3-Sulfonyl-1-carba-1-dethiacephems

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The stability of the 1-carba-1-dethiacephalosporin framework has allowed the synthesis of a range of 3-sulfonyl-1-carba-1-dethiacephems unavailable for a variety of reasons in the cephem arena. The known *p*-nitrobenzyl 7β-(phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate served as a precursor to this series of compounds. Displacement of the enol triflate with various sulfinates in acetonitrile or DMF and deprotection of the intermediates led to 7β-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[alkyl(aryl)sulfonyl]-1-carba-1-dethia-3-cephem-4-carboxylic acids. The 3-sulfonyl-1-carba-1-dethiacephems display potent activity against both Gram-positive and Gram-negative bacteria. The following MIC's (μg/mL) for the 3-cyclopropyl sulfone are representative: *Staphylococcus aureus* = 4, *Streptococcus pyogenes* = 1, *Haemophilus influenzae* = 0.25, *Escherichia coli* = 0.03, *Enterobacter cloacae* = 0.25, *Proteus rettgeri* = 0.25. The excellent in vitro antibacterial activity of this series indicates the potential of the carbacephalosporin framework for exploring substituents which are unknown or which produce unstable cephems.

The 1-carba-1-dethiacephalosporins have been known for some time,[1] the first complete cephalosporin mimic having been synthesized by Guthikonda et al. in 1974.[2] These workers showed that the methylene analogue of cephalothin (**1**), 1-carbacephalothin (**2**), (Figure 1), had antibacterial activity equivalent to that of the corresponding cephalosporin when normalized for the potency of the correct enantiomer. A number of other publications have appeared over the years concerning various aspects of 1-carba-1-dethiacephalosporin bioactivity and synthesis.[3] Our interest in this area was stimulated by the recent observation that 3-chloro-7-phenylglycyl-1-carba-1-dethiacephem (loracarbef, **4**) shows a dramatic stability increase over the corresponding cephem, cefaclor (**3**), in both water and serum.[4]

This dramatic stability increase of the carbacephem over the analogous cephem is dramatized in a number of pairs of compounds synthesized and described in a forthcoming publication.[5] We have been pursuing a number of leads in the 1-carba-1-dethiacephem series in an effort to take advantage of the inherent stability of this nucleus over that of the cephem parent.[6] The particular structure–activity relationship described in this paper is for the 3-sulfonyl-1-carba-1-dethiacephem series. There has only been a single instance of a 3-sulfone prepared in the cephem art. This is 7-phenylglycylamido compound **5** made at Ciba-Geigy.[7] The compound was chemically quite labile and showed only traces of microbiological activity due to this instability. We hoped to take advantage of the stability of the carbacephem framework and use this handle to explore new compounds unavailable as cephems.

Synthesis of 3-Sulfonyl-1-carba-1-dethiacephems. Synthesis began with *p*-nitrobenzyl 7-(phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethiacephem-4-carboxylate (**6**) (cephem numbering). This material was prepared essentially as described by Evans et al.[8] The first compound prepared in this series was by the direct displacement of the 3-enol triflate of **6** with sodium methanesulfinate (Figure 2).

This gave sulfone **7**, after hydrogenolysis, which displayed the microbiological activity shown in Table I (as compared with that of its 3-Cl-cephem counterpart) and convinced us to pursue the further elaboration of this series. We desired to replace the 7-phenoxyacetamido substituent with an appropriately protected third-generation side chain (2-(2-aminothiazol-4-yl)-2(*Z*)-(methoximinoacetamido): ATMO) at C-7 and to reprotect the C-4 acid with a protecting group more readily removed in the presence of the ATMO side chain (Figure 3). Treatment of *p*-nitrobenzyl ester **6** with Zn dust in DMF/1 N HCl gave the free acid, which was esterified directly with diphenyldiazomethane to give **8a**. Alternatively, the free acid could be converted to its tetra-*n*-butylammonium salt and alkylated with allyl bromide to yield **8b**. Cleavage of the amide at C-7 was accomplished by sequential treatment with PCl_5 in pyridine, isobutanol, and water.[9] The relatively unstable free amines **9a,b** were then immediately acylated by treatment with the active ester of the *tert*-butoxycarbonyl, *t*-Boc (or allyloxycarbonyl, alloc), protected 2-(2-aminothiazol-4-yl)-2(*Z*)-methoximinoacetic acid. 6-Chloro-2,4-dimethoxy-1,3,5-triazine was used to

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Table I. Minimal Inhibitory Concentrations for **6a–i**[a]

compd	S.a.	S.e.	S.py.	S.pn.	H.i.	E.c.	E.c.+	K.	K.+	E.cl.	E.cl.+	S.	Ps.	P.m.	P.r.
7	0.25	0.50	0.015	0.06	16	4.0	>128	8.0	>128	>128	>128	8.0	>128	>128	>128
7(1-*S*)	0.25	0.25	0.125	0.25	1.0	64	128	8.0	128	128	128	64	128	128	128
3	2.0	4.0	0.25	1.0	2.0	0.50	1.0	0.25	>128	16	>128	2.0	>128	>128	64
11a	16	32	0.06	0.06	0.25	0.25	1.0	0.06	64	2.0	>128	0.125	>128	1.0	0.50
11b	8.0	16	0.03	0.03	0.25	0.06		0.06	>128	1.0	>128	0.06	>128	2.0	0.125
11c	8.0	8.0	0.03	0.03	0.25	0.125	1.0	0.125	>128	1.0	>128	0.125	>128	2.0	4.0
11d	8.0	16	2.0	0.06	0.50	0.25	1.0	0.125	>128	1.0	>128	0.06	>128	4.0	0.25
11e	4.0	8.0	0.015	0.03	0.25	0.06	0.50	0.06	>128	0.50	>128	0.125	>128	2.0	1.0
11f	8.0	16	1.0	0.06	0.25	2.0	8.0	1.0	>128	8.0	>128	0.25	>128	>128	1.0
11g	4.0	16	0.015	0.03	1.0	2.0	128	2.0	>128	8.0	>128	0.50	>128	64	64
11h	16	32	0.06	0.125	1.0	1.0	4.0	2.0	>128	16	>128	2.0	>128	>128	>128
11i	4.0	8.0	0.03	0.03	0.25	2.0	8.0	1.0	>128	8.0	>128	4.0	>128	2.0	16
12	2.0	2.0	0.015	0.015	0.015	0.03	0.03	0.008	2.0	0.125	32	0.03	32	0.25	0.125

[a] S.a. = *Staphylococcus aureus* (X1.1), S.e. = *Staphylococcus epidermidis* (222), S.py. = *Streptococcus pyrogenes* (C203), S.pn. = *Streptococcus pneumoniae* (PARK), H.i. = *Haemophilus influenzae* (C.L.), E.c. = *Escherichia coli* (EC14), E.c. + = *Escherichia coli* (TEM β-lactamase containing), K. = *Klebsiella* (X26), K.+ = *Klebsiella* (KAE β-lactamase containing), E.cl. = *Enterobacter cloacae* (EB5), E.cl.+ = *Enterobacter cloacae* (265A β-lactamase containing), S. = *Salmonella* (X514), Ps. = *Pseudomonas aeruginosa* (X528), P.m. = *Proteus morganii* (PR 15), P.r. = *Proteus rettgeri* (C24).

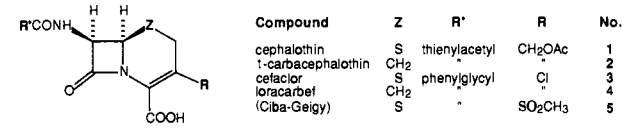

Figure 1.

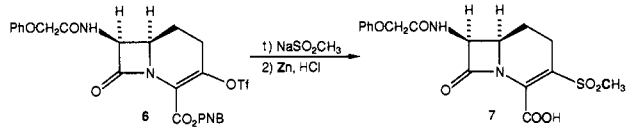

Figure 2.

