40, 22476-74-0; 41, 126458-10-4; 42, 5435-12-1; 43, 84477-72-5; (±)-44, 126458-11-5; (±)-45, 126458-12-6; (±)-46, 126458-13-7; (±)-47, 126458-14-8; (±)-48, 126458-36-4; (±)-49, 126458-37-5; (±)-50, 126458-38-6; $C_6H_5CH_2OH$, 100-51-6; NaSMe, 5188-07-8; $MeOC_6H_4$-4-CH_2SH, 6258-60-2; $C_6H_5CH_2NH_2$, 100-46-9; $HOCH_2CH_2NH_2$, 141-43-5; (±)-2-methylpiperazine, 75364-79-3; (S)-(+)-2-methylpiperazinium D-(-)-tartarate, 126458-15-9; (S)-(+)-2-methylpiperazine, 74879-18-8; D-(-)-tartaric acid, 147-71-7; (R)-(-)-2-methylpiperazine, 75336-86-6; L-(+)-tartaric acid, 87-69-4; (R)-(-)-2-methylpiperazinium L-(+)-tartarate, 126458-16-0; cis-2,6-dimethylpiperazine, 21655-48-1; N,N-dimethylethylenediamine, 108-00-9; 2,5-dimethoxytetrahydrofuran, 696-59-3; piperazine, 110-85-0; (±)-1-(ethoxycarbonyl)-3-methylpiperazine, 126458-34-2; (±)-cis-2,3-dimethylpiperazine, 57193-34-7; (±)-1,2-dimethylpiperazine, 126458-35-3; (±)-trans-2,5-dimethylpiperazine, 2815-34-1; N-methylpiperazine, 109-01-3; (±)-trans-2,6-dimethylpiperazine, 126458-39-7.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **36k** (11 pages). Ordering information is given on any current masthead page.

Comparative Reactivity of 1-Carba-1-dethiacephalosporins with Cephalosporins

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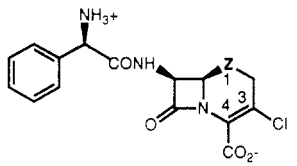
Received October 2, 1989

Nine matched pairs of cephalosporins and their 1-carba-1-dethiacephalosporin analogues have been compared with regard to microbiological activity, β-lactam carbonyl infrared absorption, and aqueous stability. In general the microbiological activity of the pairs of compounds were very similar across a broad range of bacteria. The infrared absorption bands for the β-lactam carbonyls of the pairs indicated a general trend for the 1-carba-1-dethiacephalosporins to absorb at lower frequencies than the corresponding cephalosporins. All of the 1-carba-1-dethiacephalosporins did however present a striking stability enhancement over their cephalosporin counterparts at pH = 10 or 11 in water. This marked contrast of MIC similarity with the observed differences in chemical reactivity clearly demonstrates hydroxide ion catalyzed hydrolysis is not a good model for transpeptidase activity unless the compounds comprise a limited domain of structural type.

The 1-carba-1-dethiacephalosporins have been known for some time, with the first complete cephalosporin mimic prepared by Guthikonda et al.[1] Further work in this area has appeared from a number of laboratories.[2] The first comparison of the stability of 1-carba-1-dethiacephems with the parent cephems was published by Narisada et al.[3] The Shionogi group provided one example which indicated an enhanced chemical stability of cephalosporins over their 1-carba-1-dethiacephalosporin counterparts. The structure studied was limited to a β-lactam derivative possessing a 7α-methoxy group, further limiting the general applicability of their conclusions. In contrast loracarbef[4] (1), the



1: Z = S

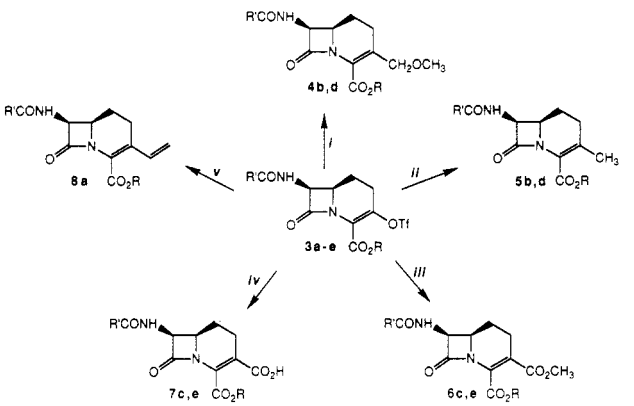
2: Z = CH_2

carba analogue of cefaclor (2), has been shown to exhibit enhanced chemical and serum stability over cefaclor.[5] In light of this apparent contradiction, we chose to study the comparative stabilities of cephalosporins and their 1-carba analogues in greater detail.

Chemistry

Preparation of all new compounds began with *p*-nitrobenzyl (7*S*,6*R*)-7-(phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (**3a**).[6] This compound could be converted via palladium-catalyzed substitution reactions to a number of derivatives with varying functional groups at C-3.[7] These conversions are depicted in Scheme I and described in the

Scheme I



[a] (i) (1) cat. $PdCl_2(CH_3CN)_2$, *n*-$Bu_3SnCH_2OCH_3$, LiCl, (2) TFA, Et_3SiH; (ii) (1) cat. $PdCl_2(CH_3CN)_2$, $(CH_3)_4Sn$, LiCl, (2) TFA, Et_3SiH; (iii) (1) cat. $PdCl_2(CH_3CN)_2$, CO, MeOH, (2) Zn/HCl; (iv) (1) cat. $PdCl_2(CH_3CN)_2$, CO, HCO_2H; (2) Zn/HCl; (v) (1) cat. $PdCl_2(CH_3CN)_2$, *n*-$Bu_3SnCHCH_2$, LiCl; (2) TFA, Et_3SiH.

Experimental Section. More detailed papers on both the chemistry and biology of the different series represented

†This paper is dedicated to the memory of Dr. Alan S. Katner—deceased November 16, 1986.

(1) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584.
(2) Firestone, R. A.; et al. *J. Med. Chem.* **1977**, *20*, 551. Finkelstein, J.; Holden, K. G.; Perchonock, C. D. *Tetrahedron. Lett.* **1978**, 1629. Doyle, T. W.; Conway, T. T.; Casey, M.; Lim, G. *Can. J. Chem.* **1979**, *57*, 222. Doyle, T. W.; Conway, T. T.; Lim, G.; Luh, B.-Y. *Ibid.* **1979**, *57*, 227. Martel, A.; Doyle, T. W.; Luh, B.-Y. *Ibid.* **1979**, *57*, 614. Doyle, T. W.; Douglas, J. L.; Belleau, B.; Conway, T. T.; Ferrari, C. F.; Horning, D. E.; Lim, G.; Luh, B.-Y.; Martel, A.; Menard, M.; Morris, R. L.; Misiek, M. *Ibid.* **1980**, *58*, 2508; Salzman, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron. Lett.* **1980**, *21*, 1193. Uyeo, S.; Ona, H. *Chem. Pharm. Bull.* **1980**, *1563*. Bremner, J. A. S.; Colvin, E. W.; Gallacher, G.; MacLeod, A. *Tetrahedron. Lett.* **1983**, *24*, 3783. Hatanaka, M.; Ishimaru, T. *Ibid.* **1983**, *24*, 4837.

