RNase T1 (100 units). The total cell lysate was applied to nitrocellulose paper with use of a 96-well, vacuum operated dot-blot apparatus. The blots were hybridized to a  $^{35}$ S-labeled d-ATP nick translated probe made by inserting full-length mouse mtDNA into pSP64 vector at the Sac1 site. The vector itself was used to generate a standard curve for each experiment. Dot blots were visualized by autoradiography and cut out, and radioactivity was determined by scintillation counting.

Flow Cytometric Analysis. Flow cytometric analysis of nuclear DNA content was performed with the RATCOM flow cytometer (RATCOM Inc., Miami, FL) interfaced with a microcomputer (IBM-XT). Cultured L1210 cells in log growth were incubated at 37 °C with 10  $\mu$ M DESPM-3 and samples removed at 0, 48, 96, and 144 h were analyzed for nuclear DNA content distributions after being stained with diamidinophenylindole in a nuclear isolation media (NIM-DAPI).<sup>20</sup>

**Cloning Assay.** L1210 cells maintained between  $10^5$  and  $10^6$  cells/mL were incubated with 10  $\mu$ M DESPM-3 for 96 h. At 24-h intervals, treated cells were washed (2 × 10 mL) and diluted in fresh complete media and plated in triplicate 96-well microtiter plates at 0.4 cell/well with each well containing 100  $\mu$ L of sample. The plates were incubated at 37 °C in a humidified incubator in an atmosphere of 5% CO<sub>2</sub> and 95% air. The plates were examined with an inverse-phase microscope at 100× magnification. The final number of colonies per plate was quantitated 7 days after plating. Groups of 50 or more cells/well were identified as having been cloned from a single viable cell. Also, at each 24-h interval, treated cell samples were washed and the cells resus-

(20) Thornwaite, J. T.; Sugerbaker, E. V.; Temple, W. J. Cytometry 1980, 1, 229-237. pended in fresh media at  $10^5$  cells/mL in duplicate 10-mL flasks. The regrowth of the treated cells was followed for up to 144 h.

**Cell Size.** Cell size was determined directly by the method of Schwartz et al.<sup>21</sup> In brief, uniform polymeric microspheres ranging from 4.72 to 10.2  $\mu$ m in diameter (Polysciences, Warrington, PA) were diluted in Hematall (Fisher Scientific Co.). Electronic size was measured on the FACS Analyzer (Becton Dickinson, Sunnyvale, CA) with the amplifier in the log mode. The peak channel number for each size microbead was plotted against the corresponding calibrated diameter and calculated volume to obtain a calibration curve. L1210 cells were treated with 10  $\mu$ M DESPM-3 for 0–144 h and samples of 10<sup>6</sup> cells were removed at 24-h intervals and pelleted. The cells were resuspended in 0.5 mL of Hematall and analyzed. The peak channel number of the treated cells was plotted on the calibration curve to obtain the approximate cell size directly.

**Registry No.** 1, 70655-37-7; 1·2HCl, 113812-27-4; 2, 113812-18-3; 2·4HCl, 113812-17-2; 3, 61345-84-4; 3·4HCl, 113812-15-0; 4, 113812-20-7; 4·4HCl, 113812-21-8; 5, 113812-11-6; 5·HCl, 113812-12-7; 6, 113812-23-0; 6·4HCl, 113812-24-1; 7, 40563-84-6; 8, 113830-94-7; 8·4HCl, 113812-26-3; 9, 113812-30-9; 10, 63958-61-2; 11, 113812-13-8; 12, 113812-16-3; 13, 113812-16-1; 14, 113812-19-4; 15, 113812-22-9; 16, 113812-25-2; 17, 113812-28-5; 18, 113812-29-6; SPM-4HCl, 306-67-2; C<sub>2</sub>H<sub>5</sub>NHCCH<sub>2</sub>)<sub>3</sub>NHC<sub>2</sub>H<sub>5</sub>, 10061-68-4; CIC-O(CH<sub>2</sub>)<sub>2</sub>COCl, 543-20-4; CH<sub>2</sub>=CHCN, 107-13-1; C<sub>2</sub>H<sub>5</sub>NH(C-H<sub>2</sub>)<sub>4</sub>NHC<sub>2</sub>H<sub>5</sub>, 19435-68-8; CH<sub>3</sub>CONH(CH<sub>2</sub>)<sub>12</sub>NHCOCH<sub>3</sub>, 31991-77-2; CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>-p-SO<sub>2</sub>NHC<sub>2</sub>H<sub>5</sub>, 80-39-7; Cl(CH<sub>2</sub>)<sub>3</sub>Cl, 142-28-9; 1,4-bis(3-aminopropyl)piperazine, 7209-38-3.

