL of EtOH. After 2 h the reaction was adjusted to pH 10 and di-*tert*-butyl dicarbonate (3.4 mL) was added. The pH of the reaction was maintained at 9–10 until it stabilized. The crude reaction was then diluted with H_2O–EtOAc and the aqueous portion washed with EtOAc. The aqueous portion was separated and acidified to pH 2.3 and then extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated to yield 1.14 g (25%) of the Boc-protected compound as an oil: NMR ($CDCl_3$) δ 1.4 (s, 9 H, Boc CH_3), 5.4–5.8 (m, 2 H, α-H and NH), 7.2–7.8 (m, 5 H, arom).

(*RS*)-2-Naphthylglycine (Method 1D). A solution of 15.6 g (0.1 mol) of 2-naphthaldehyde in 700 mL of 50% EtOH–H_2O containing 14.7 g (0.3 mol) of NaCN and 38.4 g (0.4 mol) of $(NH_4)_2CO_3$ was heated at 50 °C for 20 h. The reaction mixture was cooled and concentrated to about 400 mL by evaporation under reduced pressure, and then the solution was acidified to pH 2.0 by the addition of concentrated HCl. The solid precipitate that formed was collected by filtration, washed with dilute HCl, and then dried to afford 22.1 g of 4-(2-naphthyl)-2,5-imidazolinedione.

A solution of 5.0 g (22 mmol) of the 4-(2-naphthyl)-2,4-imidazolidinedione in 100 mL of 16% (w/v) aqueous NaOH was heated at reflux for 2.5 h. The reaction mixture was then filtered, cooled, and washed with EtOAc. The aqueous solution was next diluted with 6 N HCl to pH 5.1 and filtered to provide 2-naphthylglycine. The reaction was repeated several times to produce larger quantities of the product.

A 10.0-g sample of 2-naphthylglycine was purified by dissolving it into 125 mL of MeOH containing 3.9 mL of acetyl chloride. The reaction mixtures was filtered and the filtrate was then diluted with 5 mL of aniline. The precipitated product was collected by filtration and dried to give 7.0 g of 2-naphthylglycine, mp 219–221 °C.

(*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-naphthylglycine. To a stirred solution of 10 g (50 mmol) of 2-naphthylglycine in 100 mL of 1 N sodium hydroxide was added 50 mL of THF followed by 30 g (140 mmol) of di-*tert*-butyl dicarbonate. The reaction mixture was stirred at 24 °C for 4 h. The product was isolated by first washing the reaction mixture three times with 50-mL portions of diethyl ether, and then the mixture was acidified to pH 2.0 with concentrated HCl. The aqueous acid mixture was extracted several times with EtOAc, the extracts were combined, washed with water, and dried, and the solvent was removed by evaporation under reduced pressure to provide 12.8 g (85% yield) of *N*-(*tert*-butoxycarbonyl)-2-naphthylglycine: NMR (Me_2SO) δ 2.5 (s, 9 H), 6.85 (s, 1 H), 7.28–7.9 (m, 7 H).

By following the general procedures the following compounds were prepared.

***N*-(*tert*-Butoxycarbonyl)(6-methoxy-2-naphthyl)glycine:** NMR ($CDCl_3$) δ 1.2 and 1.4 (2 br s, 9 H), 5.4 (br s, 1 H), 6.7 (br s, 1 H), 7.03–7.8 (m, 6 H).

***N*-(*tert*-Butoxycarbonyl)(6-chloro-2-naphthyl)glycine:** NMR ($CDCl_3$) δ 1.15 (s, 9 H), 5.3–5.7 (m, 1 H), 7.3–8.3 (m, 8 H).

α-Amino-α-(2-naphthyl)acetyl Chloride Hydrochloride.

Hydrogen chloride was bubbled through a cold (0 °C) solution of 5.0 g (25 mmol) of 2-naphthylglycine in 150 mL of CH_2Cl_2 for 20 min. The reaction mixture was then stirred while 7.6 g (38 mmol) of PCl_5 was added in one portion and stirring was continued at 0–10 °C for 2 h. The solution was filtered and dried, and the solvent was evaporated under reduced pressure to give 5.2 g (81% yield) of α-amino-α-(2-naphthyl)acetyl chloride hydrochloride: IR (mull) 1795 cm^{-1}. Anal. Calcd for $C_{12}H_{11}Cl_2NO$: Cl, 27.68. Found: Cl, 27.69.

***N*-(*tert*-Butoxycarbonyl)(5-chloro-3-benzothienyl)glycine (Method 2B).** Reaction of chloroacetone with 4-chlorothiophenol gave [(4-chlorophenyl)thio]methyl methyl ketone, which was cyclized by reaction with polyphosphoric acid to 5-chloro-3-methylbenzothiophene. Bromination of the latter compound by photochemical reaction with *N*-bromosuccinimide provide 5-chloro-3-(bromomethyl)benzothiophene, which was reacted with sodium cyanide, then hydrolyzed with formic acid, and esterified with ethyl orthoformate, ethanol, and a catalytic amount of HCl to give ethyl α-(5-chloro-3-benzothienyl)acetate. Reaction of the ester with sodium methoxide and *n*-butyl nitrite afforded ethyl α-(hydroxyimino)-α-(5-chloro-3-benzothienyl)acetate. Reduction of the oxime by reaction with zinc and formic acid and subsequent basic hydrolysis of the ester and reaction with di-*tert*-butyl dicarbonate gave *N*-(*tert*-butoxycarbonyl)(5-chloro-3-benzothienyl)glycine: NMR ($CDCl_3$) δ 1.1–1.5 (br s, 9 H), 5.4–5.7 (br s, 1 H), 7.2–8.0 (m, 4 H).

B. Preparation of Bicyclic α-Methoximinoacetic Acids. α-Methoximino-α-(6-fluoro-3-benzothienyl)acetic Acid (Method 2B). A solution of 25.6 g of ethyl α-(6-fluoro-3-benzothienyl)acetate in 100 mL of EtOH containing 107 mL of 1 M ethanolic sodium ethoxide and 17.5 mL of *n*-butyl nitrite was stirred at 24 °C for about 20 h. The reaction mixture was diluted by addition of 300 mL of EtOH and 9.2 mL of glacial acetic acid and stirred for an additional 1 h. The reaction mixture was then concentrated diluted with water and the product was extracted into EtOAc. The EtOAc solution was washed with aqueous $NaHCO_3$ and dried and the solvent was removed to provide, following crystallization from *n*-hexane and diethyl ether, 7.99 g of ethyl α-(hydroxyimino)-α-(6-fluoro-3-benzothienyl)acetate: mp 168–171 °C. Second crop of 10.25 g was also recovered; yield 64%.