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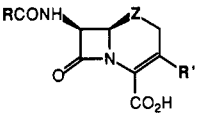
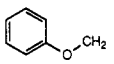
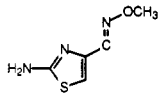
Table I. Stabilities of Cephalosporin and Carbacephalosporin Pairs



R	no.	R′	Z	IR, cm^{-1}	k,[a] h^{-1}	K_s/K_c	$t_{1/2}$, h
	**1**	Cl	S	1781	0.944 ± 0.074[b]	29.1	0.734
	2	Cl	CH_2	1778	0.0324 ± 0.0027		21.4
	**14**[9]	OMs	S	1789	1.91 ± 0.15	21.4	0.363
	15[10]	OMs	CH_2	1777	0.0890 ± 0.0057		7.79
	16[11]	Cl	S	1788	0.895 ± 0.107	20.4	0.774
	17[12]	Cl	CH_2	1783	0.0438 ± 0.0035		15.8
	18[13]	CH_2OCH_3	S	1789	0.368 ± 0.002[c]	24.7	1.88
	4d	CH_2OCH_3	CH_2	1762	0.0149 ± 0.0006[c]		46.5
	19[14]	CH_3	S	1759	0.0793 ± 0.0017[c]	49.6	8.74
	5d	CH_3	CH_2	1742	0.00160 ± 0.00015[c]		433
	**20**[15]	CO_2CH_3	S	1798	6.27 ± 0.25	7.8	0.111
	6e	CO_2CH_3	CH_2	1774	0.799 ± 0.088		0.867
	21[15]	CO_2H	S	1781	0.340	32.3	2.04
	7e	CO_2H	CH_2	1760	0.0105		66.0
	**22**[16]	H	S	1745	0.114 ± 0.002[c]	20.2	6.08
	2	H	CH_2	1775	0.00565 ± 0.00064[c]		123
	24[17]	$CH_2{}^+NC_5H_5$	S	1777	1.85 ± 0.05	29.5	0.375
	13	$CH_2{}^+NC_5H_5$	CH_2	1758	0.0628 ± 0.0079		11.0

[a] Pseudo-first-order rate constants at pH 10, μ = 0.5, 35 °C. [b] See ref 33. [c] Experimentally measured at pH 11 and calculated as $^1/_{10}$ the observed rate constant assuming K_{obs} is directly proportional to [$^-$OH]. [d] Sodium salt.

by these individual compounds will be presented in further publications.

Compounds **4b**, **5b**, and **8a** were prepared from derivatives **3a,b**, by palladium-catalyzed coupling reactions with methoxymethyl, methyl, and vinyltri-*n*-butylstannanes, respectively. Subsequent treatment of compounds **4b** and **5b** with trifluoroacetic acid and triethylsilane gave acids **4d** and **5d**. Carbonylation of *p*-nitrobenzyl (7*S*,6*R*)-7-(thienylacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethiacephalosporinate (**3c**) in the presence of methanol or formic acid gave the corresponding C-3 methyl ester **6c** and C-3 acid **7c**, respectively. Deesterification at C-4 with Zn/HCl afforded acids **6e** and **7e**. The following sequence (outlined in Scheme II) was required for the preparation of the quaternary carbacephem **13**. Olefin **8a** upon ozonolysis gave C-3 formyl compound **9**. Reduction with lithium tri-*tert*-butoxyaluminum hydride at −40 °C and *in situ* trapping of the intermediate alcohol with acetic anhydride gave acetate **10**. This acetate was then converted via standard cephem manipulations to produce carbacephem **13**.[8]

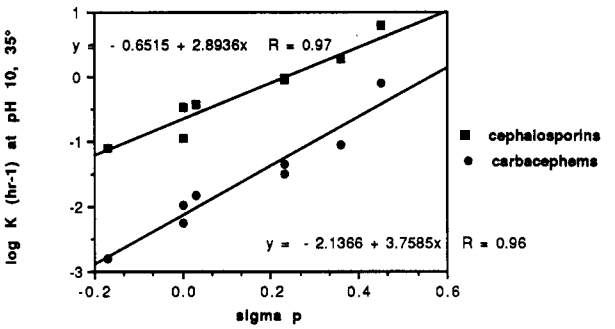


Figure 1. Correlation of hydrolysis rates with σ_p.

Rates of Hydrolysis and Infrared Spectroscopy

Since β-lactams exert their biological effects by acylating the serine hydroxyl of penicillin-binding proteins,[18] many

(3) Narisada, M.; Yoshida, T.; Ohtnai, M.; Ezumi, K.; Takasuka, M. *J. Med. Chem.* **1983**, *26*, 1577.
(4) This compound has also been referred to in the literature as LY163892 and KT3777.
(5) Hirata, T.; Matsukuma, I.; Mochida, K.; Sato, K. 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1987, Abstract No. 1187. Gray, G.; Ramotar, K.; Krulicki, W.; Louie, T. J. *Ibid.* Abstract No. 1200. Quay, J. F.; Coleman, D. L.; Finch, L. S.; Indelicato, J. M.; Pasini, C. E.; Shoufler, J. R.; Sullivan, H. R.; Turner, J. C. *Ibid.* Abstract No. 1205. Pasini, C. E.; Indelicato, J. M. American Association of Pharmaceutical Scientists, Western Regional Meeting, 1989, Abstract No. 25. Matsukuma, I.; Yoshiiye, S.; Mochida, K.; Hashimoto, Y.; Sato, K.; Okachi, R.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 1239.
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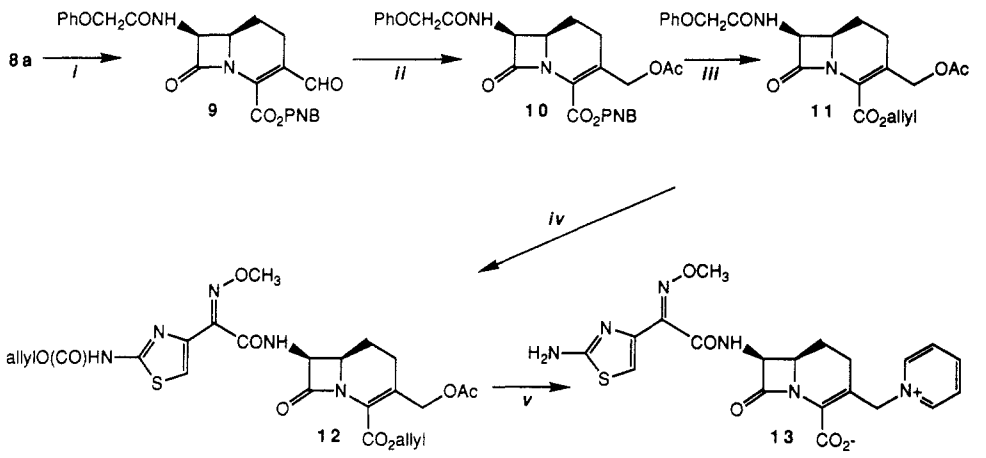
(7) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H., III; Munroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828.
(8) Bonjouklian, R.; Phillips, M. L. *Tetrahedron Lett.* **1981**, *22*, 3915.
(9) Spitzer, W. A., Lilly Research Laboratories, Eli Lilly and Company, personal communication, 1988.
(10) U.S. Patent 4,335,211, Kyowa Hakko Kogyo Co. Ltd., June 15, 1982.
(11) Chauvette, R. B.; Pennington, P. A. *J. Med. Chem.* **1975**, *18*, 403.
(12) Eur. Pat. Appl. 154253, Al, Kyowa Hakko Kogyo Co. Ltd., Nov. 9, 1985.
(13) Fujumoto, K.; Ishihara, S.; Yanagisawa, H.; Ide, J.; Nakayama, E.; Nakao, H.; Sugawara, S.; Iwata, M. *J. Antibiot.* **1987**, *40*, 370.
(14) Flynn, E. H. In *Cephalosporins and Penicillins Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; pp 664–665.
(15) Spry, D. O. *J. Chem. Soc. Chem. Commun.* **1974**, 1012.
(16) Uyeo, S.; Ona, H. *Chem. Pharm. Bull.* **1980**, *28*, 1563.
(17) Perronnet, J.; Bucort, R.; Heymes, R.; Bormann, D.; Durckheimer, W. 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1978, Abstract No. 75.