(21) Schwartz, A.; Sugg, H.; Ritter, T. W.; Fernandez-Repollet, E. Cytometry 1983, 3, 456-458.

## An Examination of O-2-Isocephems as Orally Absorbable Antibiotics

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The synthesis and structure-activity relationships of a series of orally absorbed O-2-isocephems are described. These compounds possessed a D-[(p-hydroxyphenyl)glycyl]amino substituent at the 7-position while the substituent at the 3-position was varied. Relative to the analogous cephems, the O-2-isocephems exhibited comparable to better activity against Gram-positive organisms. Against Gram-negative organisms, their activity was variable but did indicate a lower  $\beta$ -lactamase stability. Following oral administration, the O-2-isocephems generally exhibited longer half-lives but lower  $C_{\max}$ 's and urinary recoveries.

The perception<sup>1</sup> that the use of orally administered antibiotics can be more cost-effective has spurred the search for new, long-acting, orally active  $\beta$ -lactam antibiotics. *O*-2-Isocephems, e.g. 1, are nuclear analogues of the cephalosporins and have been extensively examined in these laboratories<sup>2a</sup> as parenterally administered antibacterials. We have conducted a reexamination of this class of compounds to see if they would show promise as orally administered antiinfectives. This consisted of examining the activity of a group of *O*-2-isocephems bearing a D-[(*p*-hydroxyphenyl)glycyl]amino substituent at the 7-position as a function of the nature of the substituent at the 3-position. The results of this effort together with the details of a new, enantioselective *O*-2-isocephem synthesis are described in this paper.

## Chemistry

Since existing syntheses<sup>2</sup> were too long and did not provide much room to vary the 3-substituent, we devised

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a new synthesis (Scheme I), which would be more suited to our needs. We believed that the O-2-isocephem 1 could

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Scrip, 1985 Chemotherapy Report; PJB Publications: Surrey, U. K., 1985; p 22.

	minimal inhibitory concentrations (MIC), <sup>a</sup> µg/mL							
compd	S. pyogenes	S. pneumoniae	S. faecalis	S. aureus <sup>b</sup>	E. coli <sup>b</sup>	K. pneumoniae	P. mirabilis	H. influenzae
45	0.016	0.03	0.5	0.13 (32)	2 (32)	8	0.5	1
46	0.016	0.03	1	0.25 (32)	2 (63)	16	1	2
47	0.016	0.03	1	0.25(125)	2 (63)	8	0.5	2
48	0.008	0.016	0.06	0.5(125)	2 (32)	32	16	2
49	0.008	0.016	0.13	0.5 (32)	4 (32)	16	16	2
50	0.008	0.03	1	0.13(125)	2 (63)	16	1	2
51	0.25	1	32	1 (16)	4 (8)	8	4	2
52	0.13	0.13	16	1 (32)	8 (16)	8	4	8
53	0.004	0.008	0.03	0.06 (63)	2(32)	16	4	
54	0.016	0.03	1	0.25(125)	4 (125)	16	2	8
55	0.03	0.03	2	0.25	4 (32)	16	4	
56	0.016	0.03	2	0.13 (32)	1 (4)	2	0.25	2
57	0.03	0.06	4	0.25(3)	8 (32)	8	1	4
58	0.016	0.03	18	0.13(32)	4 (8)	4	1	1
cefalexin	0.5	0.5	32	0.5	8 (16)	16	4	4
cefaclor	0.25	0.5	16	0.25	1(32)	1	0.25	1

Chart I

Tahla I	้ไท่	Vitro	Antihact	orial	Activity
TADIG	. 111	VILLO	AIIUUaci	eriai	ACTIVITY

<sup>a</sup> MIC determined by 2-fold microdilution technique.  ${}^{b}\beta$ -Lactamase producing strain in parentheses,

be derived from the  $\beta$ -keto ester 2 and that the latter could be obtained by condensation<sup>3</sup> of the ester enolate of 3 with the activated form of a carboxylic acid. If successful, this approach would allow us to introduce the 3-substituent as an acid derivative at a late stage of the synthesis and would thereby facilitate the preparation of this series of analogues. It would, however, require access to a source of the chiral azetidinone 4. For the sake of expediency, we turned to an existing synthesis<sup>4</sup> of this material.