Reaction of 7.82 g of the compound thus prepared with 4.16 mL of dimethyl sulfate and 5.53 g of potassium carbonate provided 3.59 g (48%) of ethyl α-(methoximino)-α-(6-fluoro-3-benzothienyl)acetate, mp 84.5–86 °C.

A solution of 3.5 g of ethyl α-methoximino-α-(6-fluoro-3-benzothienyl)acetate in 75 mL of EtOH containing 40 mL of 0.5 N NaOH was stirred at 24 °C for 19 h. The solution was then concentrated to a volume of about 50 mL, and 50 mL of water was added. The aqueous solution was washed with CH_2Cl_2, filtered, and then acidified to pH 2 by addition of 6 N HCl. The precipitate that formed was collected by filtration and identified as 3.02 g (95%) of α-methoximino-α-(6-fluoro-3-benzothienyl)-acetic acid, mp 150–151 °C.

Similarly prepared were α-methoximino-α-(4-fluoro-3-benzothienyl)acetic acid, α-methoximino-α-(5-fluoro-3-benzothienyl)-acetic acid, α-methoximino-α-(7-fluoro-3-benzothienyl)acetic acid, and α-methoximino-α-(5,6-dichloro-3-benzothienyl)acetic acid.

α-Methoximino-α-(6-methoxy-3-benzothienyl)acetic Acid (Method 2C). To a stirred solution of sodium 3-methoxythiophenoxide in 150 mL of EtOH (prepared by reacting 14 g of 3-methoxythiophenol with 5.94 g of sodium methoxide) was added dropwise over 10 min 27.7 g of ethyl 2-methoximino-3-oxo-4-bromobutyrate. The reaction mixture was stirred at 25 °C for 16 h, and then the solvent was removed by evaporation under reduced pressure to give an oil. The oil was dissolved in EtOAc and washed several times with water. The organic layer was dried and the solvent was evaporated to afford 16.28 g of ethyl 2-methoximino-3-oxo-4-[(3-methoxyphenyl)thio]butyrate as a yellow oil: NMR ($CDCl_3$) δ 1.32 (t, 3 H), 3.79 (s, 3 H), 4.05 (s, 3 H), 4.34 (q, 2 H), 6.7–7.3 (m, 4 H).

Five grams of the compound from above was added to 40 mL of methanesulfonic acid, and the solution was stirred for 15 min at 25 °C. The reaction mixture then was added to 400 mL of ice water, and the aqueous mixture was extracted several times with diethyl ether. The ethereal extracts were combined, washed with water and with aqueous $NaHCO_3$, and dried, and the solvent was removed by evaporation to give 4.31 g of ethyl α-methoximino-α-(6-methoxy-3-benzothienyl)acetate as a dark oil: NMR ($CDCl_3$) δ 1.36 (t, 3 H), 3.80 (s, 3 H, 4.02 (s, 3 H), 4.3 (q, 2 H), 6.8–7.2 (m, 3 H), 8.3 (d, 1 H).

A solution of 2.65 g of the compound thus prepared in 50 mL of EtOH containing 3.6 mL of 5 N NaOH was stirred at 25 °C for 3.5 h. The solvent was then removed by evaporation to provide an oil, which was dissolved in EtOAc and water. The aqueous layer was separated and the organic layer was extracted with aqueous $NaHCO_3$. The aqueous portions were combined, acidified to pH 1.8 with 1 H HCl, and extracted with fresh EtOAc. The organic extract was dried and concentrated to give 1.39 g of α-methoximino-α-(6-methoxy-3-benzothienyl)acetic acid as an amorphous solid: NMR (Me_2SO-d_6) δ 3.82 (s, 3 H), 4.02 (s, 3 H), 7.04–8.41 (m, 4 H).

α-Methoximino-α-(5-chloro-2-benzothienyl)acetic Acid (Method 2D). Methylthio α-oxo-α-(5-chloro-2-benzothienyl)-acetate was prepared by reacting 26.8 g of methyl (5-chloro-2-benzothienyl)formate with 21.4 g of sodium hydride (50% dispersion) and 20.4 g of methyl (methylthio)methyl sulfoxide in 500 mL of DMF to give 1-oxo-1-(5-chloro-2-benzothienyl)-2-(methylthio)-2-(methylsulfinyl)ethane, which was then reacted with sodium paraperiodate in acetic anhydride and formic acid.

A solution of 2.6 g of methylthio α-oxo-α-(5-chloro-2-benzothienyl)acetate in 180 mL of MeOH containing 840 mg of methoxylamine hydrochloride and 10 mL of 1 N NaOH was stirred at 25 °C for 16 h. The reaction solvent was removed by evaporation under reduced pressure to give an oil. The oil was dissolved in 100 mL of EtOAc and 100 mL of water, and the mixture was made alkaline to pH 10.4 by addition of 1 N NaOH. The aqueous layer was separated, washed with fresh EtOAc, and then made acidic to pH 2 by addition of 1 N HCl. The aqueous acid mixture was extracted with fresh EtOAc which was then washed with water and dried and the solvent was removed to provide 2.5 g of α-methoximino-α-(5-chloro-2-benzothienyl)acetic acid: NMR ($CDCl_3$) δ 4.10 and 4.22 (2 s, 3 H), 7.20–8.19 (m, 4 H), 10.15 (br s, 1 H). Anal. ($C_{11}H_8NO_3SCl$) C, H, N.