Scheme II



[a] (i) O_3/Me_2S; (ii) Li(t-BuO)$_3$AlH, Ac_2O; (iii) (1) Zn/HCl, (2) allyl bromide, NMM; (iv) (1) PCl_5, *i*-BuOH, H_2O, (2) alloc-ATMO-acetic acid, 2-chloro-4,6-dimethoxytriazine, NMM, (v) (1) MSTFA, TMSI, pyridine, (2) cat. $Pd(OAc)_2$, Ph_3P, *n*-Bu_3SnH, HOAc.

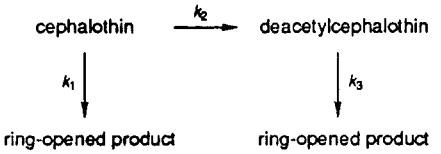
studies of β-lactams have focused on the chemical reactivity of the azetidinone. Alkaline-hydrolysis rates have been used to understand this chemical reactivity as well as the changes induced by various substituents on bicyclic β-lactams. The hydrolysis data presented here were determined by HPLC-monitored disappearance of the starting intact nucleus. The rates and corresponding half-lives are listed in Table I. The methodology utilized consisted of exposing millimolar concentrations of the various compounds to a constant basic pH (10 or 11) by the continual addition of NaOH. HPLC on reverse-phase columns allowed the direct determination of rates for disappearance of starting material. Hydrolyses of **6** and **20** were complicated by two possible modes of decomposition; hydrolysis of either the β-lactam ring or the 3-carboxymethyl ester moieties. The HPLC method used to measure the hydrolysis kinetics merely measured disappearance of starting material and did not directly distinguish between the two possible hydrolysis reactions. However, a slight modification of the HPLC system did allow for the quantitation of the β-lactam intact products which would result from ester hydrolysis in these cases. Thus, the appearance of the two known compounds, cephalosporin **21** and carbacephalosporin **7**, could be monitored.[19] In the case of the hydrolyses of **20** and **6**, analysis of the data is more straightforward than for cephalothin. The product of ester hydrolysis in each case, **21** and **7**, is relatively stable [K(β-lactam hydrolysis) = 0.05 X K_{obs} for **21** and K(β-lactam hydrolysis) = 0.01 X K_{obs} for **6**, determined in independent experiments] to β-lactam hydrolysis compared to the intact parent ester and is assumed to accumulate but not hydrolyze during the time period of data collection. This assumption simplifies analysis of the rate data. In the case of the hydrolysis of **20**, no compound **21** is observed to form (<1%) and the rate K(β-lactam hydrolysis) is equal to K_{obs}. In the case of the hydrolysis of derivative **6** a small amount of derivative **7** (~3%) is formed and K_{obs} must be corrected to account for this minor reaction pathway (K_{obs} = 0.825 h^{-1} and K(β-lactam hydrolysis) = 0.799 h^{-1}).

The graph of the log of the rate constant for base-catalyzed hydrolysis versus the σ_p values[21,22] for the C-3 substituent of these matched pairs is shown in Figure 1. (Use of σ_{p+} has very little effect on the relative slopes or values of r.) Good correlations for both the cephalosporins and the carbacephalosporins were obtained, r = 0.97 and 0.96, respectively, thus signifying a linear free energy relationship of substituents on the rate of hydrolysis. In both cases the value of ρ is positive, confirming the expectation that electron-withdrawing groups at C-3 enhance the rate of reaction. The large ρ values indicate a significant charge separation in the transition state for the rate-limiting step, which would be consistent with the decomposition of the tetrahedral intermediate.[23] The difference in slopes for the carbacephem and cephem indicate an enhanced effect of C-3 substituents on the carbacephalosporin hydrolysis rates.

Infrared absorption spectroscopy of the β-lactam carbonyl has been studied since the first work of Sheehan et al.[24] on the penicillins. This and later work on other β-

(18) Waxman, D. J.; Strominger, J. L. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Ed.; Academic Press: New York, 1982; Vol. 3, pp 210–285.

(19) A similar situation has been studied for the reaction of cephalothin.[20] At pH 10 reaction occurs both at the β-lactam ring and at the 3′-acetate function. Separation of these rate constants is not straightforward because the product of acetate cleavage, deacetylcephalothin, is also subject to β-lactam hydrolysis and at a rate of the same order, approximately half the rate, as that of cephalothin. However, from the disappearance



of cephalothin, k_{obs} (where $k_{obs} = k_1 + k_2$ by HPLC), from k_3 (determined in an independent experiment by the disappearance of authentic deacetylcephalothin), and from the experimental data points for the solution time courses for cephalothin and deacetylcephalothin, the values of k_1 and k_2 were calculated with the MLAB software (National Institutes of Health): k_1 = 0.317 h^{-1}, k_2 = 0.485 h^{-1}, and k_3 = 0.158 h^{-1}.

(20) Indelicato, J. M.; Pasini, C. E. *J. Med. Chem.* **1988**, *31*, 1227.

(21) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96; Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience, New York, 1979.

(22) Boyd, D. B., unpublished work. A 1032 database of substituent parameters adapted from the Pomona College Medchem Files.