The 4-(hydroxymethyl)azetidinone 6 was prepared according to the literature procedure.<sup>4a</sup> Conversion (Chart I) of this material to the allyl acetate 10 was accomplished by the following sequence of reactions: oxidative removal of the dimethoxybenzyl group of 6, protection of the alcohol function of 7 as a silvl ether, replacement of the benzyloxycarbonyl protecting group on 8 with a trityl group, and attachment of the allyl acetate group onto the nitrogen atom of the azetidinone 9. With the acetate 10 in hand, we were ready to examine the proposed condensation reaction. We were pleased to find that the lithium enolate of 10 would indeed react with a variety of acid chlorides to give the  $\beta$ -keto esters 11-17 in good yield (48-95%). Removal of the silvl protecting group furnished the 3-hydroxymethyl compounds 18-24, and these, when subjected to the conditions of the Mitsunobu reaction,<sup>5</sup> readily underwent cyclization to give the O-2-isocephems 25-31 (Chart II). The trityl group was then replaced by an (R)-N-(allyloxycarbonyl)(p-hydroxyphenyl)glycyl side chain to give the 7-acylamido derivatives 32-38. At this stage, some additional functional group manipulation of

- (2) (a) 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, L. R. Can. J. Chem. 1980, 58, 2508 and earlier papers in the series. (b) Other racemic O-2-isocephem syntheses: Hakimelahi, G. H.; Just, G.; Ugolini, A. Helv. Chim. Acta 1982, 65, 1368. McCombie, S. W.; Metz, W. A.; Afonso, A. Tetrahedron Lett. 1986, 27, 305. Hrytsak, M.; Durst, T. Heterocycles 1987, 26, 2393. (c) Enantioselective syntheses: Tenneson, S. M.; Belleau, B. Can. J. Chem. 1980, 58, 1605. Natta, H.; Hatanaka, M.; Ishimaru, T. J. Chem. Soc., Chem. Commun. 1987, 51. A preliminary account of this work has appeared: Mastalerz, H.; Vinet, V. J. Chem. Soc., Chem. Commun. 1987, 1283.
- (3) A similar condensation has been used to synthesize a clavulanic acid derivative: Eglington, J. J. Chem. Soc., Chem. Commun. 1977, 720.
- (4)(a) Hubschwerlen, C. Synthesis 1986, 962 and references therein. (b) Evans, D. A.; Sjogren, E. B. Tetrahedron Lett. 1985, 3783.
- (5) For the O-alkylation of  $\beta$ -diketones under these conditions see: Mitsunobu, O. Synthesis 1981, 1.



**5**: H = 0; H = 2,4-(MeO)<sub>2</sub>O<sub>6</sub> $H_3$ OH<sub>2</sub>;  $H = CO_2$ OH<sub>2</sub>: $H'' = CO_2$ CH<sub>2</sub>Ph **6**: R = H, OH; R' = 2,4-(MeO)<sub>2</sub>C<sub>6</sub> $H_3$ CH<sub>2</sub>;  $R'' = CO_2$ CH<sub>2</sub>Ph **7**: R = H, OH; R' = H;  $R'' = CO_2$ CH<sub>2</sub>Ph **8**: R = H, OTBDMS; R' = H;  $R'' = CO_2$ CH<sub>2</sub>Ph **9**: R = H, OTBDMS; R' = H;  $R'' = CPh_3$ 10: R = H, OTBDMS;  $R' = CH_2CO_2CH_2CH = CH_2$ ;  $R'' = CPh_3$ 