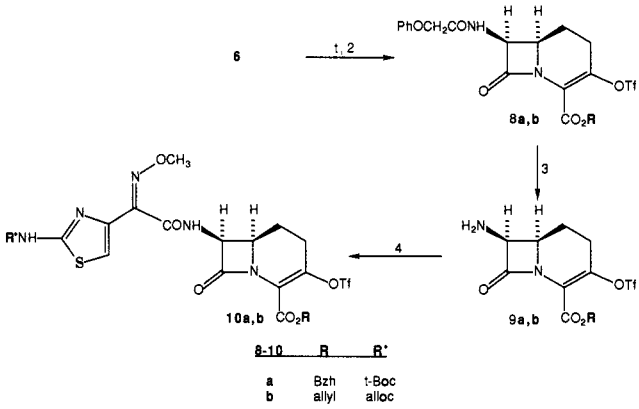

Figure 3. (1) Zn, HCl, DMF/THF; (2) (a) Ph_2CN_2 or (b) $Bu_4NHSO_4/NaHCO_3$, CH_2CHCH_2Br; (3) (a) PCl_5, py, (b) *i*-BuOH, (c) H_2O; (4) *t*-Boc (or alloc)(2-aminothiazol-4-yl)-2(*Z*)-oximinoacetyl-$OCO_2C_3N_3(MeO)_2$, *N*-methylmorpholine, CH_2Cl_2.

activate the free acid in the presence of *N*-methylmorpholine.[10] The resultant carbacephems (**10a,b**) were then ready for conversion to the desired sulfones **11a–i.**

The conversion to the sulfones was accomplished by an addition–elimination reaction at C-3 with the salt of the corresponding sulfinic acid (Figure 4). Two of these sulfinic acid salts were commercially available: CH_3SO_2Na and $PhSO_2Na$ only required azeotropic drying with CH_3CN prior to use. The lithium cyclopropanesulfinate was synthesized by quenching cyclopropyllithium[11] with SO_2.[12] The remainder of the sulfinates, except the 3-pyridinesulfinate, were prepared from the corresponding com-

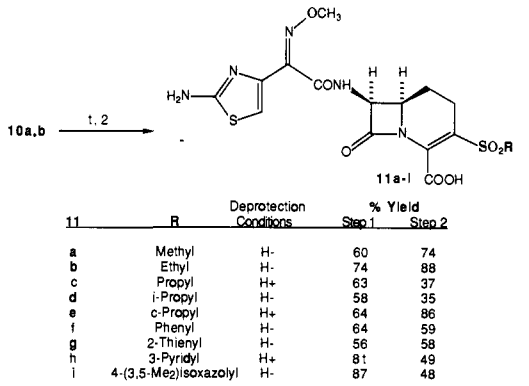

Figure 4. (1) RSO_2M, DMF, or CH_3CN; (2) TFA, Et_3SiH, or cat. $Pd(OAc)_2$, Ph_3P, *n*-Bu_3SnH.

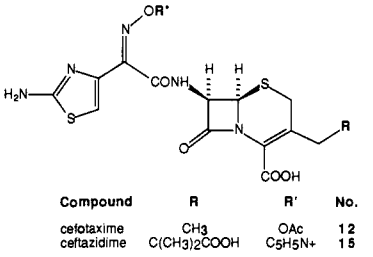

Figure 5.

mercially available sulfonyl chlorides by reduction in aqueous sodium bicarbonate with sodium bisulfite.[13] This procedure often gave sulfinates contaminated with inorganic salts, but since these did not seem to interfere with the displacement chemistry, no effort was made to further purify these sulfinates. Sodium 3-pyridinesulfinate was also prepared by this reduction, but it was necessary to first convert the commercially available 3-pyridinesulfonic acid to the sulfonyl chloride. The displacements were carried out in acetonitrile or dimethylformamide at room temperature except for the less nucleophilic sulfinates (i.e. 3-pyridinesulfinate) which required gentle heating. The displacements proceeded in good yield and the product sulfones were purified by flash chromatography.[14] Deprotection at both ends of the molecule was accomplished with trifluoroacetic acid/triethylsilane in the case of the

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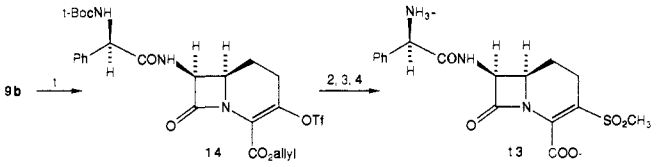

Figure 6. (1) *t*-Boc(D)-phenylglycyl-$OCO_2C_3N_3(MeO)_2$, *N*-methylmorpholine, CH_2Cl_2. (2) CH_3SO_2Na, DMF; (3) cat. $Pd(OAc)_2$, Ph_3P, *n*-Bu_3SnH; (4) TFA, Et_3SiH.

benzhydryl ester/*t*-Boc-protected materials. Triethylsilane was used as a carbonium ion scavenger. Removal of the *t*-Boc group preceded benzhydryl cleavage as the benzhydryl ester was often observed by TLC and could be isolated in low yield. The bis-allyl-protected intermediates were deprotected by treatment with a catalytic amount of $Pd(OAc)_2$ in the presence of *n*-Bu_3SnH.[15] All of the final products were isolated as lyophilizates after purification by reverse-phase chromatography either on C_{18} or on HP20ss with acetonitrile/water gradients.

Evaluation of the 3-Sulfonyl-1-carba-1-dethiacephems. The in vitro activity is displayed in Table I and shows some clear trends. The activity is quite good, as compared with that of cefotaxime (**12**) (Figure 5) for most of the sulfones. The antimicrobial MIC's compare favorably with the best cephalosporins demonstrating good activity against *S. aureus*, *H. influenza*, and *E. coli*. There is no activity seen against those Gram-negative microbes possessing cephalosporinases (K. vs K.+ and E.cl. vs E.cl.+ of Table I, in both cases the β-lactamases indicated by the + are cephalosporinases) or *P. aeruginosa*. This is due presumably to both a poor stability to these cephalosporinases and to poor permeability across the outer membrane of the more impermeable Gram-negative microbes. Gram-positive activity improves as one might expect on increasing lipophilicity (e.g. methyl to ethyl to propyl and cyclopropyl). This occurs with little loss of Gram-negative activity.

This class of compounds is slightly less stable than ceftazidime (**15**), a relatively unstable cephalosporin. Ethyl sulfone **11b** shows a hydrolysis rate of $K = 4.34\ h^{-1}$ at pH = 10, at an ionic strength $m = 0.5$, and 35 °C. This corresponds to a $t_{1/2} = 0.16$ h. Ceftazidime under identical conditions shows $K = 1.23\ h^{-1}$ and $t_{1/2} = 0.562$ h (pH = 10). Noting the 10–30-fold enhancement in stability for carbacephems relative to their cephem counterparts,[5] it is quite clear that these compounds, though comparable in stability to the least stable of marketed parenteral cephalosporins, are still viable compounds.

7-Phenylglycyl-3-sulfonyl-1-carba-1-dethiacephems. 3-(Methylsulfonyl)-7-phenylglycylamido-1-carba-1-dethiacephem-4-carboxylate (**13**) was also prepared in order to pursue the possibility of orally bioavailable antibacterials. The starting triflate was prepared as above, except the acylation was performed with the *t*-Boc-protected phenylglycine-active ester to give **14** (Figure 6). Displacement of the enol triflate with sodium methanesulfinate in DMF (77%), palladium-catalyzed deesterification (73%), and TFA deprotection (24%) proceeded smoothly to give the zwitterion, which crystallized from methanol. This material was quite unstable in pH = 7 buffer and decomposed with a $t_{1/2}$ of less than 1 h as compared with cefaclor, whose $t_{1/2}$ was about 22 h under these conditions. Even the stability of the carbacephem nucleus was overcome by these extremes in β-lactam activation: a strong electron withdrawer at C-3[16] and a good intramolecularly disposed nucleophile—the side-chain amine.