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Table II. Microbiological Activity of Cephalosporin and Carbacephalosporin Pairs[a]

	Staphylococcus aureus X1.1	*Streptococcus pyogenes* Park	*Haemophilus influenza* C.L.	*Escherichia coli* EC14	*Klebsiella* X26	*Enterobacter cloacae* EB5	*Pseudomonas aeruginosa* X258	*Proteus rettgeri* C24
1	1.0	0.5	1.0	0.25	0.25	32	128	128
2	2.0	1.0	0.5	0.25	0.25	4.0	128	128
14	0.125	0.015	4.0	64	8.0	128	128	128
15	0.5	0.5	8.0	32	8.0	128	128	128
16	0.25	0.25	2.0	64	8.0	128	128	128
17	1.0	0.25	4.0	8.0	8.0	128	128	128
18	0.25	0.12	2.0	128	32	128	128	128
4	0.5	0.25	8.0	32	8.0	128	128	128
19	4.0	1.0	16	128	64	128	128	128
5	4.0	1.0	32	128	32	128	128	128
20	0.5	0.03	2.0	2.0	2.0	128	128	128
6	0.25		1.0	1.0	0.25	128	128	8.0
22	4.0	0.015	0.015	0.015	0.008	0.06	32	0.008
23	16	0.015	0.008	0.008	0.008	0.06	32	0.008
24	1.0	0.03	0.06	0.03	0.03	0.06	2.0	0.03
13	4.0	0.015	0.5	0.03	0.03	0.06	2.0	0.06

[a] MIC end points were recorded as the lowest antibiotic concentrations (μg/mL) that inhibited the development of visible growth on the plates.

lactams has demonstrated the effects of β-lactam strain, ring fusion, and lack of amide resonance on the frequency of the amide I band.[25] In addition, these studies have often shown that an increase in absorption frequency corresponds to a decrease in chemical stability,[26] though recently this correlation has been questioned.[27] The stretching frequencies of the β-lactam carbonyls are compiled in Table I. The compounds of our report demonstrate that carbacephalosporins in general are more stable and have lower IR stretching frequencies than their cephem counterparts. In contrast, the Shionogi study of one 7α-methoxylated β-lactam reported the β-lactam carbonyl stretching frequency to be lower for the less stable carbacephalosporin.

Microbiological Activity

In most examples the in vitro MIC's of cephems and carbacephems are comparable. Comparative MIC's for the matched pairs in this study are shown in Table II. As is generally the case, the MIC's are very similar and in most cases the differences are within the margin of error of the experimental protocol.

Discussion

The chemical uniqueness of the β-lactam was first discussed in the 1949 paper of Johnson, Woodward, and Robinson.[28] The unusual chemical reactivity and spectral properties of the amide bond in penicillin were attributed to a decrease in amide resonance due to ring strain in the β-lactam as compared with normal amides. Medicinal chemists have extended this analysis to account for the biological activity of β-lactam antibiotics.[29] This intuitive reasoning has led several groups to calculate[30] or measure[31-36] rates of cephalosporin β-lactam hydrolysis (by hydroxide ion) and to correlate this kinetic data with antimicrobial activity. Several such studies have been successful in showing qualitative correlations between reactivity and antimicrobial activity when the compounds in the series are limited to changes in the C-3 or C-3′ position of cephalosporins and 1-oxacephalosporins or the C-3 position of bicyclic pyrazolidinones. The existence of even a qualitative correlation is somewhat remarkable since many factors contribute to antibacterial activity such as "fit" within the active site of the enzyme, stability of the acylated enzyme, permeability through the bacterial outer membrane, and β-lactamase stability. When rates of β-lactam hydrolysis of different classes of β-lactam antibiotics are compared with antimicrobial activity, no correlation, even qualitative, is observed.[37-39]

From the rate data in Table I, β-lactam reactivity cannot be used to explain the equipotent antimicrobial activity of analogous carbacephalosporins and cephalosporins. This is reasonable since the differences in chemical reactivity of carbacephalosporins and cephalosporins are trivial when compared to the chemical reactivity of the amide bond of X-*d*-Ala-*d*-Ala, the natural enzyme substrate.[40] This marked contrast of MIC similarity with the observed differences in chemical reactivity clearly demonstrate hydroxide ion catalyzed hydrolysis is not a good model for transpeptidase activity. The important parameters for the similar antibacterial activity of these two β-lactam classes

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appear to be recognition as identical substrates by the relevant penicillin-binding proteins (both affinities and off-rates), equivalent recognition by any β-lactamases present, identical diffusion through the porins of the Gram-negative organisms, and in some cases chemical stability under the testing conditions. This virtual identity of structure, as viewed by the bacteria, holds true over a broad range of C-7 side chains, as well as over a formidable group of bacteria with large variations in all of the relevant proteins. The decreased hydrolytic reactivity of the carbacephalosporins relative to the cephalosporins can be attributed to a number of possibilities. These include (1) the lack of the sulfur atom's additional inductive electronegativity[21] as evidenced by σ_i's, (2) the participation of different conformations in the rate-determining transition states for hydrolysis, (3) the steric differences[41] resulting from substitution of CH_2 for S in the same transition state, and (4) differential solvation of the two transition states.

Experimental Section

Reagents were used as supplied unless otherwise noted. Reactions were run under an atmosphere of dry nitrogen or argon unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL FX-90X, Bruker WM-270, Bruker WH-360, or General Electric QE-300 instrument. Chemical shifts are recorded in parts per million (δ) relative to Me_4Si or DSS as internal standard. Infrared (IR) spectra were determined on a Nicolet MX-1 FT-IR, optical rotations were done on a Perkin-Elmer 241 spectrometer, and ultraviolet (UV) spectra were obtained on a Cary 219. Mass spectral data (MS) were obtained on either a CEC-21-140 or a Varian MAT-731 spectrometer. 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 either with ethyl acetate/hexane solvent mixtures or for polar compounds with 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%.

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 end points were recorded as the lowest antibiotic concentrations that inhibited the development of visible growth on the plates.

Determination of Base-Catalyzed-Hydrolysis Rates. The hydrolysis rates 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 $\mu = 0.5$ 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 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 mobile phases (v/v) were as follows. MeCN/0.025 M NH_4OAc: **6e** (16:84); **7e** (7:93); **14**, **15** (22:78); **16**, **17**, **20** (20:80); **21** (8:92). MeCN/0.025 M $NH_4H_2PO_4$: **2**, **13**, **22**, **23**, **24** (10:90). MeCN/0.5% H_3PO_4: **4d**, **5d** (38:62); **18**, **19** (40:60).

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Diphenylmethyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-[[(trifluoromethylsulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (3b). A solution of ester **3a** (25.74 g, 43.00 mmol) in 650 mL of THF and 650 mL of DMF was cooled in an ice/ethanol bath to 0 °C and 650 mL of 1 N HCl was added. When the temperature of the solution returned to 0 °C, zinc dust (10.69 g, 163.2 mmol) was added in portions over 1 h. After stirring for an additional hour at 0 °C, the reaction mixture was poured into 4000 mL of ethyl acetate and washed with 1600 mL of 1 N HCl and with 1600 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 20.4 g of crude acid **3d**, which was esterified directly without purification. The crude product was homogeneous by TLC in 90% ethyl acetate/10% methanol. A solution of acid **3d** in 300 mL of anhydrous CH_3CN was treated with diphenyldiazomethane (8.54 g, 44.0 mmol). After 30 min the mixture was quenched with acetic acid. Concentration gave 28.6 g of a crude brown oil, which was purified by chromatography on silica gel (elution with 40:60 ethyl acetate/hexane). This produced 21.3 g of an off-white solid, which was recrystallized from hexane to yield 19.84 g (80%) of **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 7 Hz, 2 H), 7.2–7.4 (m, 10 H), 7.13 (d, J = 7 Hz, 1 H), 7.04 (t, J = 7 Hz, 1 H), 7.00 (s, 1 H), 6.90 (d, J = 8 Hz, 2 H), 5.44 (t, J = 6 Hz, 1 H), 4.54 (s, 2 H), 3.98 (dt, J = 5, 12 Hz, 1 H), 2.6–2.7 (m, 2 H), 2.0–2.1 (m, 1 H), and 1.5–1.7 (m, 1 H); IR ($CHCl_3$) 1784 cm^{-1}; 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.