α-Methoximino-α-(8-chloro-2-naphthyl)acetic Acid (Method 2D). A suspension of 9.2 g sodium hydride in 50 mL of DMF was added in one portion to a stirred solution of 5.6 g (24 mmol) of ethyl 8-chloro-2-naphthylformate and 4.4 g (36 mmol) of methyl (methylthio)methyl sulfoxide in 10 mL of DMF. The reaction mixture was stirred for 4 h at 25 °C and then concentrated to dryness. The product was dissolved in 250 mL of EtOAc and the solution was washed with 5% HCl, saturated $NaHCO_3$, and brine. The solution was dried and the solvent evaporated to give 4.73 g (63% yield) of 1-oxo-1-(8-chloro-2-naphthyl)-2-(methylthio)-2-(methylsulfinyl)ethane. A solution of 3.12 g (10 mmol) of the product in 150 mL of formic acid and 12 mL of acetic anhydride was stirred at 65 °C for 30 min. To the reaction mixture was added 856 mg (4 mmol) of sodium periodate and stirring was continued for an additional 15 min. The reaction mixture was cooled and concentrated to dryness, and the product was dissolved in EtOAc and washed with $NaHCo_3$ and brine, and the solvent was removed to give 1.2 g (46% yield) of methylthio α-oxo-α-(8-chloro-2-naphthyl)acetate.

A solution of 220 mg of the product from above in 15 mL of MeOH and 15 mL of water containing 0.83 mL of 1 N NaOH and 70 mg of methoxyamine hydrochloride was stirred for 16 h at 25 °C. The reaction mixture was acidified to pH 2 by addition of 1 N HCl. The acid solution was extracted with EtOAc which was dried and concentrated to give 170 mg of α-(8-chloro-2-naphthyl)-α-methoximinoacetic acid.

C. Coupling of Protected Amino Acids with 7-ADCA (or Esters) and Removal of Protecting Groups. (*RS*)-Allyl 7-[*N*-[(Allyloxy)carbonyl]-3-benzothienylglycylamido]-3-methyl-3-cephem-4-carboxylate. A solution of 5.82 g (20 mmol) of (*RS*)-*N*-[(allyloxy)carbonyl]-3-benzothienylglycine in 200 mL of THF containing 5.18 g (21 mmol) of EEDQ was added in one portion to a solution of 5.6 g (24 mmol) of allyl 7-amino-3-methyl-3-cephem-4-carboxylate in 200 mL of CH_3CN. The reaction mixture was stirred at 25 °C for 16 h and then concentrated to an oil by evaporation of the solvent. The oil was dissolved in 1 L of EtOAc and washed once with 500 mL of water, twice with 250-mL portions of 5% aqueous $NaHCO_3$, twice with 5% HCl,

again with 250 mL of water, and finally with 250 mL of brine. The solution was dried and the solvent was removed by evaporation under reduced pressure to give 10.47 g (99% yield) of (*RS*)-allyl 7-[*N*-[(allyloxy)carbonyl]-3-benzothienylglycylamido]-3-methyl-3-cephem-4-carboxylate as an amorphous solid: NMR (Me_2SO-d_6) δ 2.00 and 2.05 (2 s, 3 H, *R* and *S* isomers), 3.18–3.80 (m, 2 H), 4.45–6.10 (m, 13 H), 7.3–8.1 (m, 6 H), 9.1–9.35 (m, 1 H). Anal. ($C_{25}H_{25}N_3O_6S_2$) C, N, N.

(*R*)-7-(2-Naphthylglycylamido)-3-cephem-4-carboxylic Acid Trifluoroacetate (14R). To a stirred suspension of 2.0 g (10 mmol) of 7-amino-3-cephem-4-carboxylic acid in 15 mL of CH_3CN was added in one portion 8 mL (30 mmol) of BSTFA. The mixture was stirred at 25 °C for 30 min and then was cooled to 0 °C and added in one portion to a stirred solution of 2.0 g (6.6 mmol) of (*RS*)-*N*-(*tert*-butoxycarbonyl)-2-naphthylglycine in 15 mL of CH_3CN containing 1.73 g (7.0 mmol) of EEDQ. The reaction mixture was stirred for 1 h at 25 °C and then was concentrated to dryness to provide an oil. The oil was dissolved in 100 mL of EtOAc, washed four times with 25-mL portions of 1 N HCl and twice with brine, and dried. The solvent was removed by evaporation under reduced pressure to provide a white foam. The foam was dissolved in 25 mL of TFA and the solution was sonicated for 5 min at 25 °C. The reaction mixture was concentrated to dryness and triturated with diethyl ether to afford 1.8 g (55% yield) of (*RS*)-7-(2-naphthylglycylamido)-3-cephem-4-carboxylic acid trifluoroacetate. The product thus produced was chromatographed over reverse-phase C_{18} silica gel, eluting with 8 L of a solution of 1% acetic acid plus a gradient of 95% water + 5% acetonitrile to 85% water + 15% acetonitrile (v/v). The appropriate fractions were combined, and the solvent was removed by lyophilization to afford 157 mg of (*R*)-7-(2-naphthylglycylamido)-3-cephem-4-carboxylic acid as an amorphous solid: IR (KBr) 1771.75 cm^{-1} (β-lactam); NMR (TFA-*d*) δ 3.55 (q, 2 H, 4.08 (s, 1 H), 5.6–6.0 (m, 2 H), 7.5–8.1 (m, 7 H).

***p*-Nitrobenzyl 7-[*N*-(*tert*-Butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylate.** A solution of 622 mg of *N*-(*tert*-butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycine from preparation 4 in 50 mL of CH_3CN containing 494 mg of EEDQ was stirred for 5 min and then added in one portion to a cold (0 °C) stirred solution of 770 mg of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 250 mL of CH_3CN. The reaction mixture was stirred at 0 °C for 30 min and then was warmed to 25 °C and stirred for an additional 12 h. The reaction mixture was concentrated to an oil by evaporation of the solvent, and the oil was dissolved in 100 mL of EtOAc. The solution was washed once with 1 N HCl, then with aqueous $NaHCO_3$, and finally with brine. After drying of the solution, the solvent was removed by evaporation under reduced pressure to give 1.23 g (59% yield) of *p*-nitrobenzyl 7-[*N*-(*tert*-butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylate as an oil: NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.79 (m, 4 H), 2.64 (m, 4 H), 3.32 (m, 2 H), 4.99 (m, 1 H), 5.31 (s, 2 H), 5.41 (s, 2 H), 5.75 (m, 1 H), 6.72 (s, 1 H), 6.99 (m, 1 H), 7.55 (d, 2 H), 8.20 (d, 2 H).