11: R = TBDMS;  $R' = CH_2CH_2SePh$ 12: R = TBDMS;  $R' = CH_2CI$ **18:**  $R = H_1 R' = CH_2CH_2SePh$ 19: R = H; R'= CH2CI 13: R = TBDMS;  $R' = CH_2CH_2CH_2SePh$  20: R = H;  $R' = CH_2CH_2CH_2SePh$ 20: H= H; H = CH2OH2O 21: R=H; R'=H 22: R=H; R'=CH3 23: R=H; R'=n-Pr 24: R=H; R'=c-C3H5 14: R = TBDMS, R'=H 15: R = TBDMS; R'=CH<sub>3</sub> **16:** R = TBDMS; R' = n - Pr**17:**  $R = TBDMS; R' = c - C_3H_5$ 

the 3-substituent was required in order to prepare certain analogues. The respective precursors of the 3-vinyl (45) and 3-allyl (50) compounds, 39 and 40, were obtained from 32 and 34 by oxidation followed by selenoxide elimination. The 3-chloromethyl compound 33 served as the precursor for the 3-propenyl and 3-trifluoropropenyl compounds 46-49. This transformation involved conversion of 33 to the iodide 41 and then reaction of the latter with triphenylphosphine to give the phosphonium salt 42. Wittig reaction of the in situ generated ylide with the appropriate aldehyde furnished mixtures of the olefin isomers 43 and 44. The last step was the palladium-catalyzed removal of the protecting groups. Purification and, where necessary, separation of olefin isomers was effected by reverse-phase column chromatography.

## **Biological Results and Discussion**

The in vitro antibacterial activity of the O-2-isocephems (45-54) and several corresponding cephems<sup>6</sup> (55-58) is summarized in Table I.

<sup>(</sup>a) Leitner, F.; Pursiano, T. A.; Buck, R. E.; Tsai, Y. H.; Chisholm, D. R.; Misiek, M.; Desiderio, J. V.; Kessler, R. E. (6)Antimicrob. Agents Chemother. 1987 31, 238. (b) Naito, T.; Hoshi, H.; Aburaki, S.; Abe, Y.; Okumura, J.; Tomatsu, K.; Kawaguchi, H. J. Antibiot. 1987, 40, 991.

**Chart II** 



Substitution at the 3-position generally enhanced activity in vitro against Gram-positive bacteria (streptococci and staphylococci) as shown by comparing 45-50 and 52-54 to 51. However, the latter was more active against the  $\beta$ -lactamase producing *Staphylococcus aureus* and *Escherichia coli*, suggesting lower  $\beta$ -lactamase stability among the substituted O-2-isocephems. There were relatively small or no differences in activity against the other Gram-negative bacteria, i.e., *E. coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*. Activity against *Proteus mirabilis* was quite variable. The fluorinated compounds (48 and 49) in particular exhibited much lower activity against *P. mirabilis*.

Comparison of the O-2-isocephems 45–47 and 50 to their corresponding cephems 55–58 showed no differences in intrinsic activity against Streptococcus pyogenes, Streptococcus pneumoniae, and S. aureus. Compounds 56 and 58 were more active than their corresponding isocephems 46 and 50 against the  $\beta$ -lactamase producing S. aureus. The O-2-isocephems were 2–8-fold more active than the cephems against Streptococcus faecalis. The results with the Gram-negative bacteria were more variable, and no generalities were possible.

A comparison of pharmacokinetic parameters in blood and urinary recoveries following oral administration of 45-49 and 55-58 is shown in Table II. Compound 45 and its corresponding cephem 55 exhibited similar  $C_{\rm max}$  values, but the half-life of 45 was longer. The other three O-2isocephems exhibited lower  $C_{\rm max}$  values than their corresponding cephems with longer half-lives for two of the three. Urinary recoveries of the three O-2-isocephems tested were significantly lower than those of the corresponding cephems.

Of these four pairs only two were compared directly in systemic infection models (Table III). Compounds 46 and 56 were similar in efficacy against *S. pneumoniae* but the cephem 56 was nearly 20-fold more effective against *E. coli*. Apparently the 3-fold higher  $C_{\text{max}}$  of 56 was more important than the somewhat longer half-life of 46 in this model.