***p*-Nitrobenzyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-vinyl-1-carba-1-dethia-3-cephem-4-carboxylate (8a).** A solution of enol trilate **3a** (37.0 g, 61.8 mmol) in 125 mL of anhydrous DMF was treated with lithium chloride (5.26 g, 124 mmol) and $(CH_3CN)_2PdCl_2$ (1.59 g, 6.1 mmol) and then degassed and purged with N_2. Tributylvinylstannane (21.56 mL, 68.0 mmol) was added in one portion. The reaction began to exotherm and was placed in a water bath. After 30 min the black solution was diluted with EtOAc/Et_2O and H_2O, stirred for 10 min, filtered through Celite, washed with H_2O and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by HPLC on a Waters Prep 500 silica gel system (elution with a gradient of toluene to 50:50 EtOAc/toluene) to afford 22.6 g (77%) of **8a** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8 Hz, 2 H), 7.63 (d, J = 8 Hz, 2 H), 7.35 (t, J = 8 Hz, 2 H), 7.08 (m, 2 H), 6.95 (d, J = 8 Hz, 2 H), 5.3–5.6 (m, 5 H), 4.56 (s, 2 H), 3.96 (m, 1 H), 2.81 (dd, J = 5, 18 Hz, 1 H), 2.35 (m, 1 H), 2.07 (m, 1 H), and 1.46 (m, 1 H); IR ($CHCl_3$) 1757, 1718, 1672, 1523, 1388, and 1347 cm^{-1}; UV (EtOH) λ_{max} 296 nm (ε 22300); MS m/e 477 (M^+). Anal. ($C_{25}H_{23}N_3O_7$) C, H, N.

Benzhydryl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-(methoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (4b). Tri-*n*-butyl(methoxymethyl)stannane was substituted as the tin reagent at 70 °C as exemplified for the conversion of **3a** to **8a**. Methyl ether **4b** was produced in 58% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 10 Hz, 1 H), 7.43 (d, J = 8 Hz, 2 H), 7.1–7.4 (m, 10 H), 7.00 (t, J = 8 Hz, 1 H), 6.96 (d, J = 8 Hz, 2 H), 6.93 (s, 1 H), 5.44 (m, 1 H), 4.53 (AB q, 2 H), 4.22 (AB q, 2 H), 3.80 (dt, J = 5, 12 Hz, 1 H), 3.21 (s, 3 H), 2.40 (dd, J = 6, 18 Hz, 1 H), 2.3 (m, 1 H), 1.8 (m, 1 H), and 1.30 (m, 1 H); IR ($CHCl_3$) 3020, 1771, 1722, 1690, 1523, and 1496 cm^{-1}; UV (EtOH) λ_{max} 268 nm (ε 10900); MS m/e 525 (M^+ -1). Anal. ($C_{31}H_{30}N_2O_6$) C, H, N.

Benzhydryl (7*S*,6*R*)-7-(Phenoxyacetamido)-1-carba-1-dethia-3-methyl-3-cephem-4-carboxylate (5b). Tetramethylstannane was substituted as the tin reagent as in the conversion of **3a** to **8a**. Carbacephem **5b** was produced in 70% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8 Hz, 2 H), 7.1–7.4 (m, 10 H), 6.98 (t, J = 8 Hz, 1 H), 6.90 (d, J = 8 Hz, 2 H), 6.88 (s, 1 H), 5.35 (m, 1 H), 4.50 (AB q, 2 H), 3.75 (dt, J = 5, 12 Hz, 1 H), 2.16 (m, 2 H), 2.01 (s, 3 H), 1.73 (m, 1 H), and 1.36 (m, 1 H); IR ($CHCl_3$) 3020, 1762, 1718, 1689, 1524, 1496, and 1387 cm^{-1}; UV (EtOH) λ_{max} 268 nm (ε 11300); MS m/e 497 (M^+ + 1). Anal. ($C_{30}H_{28}N_2O_5$) C, H, N.

(7*S*,6*R*)-7-(Phenoxyacetamido)-3-(methoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylic Acid (4d). Ester **4b** was treated as exemplified for the conversion of **5b** to **5d** below. Acid **4d** was produced in 76% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 3 H), 7.00 (t, J = 8 Hz, 1 H), 6.89 (d, J = 8 Hz, 2 H), 5.4 (m, 1 H), 4.55 (s, 2 H), 4.37 (s, 2 H), 3.85 (m, 1 H), 3.30 (s, 3 H), 2.61 (m, 1 H), 2.3 (m, 1 H), 1.8 (m, 1 H), and 1.27 (m, 1 H);

IR ($CHCl_3$) 1762, 1756, 1725, 1688, and 1261 cm^{-1}; UV (EtOH) λ_{max} 261 nm (ϵ 5700); MS m/e 361 ($M^+ + 1$). Anal. ($C_{18}H_{20}N_2O_6$) C, H, N.

(7*S*,6*R*)-7-(Phenoxyacetamido)-1-carba-1-dethia-3-methyl-3-cephem-4-carboxylic Acid (5d). Trifluoroacetic acid (0.8 mL) and triethylsilane (0.3 mL) were cooled under N_2 with an ice/EtOH bath. Benzhydryl ester **5b** was added in one portion and stirred for 20 min. Acetonitrile (5 mL) was added and the solution was stripped to a volume of 1 mL. This was repeated with CH_3CN and then the solution was diluted with toluene (5 mL) and stripped to dryness. The residue was purified by flash chromatography on silica gel (elution with 60:38:2 EtOAc/hexane/HOAc). The combined fractions were diluted with toluene and concentrated, producing 0.032 g of acid **5d** as a white powder (48%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 3 H), 6.97 (t, J = 8 Hz, 1 H), 6.85 (d, J = 8 Hz, 2 H), 5.35 (m, 1 H), 4.50 (s, 2 H), 3.85 (m, 1 H), 2.20 (m, 2 H), 2.10 (s, 3 H), 1.87 (m, 1 H), and 1.50 (m, 1 H); IR ($CHCl_3$) 1742, 1713, 1656, 1633, 1546, 1495, 1391, and 1220 cm^{-1}; UV (EtOH) λ_{max} 262 nm (ϵ 9720); MS m/e 331 ($M^+ + 1$). Anal. ($C_{17}H_{18}N_2O_5$) C, H, N.