In conclusion, we have shown that the carbacephem nucleus can serve as a framework for exploring new substituents. Carbacephem **6** has allowed the preparation and microbiological testing of a series of 3-sulfonyl-1-carba-1-dethiacephems with good, third-generation activity against both Gram-positive and Gram-negative bacteria. Unfortunately, the carbacephems of this series do not show stability to the cephalosporinases present in many Gram-negative species, nor do they display any activity against *P. aeruginosa*. The introduction of the phenylglycyl substituent at C-7 led to a relatively unstable compound which displayed no microbiological activity, similar to its cephem counterpart.[7]

Experimental Section

IR spectra were recorded on a Nicolet FT-IR Model 10-DX instrument. Mass spectra were determined with a Varian MAT 731. Mass spectra were recorded by either one of two methods, fast atom bombardment (FAB) or field desorption (FD). Proton NMR spectra were recorded on a General Electric QE-300 instrument. UV spectra were determined on a Cary Model 219 spectrometer in EtOH. Analytical HPLC was carried out on a C_{18} column eluted with aqueous 1–20% acetonitrile (constant or gradient) in aqueous ammonium acetate (1–2%) buffer and monitored at 254 nm. Thin-layer chromatography was performed on Merck F254 silica gel plates eluted with either ethyl acetate/hexane solvent mixtures or for polar compounds a mixture of ethyl acetate, acetonitrile, acetic acid, and water (25:7:9:9) sometimes diluted with varying amounts of ethyl acetate. Analytical results indicated by elemental symbols were within ±0.4% of the theoretical values.

Determination of Minimal Inhibitory Concentrations (MIC). Test compounds were diluted to an appropriate range of concentrations in 0.1 M phosphate buffer, pH 7.0, incorporated into Mueller-Hinton agar (Difco) supplemented with 1% Bacto-Supplement C (Difco) at 50 °C and allowed to solidify in petri dishes. Fresh overnight cultures of test bacteria were diluted to approximately 1×10^4 cells/μL and applied in 1-μL volumes to the surfaces of the agar plates. The inoculated plates were incubated overnight at 35 °C in ambient air. MIC endpoints were recorded as the lowest antibiotic concentrations that inhibited the development of visible growth on the plates.

Determination of Stabilities. The hydrolysis rates for the ATMO sulfones were determined by following the loss of parent β-lactam. Constant pH was maintained by a pH stat consisting of a Metrohm 655 dosimat, 614 implusomat, and a 632 pH meter fitted with a combination electrode. Initial β-lactam concentrations were 3.9×10^{-4}–1×10^{-3} M. The pH was maintained at 10 or 11 by addition of NaOH. The ionic strength was adjusted to 0.5 with KCl. The chromatography system consisted of a Beckman 332 chromatograph, a Rheodyne 7125 injection valve fitted with a 20-μL loop, a Waters 450 or a Kratos Spectroflow 773 detector, and a Hewlett-Packard 3390A integrator. The stationary phase was a 4.4 × 250 mm Zorbax ODS (Du Pont) reverse-phase column and the detector was set at 254 nm. The flow rate was 1 mL/min. The hydrolysis rate for cefaclor and **14** were determined by dissolution of the particular salt in pH 7.0 phosphate buffer (2 mM in β-lactam and 0.05 M in PO_4^{2-}). The solutions were monitored by reverse-phase HPLC consisting of an Altex 110A pump at 1 mL/min, the same injector as above, an LDC Spectromonitor III variable-wavelength UV detector set to 254 nm, a Spectra-Physics SP4270 integrator, and a 3 × 250 mm Soft Seal 5-μm C_{18} reverse-phase column eluted with 10% CH_3CN/1% NH_4OAc/89% H_2O.

***p*-Nitrobenzyl 7β-(Phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (6).** A solution of 4.59 g of *p*-nitrobenzyl 7β-

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[(phenoxyacetyl)amino]-3-hydroxy-1-carba-1-dethia-3-cephem-4-carboxylate in 98 mL of distilled CH_2Cl_2 was cooled to −40 °C by means of an external acetonitrile/dry ice bath. With stirring, 1.49 g of triethylamine was added followed by the rapid addition of 2.91 g of triflic anhydride. After 5 min, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution. The layers were separated, and the organic layer was washed twice with 0.1 N hydrochloric acid and once with distilled water, and then dried over $MgSO_4$, filtered, and concentrated in vacuo. Hexane was added and the mixture was again evaporated in vacuo. The residue was triturated with 100 mL of hexane, providing 5.5 g of the desired intermediate as light pink/beige crystals. ^1H NMR ($CDCl_3$): 1.8–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.6–2.8 (2 H, m), 3.98 (1 H, dt, $J_{1,2}$ = 5 and 12 Hz), 4.60 (2 H, s), 5.41 (1 H, d, $J_{1,2}$ = 14 Hz), 5.52 (1 H, d, $J_{1,2}$ = 14 Hz), 5.56 (1 H, dd, $J_{1,2}$ = 5 and 10 Hz), 6.92–7.0 (3 H, m), 7.31 (2 H, t, $J_{1,2}$ = 7 Hz), 7.71 (2 H, d, $J_{1,2}$ = 10 Hz), 8.26 (2 H, d, $J_{1,2}$ = 10 Hz), 8.94 (1 H, d, $J_{1,2}$ = 10 Hz). IR (KBr): 1784.7 cm^{-1} (β-lactam carbonyl). MS (FAB): *m/e* (M + 1) 600. UV (EtOH): λ_{max} 269 nm (ε 19700). Anal. ($C_{24}H_{20}F_3N_3O_{10}S$): C, H, F, N, S.

7β-[(Phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylic Acid. *p*-Nitrobenzyl 7β-[(phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (20 g) was dissolved in a mixture of 200 mL of 1 N HCl, 200 mL of DMF and 400 mL of THF. Zinc (4 g) was added at room temperature to the solution with stirring. After 1 h, 2 g more of zinc were added and the mixture was stirred for 3 h at room temperature. The mixture was diluted with ethyl acetate and washed 3 times with aqueous HCl, water, and brine, dried over sodium sulfate, and evaporated to dryness. The product (15.07 g) was obtained and used without further purification. The crude product was homogeneous by TLC in 90% ethyl acetate/10% methanol.

Diphenylmethyl 7β-[(Phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (8a). A solution of 21.62 g of 7β-[(phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylic acid in 300 mL of acetonitrile was maintained under nitrogen and 9 g of diphenyldiazomethane was added portionwise at room temperature. After 2 h, acetic acid was added to remove the color of the reaction mixture and 100 mL of toluene was added. The mixture was evaporated to dryness under vacuum and the residue was chromatographed over silica using 60/40 hexane/ethyl acetate. The ester (22.1 g) was obtained in a yield of 75%. ^1H NMR ($CDCl_3$): 1.5–1.7 (1 H, m), 2.0–2.1 (1 H, m), 2.6–2.7 (2 H, m), 3.98 (1 H, dt, $J_{1,2}$ = 5 and 12 Hz), 4.54 (2 H, s), 5.44 (1 H, t, $J_{1,2}$ = 6 Hz), 6.90 (2 H, d, $J_{1,2}$ = 8 Hz), 7.00 (1 H, s), 7.04 (1 H, t, $J_{1,2}$ = 7 Hz), 7.13 (1 H, d, $J_{1,2}$ = 7 Hz), 7.2–7.4 (10 H, m), 7.48 (2 H, d, $J_{1,2}$ = 7 Hz). IR ($CHCl_3$): 1784.4 cm^{-1} (β-lactam carbonyl). MS (FAB): *m/e* (M − 1) 629. UV (EtOH): λ_{max} 269 nm (ε 10600). Anal. ($C_{30}H_{25}F_3N_2O_8S$): C, H, N.