Table II.	Pharmacoki	netic Parai	neters of S	elected Ce	phems
and O-2-Is	ocephems in	Mice after	an Oral D	ose of 50 r	ng/kg

				0,0
no.	$C_{ m max},\mu { m g}/{ m mL}$	$T_{1/2}$ , min	AUC, µg/mL	percentage of dose recovered, 0-6 h in urine
45	26	39	30	73
46	15	52	23	25
47	11	110	30	5
50	31	32	32	46
55	22	29	21	$ND^a$
56	46	29	42	85
57	35	47	45	65
58	45	34	41	79

 $^{a}$  ND = not done.

Table III.	Oral Th	erapeutic l	Efficac	y of Selec	ted	
O-2-Isoceph	ems and	Cephems	in Syst	temically	Infected	Mice

	<i>E. c</i>	oli	S. pneumoniae		
no.	MIC, µg/mL	PD <sub>50</sub> , <sup>b</sup> mg/kg per dose	MIC, µg/mL	PD <sub>50</sub> , mg/kg per dose	
45	2	2.1	0.03	0.8	
46	2	19	0.03	0.30	
47	2	>50	0.03	1.8	
48	2	>50	0.016	2.7	
49	4	>50	0.016	>12.5	
50	4	9.2	0.016	1.0	
51	4	6.2	1	33	
52	8	11	0.13	2.1	
<b>54</b>	4	>50	0.03	3.6	
56	2	1.2	0.016	0.4	
57	8	ND°	0.06	0.5	

<sup>a</sup> Mice treated twice at 0 and 2 h after infection for *E. coli*, 1 and 3.5 h for *S. pneumoniae*. <sup>b</sup> PD<sub>50</sub> = protective dose for 50% of animals tested. <sup>c</sup> ND = not done.

The relative importance of  $C_{\max}$  was also seen with the comparison of 57 (3-fold higher  $C_{\max}$ ) and 47 (2-3-fold longer half-life) against S. pneumoniae.

Compound 45 showed the best balance in activity in vivo against E. coli and S. pneumoniae (Table III) of the O-2-isocephems and was nearly as active as 56, which is currently in clinical trials.

## **Experimental Section**

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The UV and IR spectra were recorded on Hewlett-Packard 8451A and Perkin-Elmer 781 spectrophotometers, respectively. The <sup>1</sup>H NMR spectra were obtained on a Bruker AC 200 instrument with tetramethylsilane as the internal standard for organic solvents and sodium 3-(trimethylsilyl)propionate-2,2,3,3-d<sub>4</sub> for deuterium oxide. TLC was performed with EM Art. 5719 Kieselgel 60 F<sub>254</sub> plates. Medium-pressure column chromatography employed EM Art. 9385 Kieselgel 60 (230-400 mesh) with EtOAc/hexane mixtures being used as eluent. Where necessary, solvents were dried and reactions were conducted under an Ar atmosphere.

The final O-2-isocephems were purified by medium-pressure column chromatography employing the absorbant from a Waters  $C_{18}$  PrepPak-500 column as the stationary phase and  $CH_3CN/$  water mixtures as eluent. The desired fractions were combined, the organic solvent was removed under high vacuum, and then the water was removed by lyophilization. This left the isocephems as amorphous powders. Since these contained varying amounts of water of hydration, which could not be removed without some product decomposition, their final purity was judged by analytical HPLC. A Waters  $C_{18}$  Bondapak column (10  $\mu$ m particle size, 3.8 mm  $\times$  30 cm) with a Waters 481 LC spectrophotometric detector was employed. Material of greater than 95% purity was used for biological evaluation.

In Vitro Antibacterial Activity. Conventional microtiter dilution procedures were used for determination of minimum inhibitory concentrations (MICs). Organisms were grown overnight in Mueller–Hinton Broth (Difco) at 37 °C. Twofold dilutions of the stock solution of each compound ( $125 \ \mu g/mL$ ) were made in Nutrient Broth (Difco) to obtain a test concentration range from 0.005 to  $125 \ \mu g/mL$ . The wells were then inoculated with approximately  $10^4$  organisms. The microtiter plates were incubated at 37 °C for 18 h. The MIC was the lowest concentration of test compound that yielded no visible growth.

In Vivo Testing. Procedures for determining pharmacokinetics in mice and therapeutic efficacy in mice have been described.<sup>6-8</sup> Briefly, male Swiss-Webster mice  $(20 \pm 2 \text{ g})$  were dosed by gavage. Determinations of blood concentrations and urine levels were done by microbiological assay. Bacterial challenges were administered intraperitoneally with sufficient numbers of bacteria to kill untreated controls within 72 h. Animals were dosed at 0 and 2 h postchallenge with *E. coli* or 1 and 3.5 h postchallenge with *S. pneumoniae*.