***p*-Nitrobenzyl (7*S*,6*R*)-7-(2-Thienylacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (3c).** A solution of triflate **3a** (15 g, 25.0 mmol) and 2,6-lutidine (5.3 mL, 45.5 mmol) in 75 mL of CH_2Cl_2 was treated with phosphorus pentachloride (6.7 g, 32.2 mmol) and the mixture was stirred at 23 °C for 3 h. This solution was added over 0.25 h to a solution of isobutyl alcohol (25 mL) in 75 mL of CH_2Cl_2 at −10 °C. After stirring for an additional 0.75 h at 0 °C, 50 mL of water was added with stirring at 23 °C. The mixture was poured into 500 mL of CH_2Cl_2 and washed with 10% aqueous sodium bicarbonate and brine, dried over $MgSO_4$, filtered, and concentrated to a volume of ca. 300 mL. 2,6-Lutidine (3.0 mL, 25.8 mmol) and 2-thienylacetyl chloride (3.5 mL, 28.1 mmol) were added, and the mixture was stirred at 23 °C for 16 h. After dilution with 400 mL of CH_2Cl_2, the organic layer was washed twice with 1 N HCl, saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed twice on silica gel (elution with 10% EtOAc/CH_2Cl_2) to afford 5.1 g (25%) of acid **3c** as a light yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8 Hz, 2 H), 7.60 (d, J = 8 Hz, 2 H), 7.30 (m, 1 H), 7.00 (dd, J = 4, 6 Hz, 1 H), 6.95 (m, 1 H), 6.15 (d, J = 6 Hz, 1 H), 5.40 (AB q, 2 H), 5.30 (t, J = 6 Hz, 1 H), 3.95 (m, 1 H), 3.82 (s, 2 H), 2.60 (dd, J = 5, 9 Hz, 2 H), 2.10 (m, 1 H), and 1.58 (m, 1 H); IR ($CHCl_3$) 3019, 1783, 1740, 1684, 1526, 1431, 1350, 1243, and 1205 cm^{-1}; UV (EtOH) λ_{max} 269 nm (ϵ 17 400); MS m/e 589 (M^+). Anal. ($C_{22}H_{18}N_3O_9S_2F_3$) C, H, N.

***p*-Nitrobenzyl (7*S*,6*R*)-7-(2-Thienylacetamido)-3-carbomethoxy-1-carba-1-dethia-3-cephem-4-carboxylate (6c).** A solution of ester **3c** (0.603 g, 1.02 mmol) and lithium chloride (0.130 g, 3.07 mmol) in 16 mL of a 1:1 mixture of anhydrous DMF and anhydrous methanol was treated with gaseous carbon monoxide for 5 min, at which time triethylamine (0.29 mL, 2.1 mmol) and $(CH_3CN)_2PdCl_2$ (0.080 g, 0.3 mmol) were added. A balloon filled with CO was attached to maintain a positive pressure of CO. After stirring for 3.5 h the resultant black solution was diluted with 250 mL of EtOAc. The separated organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, 1 N HCl, and brine, dried over $MgSO_4$, and filtered. Toluene (300 mL) was added (to aid the removal of methanol, thereby minimizing β-lactam cleavage during isolation) and the mixture was concentrated. Flash chromatography on silica gel (elution with 10% to 15% EtOAc/CH_2Cl_2) afforded 0.140 g (27%) of **6c** as a white solid after trituration with hexane: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8 Hz, 2 H), 7.60 (d, J = 8 Hz, 2 H), 7.25 (m, 1 H), 7.00 (dd, J = 4, 6 Hz, 1 H), 6.95 (m, 1 H), 6.05, (d, J = 6 Hz, 1 H), 5.40 (AB q, 2 H), 5.35 (dd, J = 5, 6 Hz, 1 H), 3.92 (m, 1 H), 3.85 (s, 2 H), 3.65 (s, 3 H), 2.80 (dd, J = 5, 18 Hz, 1 H), 2.30 (m, 1 H), 2.05 (m, 1 H), and 1.30 (dq, J = 5, 12 Hz, 1 H); IR ($CHCl_3$) 1783, 1743, 1714, 1685, 1525, 1391, 1350, 1226, and 1205 cm^{-1}; UV (EtOH) λ_{max} 278 nm (ϵ 20 200); MS m/e 499 (M^+). Anal. ($C_{23}H_{21}N_3O_8S$) C, H, N.

(7*S*,6*R*)-7-(2-Thienylacetamido)-3-carbomethoxy-1-carba-1-dethia-3-cephem-4-carboxylic Acid (6e). To a solution of ester **6c** (0.130 g, 0.22 mmol) in 7 mL of DMF and 3 mL of 1 N HCl was added zinc dust (0.064 g, 1.0 mmol) at 23 °C and the resultant mixture was stirred for 2 h. After dilution with 150 mL of EtOAc, the mixture was washed with 1 N HCl and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel (elution with 1% HOAc in EtOAc) afforded 0.034 g of material which was further purified on HP-20ss (elution with 1:10:89 HOAc/CH_3CN/H_2O changing to 1:20:79 HOAc/CH_3CN/H_2O) to afford 0.024 g (30%) of product **6e** as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 1 H), 7.00 (dd, J = 4, 6 Hz, 1 H), 6.95 (m, 1 H), 6.05, (d, J = 6 Hz, 1 H), 5.35 (dd, J = 5, 6 Hz, 1 H), 3.92 (m, 1 H), 3.85 (s, 2 H), 3.65 (s, 3 H), 2.80 (dd, J = 5, 18 Hz, 1 H), 2.30 (m, 1 H), 2.05 (m, 1 H), and 1.30 (dq, J = 5, 12 Hz, 1 H); IR ($CHCl_3$) 3019, 1774, 1711, 1682, 1619, 1535, 1260, 1226, and 1142 cm^{-1}; UV (EtOH) λ_{max} 285 nm (ϵ 12 600); MS m/e 364 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 51.60; H, 4.37; N, 7.79 (correct for $C_{16}H_{16}N_2O_6S \cdot {}^1/_2H_2O$).

***p*-Nitrobenzyl (7*S*,6*R*)-7-(2-Thienylacetamido)-3-carboxy-1-carba-1-dethia-3-cephem-4-carboxylate (7c).** Gaseous CO was bubbled through a solution of triflate **3c** (1.88 g, 3.19 mmol) and $(CH_3CN)_2PdCl_2$ (0.250 g, 0.9 mmol) in 45 mL of anhydrous DMF for 5 min at 23 °C, after which time triethylamine (2.2 mL, 16 mmol) and formic acid (0.24 mL, 6 mmol) were added. A balloon filled with CO was attached to maintain a positive pressure of CO. After stirring for 1 h the resultant black solution was diluted with 750 mL of EtOAc, washed with 1 N HCl, saturated aqueous $NaHCO_3$, 1 N HCl, and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel (elution with 1% HOAc in 10% EtOAc/CH_2Cl_2 changing to 1% HOAc in 30% EtOAc/CH_2Cl_2 and then to 1% HOAc in EtOAc) afforded 0.134 g (9%) of **7c** as a white solid after trituration with hexane: ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8 Hz, 2 H), 7.55 (d, J = 8 Hz, 2 H), 7.25 (m, 1 H), 7.00 (m, 2 H), 6.60, (d, J = 6 Hz, 1 H), 5.45 (dd, J = 5, 6 Hz, 1 H), 5.38 (AB q, 2 H), 3.95 (m, 1 H), 3.85 (s, 2 H), 2.80 (dd, J = 5, 18 Hz, 1 H), 2.25 (m, 1 H), 2.05 (m, 1 H), and 1.45 (dq, J = 5, 12 Hz, 1 H); IR ($CHCl_3$) 1783, 1748, 1685, 1525, 1387, 1350, and 1205 cm^{-1}; UV (EtOH) λ_{max} 274 nm (ϵ 19 600); MS m/e 332 (M^+ − 153), 153 (M^+ − 332). Anal. ($C_{22}H_{19}N_3O_8S$) C, H, N.