Diphenylmethyl 7β-[2-[2-[[(*tert*-Butyloxy)carbonyl]amino]thiazol-4-yl]-2(*Z*)-(methoxyimino)acetamido]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (10a). A solution of 22.1 g of diphenylmethyl 7β-[(phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate in 300 mL of methylene chloride was cooled in an ice/ethanol bath and 3.4 mL of pyridine and 8.0 g of phosphorus pentachloride were added. After stirring for about 2 h, the cold solution was added to a solution of 300 mL of isobutyl alcohol in 300 mL of methylene chloride cooled to −20 °C. After stirring for 30 min, 400 mL of water was added to the reaction mixture and after stirring for 30 min the mixture was extracted three times with methylene chloride. The extracts were combined and washed three times with aqueous sodium bicarbonate solution, water and brine, dried over sodium sulfate, and evaporated under vacuum to a volume of 100 mL. The concentrate contained the free amine, which was not isolated but used in the following acylation. A solution of 10.6 g of 2-[2-[[(*tert*-butyloxy)carbonyl]amino]thiazol-4-yl]-2-(*Z*)-(methoxyimino)acetic acid in 100 mL of methylene chloride was treated with 3.84 mL of *N*-methylmorpholine, cooled in an ice bath, and next treated with 6.2 g of 2-chloro-4,6-dimethoxy-*s*-triazine. The mixture was stirred at room temperature for 30 min and cooled in an ice/ethanol bath. The 100-mL solution from above was added to the cold solution of the active ester, and the mixture was stirred at room temperature over 2 days. The reaction mixture was evaporated to dryness under vacuum and the residue was dissolved in ethyl acetate. The solution was washed three times with 1 N HCl, once with water, three times with aqueous sodium bicarbonate, and once with brine, was dried over sodium sulfate, and chromatographed twice over silica gel using 60% hexane in ethyl acetate, and 3.67 g of product was obtained. MP: 138–140 °C. ^1H NMR ($CDCl_3$): 1.5 (9 H, s), 1.7–1.8 (1 H, m), 2.1–2.2 (1 H, m), 2.6 (2 H, m), 4.0 (1 H, m), 4.05 (3 H, s), 4.19 (1 H, s), 5.60 (1 H, t, $J_{1,2}$ = 6 Hz), 6.94 (1 H, s), 7.2–7.5 (10 H, m). IR ($CHCl_3$): 1774 cm^{-1} (β-lactam carbonyl). MS (FAB): *m/e* (M + 1) 780. UV (EtOH): λ_{max} (265 nm (ε 100000). Anal. ($C_{33}H_{32}F_3N_5O_{10}S_2$) C, H, N.

Allyl 7β-(Phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (8b). To a suspension of 4.30 g (9.26 mmol) of 7β-[(phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylic acid in 270 mL of saturated aqueous sodium bicarbonate solution was added 3.22 g (9.50 mmol) of tetra-*n*-butylammonium sulfate. The mixture was extracted three times with 100-mL portions of methylene chloride. The extracts were combined, dried over sodium sulfate, and evaporated to dryness under vacuum to provide 5.50 g of the tetra-*n*-butylammonium salt as a foam. The salt was dissolved in 35 mL of acetonitrile under nitrogen and 708 μL (8.18 mmol) of allyl bromide was added to the solution. After the reaction mixture was allowed to sit at room temperature for 2 days, the mixture was poured into water and extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated to dryness under vacuum, yielding 4.0 g of crude allyl ester. The crude ester was purified by flash chromatography on silica gel using 50% ethyl acetate/hexane for elution, yielding 3.45 g (74%). ^1H NMR ($CDCl_3$): 1.6–1.7 (1 H, m), 2.0–2.1 (1 H, m), 2.6–2.7 (2 H, m), 3.98 (1 H, m), 4.57 (2 H, s), 4.81 (2 H, m), 5.3–5.5 (3 H, m), 5.9–6.1 (1 H, m), 6.90 (2 H, d, $J_{1,2}$ = 9 Hz), 7.06 (1 H, t, $J_{1,2}$ = 9 Hz), 7.12 (1 H, d, $J_{1,2}$ = 8 Hz), 7.24 (2 H, t, $J_{1,2}$ = 9 Hz). IR ($CHCl_3$): 1785.7 cm^{-1} (β-lactam carbonyl). MS (FD): *m/e* (M) 504. UV (EtOH): λ_{max} 269 nm (ε 10759.7). Anal. ($C_{20}H_{19}F_3N_2O_8S$): C, H, N.

Allyl 7β-Amino-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (9b). The ester (0.80 g, 1.59 mmol) from above was dissolved in 16 mL of anhydrous methylene chloride under N_2 and 158 μL (1.95 mmol) of pyridine and 375 mg (1.80 mmol) of phosphorus pentachloride were added with stirring. The mixture was stirred at room temperature for 1.5 h. When a thin-layer chromatogram indicated the presence of some remaining starting material after an aliquot was treated with methanol, an additional 0.52 μL of pyridine and 125 mg of phosphorus pentachloride were added to the reaction mixture. The reaction was allowed to continue for 30 min and was then added via a syringe to a solution of 1.47 mL (15.9 mmol) of isobutanol in 65 mL of methylene chloride maintained under N_2 at −10 °C. The cold mixture was stirred for 1 h as the temperature increased to 0 °C. Water (40 mL) was added and the mixture was stirred vigorously at room temperature for 15 min. The organic layer was separated and extracted three times with 1 N HCl. The pH of the aqueous acid extract was adjusted to 7.5 with sodium bicarbonate and extracted three times with methylene chloride. The extract was dried over sodium sulfate and evaporated to dryness under vacuum to provide 0.49 g of product as a clear oil. This material was used immediately in the following acylation.

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(*Z*)-(methoxyimino)acetamido]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (10b). To a suspension of 456 mg (1.60 mmol) of 2-[2-[[(allyloxy)carbonyl]amino]thiazol-4-yl]-2(*Z*)-(methoxyimino)acetic acid in 11.2 mL of anhydrous methylene chloride maintained under N_2 at 0 °C were added 281 mg (1.60 mmol) of chlorodimethoxytriazine and 176 μL (1.60 mmol) of *N*-methylmorpholine. The mixture was stirred at 0 °C for about 2 h before a solution of 0.49 g (1.32 mmol) of allyl 7β-amino-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate in 5 mL of anhydrous methylene chloride was added. The reaction mixture was stirred for about 14 h at room temperature, diluted with methylene chloride, washed twice with 0.1 N HCl and once with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and

evaporated under vacuum, yielding 740 mg of product as a yellow foam. The product was purified by flash chromatography on silica gel with 250 mL of 50% ethyl acetate/hexane, yielding 690 mg. ^{1}H NMR ($CDCl_3$): 1.83–2.00 (1 H, m), 2.18–2.30 (1 H, m), 2.62–2.74 (2 H, m), 4.0 (3 H, s), 4.01–4.10 (1 H, m), 4.80 (4 H, dd, $J_{1,2}$ = 4 and 12 Hz), 5.28–5.44 (4 H, m), 5.62–5.68 (1 H, m), 5.90–6.02 (2 H, m), 7.14 (1 H, s), 7.96 (1 H, br s), 9.50 (1 H, s). MS (FAB): m/e (M + 1) 638. IR ($CHCl_3$): 1774 cm^{-1} (β-lactam carbonyl). UV (EtOH): λ_{max} 267 (ϵ 19948), 230 nm (ϵ 19196.8).