***p*-Nitrobenzyl 7-[*N*-(*tert*-Butoxycarbonyl)(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylate.** To a stirred solution of 662 mg (2 mmol) of *N*-(*tert*-butoxycarbonyl)(6-methoxy-2-naphthyl)glycine in 100 mL of CH_3CN containing 500 mg (2 mmol) of EEDG was added in one portion 770 mg (2.2 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate. The reaction mixture was stirred at 25 °C for 16 h and then concentrated to dryness to provide an oil. The oil was dissolved in 50 mL of EtOAc and the solution was washed with 25 mL of 1 N HCl, 25 mL of aqueous $NaHCO_3$, and water. The solution was dried and concentrated to dryness to provide 1.3 g of *p*-nitrobenzyl 7-[*N*-(*tert*-butoxycarbonyl)(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylate as an oil: NMR ($CDCl_3$) δ 1.39 (s, 9 H), 2.08 and 2.15 (2 s, 3 H), 3.34 (q, 2 H), 3.90 (s, 3 H), 4.9 (m, 1 H), 5.29 (s, 2 H), 5.31 (s, 1 H), 5.68 (m, 1 H), 7.08–8.25 (m, 12).

7-[(5-Chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (6R). A solution of 766 mg (2.2 mmol) of *N*-(*tert*-butoxycarbonyl)(5-chloro-3-benzothienyl)glycine and 844 mg (2.4 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 380 mL of CH_3CN containing 544 mg (2.2 mmol) of EEDQ was stirred at 0 °C for 1 h and at 25 °C for 4 h. The reaction mixture was concentrated to dryness by evaporation of the solvent, and the product was dissolved in 200 mL of EtOAc. The organic solution was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and water. The solution was dried and the solvent was removed by evaporation under reduced pressure to give 1.28 g (87% yield) of *p*-nitrobenzyl (*RS*)-7-[*N*-(*tert*-butoxycarbnyl)(5-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylate as an oil: NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.13 and 2.19 (2 s, 3 H), 3.1–3.5 (m, 2 H), 4.9 and 5.01 (2 d, 1 H), 5.3 (br s, 2 H), 5.5–5.9 (m, 3 H), 6.9–8.3 (m, 9 H).

A suspension of 1.8 g of 5% palladium on carbon in 30 mL of MeOH and 10 mL of EtOH was shaken for 30 min at 25 °C under 55 psi H_2. A solution of 1.28 g of the compound from above in 100 mL of THF was added to the reaction mixture, and the mixture was shaken at 25 °C for 45 min under 57 psi H_2. The reaction mixture was filtered and the solvent was removed from the filtrate. The product was dissolved in 50 mL of diethyl ether and 50 mL of water. The mixture was made alkaline to pH 7.7 and the organic layer was separated. The aqueous layer was washed with fresh diethyl ether and then was acidified to pH 2 by addition of 1 N HCl. The aqueous acid layer was extracted three times with 50-mL portions of EtOAc, and the extracts were combined, dried, and concentrated to dryness to give 700 mg (70% yield) of (*RS*)-7-[*N*-(*tert*-butoxycarbonyl)(5-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as an oil: NMR ($CDCl_3$) δ 1.43 (s, 9 H), 2.09 and 2.12 (2 s, 3 H), 3.1–3.5 (m, 2 H), 4.8–5.3 (m, 1 H), 5.4–6.1 (m, 3 H), 7.0–8.4 (m, 5 H).

A solution of 700 mg of the compound from above in 8 mL of TFA was stirred at 25 °C for 5 min. The solution was added to 20 mL of water and the pH was adjusted to 6 by addition of 1 N NaOH. The precipitate that formed was collected by filtration and air-dried to give (*RS*)-7-[(5-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid. The isomers were separated by chromatography over a C_{18} reverse-phase silica gel column, eluting with a gradient of 1% CH_3CO_2H, 0–30% CH_3CN and 99–69% water. Appropriate fractions were combined, concentrated in volume by evaporation of solvents, and lyophilized to give: (*S*)-7-[(5-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid and (*R*)-7-[(5-chloro-3-benzothienyl)glycylamido]-3-cephem-4-carboxylic acid as amorphous solids.

(*R*)-7-[(6-Chloronaphth-2-yl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (15R) (Method 1A). 2-Chloronaphthalene was acylated with ethyl chlorooxalyate to produce ethyl α-keto-α-(6-chloronaphth-2-yl)acetic acid. Reaction of the latter compound with hydroxylamine, followed by reduction and hydrolysis, provided 6-chloronaphth-2-ylglycine. This was converted to the *N*-*tert*-butoxycarbonyl-protected derivative.

To a stirred cold (0 °C) solution of 523 mg (1.5 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 300 mL of acetonitrile was added a solution of 500 mg (1.5 mmol) of *N*-(*tert*-butoxycarbonyl)-6-chloronaphth-2-ylglycine in 100 mL of CH_3CN containing 369 mg EEDQ. The reaction mixture was stirred 1 h at 0 °C and then was warmed to room temperature and stirred for an additional 48 h. The reaction solvent was next removed by evaporation under reduced pressure to provide the product as an oil. The oil was dissolved in 100 mL of EtOAc, washed with 1 N HCl, aqueous $NaHCO_3$, and water, and then dried. Removal of the solvent by evaporation afforded 770 mg of a white solid (77% yield) of *p*-nitrobenzyl 7-[*N*-(*tert*-butoxycarbonyl)-6-chloronaphth-2-ylglycylamido]-3-methyl-3-cephem-4-carboxylate: NMR ($CDCl_3$) δ 1.40 (s, 9 H), 2.12 (2 s, 3 H), 3.40 (q, 2 H), 4.68 and 4.90 (2 d, 1 H), 5.30 (br s, 3 H), 5.6–6.0 (m, 1 H), 7.2–8.3 (m, 10 H).

Removal of the *p*-nitrobenzylcarboxy protecting group was accomplished by hydrogenation of 770 mg of the compound from above with 1.0 g of 5% palladium on carbon in 50 mL of MeOH containing 20 mL of EtOH with an initial hydrogen pressure of 55 psi. The reaction was complete after 55 min, and the reaction mixture was filtered and the solvent was removed from the filtrate to give an oil. The oil was dissolved in 50 mL of ethyl acetate containing pH 7 buffer, and the aqueous layer was acidified to pH 2.3 with 1 N HCl. The product was extracted into EtOAc, which was then washed with water, dried, and concentrated to dryness to afford 220 mg (36% yield) of 7-[*N*-(*tert*-butoxycarbonyl)6-chloronaphth-2-ylglycylamido]-3-methyl-3-cephem-

4-carboxylic acid: NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.15 (2 s, 3 H), 3.35 (m, 2 H), 7.2–8.1 (m, 8 H).