(7*S*,6*R*)-7-(2-Thienylacetamido)-3-carboxy-1-carba-1-dethia-3-cephem-4-carboxylic Acid (7e). To a solution of ester **7c** (0.125 g, 0.26 mmol) in 4 mL of DMF and 2 mL of 1 N HCl was added zinc dust (0.090 g, 1.41 mmol) at 23 °C and the mixture was stirred for 4 h. After dilution with 100 mL of EtOAc, the mixture was washed with 1 N HCl. The organic layer was extracted with 10% aqueous $NaHCO_3$, and the combined aqueous layers were acidified with 1 N HCl to pH 1.5, saturated with NaCl, and extracted with 25% 2-propanol/$CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Chromatography on HP-20ss (elution with 1:10:89 HOAc/CH_3CN/H_2O) afforded 0.025 g (28%) of acid **7e**: ^1H NMR (300 MHz, D_2O) δ 7.40 (m, 1 H), 7.05 (m, 2 H), 5.35 (d, J = 5 Hz, 1 H), 3.95 (m, 3 H), 2.80 (m, 1 H), 2.30 (m, 1 H), 2.05 (m, 1 H), 2.02 (s, 1.3 H, CH_3CN), and 1.50 (m, 1 H); IR ($CHCl_3$) 3260, 1760, 1662, 1544, 1408, and 1202 cm^{-1}; UV (EtOH) λ_{max} 236 nm (ϵ 8880); MS m/e 351 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.43; H, 4.03; N, 8.00. Found: C, 49.41; H, 4.44; N, 9.02 (correct for $C_{15}H_{14}N_2O_6S \cdot H_2O \cdot {}^1/_2CH_3CN$).

***p*-Nitrobenzyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-formyl-1-carba-1-dethia-3-cephem-4-carboxylate (9).** O_3 (0.7 mmol/min) was bubbled through a solution of vinylcarbacephem **8a** (15.00 g, 3.4 mmol) in 1500 mL of CH_2Cl_2 and 3.81 mL of MeOH at −78 °C for 30 min. The reaction was carefully monitored by TLC after two additional 5-min treatments with ozone. When only a trace of starting material could be seen by TLC (28.3 mmol total ozone), the reaction was maintained at −78 °C for 1 h and then flushed with N_2 for 15 min. Dimethyl sulfide (2.26 mL, 30.8 mmol) was added via syringe and the reaction was allowed to warm to 23 °C. The reaction was concentrated after the addition of toluene (250 mL). HPLC with a Waters Prep 500 silica gel system (elution with a gradient of toluene to 50:50 EtOAc/toluene) gave 10.8 g (72%) of **9** as a white solid along with 1.82 g (12%) of starting material: ^1H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1 H), 8.26 (d, J = 8 Hz, 2 H), 7.63 (d, J = 8 Hz, 2 H), 7.34 (t, J = 8 Hz, 2 H), 7.05 (t, J = 8 Hz, 2 H), 6.91 (d, J = 8 Hz, 2 H), 5.52 (t, J = 6 Hz, 1 H), 5.45 (AB q, 2 H), 4.57 (s, 2 H), 4.13 (q, J = 12 Hz, 1 H, EtOAc), 4.0 (m, 1 H), 2.97 (m, 1 H), 2.30 (m, 1 H), 2.15 (m, 1 H), 2.04 (s, 1.5 H, EtOAc), 1.70 (m, 1 H), 1.26 (t, J =

12 Hz, 1.5 H, EtOAc), and 1.15 (m, 1 H); IR ($CHCl_3$) 3020, 1788, 1733, 1692, 1674, 1601, 1526, 1496, 1385, 1362, 1350, 1229, and 1083 cm^{-1}; UV (EtOH) λ_{max} 298 (ϵ 5880), 275 (ϵ 5610), and 268 nm (ϵ 5710); MS *m/e* 480 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{21}N_3O_8$: C, 60.12; H, 4.41; N, 8.76. Found: C, 59.80; H, 4.42; N, 7.94 (correct for $C_{24}H_{21}N_3O_8 \cdot {}^1/_2EtOAc$).

p-Nitrobenzyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-(acetoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (10). A solution of the aldehyde **9** (3.30 g, 6.89 mmol) in 70 mL of anhydrous THF was cooled to −35 °C and treated with lithium tri(*tert*-butoxy)aluminum hydride (1.84 g, 7.23 mmol) portionwise over 1 h. After an additional hour at −35 °C, pyridine (1.11 mL, 13.8 mmol) and acetic anhydride (3.25 mL, 34.5 mmol) were added. The reaction was warmed to 0 °C over 45 min and kept at this temperature for 18 h. The reaction was then diluted with ethyl acetate and treated with 1 N HCl. After stirring for 1 h the organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 45:55 EtOAc/hexane followed by 55:45 EtOAc/hexane) to give 1.65 g (46%) of acetate **10**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8 Hz, 2 H), 7.63 (d, J = 8 Hz, 2 H), 7.33 (t, J = 8 Hz, 2 H), 7.08 (m, 2 H), 6.91 (d, J = 8 Hz, 2 H), 5.43 (t, J = 6 Hz, 1 H), 5.36 (AB q, 2 H), 4.98 (AB q, 2 H), 4.56 (s, 2 H), 3.92 (m, 1 H), 2.2 (m, 2 H), 2.08 (s, 3 H), 2.01 (m, 1 H), 1.4 (m, 1 H); IR ($CHCl_3$) 3020, 1774, 1734, 1691, 1525, 1496, 1391, 1350, and 1233 cm^{-1}; UV (EtOH) λ_{max} 269 nm (ϵ 21 900); MS *m/e* 524 ($M^+ + 1$). Anal. ($C_{26}H_{25}N_3O_9$) C, H, N.

Allyl (7*S*,6*R*)-7-(Phenoxyacetamido)-3-(acetoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (11). A solution of ester **10** (0.200 g, 0.382 mM) in 4.2 mL of CH_2Cl_2/HOAc (10:1) under N_2 at 0 °C was treated with zinc (0.300 g, 4.59 mmol). After 2 h at 23 °C the resultant suspension was filtered through Celite, the Celite was rinsed with CH_2Cl_2, and the filtrate was concentrated. The resultant orange oil was purified by chromatography on silica gel (elution with 4:96 HOAc/EtOAc) to give 0.104 g (70%) of the acid as a yellow solid. A solution of this acid (0.050 g, 0.129 mmol) in anhydrous DMF at 0 °C under N_2 was treated with allyl bromide (0.013 mL, 0.155 mmol) and *N*-methylmorpholine (0.023 mL, 0.206 mmol). After 0.25 h at 0 °C the reaction mixture was maintained at 23 °C for 2 h and at 40 °C for 12 h. After cooling to 23 °C the solution was diluted with EtOAc, washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The resultant oil was purified by chromatography on silica gel (elution with 55:45 EtOAc/hexane) to give 0.036 g (65%) of ester **11** as an off-white oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, J = 8 Hz, 2 H), 7.02 (m, 2 H), 6.88 (d, J = 8 Hz, 2 H), 5.95 (m, 1 H), 5.42 (m, 3 H), 4.92 (AB q, 2 H), 4.75 (m, 2 H), 4.57 (s, 2 H), 3.86 (m, 1 H), 2.3 (m, 2 H), 2.05 (s, 3 H), 1.98 (m, 1 H), and 1.4 (m, 1 H); IR ($CHCl_3$) 1773, 1732, 1690, 1522, 1496, 1391, 1387, and 1234 cm^{-1}; UV (EtOH) λ_{max} 268 nm (ϵ 11 360); MS *m/e* 429 ($M^+ + 1$). Anal. Calcd for ($C_{22}H_{24}N_2O_7$): C, 61.68; H, 5.65; N, 6.54. Found: C, 61.31; H, 5.88; N, 5.85.