Sodium Ethanesulfinate. Ethanesulfonyl chloride (25 g, 194 mmol) was added via an addition funnel with concurrent addition of Na_2CO_3 (36.7 g, 346 mmol) via a second addition funnel to a suspension of 55.1 g (437 mmol) of Na_2SO_3 in 130 mL of water at 80 °C. The simultaneous additions took ~45 min and evolved significant quantities of CO_2. The solution was heated at 80 °C for an additional hour. The water was removed in vacuo at 60 °C, and the remaining solids were refluxed in anhydrous EtOH for 1 h. The resultant suspension was filtered through Celite and the filtrate was stripped of solvent in vacuo. This gave 12.7 g (56%) of a white solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): 0.90 (3 H, t, $J_{1,2}$ = 8 Hz), 1.78 (2 H, q, $J_{1,2}$ = 8 Hz). IR (KBr): 1465, 1223, 1039, 1007, 989, 975 cm^{-1}. MS (FD): m/e (M) 116. Anal. ($C_2H_5NaO_2S$): C, H, N.

The following sulfinates were prepared analogously from the commercially available sulfonyl chlorides.

Sodium 1-Propanesulfinate. ^{1}H NMR (DMSO-d_6): 0.87 (3 H, t, $J_{1,2}$ = 8 Hz), 1.41 (2 H, q, $J_{1,2}$ = 8 Hz), 1.80 (2 H, t, $J_{1,2}$ = 8 Hz). IR (KBr): 1460, 1209, 1038, 1020, 1013, 991, 977 cm^{-1}. MS (FAB): m/e (M + Na, 153).

Sodium 2-Propanesulfinate. ^{1}H NMR (DMSO-d_6): 1.85 (6 H, d, $J_{1,2}$ = 8 Hz), 1.58 (1 H, septet, $J_{1,2}$ = 8 Hz). IR (KBr): 1461, 1208, 1049, 1012, 982 cm^{-1}. MS (FAB): m/e (M + Na, 153).

Sodium 2-Thienylsulfinate. ^{1}H NMR (DMSO-d_6): 6.95 (2 H, m), 7.41 (1 H, d, $J_{1,2}$ = 4 Hz). IR (KBr): 1405, 1220, 1023, 989, 978 cm^{-1}. MS (FD): m/e (M + Na) 193. UV (EtOH): λ_{max} 274 (ϵ 1530); 236 nm (ϵ 8060). Anal. ($C_4H_3NaO_2S_2$): C, H, S.

Sodium 3,5-Dimethylisooxazole-4-sulfinate. ^{1}H NMR (DMSO-d_6): 2.20 (3 H, s), 2.37 (3 H, s), IR (KBr): 1605, 1413, 1358, 1250, 1052, 1042, 988, 976 cm^{-1}. MS FAB): m/e (M + Na, 206). UV (EtOH): λ_{max} 218 nm (ϵ 4220).

Sodium 3-Pyridinesulfinate. 3-Pyridinesulfonic acid (20 g, 125 mmol) was mixed with 40 g of PCl_5 and heated in an oil bath to 130 °C for 2 h. The volatiles were then removed on the rotary evaporator and the residue was triturated with ether. The precipitate was collected and used immediately. The solid sulfonyl chloride/hydrochloride was added to a solution of 32 g (250 mmol) of Na_2SO_3 and 21 g (250 mmol) of $NaHCO_3$ in 100 mL of water that was maintained at 80 °C. After about half of the sulfonyl chloride had been added, an additional 21 g of $NaHCO_3$ was added. After addition was complete, the solution was heated for another hour and then stripped to dryness. The residue was leached with refluxing EtOH and decanted. After cooling, the ethanolic suspension was filtered and the filtrate was stripped to dryness. The solids were recrystallized from 2-propanol, resulting in a yield of ~20%. The material was utilized in this rather impure state. ^{1}H NMR (DMSO-d_6): 7.35 (1 H, m), 7.80 (1 H, m), 8.43 (1 H, d, $J_{1,2}$ = 8 Hz), 8.65 (1 H, s). IR (KBr): 1580, 1411, 1198, 1049, 1035, 984. MS (FAB): m/e (M + Na) 188, (M + H) 166. UV (EtOH): λ_{max} 295 (ϵ 560), 260 nm (ϵ 2508).

Lithium Cyclopropanesulfinate. A lithium dispersion (30% in mineral oil; 5.13 g, 220 mM) was suspended in 40 mL of anhydrous ether and cooled to 0 °C under N_2. Cyclopropyl bromide, dissolved in 40 mL of anhydrous ether, was added dropwise to maintain the internal temperature below 5 °C. After 3 h, the suspension was filtered through a Schlenk type fritted funnel under a positive pressure of N_2. In a separate flask, 4.7 mL of SO_2 was condensed and then warmed, allowing the boiling SO_2 to bubble through the ethereal solution of cyclopropyllithium. The precipitate which formed was filtered off and washed with ether and dried in a vacuum oven, giving the product in 19% yield. ^{1}H NMR (DMSO-d_6): 0.50–0.62 (4 H, m); 1.90 (1 H, m); IR (KBr): 1635, 1225, 1205, 1054, 1032, 985 cm^{-1}. MS (FAB): m/e (M + Na) 135.

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-methylsulfonyl-1-carba-1-dethia-3-cephem-4-carboxylate. Sodium methanesulfinate (17 mg, 0.16 mmol) was dried in a small vial via azeotropic distillation with acetonitrile and then maintained under N_2. Dry dimethylformamide (320 μL) and 50 mg (0.078 mmol) of allyl 7β-[2-[2-[[(allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate were added to the vial. The mixture was stirred for 3 h, diluted with 1 mL of ether acetate, and washed with water. The aqueous wash was extracted with ethyl acetate and the extract was combined with the washed reaction mixture. The mixture was filtered through sodium sulfate and evaporated to dryness under vacuum, yielding 52 mg of a brown oil. The oil was chromatographed on silica gel with 100 mL of 75% ethyl acetate/hexane and yielded 33 mg (0.058 mM) of product. ^{1}H NMR (90 MHz, $CDCl_3$): 1.2–1.4 (1 H, m), 1.7–1.9 (1 H, m), 2.0–2.4 (1 H, m), 2.6–2.8 (1 H, m), 3.08 (3 H, s), 4.01 (3 H, s), 4.95 (4 H, br t, $J_{1,2}$ = 5 Hz), 5.2–6.2 (7 H, m), 7.14 (1 H, s), 7.82 (1 H, d, $J_{1,2}$ = 8 Hz).

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-(ethylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. ^{1}H NMR (90 MHz, $CDCl_3$): 1.2–1.4 (1 H, m), 1.35 (3 H, t, $J_{1,2}$ = 7 Hz), 1.7–1.95 (1 H, m), 2.5–2.8 (2 H, m), 3.16 (2 H, q, $J_{1,2}$ = 7 Hz), 3.76 (3 H, s), 4.75 (4 H, t, $J_{1,2}$ = 5 Hz), 5.2–6.2 (7 H, m), 7.12 (1 H, s), 7.82 (1 H, d, $J_{1,2}$ = 8 Hz), 8.4 (1 H, br m).

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-(2-propylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. ^{1}H NMR ($CDCl_3$): 1.3 (1 H, m), 1.33 (3 H, d, $J_{1,2}$ = 9 Hz), 1.38 (3 H, d, $J_{1,2}$ = 9 Hz), 1.7 (1 H, m), 2.2–2.3 (1 H, m), 2.6 (1 H, m), 3.48 (1 H, septet), 4.05 (3 H, s), 4.1 (1 H, m), 4.76 (2 H, d, $J_{1,2}$ = 5 Hz), 4.83 (2 H, d, $J_{1,2}$ = 5 Hz), 5.3–5.5 (4 H, m), 5.98 (1 H, t, $J_{1,2}$ = 6 Hz), 6.0 (2 H, m), 7.15 (1 H, s), 7.25 (1 H, d, $J_{1,2}$ = 8 Hz), 8.8 (1 H, m), MS (FAB): m/e (M + 1) 596.