(3S,4S)-3-(Benzyloxycarboxamido)-1-(2,4-dimethoxybenzyl)-4-(hydroxymethyl)-2-azetidinone (6). A solution of (3S,4S)-3-(benzyloxycarboxamido)-1-(2,4-dimethoxybenzyl)-4formyl-2-azetidine (5)<sup>4a</sup> (170 g, 0.43 mol) in CH<sub>2</sub>Cl<sub>2</sub> (1.90 L) was placed in a water bath, and then NaBH<sub>4</sub>/Al<sub>2</sub>O<sub>3</sub><sup>9</sup> (850 g, 1 g of NaBH<sub>4</sub>/10 g of Al<sub>2</sub>O<sub>3</sub>) was added slowly with vigorous stirring. After 40 min, the alumina was removed by filtration and washed with EtOAc. The solvent was then removed from the filtrate to leave the crude alcohol 6 (170 g), which was used as such without further purification. A sample was crystallized from EtOAc: mp 129–130 °C;  $[\alpha]^{21}_D$ -12° (c 1.0, CHCl<sub>3</sub>); IR (KBr) 3480, 3340, 1730 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  3.47–3.72 (m, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.35 (q, 2 H,  $\delta_A$  4.28,  $\delta_B$  4.42,  $J_{AB}$  = 14.4 Hz), 5.07 (m, 3 H), 6.42–7.31 (m, 8 H). Anal. (C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>) C, H, N.

(3S,4S)-3-(Benzyloxycarboxamido)-4-[[(tert-Butyldimethylsilyl)oxy]methyl]-2-azetidinone (8). A stirred suspension of the crude alcohol 6 (170 g, ca. 0.45 mol),  $K_2S_2O_8$  (161 g, 1.4 equiv), and  $K_2$ HPO<sub>4</sub> (96 g, 1.3 equiv) in a mixture of CH<sub>3</sub>CN (4.4 L) and water (2.25 L) was heated at ca. 95 °C for 1 h.<sup>10</sup> At this point, additional quantities of  $K_2S_2O_8$  (32 g, 0.28 equiv) and  $K_2$ HPO<sub>4</sub> (19 g, 0.26 equiv) were added, and heating was continued for an additional 3 h. After cooling, the organic solvent was removed, and the residual mixture was saturated with NaCl. This was extracted with EtOAc ( $4 \times 900$  mL), and then the combined organic phases were washed with aqueous NaHCO<sub>3</sub> ( $2 \times 500$  mL, 2.5%). After extraction of the aqueous phase with EtOAc (500 mL), the combined organic phases were dried, and the solvents were removed. Chromatography afforded the alcohol 7 (73.0 g, 69% yield), which had physical properties that were in agreement with those reported.4b

Triethylamine (114 mL, 2.20 equiv) was added over 0.5 h to an ice-cooled, stirred solution of the alcohol 7 (93.0 g, 0.372 mol), tert-butyldimethylsilyl chloride (127 g, 2.20 equiv), and 4-(dimethylamino)pyridine (8.0 g, 0.2 equiv) in DMF (900 mL). The bath was removed, and the reaction mixture was left stirring for 1 h. It was then diluted with  $\rm CH_2\rm Cl_2$  (3 L) and washed with water  $(3 \times 600 \text{ mL})$  followed by brine (600 mL). After drying, the solvents were removed, and the residual oil was taken up in HOAc (325 mL). KF (28.1 g, 1.30 equiv) was added, and the reaction mixture was left stirring for 1 h. The reaction was then diluted with  $CH_2Cl_2$  (3 L), and this was washed with water (5 × 1 L). After drying and removal of the solvents, the crude material was chromatographed to give the monosilylated product 8 (113 g, 84% yield) as an oil:  $[\alpha]^{21}{}_{\rm D}$  30° (c 1.0, CHCl<sub>3</sub>); IR (neat) 3200, 1765, 1720 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  0.05 (s, 6 H), 0.86 (s, 9 H), 3.70–3.91 (m, 3 H), 5.10 (s, 2 H), 5.18 (q, 1 H, J = 5.1, 10.2 Hz), 5.92 (d, 1 H, exchangeable, J = 10.2 Hz), 6.05 (s, 1 H, exchangeable), 7.30 (s, 5 H). Anal.  $(C_{18}H_{28}O_4N_2Si)$  C, H, N.