The product thus formed was dissolved in 5 mL of TFA and the solution was stirred at room temperature for 5 min. Evaporation of the solvent and purification of the product by high-pressure liquid chromatography provided (*R*)-7-[(6-chloronaphth-2-yl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid.

(*R*)-7-[(6-Methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (17R). To a stirred suspension of 1.4 g of 5% palladium on carbon in 50 mL of EtOH was added in one portion 1.3 g of *p*-nitrobenzyl 7-[*N*-(*tert*-butoxycarbonyl)(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylate. The reaction mixture was stirred 3 h at 25 °C under 55 psi H_2. The reaction mixture was then filtered and the filter cake was washed with fresh EtOH. The filtrate was evaporated under reduced pressure to provide 1.1 g of 7-[*N*-(*tert*-butoxycarbonyl)(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid.

The acid thus formed was dissolved in 5 mL of TFA and the solution was stirred at 25 °C for 5 min. The reaction mixture was added to 20 mL of water and the aqueous solution was lyophilized to give (*RS*)-7-[(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid trifluoroacetate. The salt thus formed was redissolved in fresh water and purified by high-performance liquid chromatography to afford (*R*)-7-[(6-methoxy-2-naphthyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid.

(*R*)- and (*S*)-7-(3-Benzothienylglycylamido)-3-methyl-3-cephem-4-carboxylic Acid (1R). A solution of 72 mg (0.32 mmol) of palladium tetraacetate in 50 mL of acetone containing 419 mg (1.6 mmol) of triphenylphosphine was stirred at 25 °C for 30 min and then was cooled at 5 °C and diluted by addition of 30 mL of acetone containing 6.74 g (12.8 mmol) of (*RS*)-allyl 7-[*N*-[(allyloxy)carbonyl]-3-benzothienylglycylamido]-3-methyl-3-cephem-4-carboxylate. The cold reaction mixture was stirred for 10 min, and then 7.36 mL (28.2 mmol) of tributyltin hydride was added in one portion. The reaction mixture was stirred for 1 h at 0–5 °C and then was diluted by addition of 5 mL of 1 N HCl and stirred for an additional 10 min. The reaction mixture was added to 25 mL of water and washed twice with 50-mL portions of *n*-hexane, and then the pH was adjusted to 4.5 with 1 N NaOH. Concentration of the solution by evaporation of the organic solvent effected precipitation of a product that was collected by filtration and lyophilized to provide 4.12 g (80% yield) of (*RS*)-7-[(3-benzothienyl)glycylamido]-3-cephem-4-carboxylic acid. A sample of the product thus formed (3.625 g) was purified further by high-pressure liquid chromatography to give 522.5 mg of the *S* isomer and 1.075 of (*R*)-7-[(3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as amorphous solids: IR (KBr) 1759 cm^{-1} (β-lactam carbonyl); MS, *m/e* 403 (M^+); UV λ_{max} (MeOH) 260 nm (ε 11 500). Anal. ($C_{18}H_{17}N_3O_4S_2$) C, H, N.

7-[*N*-(*tert*-Butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid. A suspension of 1.8 g of 5% palladium on carbon in 10 mL of EtOH and 30 mL of MeOH was stirred at 25 °C for 30 min under H_2 at 60 psi. A solution of 1.23 g of *p*-nitrobenzyl 7-[*N*-(*tert*-butoxycarbonyl)(4,5,6,7-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylate in 60 mL of THF was added in one portion to the reaction mixture and stirring was continued under H_2 at 50 psi for 50 min. The reaction mixture was filtered and the filter cake was washed with EtOAc. The filtrate was then added to 50 mL of water and the mixture was made alkaline to pH 7.8. The aqueous layer was separated, acidified to pH 2.2 by addition of 1 N HCl, and then extracted several times with EtOAc. The organic extracts were combined, dried, and concentrated to dryness to give 650 mg of (*RS*)-7-[*N*-(*tert*-butoxycarbonyl)(4,5,6,6-tetrahydro-2-benzothienyl)-glycylamido]-3-methyl-3-cephem-4-carboxylic acid: NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.80 (m, 4 H), 2.18 (s, 3 H), 2.60 (m, 4 H), 3.29 (q, 2 H), 5.00 (m, 1 H), 5.4–5.9 (m, 3 H), 6.72 (2 s, 1 H), 8.62 (br, 2 H).

7-[(4,5,6,7-Tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (13R). A solution of 650 mg of (*RS*)-7-[*N*-(*tert*-butoxycarbonyl)(4,5,6,6-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid in 8 mL of TFA stood at room temperature for 5 min. The reaction mixture was added to 10 mL of water and the pH was adjusted to 7 by addition of dilute NH_4OH. The neutral reaction mixture was filtered and the filtrate was concentrated in volume and then chromatographed over high-pressure liquid chromatography, eluting with a mixture of 15% v/v CH_3CN, 1% ammonium acetate, and 84% water to give the *S* isomer and (*R*)-7-[(4,5,6,6-tetrahydro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as amorphous solids.

D. Acylation of 7-ADCA via Acid Chlorides. 7-[α-Methoximino-α-(6-methoxy-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic Acid. A solution of 610 mg (3.7 mmol) of α-methoximino-α-(6-methoxy-3-benzothienyl)acetic acid in 50 mL of benzene containing 1.1 mL (12.6 mM) of oxalyl chloride and 2 drops of DMF was stirred at room temperature for 1 h. The solvent was removed by evaporation under reduced pressure to provide α-methoximino-α-(6-methoxy-3-benzothienyl)acetyl chloride as an oil.