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-(phenylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. ^{1}H NMR ($CDCl_3$): 1.4 (1 H, m), 2.1 (1 H, m), 2.3–2.5 (2 H, m), 3.95 (1 H, m), 4.20 (3 H, s), 4.76 (2 H, d, $J_{1,2}$ = 5 Hz), 4.92 (2 H, m), 5.3–5.5 (4 H, m); 5.9–6.1 (2 H, m), 7.5–7.7 (3 H, m), 8.00 (2 H, d, $J_{1,2}$ = 9 Hz). IR (KBr): 1789.8 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + 1) 630. UV (EtOH): λ_{max} 274 (ϵ 23900), 226 nm (ϵ 23100). Anal. ($C_{27}H_{27}N_5O_9S_2$): C, H, N, S.

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-(2-thienylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. ^{1}H NMR ($CDCl_3$): 2.2 (1 H, m), 2.4–2.6 (1 H, m), 2.65–2.75 (1 H, m), 4.00 (3 H, s), 4.77 (2 H, d, $J_{1,2}$ = 4 Hz), 4.90 (2 H, t, $J_{1,2}$ = 4 Hz), 5.3–5.5 (4 H, m), 5.58 (1 H, t, $J_{1,2}$ = 6 Hz), 5.9–6.1 (2 H, m), 7.17 (1 H, t, $J_{1,2}$ = 4 Hz), 7.20 (1 H, s), 7.73 (1 H, d, $J_{1,2}$ = 4 Hz), 7.80 (1 H, d, $J_{1,2}$ = 4 Hz), 8.8 (1 H, m). MS (FAB): m/e (M + 1) 636.

Allyl 7β-[2-[2-[[(Allyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-1-carba-1-dethia-3-cephem-4-carboxylate. To a solution of 200 mg (0.256 mmol) of the allyloxycarbonyl-protected allyl ester intermediate in 10 mL of acetonitrile was added 200 mg of sodium 3,5-dimethylisoxazole-4-sulfinate and the solution was stirred at room temperature for about 12 h. When thin-layer chromatography of the solution showed the presence of starting material, 100 mg of 18-crown-6 was added and the mixture was stirred for another 12 h at room temperature. When starting material was still detected, the mixture was warmed to 50 °C for 4 h. Thereafter the reaction was evaporated to dryness and the residue was extracted from salt water with ethyl acetate. The extract was flushed through silica gel to provide 177 mg (0.240 mmol) of the allyloxycarbonyl-protected allyl ester sulfone. ^{1}H NMR ($CDCl_3$): 1.5 (1 H, m), 2.1–2.2 (2 H, m), 2.36 (3 H, s), 2.55 (1 H, m), 2.60 (3 H, s), 3.95 (1 H, m), 3.99 (3 H, s), 4.68 (2 H, d, $J_{1,2}$ = 6 Hz), 4.86 (2 H, m), 5.2–5.4 (5 H, m), 5.8–6.0 (2 H, m), 7.10 (1 H, m), 7.22 (1 H, s), 8.52 (1 H, m). IR (KBr): 1791.2 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M − 1) 649. UV (EtOH): λ_{max} 273 (ϵ 22000), 225 nm (ϵ 19900). Anal. ($C_{26}H_{30}N_6O_{10}S_2$): C, H, N, S.

Diphenylmethyl 7β-[2-[2-[[(*tert*-Butyloxy)carbonyl]amino]thiazol-4-yl]-2(Z)-(methoxyimino)acetamido]-3-(1-propylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. To a solution of 200 mg (0.326 mmol) of the *t*-Boc-protected

diphenylmethyl ester intermediate in 2 mL of dry acetonitrile was added 100 mg of sodium *n*-propanesulfinate and the mixture was stirred at room temperature for about 12 h. The solution was evaporated to remove the solvent. DMF was added and the solution was stirred an 2 additional hours. The DMF was partially removed by evaporation under vacuum and the concentrate was diluted with ethyl acetate. The solution was washed four times with water and three times with 1 N HCl, dried over sodium sulfate, and evaporated under vacuum. The residue containing the displacement product was chromatographed over silica gel using 50:50 ethyl acetate/hexane. This gave 107 mg of product. ^{1}H NMR ($CDCl_3$): 0.80 (3 H, t, $J_{1,2}$ = 5 Hz), 1.50 (9 H, s), 1.6 (4 H, m), 2.1 (1 H, m), 2.5 (2 H, m), 2.8 (2 H, m), 3.8–4.0 (1 H, br m), 3.92 (3 H, s), 5.40 (1 H, t, $J_{1,2}$ = 6 Hz), 6.80 (1 H, s), 7.1–7.5 (12 H, m), 8.7 (1 H, br s).

Diphenylmethyl 7β-[2-[2-[[(*tert*-Butyloxy)carbonyl]amino]thiazol-4-yl]-2(*Z*)-(methoxyimino)acetamido]-3-(3-pyridylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. To a solution of 200 mg (0.326 mmol) of the *t*-BOC protected diphenylmethyl ester intermediate in 4 mL of dry DMF was added 75 mg of sodium 3-pyridinesulfinate and the solution was stirred at room temperature for 6 days. The solution was diluted with 2 mL of ethyl acetate and was washed three times with water, three times with 1 N HCl and brine. The solution was chromatographed over silica gel to provide 111 mg (0.144 mmol) of product. ^{1}H NMR ($CDCl_3$): 1.50 (9 H, s), 2.1 (1 H, m), 2.4 (2 H, m), 3.89 (3 H, s), 4.05 (1 H, m), 5.38 (1 H, t, $J_{1,2}$ = 6 Hz), 7.00 (1 H, s), 7.2–7.5 (~12 H, m), 7.92 (1 H, s), 8.00 (1 H, br d, $J_{1,2}$ = 9 Hz), 8.69 (1 H, d, $J_{1,2}$ = 4 Hz), 8.88 (1 H, s).

The following compound was prepared analogously.

Diphenylmethyl 7β-[2-[2-[[(*tert*-Butyloxy)carbonyl]amino]thiazol-4-yl]-2(*Z*)-methoxyiminoacetamido]-3-(cyclopropylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. ^{1}H NMR ($CDCl_3$): 0.8 (2 H, m), 1.04 (1 H, m), 1.2 (1 H, m), 1.50 (9 H, s), 1.6–1.7 (2 H, m), 2.1–2.2 (1 H, m), 2.4–2.6 (2 H, m), 3.95 (1 H, m), 4.02 (3 H, s), 5.49 (1 H, t, $J_{1,2}$ = 6 Hz), 6.92 (1 H, s), 7.2–7.4 (~11 H, m), 9.05 (1 H, br s).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11a). To a solution of 130 mg (0.229 mmol) of the bis-allyl-protected sulfone from above in 1.4 mL of acetonitrile containing 0.92 mL of diethyl ether maintained under N_2 were added 6.0 mg (0.024 mmol) of palladium acetate and 48 mg (0.148 mmol) of triphenylphosphine, and the mixture was stirred at room temperature under N_2 for 20 min. The reaction mixture was cooled to 0 °C and 128 μL (0.477 mmol) of tri-*n*-butyltin hydride was added. The cooling bath was removed and the mixture was stirred at room temperature for 1 h. Concentrated HCl (39.4 μL, 0.447 mmol) was added to the mixture and a brown precipitate formed. The mixture was diluted with diethyl ether and the precipitate was separated by centrifugation. The precipitate was washed twice with diethyl ether, and the washes and precipitate were dissolved in hot 1:1 2-propanol/acetonitrile. The solution was filtered to remove the dark-brown solid. The filtrate was diluted with diethyl ether and the precipitate was separated by centrifugation, yielding 75 mg of the title compound. The product was purified via reverse-phase C_{18} HPLC using 5% acetonitrile/1% acetic acid/water. ^{1}H NMR (DMSO-d_6): 1.60 (1 H, m), 2.00 (1 H, m), 2.40 (1 H, m), 2.70 (1 H, m), 3.10 (3 H, s), 3.85 (3 H, s), 3.9–4.0 (1 H, m), 5.55 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.76 (1 H, s), 7.20 (2 H, br s), 7.8 (2 H, m), 9.32 (1 H, d, $J_{1,2}$ = 8 Hz). IR (KBr): 1779 cm^{-1} (β-lactam carbonyl). MS (FD): m/e (M + 1) 444, (M – CO_2) 399. UV (EtOH): λ_{max} 268 (ε 15106), 230 nm (ε 16836).