Allyl (7*S*,6*R*)-7-[[[2-[[(Allyloxy)carbonyl]amino]-4-thiazolyl]methoximinoacetyl]amino]-3-(acetoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (12). Pyridine (0.75 mL, 9.25 mmol) and PCl_5 (1.77 g, 8.50 mmol) were added to a solution of the ester **11** (3.00 g, 7.5 mmol) in 45 mL of CH_2Cl_2 at 5 °C under N_2. After stirring for 15 min the bath was removed and the reaction was allowed to warm to 23 °C over 1.5 h. In a separate flask, isobutyl alcohol (7.0 mL, 76 mmol) in 300 mL of CH_2Cl_2 was cooled to −20 °C and the imino chloride solution from above was added via a cannula at a moderate rate. This reaction mixture was stirred for 2 h as the temperature rose to 23 °C and then stirred for an additional hour. Water (200 mL) was added and the resultant biphasic mixture was vigorously stirred for 0.5 h. The separated organic layer was extracted with 1 N HCl. The aqueous layer was adjusted to pH 7.5 with $NaHCO_3$ and then extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and concentrated to afford 1.49 g of crude amine as a clear oil, which was used immediately without purification. A suspension of [2-[[(allyloxy)carbonyl]amino]-4-thiazolyl]-methoximinoacetic acid (1.49 g, 7.4 mmol) in 43 mL of anhydrous CH_2Cl_2 at 0 °C was treated with *N*-methylmorpholine (0.81 mL, 7.4 mmol). 2-Chloro-4,6-dimethoxytriazine (1.37 g, 7.4 mmol) was added and the reaction was stirred at 0 °C for 1 h. This solution of active ester was added dropwise via an addition funnel to a solution of the amine in 10 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 3 h at 0 °C and for 2 h at 23 °C. The resultant precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 60:40 and then 70:30 EtOAc/hexane), giving 0.920 g (22%) of acetate **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (br, s, 1 H), 8.10 (br, s, 1 H), 7.15 (s, 1 H), 5.9 (m, 2 H), 5.62 (dd, J = 6, 8 Hz, 1 H), 5.42 (m, 1 H), 5.37 (m, 1 H), 5.29 (dd, J = 5, 8 Hz, 2 H), 4.99 (AB q, 2 H), 4.7 (m, 4 H), 4.00 (m, 1 H), 3.93 (s, 2 H), 2.45 (m, 2 H), 2.15 (m, 1 H), 2.08 (s, 3 H), and 1.7 (m, 1 H); IR ($CHCl_3$) 3026, 1762, 1731, 1679, 1554, 1394, 1294, 1286, 1229, and 1043 cm^{-1}; UV (EtOH) λ_{max} 266 (ϵ 22 700) and 229 nm (ϵ 20 300); MS *m/e* 562 ($M^+ + 1$). Anal. ($C_{24}H_{27}N_5O_9S$) C, H, N.

(7*S*,6*R*)-7-[[(2-Amino-4-thiazolyl)methoximinoacetyl]amino]-3-((1-pyridiniumyl)methyl)-1-carba-1-dethia-3-cephem-4-carboxylate Inner Salt (13). To a solution of acetate **12** (0.050 g, 0.104 mmol) in 0.32 mL of dry CH_2Cl_2 at 0 °C was added iodotrimethylsilane (0.022 mL, 0.156 mmol). The resultant mixture was stirred at 0 °C for 0.5 h and then at 23 °C for 1 h. The reaction was concentrated and the resultant brown oil was dissolved in 0.35 mL of CH_3CN. Tetrahydrofuran (0.0126 mL, 0.156 mmol) was added and the reaction was stirred for 10 min. After cooling to 0 °C, the reaction mixture was treated with a solution of pyridine (0.0101 mL, 0.125 mmol) in 0.1 mL of CH_3CN. After 10 min at 0 °C, the mixture was warmed to 23 °C. After 50 min the reaction was diluted with Et_2O, precipitating the quaternary salt, which was collected by centrifugation. The solid was dissolved in CH_2Cl_2 and twice precipitated with Et_2O. This material was used without further purification. A solution of triphenylphosphine (0.0021 g, 0.008 mmol) and palladium(II) acetate (0.0004 g, 0.0016 mmol) in 1.0 mL of anhydrous CH_3CN and 0.3 mL of Et_2O under N_2 was cooled to 0 °C and the quaternary salt (0.025 g, 0.04 mmol) was added followed by tributyltin hydride (0.022 mL, 0.0082 mmol). An additional 0.5 mL of CH_3CN and 0.2 mL of Et_2O were added in order to maintain a solution. The reaction was stirred at 0 °C for 0.5 h and then at 23 °C for 0.25 h. The mixture was cooled to 0 °C, then acetic acid (0.005 mL, 0.0088 mmol) was added and the solution was warmed to 23 °C. Et_2O (2 mL) was added and the solid was isolated by centrifugation. This solid was washed with Et_2O and then purified by chromatography on HP-20ss (gradient elution with H_2O to 8:92 CH_3CN/H_2O). Lyophilization provided 0.0075 g of product **13**: ^1H NMR (300 MHz, DMSO-d_6) δ 9.47 (br d, J = 6 Hz, 1 H), 9.10 (d, J = 10 Hz, 1 H), 8.60 (t, J = 8 Hz, 1 H), 8.13 (t, J = 8 Hz, 2 H), 7.13 (br s, 1 H), 6.65 (s, 1 H), 5.66 (d, J = 13 Hz, 1 H) 5.25 (m, 1 H), 4.97 (d, J = 13 Hz, 1 H), 3.72 (s, 3 H), 2.10 (m, 1 H), 1.8 (m, 2 H), and 1.40 (m, 1 H); ^{13}C NMR (75 MHz, D_2O) δ 165.5, 142.7, 144.8, 138.3, 137.9, 133.8, 133.3, 132.5, 128.3, 127.5, 117.9, 113.3, 62.9, 62.1, 58.3, 53.3, 23.6, and 20.8; IR (KBr) 3300, 1758, 1662, 1609, 1580, 1535, 1384, 1338, 1152, and 1036 cm^{-1}; UV (EtOH) λ_{max} 257 nm (ϵ 18 700); MS *m/e* 457 ($M^+ + 1$); high-resolution MS calcd for $C_{20}H_{21}N_6O_5S$, 457.12929; found, 457.12919.

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