The product thus formed was dissolved in 40 mL of acetone and added dropwise over 30 min to a stirred cold (10 °C) solution of 830 mg (3.85 mmol) of 7-amino-3-methyl-3-cephem-4-carboxylic acid in 40 mL of acetone and 75 mL of water containing 932 mg (11.1 mmol) of $NaHCO_3$. The reaction mixture was warmed to 25 °C following the addition and was stirred for an additional 90 min. The organic solvent was then removed by evaporation and the aqueous mixture was layered with EtOAc and made acidic to pH 2.5 with 1 N HCl. The organic layer was separated, washed with water, dried, and evaporated to afford 856 mg of 7-[α-methoximino-α-(6-methoxy-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid: NMR (Me_2SO-d_6) δ 2.02 (s, 3 H), 3.34, 3.54 (AB, *J* = 18.03 Hz, 2 H), 3.83 (s, 3 H), 3.98 (s, 3 H), 5.13 (d, *J* = 4.4 Hz, 1 H), 5.74 (dd, *J* = 4.4, 7.9 Hz, 1 H), 7.05 (dd, *J* = 2.4, 8.79 Hz, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.65 (s, 1 H), 8.41 (d, *J* = 8.79 Hz, 1 H), 9.73 (d, *J* = 7.9 Hz, 1 H); IR (KBr) 1775 cm^{-1} (β-lactam carbonyl); MS, *m/e* 461 (M^+). Anal. ($C_{20}H_{19}N_3O_6S_2$) C, H, N.

7-[α-Methoximino-α-(6-fluoro-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic Acid. A solution of 2.70 g (10.7 mmol) of α-methoximino-α-(6-fluoro-3-benzothienyl)acetic acid in 60 mL of benzene containing 2.8 mL of oxalyl chloride and 4 drops of DMF was stirred under N_2 at 25 °C for 2 h. The solvent was then removed by evaporation under reduced pressure to give α-methoximino-α-(6-fluoro-3-benzothienyl)acetyl chloride. The acid chloride was dissolved in 60 mL of acetone and added dropwise over 5 min to a stirred cold (5 °C) solution of 2.41 g (11.3 mmol) of 7-amino-3-methyl-3-cephem-4-carboxylic acid in 60 mL of acetone and 120 mL of water containing 2.84 g (33.8 mmol) of $NaHCO_3$. The reaction mixture was stirred for 2 h at 5 °C and then warmed to 25 °C and stirred for an additional 2 h. The reaction mixture was diluted with 1 N HCl to pH 7.5 and stored to 0 °C for 12 h. Following removal of acetone from the reaction mixture by evaporation, the aqueous mixture was acidified to pH 2 with 1 H HCl, and the aqueous acid layer was extracted several times with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried, and the solvent was removed by evaporation under reduced pressure to provide 5.02 g (100%) of 7-[α-methoximino-α-(6-fluoro-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid: NMR ($CDCl_3$) δ 2.24 (s, 3 H), 4.04 and 4.15 (2 s, 3 H), 5.08 and 5.11 (2 dd, 1 H); IR ($CHCl_3$) 1774 cm^{-1} (β-lactam).

By following the general procedure, the following compounds were prepared: 7-[α-methoximino-δ-(7-fluoro-3-benzothienyl)-acetamido]-3-methyl-3-cephem-4-carboxylic acid [IR ($CHCl_3$) 1782 cm^{-1} (β-lactam)], 7-[α-methoximino-α-(4-fluoro-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid [Anal. ($C_{19}H_{16}N_3O_6S_2F$) C, H, N, F. NMR ($CDCl_3$) δ 2.22 (s, 3 H), 4.04 (s, 3 H), 5.09 (d, 1 H), 5.9 (dd, 1 H), 6.98–7.63 (m, 6 H)], 7-[α-methoximino-α-(5-fluoro-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid [IR ($CHCl_3$) 1778 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.23 (s, 3 H), 4.09 (s, 3 H), 5.1 and 5.13 (2 d, 1 H), 5.9 and 5.94 (2 dd, 1 H).

7-[α-Methoximino-α-(8-chloro-2-naphthyl)acetamido]-3-methyl-3-cephem-4-carboxylic Acid. α-Methoximino-α-(8-chloro-2-naphthyl)acetic acid (420 mg) was converted to the acid chloride by reaction with excess chlorine and 500 mg of triphenyl phosphite in 20 mL of CH_2Cl_2. The reaction mixture was added in one portion to a stirred solution of 350 mg of 7-amino-3-

methyl-3-cephem-4-carboxylic acid in 5 mL of CH_2Cl_2 containing 2 mL of BSTFA. The reaction mixture was stirred at 25 °C for 6 h and then diluted by addition of 20 mL of MeOH. The solvent was evaporated under reduced pressure to provide 7-[α-methoximino-α-(8-chloro-2-naphthyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid. The product thus formed was dissolved in formic acid containing zinc dust to give, following isolation and purification, 7-[(8-chloro-2-naphthyl)glycylamido]-3-cephem-4-carboxylic acid.

7-[α-Methoximino-α-(4-chloro-2-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic Acid. A solution of 539 mg (2 mmol) of α-methoximino-α-(4-chloro-2-benzothienyl)acetic acid in 10 mL of benzene containing 0.72 mL (8 mmol) of oxalyl chloride and 2 drops of DMF was stirred at 25 °C for 30 min. The solvent was then removed by evaporation to leave an oil, which was then purged three times with fresh benzene. The oil was next dissolved in 10 mL of acetone and added dropwise to a cold (0 °C) stirred solution of 428 mg (2 mmol) of 7-amino-3-methyl-3-cephem-4-carboxylic acid in 20 mL of water and 10 mL of acetone containing 420 mg (5 mmol) of $NaHCO_3$. The reaction mixture was stirred at 0 °C for 30 min and then for 3 h at room temperature. The reaction mixture was concentrated to a volume of about 20 mL and then diluted with 50 mL of EtOAc and the pH was adjusted to 2.4 with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with fresh EtOAc. The organic extracts were combined, washed with water, and dried, and the solvent was removed by evaporation to give 760 mg (81% yield) of 7-[α-methoximino-α-(4-chloro-2-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid as an amorphous tan solid: NMR ($CDCl_3$) δ 2.19 (s, 3 H), 3.39 (q, 2 H), 4.07 and 4.23 (2 s, 3 H), 5.02–5.14 (m, 1 H), 5.8–6.0 (m, 1 H), 7.1–7.8 (m, 5 H).