The following compounds were obtained similarly.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(ethylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11b). ^{1}H NMR (DMSO-d_6): 1.18 (3 H, t, $J_{1,2}$ = 8 Hz), 1.6–1.7 (1 H, m), 1.9–2.0 (1 H, m), 2.35–2.5 (1 H, m), 2.6–2.7 (1 H, m), 3.20 (2 H, m), 3.84 (3 H, s), 3.90–4.00 (1 H, m), 5.65 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.76 (1 H, s), 7.20 (2 H, br s), 9.33 (1 H, d, $J_{1,2}$ = 8 Hz). IR (KBr): 1780 cm^{-1} (β-lactam carbonyl). MS (FD): m/e (M – CO_2) 413. UV (EtOH): λ_{max} 268 (ε 16320); 230 nm (ε 18568).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(isopropylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11d). ^{1}H NMR (DMSO-d_6): 1.11 (3 H, d), 1.14 (3 H, d, $J_{1,2}$ = 9 Hz), 1.5–1.7 (1 H, m), 1.7–1.9 (1 H, m), 2.2–2.4 (2 H, m), 3.83 (3 H, s), 4.1–4.2 (1 H, m), 5.39 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.74 (1 H, s), 7.18 (2 H, br s), 9.30 (1 H, d, $J_{1,2}$ = 8 Hz). IR (KBr): 1772 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + Na) 494, (M + H) 472. UV (EtOH): λ_{max} 268 (ε 13654); 237 nm (ε 12676).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(phenylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11f). ^{1}H NMR (DMSO-d_6): 1.22–1.28 (1 H, m), 1.75–1.85 (1 H, m), 2.1–2.3 (2 H, m), 3.78 (3 H, s), 5.39 (1 H, dd), 6.70 (1 H, s), 7.18 (2 H, br s), 7.2 (1 H, s), 7.5–7.7 (3 H, m), 8.17 (2 H, br d), 9.23 (1 H, br d, $J_{1,2}$ = 9 Hz). IR (KBr): 1777.1 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + 1) 506. UV (EtOH): λ_{max} 268 (ε 19746), 225 nm (ε 18678).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(2-thienylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11g). ^{1}H NMR (DMSO-d_6): 1.4 (1 H, m), 2.4 (2 H, m), 3.77 (3 H, s), 3.86 (1 H, m), 5.45 (1 H, m), 6.68 (1 H, s), 7.14 (2 H, s), 7.20 (1 H, t, $J_{1,2}$ = 3 Hz), 7.8 (1 H, br s), 8.0 (1 H, br s), 9.18 (1 H, d, $J_{1,2}$ = 9 Hz). IR (KBr): 1779 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + H) 512. UV (EtOH): λ_{max} 288 (ε 20116), 237 nm (ε 21963).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-[(3,5-dimethylisoxazol-4-yl)sulfonyl]-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11i). ^{1}H NMR (DMSO-d_6): 1.6 (1 H, m), 1.9 (1 H, m), 2.18–2.3 (1 H, m), 2.33 (3 H, s), 2.46 (1 H, br m), 2.62 (3 H, s), 3.83 (3 H, s), 3.95 (1 H, m), 5.5 (1 H, dd, $J_{1,2}$ = 6 and 9 Hz), 6.76 (1 H, s), 7.2 (2 H, br s), 9.25 (1 H, d, $J_{1,2}$ = 9 Hz). IR (KBr): 1782 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + 1) 525. UV (EtOH): λ_{max} 275 (ε 18500), 230 nm (ε 17000).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(1-propylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11c). To a solution of 107 mg of diphenylmethyl 7β-[2-[2-[[(*tert*-butyloxy)carboxyl]amino]thiazol-4-yl]-2-(*Z*)-(methoxyimino)acetamido]-3-(*n*-propylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate in 2 mL of anhydrous methylene chloride was added 0.1 mL of triethylsilane. The mixture was cooled in an ice bath and 1 mL of trifluoroacetic acid was added. The ice bath was removed after 10 min and the mixture was stirred for 5 h at room temperature. The mixture was diluted with acetonitrile and evaporated to dryness under vacuum. The residue was diluted with toluene and the solution was evaporated to dryness in vacuo. The residue of product was chromatographed over HP20ss using 20% acetonitrile in water. There was obtained 18.9 mg of product. ^{1}H NMR (DMSO-d_6): 0.95 (3 H, t, $J_{1,2}$ = 7 Hz), 1.8–1.9 (1 H, m), 2.2–2.4 (2 H, m), 3.7–3.8 (1 H, m), 3.82 (3 H, s), 5.38 (1 H, dd, $J_{1,2}$ = 6 and 9 Hz), 6.75 (1 H, s), 7.2 (2 H, br s), 9.3 (1 H, br d, $J_{1,2}$ = 9 Hz). IR (KBr): 1773 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + H) 472, (M + Na) 494. UV (EtOH): λ_{max} 269 (ε 13800), 237 nm (ε 12600).

The following were obtained similarly.

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(3-pyridylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11h). ^{1}H NMR (DMSO-d_6): 1.4–1.5 (1 H, m), 1.85 (1 H, m), 2.4–2.5 (2 H, m), 3.75 (3 H, s), 3.95 (1 H, m), 5.49 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.67 (1 H, s), 7.2 (2 H, br s), 7.65 (1 H, dd, $J_{1,2}$ = 6 and 9 Hz), 8.29 (1 H, d, $J_{1,2}$ = 9 Hz), 8.85 (2 H, br d, $J_{1,2}$ = 5 Hz), 9.04 (1 H, s), 9.16 (2 H, d, $J_{1,2}$ = 9 Hz). IR (KBr): 1774 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M – $HSO_2C_6H_4N$) 363. UV (EtOH): λ_{max} 435 (ε 113), 288 (ε 11200), 235 nm (ε, 11300).

7β-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-(cyclopropylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (11e). ^{1}H NMR (DMSO-d_6): 1.6–1.7 (1 H, m); 1.9 (1 H, m), 2.4–2.5 (1 H, m), 2.6 (1 H, m), 2.9 (1 H, br s), 3.86 (3 H, s), 3.9–4.0 (1 H, m), 5.52 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.76 (1 H, s), 7.10 (2 H, br s), 9.32 (1 H, d, $J_{1,2}$ = 8 Hz). IR (KBr): 1782 cm^{-1} (β-lactam carbonyl). MS (FAB): m/e (M + 1) 470. UV (EtOH): λ_{max} 269 (ε 19882), 237 nm (ε 16959).