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(3S, 4S)-4-[[(tert-Butyldimethylsilyl)oxy]methyl]-3-(tritylamino)-2-azetidinone (9). A stirred suspension of the benzyloxycarboxamido compound 8 (113 g, 0.310 mol) and Pd catalyst (29 g, 10% on charcoal) in EtOAc (1.2 L) was maintained under a H<sub>2</sub> atmosphere until the starting material had disappeared (ca. 3 h). The catalyst was removed by filtration, and then the solvent was removed from the filtrate. The white residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 L), and trityl chloride (90.0 g, 1.04 equiv) followed by NEt<sub>3</sub> (46.0 mL, 1.05 equiv) was added. After being stirred for 1.5 h, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (1.5 L) and washed with water (3 × 600 mL) and brine (100 mL). It was then dried, and the solvent was removed. Chromatography afforded the product 9 (115 g, 79%) as a pale yellow solid: mp 203-205 °C; [ $\alpha$ ]<sup>21</sup><sub>D</sub> 34° (c 1.0, CHCl<sub>3</sub>); IR (KBr) 3350, 3300, 1770, 1735 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  -0.12 (s, 3 H), -0.06 (s, 3 H), 0.82 (s, 9 H), 2.38-3.15 (m, 3 H), 4.32 (d, 1 H, J = 4.6 Hz), 7.13-7.54 (m, 15 H). Anal. (C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>Si) C, H, N.

Allyl 2-[(3S,4S)-4-[[(tert-Butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]acetate (10). A solution of allyl 2-bromoacetate (4.30 g, 2 equiv) in dry THF (24 mL) was added over ca. 0.5 h to a stirred suspension of the azetidinone 9 (5.66 g, 12 mmol), tetrabutylammonium bromide<sup>11</sup> (786 mg, 0.20 equiv), and freshly powdered KOH (876 mg, 1.30 equiv) in dry THF (24 mL). This was left stirring for 20 h after which it was diluted with EtOAc and washed with water and brine. After drying and removal of the solvents, the residual oil was chromatographed to give the acetate 10 (4.04 g, 59%) as white crystals: mp 98–101 °C; [α]<sup>21</sup><sub>D</sub> 0° (c 1.0, CHCl<sub>8</sub>); IR 3360, 1765, 1745 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  -0.14 (s, 3 H), -0.09 (s, 3 H), 0.81 (s, 9 H), 2.47 (dd, 1 H, J = 3.6, 11.7 Hz), 3.10 (dd, 1 H, J= 2.3, 11.7 Hz), 3.32 (ddd, 1 H, J = 3.6, 2.3, 4.9 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 4.36 (d, 1 H, J = 18.0 Hz), 4.43 (d, 1 H, J = 4.9Hz), 4.52 (m, 2 H), 5.18-5.30 (m, 2 H), 5.76-5.90 (m, 1 H), 7.13-7.53 (m, 15 H). Anal.  $(C_{34}H_{42}N_2O_4Si)$  C, H, N.

Allyl (65,7S)-8-Oxo-3-[2-(phenylseleno)ethyl]-7-(tritylamino)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (25). A suspension of 3-(phenylseleno)propionic acid<sup>12</sup> (19.0 g, 0.083 mol) in oxalyl chloride (7.60 mL, 1.05 equiv) was left stirring for 4 h. The resulting solution was then distilled to give 3-(phenylseleno)propionyl chloride (13.8 g, 67% yield) as a yellow liquid: bp 102-112 °C (0.11 mm); NMR (CDCl<sub>3</sub>)  $\delta$  3.17 (m, 4 H), 7.39 (m, 5 H).