7-[α-Methoximino-α-(5-chloro-2-benzothienyl)acetamido]-3-cephem-4-carboxylic Acid. A solution of 255 mg (1 mmol) of α-methoximino-α-(5-chloro-2-benzothienyl)acetic acid in 10 mL of oxalyl chloride containing 3 drops of DMF was stirred at 0 °C for 2 h. The excess oxalyl chloride was evaporated under reduced pressure and by azeotroping with three 50-mL portions of CH_3CN. The residue was dissolved in 15 mL of CH_3CN and added in one portion to a cold (0 °C) stirred solution of 428 mg of 7-amino-3-methyl-3-cephem-4-carboxylic acid in 50 mL of acetonitrile containing 2.5 mL of BSTFA. The reaction mixture was stirred for 3 h at 0 °C and then stored at −5 °C for 12 h. The reaction mixture was warmed to 25 °C and then diluted by addition of 5 mL of dilute NH_4OH and filtered. The filtrate was concentrated to dryness to give a gum, which was then dissolved in 20 mL of aqueous $NaHCO_3$ and 20 mL of EtOAc. The mixture was acidified to pH 2 by addition of dilute HCl. The organic layer was separated and dried, and the solvent was removed by evaporation to give 400 mg of 7-[α-methoximino-α-(5-chloro-2-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid: NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.50 (m, 2 H), 4.05 (s, 3 H), 5.10 (m, 1 H), 5.90 (m, 1 H), 6.2–6.7 (br, 1 H), 7.22–8.6 (m, 4 H).

7-[(6-Chloro-3-benzothienyl)glycylamido]-3-cephem-4-carboxylic Acid (7R). α-Methoximino-α-(6-chloro-3-benzothienyl)acetic acid (2.8 g, 10.39 mol) was coverted to the acid chloride and reacted with 2.33 g (10.91 mmol) of 7-amino-3-methyl-3-cephem-4-carboxylic acid to provide 3.85 g (80% yield) of 7-[α-methoximino-α-(6-chloro-3-benzothienyl)acetamido]-3-cephem-4-carboxylic acid as an amorphous solid: NMR ($CDCl_3$) δ 2.02 and 2.21 (2 s, 3 H), 3.1–3.85 (m, 2 H), 4.01 (s, 3 H), 5.06 (d, 1 H), 5.86 (dd, 1 H), 7.2–7.8 (m, 4 H), 8.3–8.7 (m, 2 H).

Reduction of 3.83 g (8.2 mmol) of the methoxime from above by reaction with 3.04 g of zinc dust in aqueous formic acid and MeOH provided, following isolation, 4.6 g of a white powder. The product was chromatographed over a C_{18} reverse-phase silica gel column. High-performance liquid chromatography provided 80 mg of (*S*)-7-[(6-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid and 49 mg of (*R*)-7-[(6-chloro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as amorphous solids.

E. Reduction of the α-Methoximino Function to the Amino Group. 7-[(4-Chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (11R). To a stirred solution of 750 mg (1.6 mmol) of 7-[α-methoximino-α-(4-chloro-2-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid in 8 mL of MeOH were added 8 mL of 98% formic acid and 5 mL of water. The solution was cooled to about 5 °C and then 386 mg (5.9 mmol) of zinc dust was added portionwise over 20 min. The reaction mixture was stirred for 3 h and then filtered through hyflo filter aid. The filtrate was concentrated to an oil which was dissolved in EtOAc and diethyl ether. A white precipitate was collected by filtration and dried at 40 °C in vacuum to give 984 mg of (*R,S*)-7-[(4-chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as an amorphous solid.

The product thus formed was suspended in 30 mL of 5% (w/v) aqueous $NaHCO_3$ and 25 mL of water. The pH was adjusted to 8.5 by addition of 1 N sodium hydroxide. High-performance liquid chromatography over a C_{18} reverse-phase silica support, eluting with 2% acetic acid and a gradient of 10–20% (v/v) CH_3CN–water. The appropriate fractions were collected, concentrated, and lyophilized to give 102 mg of (*R*)-7-[(4-chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid and 123 mg of (*S*)-7-[(4-chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as amorphous solids.

(*R*)-7-[(5-Chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (12R). To a cold (0 °C) stirred solution of 400 mg of 7-[α-methoximino-α-(5-chloro-2-benzothienyl)acetamido]-3-cephem-4-carboxylic acid in 8 mL of mEOH containing 8 mL of 90% HCO_2H and 5 mL of water was added portionwise over 25 min 230 mg of zinc dust. The reaction mixture was stirred for 2.5 h at 0 °C following complete addition. The reaction mixture was filtered and the solvent was evaporated under reduced pressure to provide 462 mg of (*RS*)-7-[(5-chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid. High-pressure liquid chromatography effected separation of isomers to provide (*R*)-7-[5-chloro-2-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid.

(*R*)-7-[(6-Fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (4R). To a stirred cold (5 °C) solution of 5.01 g (11.1 mmol) of 7-[(α-methoximino-α-(6-fluoro-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid in 50 mL of MeOH containing 25 mL of water and 50 mL of HCO_2H was added portionwise over 25 min 2.70 g (41.3 mmol) of zinc dust. The reaction mixture was stirred for an additional 2 h and then was filtered. The filtrate was concentrated to dryness by evaporation of the solvent under reduced pressure to provide a yellow gum. The gum was triturated with diethyl ether to afford, following drying in vacuum, 5.36 g of (*RS*)-7-[(6-fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid. One gram of the product was purified by high-pressure liquid chromatography over silica gel, eluting with an CH_3CN–CH_3CO_2H gradient, to afford 149 mg of (*S*)-, 60 mg of (*RS*)-, and 318 mg of (*R*)-7-[(6-fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid: IR ($CHCl_3$) 1763 cm^{-1} (β-lactam).

By following the general procedure, the following compounds were prepared: (*R*)-7-[(5-fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid (**3R**) [IR ($CHCl_3$) 1761 cm^{-1} β-lactam], (*R*)-7-[(4-fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid (**2R**), and (*R*)-7-[(7-fluoro-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid (**5R**).

(*R*)-7-[(6-Methoxy-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic Acid (9R). To a cold (5 °C) stirred solution of 309 mg (0.67 mmol) of 7-[(α-methoximino-α-(6-methoxy-3-benzothienyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid in 0.5 mL of DMF and 10 mL of HCO_2H was added in one portion 170 mg (2.6 mmol) of zinc dust. The reaction mixture was stirred for 1 h and then was filtered through Celite filter aid. The filter cake was washed twice with 10-mL portions of MeOH, once with 10 mL of water, and again with 10 mL of MeOH. The filtrate was then evaporated to dryness, and the product was triturated with 25 mL of diethyl ether and then suspended in 20 mL of water and lyophilized to provide 290 mg of (*RS*)-7-[(6-methoxy-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid. This product was purified to separate the isomers by high-pressure liquid chromatography to give 42.4 mg of (*R*)-7-[(6-methoxy-3-benzothienyl)glycylamido]-3-methyl-3-cephem-4-carboxylic acid as an amorphous solid.