***p*-Nitrobenzyl 7β-[(Phenoxyacetyl)amino]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate.** To a solution of 600 mg (1.00 mM) of *p*-nitrobenzyl 7β-[(phenoxyacetyl)amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate in 10 mL of acetonitrile and 2 mL

of dimethylformamide under N_2 were added 108 mg (1.06 mmol) of sodium methanesulfinate and the mixture was stirred at room temperature under N_2 for 16 h. The mixture was poured into ethyl acetate and the solution was washed with water and brine, dried over magnesium sulfate, and evaporated under vacuum, yielding 0.82 g of crude product. This material was purified by chromatography on silica gel with ethyl acetate, giving 0.47 g (89% yield). ^{1}H NMR ($CDCl_3$): 1.9 (1 H, m), 2.1 (1 H, m), 2.6 (2 H, m), 3.00 (3 H, s), 4.54 (2 H, s), 5.40 (3 H, m), 6.8–7.4 (5 H, m), 7.55 (2 H, d, $J_{1,2}$ = 8 Hz), 8.20 (2 H, d, $J_{1,2}$ = 8 Hz).

7β-[(Phenoxyacetyl)amino]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (7). *p*-Nitrobenzyl 7β-[(phenoxyacetyl)amino]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate (0.49 g, 0.89 mmol) was dissolved in 13 mL of DMF, 13 mL of THF, and 13 mL 1 N HCl. The solution was chilled to 0 °C and 0.40 g of powdered zinc was added in two portions. After stirring in the cold for 1 h, the mixture was poured into 175 mL of ethyl acetate and the solution was washed twice with 1 N HCl. The colorless ethyl acetate layer was dried over magnesium sulfate and evaporated to dryness under vacuum to provide the product as a yellow oil. The oil crystallized on standing to provide 265 mg (75% yield). ^{1}H NMR (DMSO-d_6): 1.8 (2 H, m), 2.4 (1 H, m), 2.6–2.7 (1 H, m), 2.72 (3 H, s), 2.90 (3 H, s), 3.10 (3 H, s), 3.91 (1 H, m), 4.59 (2 H, s), 5.53 (1 H, dd, $J_{1,2}$ = 5 and 8 Hz), 6.95 (3 H, m), 7.32 (3 H, t, $J_{1,2}$ = 7 Hz), 7.96 (1 H, s), 9.05 (1 H, d, $J_{1,2}$ = 8 Hz). IR ($CHCl_3$): 1780 cm^{-1} (β-lactam carbonyl). MS (FD): *m/e* (M + 1) 395, (M) 394. UV (EtOH): λ_{max} 269 nm (ε 12 908).

Allyl 7β-[[D-α-[[(*tert*-Butyloxy)carbonyl]amino]phenylacetyl]amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (14). A solution of 1.005 g (4.0 mM) of *tert*-butyloxycarbonyl-protected D-phenylglycine, 702 mg (4.0 mM) of chlorodimethoxytriazine, and 440 μL (4.0 mM) of *N*-methylmorpholine in 28.6 mL of anhydrous methylene chloride was stirred under N_2 for 2 h at 0 °C. A solution of allyl 7β-amino-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (~3.77 mM) in 14 mL of methylene chloride was added to the cold solution and the reaction mixture was allowed to warm to room temperature and was stirred for 2 days. The mixture was diluted with methylene chloride, extracted with 0.1 N HCl and with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated to dryness under vacuum. The crude acylation product was chromatographed over silica gel with 35% ethyl acetate/hexane, yielding 513 mg of product (23% yield). ^{1}H NMR ($CDCl_3$): 1.2–1.3 (1 H, br m), 1.43 (9 H, s), 1.7–1.9 (1 H, br m), 2.5–2.7 (2 H, m), 3.90 (1 H, m), 4.07 (1 H, s), 4.80 (2 H, m), 5.2–5.6 (3 H, m), 5.9–6.1 (1 H, m), 7.2 (5 H, br s).

Allyl 7β-[[D-α-[[(*tert*-Butyloxy)carbonyl]amino]phenylacetyl]amino]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylate. The product of acylation was dissolved in 0.9 mL of anhydrous DMF under N_2. To this solution was added about 100 mg (1 mmol) of dry sodium methanesulfinate and the mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water. The washes were extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate. Chromatography of the oil obtained after solvent removal was carried out on silica gel with 50% ethyl acetate/hexane (500 mL) followed by 75% ethyl acetate/hexane (300 mL) and gave 350 mg (77%) of the desired material. ^{1}H NMR ($CDCl_3$): 1.42 (9 H, s), 1.38–1.45 (1 H, m), 1.75–1.90 (1 H, m), 2.4–2.6 (2 H, m), 3.02 (3 H, s), 3.90 (1 H, m), 4.8 (2 H, m), 5.2–5.5 (4 H, m), 5.7 (1 H, m), 6.0 (1 H, m), 7.10 (1 H, br s), 7.40 (5 H, br s).

7β-[(D-α-Aminophenylacetyl)amino]-3-(methylsulfonyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (13). The sulfone from above (350 mg, 0.66 mmol) was dissolved in 4 mL of acetonitrile and 2.6 mL of diethyl ether under N_2 and 16.2 mg of palladium(II) acetate and 138 mg (0.528 mmol) of triphenylphosphine were added. The reaction was stirred at room temperature for 20 min and cooled to 0 °C, and 0.186 mL (0.69 mmol) of tri-*n*-butyltin hydride was added. The cooling bath was removed and the mixture was stirred for 1 h and became increasingly cloudy and green. The mixture was treated with 0.057 mL (0.69 mmol) of concentrated HCl and was diluted with diethyl ether. The product formed as a gummy precipitate and after solvent removal 239 mg (73% yield) of crude product was isolated. This material was not characterized but was used directly in the next reaction. A portion of this crude material (50 mg, 0.10 mM) was dissolved in 1.0 mL of anhydrous methylene chloride and cooled to 0 °C. Trifluoroacetic acid (1 mL) was added and after 45 min acetonitrile was added, and the volatiles were removed in vacuo. This addition of acetonitrile and solvent removal was repeated three times, producing a yellow oil. The oil was dissolved in 4 mL of methanol and the crystalline trifluoroacetate salt was separated by centrifugation. The crystals were washed with diethyl ether and dried, yielding 12 mg of product. ^{1}H NMR (D_2O): 1.0–1.2 (1 H, m), 1.8 (1 H, m), 2.3–2.5 (2 H, m), 3.12 (3 H, s), 4.0 (1 H, dt, $J_{1,2}$ = 5 and 8 Hz), 5.22 (1 H, s), 5.46 (1 H, d, $J_{1,2}$ = 5 Hz), 7.55–7.6 (5 H, m). IR (KBr): 1787 cm^{-1} (β-lactam carbonyl). MS (FAB): *m/e* (M) 394. UV (EtOH): λ_{max} 270 nm (ε 15 207).

3-Quaternary Ammonium 1-Carba-1-dethiacephems

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A series of structurally unique 1-carba-1-dethiacephems is described. The structural stability of the 1-carba-1-dethiacephem nucleus was essential for the preparation of this series of 3-quaternary ammonium carbacephems. The known *p*-nitrobenzyl 7β-(phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate served as both a quaternization substrate as well as a precursor to derivatives such as allyl 7β-[[[2-[[(allyloxy)carbonyl]amino]-4-thiazolyl](methoxyimino)acetyl]amino]-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate. Quaternization of these enol triflates was accomplished either by dissolution in acetonitrile containing the base or by dissolution in the base, with or without warming to 50 °C. Bases nucleophilic enough to displace the triflate include a variety of substituted pyridines and *N*-methylimidazole. Deprotection then produced a very active series of 1-[7β-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-1-azabicyclo[4.2.0]oct-2-en-3-yl] quaternary ammonium hydroxide inner salts. These compounds were extremely potent antibacterials against a broad range of Gram-positive and -negative bacteria including constitutive cephalosporinase producers, such as *Enterobacter cloacae*. The compounds exhibit similar hydrolysis kinetics and pharmacokinetics to the analogous cephalosporin-3′-quaternary ammonium salts.

The 1-carba-1-dethiacephalosporins have been known for some time,[1] the first complete cephalosporin mimic having been synthesized by Guthikonda, et al. in 1974.[2] These workers showed that the methylene analogue of

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