Acknowledgment. We express our appreciation to Dr. Lowell D. Hatfield for valuable discussions and guidance,

to Dr. Larry C. Blaszczak for helpful suggestions, to Dr. J. L. Ott for the MIC's, to Dr. Fred T. Counter for obtaining the ED_{50} values in mice, to Donnis M. Berry and Lyell Huckstep for analytical and preparatie HPLC, and to the analytical and physical chemistry sections for elemental analyses, UV, IR, and NMR spectroscopy. One of us (S.K.) is grateful to Robert R. Chauvette for his counsel and critical reading of this manuscript.

Orally Absorbable Cephalosporin Antibiotics. 2.[1] Structure–Activity Studies of Bicyclic Glycine Derivatives of 7-Aminodeacetoxycephalosporanic Acid

Stjepan Kukolja,* Susan E. Draheim, Bernard J. Graves, David C. Hunden, Janice L. Pfeil, Robin D. G. Cooper, John L. Ott, and Fred T. Counter

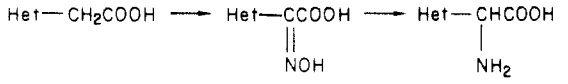
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285. *Received December 17, 1984*

Three positional analogues (4-, 5-, and 7-) of benzothienylglycine and (*N*-acetylindolinyl)-5-glycine were prepared and coupled to 7-aminodeacetoxycephalosporanic acid (7-ADCA) to give the cephalosporins **17a–c**. In addition two isomeric (2,3-*b* and 3,2-*b*) thienothiopheneglycines were synthesized and coupled to 7-ADCA to yield cephalosporins **30d** and **30e**. In vitro testing of these new cephalosporins indicates good activity against Gram-positive bacteria. Against *Streptococcus pneumoniae* infections compound **25** displayed better mouse protection (both orally and subcutaneously) than cephalexin.

In the preceding paper we described some of our recent efforts in the field of orally absorbable cephalosporins.[1] The first part dealt mainly with functional derivatives of benzothienyl- and naphthylglycine side chains. Here we would like to report the synthesis and biological activities of the positional analogues (4-, 5-, and 7-) of benzothienylglycine and the (*N*-acetylindolinyl)-5-glycine derivative of 7-aminodeacetoxycephalosporanic acid (**17a–c** and **25**). In addition two thienothiophene-2-glycine cephalosporins **30d** and **30e** were prepared and tested.

Chemistry

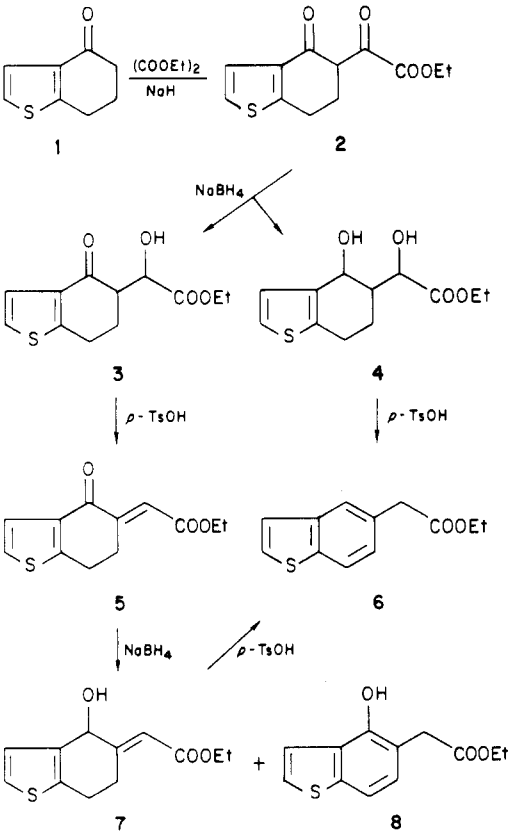
Among various possibilities for the synthesis of the described benzothienylglycines, we chose nitrosation of the pertinent heteroaromatic acetic acids to give the corresponding α-oximinoacetic acids and the subsequent reduction of the imino group to the desired amino acids, as illustrated in the following general scheme:



Het = heteroaromatic ring

The benzothienyl-4-acetate was commercially available, but the other two had to be synthesized. We began our synthesis of benzothienyl-5-acetate with 4-ketotetrahydrothianaphthene (1). By treatment of the ketone **1** with diethyl oxalate in the presence of sodium hydride the α,γ-diketo ester **2** was obtained in 88% yield. The reduction of **2** with 2.25 equiv of sodium borohydride gave a mixture of two products and the unreacted starting material. The mixture was separated by chromatography and three compounds were isolated: the starting diketone **2** (4%), a monoalcohol (31%), and a diol (27%). Physical chemical data indicate that in the case of the monoalcohol only the α-keto group was reduced to give **3** and further reduction of the 4-keto group gave the diol **4**. None of the 4-hydroxy α-keto ester was obtained. When the reduction of **2** was repeated with a larger excess of sodium borohydride (8 equiv), compound **4** was obtained in 87% yield without chromatography.

Scheme I



Our intended route from this point was a sequence starting with the monoalcohol **3** and leading to the benzothienyl-5-acetate **6** (Scheme I). Compound **3** was dehydrated by refluxing in toluene with *p*-toluenesulfonic acid and **5** was isolated in 88% yield. Treatment of **5** with sodium borohydride gave the olefinic alcohol **7**; interestingly, the phenolic benzothienyl-5-acetate **8** was also obtained. Reflux of **7** with *p*-toluenesulfonic acid afforded the benzothienyl-5-acetate **6**. However, similar reflux of the dihydroxy compound **4** gave 21% of **6** in one step.

(1) Kukolja, S.; Draheim, S. E.; Pfeil, J. L.; Cooper, R. D. G.; Graves, B. J.; Holmes, R. E.; Neel, D. A.; Huffman, G. W.; Webber, J. A.; Kinnick, M. D.; Vasileff, R. T.; Foster, B. J. *J. Med. Chem.*, preceding paper in this issue.

0022-2623/85/1828-1896$01.50/0