A solution of allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]acetate (10) (3.91 g, 6.86 mmol) in dry THF (75 mL) under argon was cooled to -78°C. To this was added a solution of lithium bis(trimethylsilyl)amide (14.1 mL, 1.0 M in THF, 2.05 equiv) dropwise. Then, after the mixture was stirred for 3 min, neat 3-(phenylseleno)propionyl chloride (1.22 mL, 1.05 equiv) was added dropwise. The reaction mixture was left stirring for 20 min after which it was quenched by the addition of a solution of acetic acid (1.30 mL, 3.3 equiv) in THF (10 mL). After being allowed to warm to 0 °C, the reaction mixture was diluted with EtOAc (200 mL), washed with brine  $(2 \times 30 \text{ mL})$ , and dried, and the solvent was removed. Chromatography afforded allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]-3oxo-5-(phenylseleno)pentanoate (11) (2.54 g, 48% yield) as an oil:  $R_f 0.55$  (EtOAc/hexane, 1:1).

To a solution of the azetidinone 11 (9.88 g, 12.7 mmol) in dry THF (190 mL) under argon was added a solution of tetrabutylammonium fluoride (15.2 mL, 1.0 M in THF, 1.2 equiv). After 15 min, acetic acid (0.95 mL, 1.3 equiv) was added. The reaction was then diluted with EtOAc (400 mL), washed with brine (40 mL), and dried. Removal of the solvent followed by chromatography afforded allyl 2-[(3S,4S)-4-(hydroxymethyl)-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-5-phenylseleno)pentanoate (18) (6.46 g, 76%) as a foam:  $R_f$  0.71 (EtOAc/hexane, 1:1).

To a solution of the alcohol 18 (6.49 g, 9.73 mmol) and triphenylphosphine (2.68 g, 1.05 equiv) in dry THF (270 mL) under argon was added diisopropyl azodicarboxylate (2.07 mL, 1.05

<sup>(10)</sup> Conditions used are modeled after those reported by: Kishimoto, S.; Sendi, M.; Tomimoto, M.; Hashigughi, S.; Matsuo, T.; Ochiai, M. Chem. Pharm. Bull. 1984, 32, 2646.

<sup>(11)</sup> Reuschling, D.; Pietsch, H.; Linkies, A.; Tetrahedron Lett. 1978, 615.

<sup>(12)</sup> Miyoshi, N.; Ishii, H.; Murai, S.; Sonoda, N.; Chem. Lett. 1979, 873.

equiv). After 15 min, the solvent was removed, and the residual oil was chromatographed to afford the O-2-isocephem **25** (5.30 g, 73% yield) as white crystals (from EtOAc/hexane): mp 128–129 °C; IR (KBr) 1770, 1710, 1610 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  2.71–3.35 (m, 8 H), 4.56–4.97 (m, 3 H), 5.20–5.42 (m, 2 H), 5.83–6.00 (m, 1 H), 7.19–7.49 (m, 20 H). Anal. (C<sub>37</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>Se) C, H, N.

(R)-N-[(Allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycine. (R)-2-(4-hydroxyphenyl)glycine (16.7 g, 0.1 mol) was dissolved in a mixture of diethyl ether (100 mL), water (200 mL), and aqueous NaOH solution (100 mL, 1 N, 1.0 equiv). This was cooled in an ice bath, and then solutions of allyl chloroformate [12.1 g, 1.0 equiv, in dry dioxane (100 mL)] and aqueous NaOH (100 mL, 1 N, 1.0 equiv) were added contemporaneously over 1 h. The mixture was left stirring in the ice bath for 1 h after which the organic phase was separated. The aqueous phase was washed with ether  $(3 \times 200 \text{ mL})$ , and then its pH was adjusted to 2.5 by the addition of concentrated  $H_3PO_4$ . This mixture was then extracted with EtOAc  $(2 \times 200 \text{ mL})$ . The combined organic extracts were washed with water (50 mL) and dried, and then the solvents were removed. Trituration of the residual gum with a mixture of benzene (50 mL) and petroleum ether (400 mL, 30-60 °C) gave a white solid. This was taken up and digested in boiling benzene (10 mL/g). After cooling, the white solid was collected and washed successively with benzene and petroleum ether. This gave the pure N-allyloxycarbonyl derivative as a white powder (12.4 g, 50% yield): mp 147–149 °C;  $[\alpha]^{21}_{D}$ –158.3° (c 1.0, MeOH); IR (KBr) 3200, 1735, 1650 cm<sup>-1</sup>; NMR (DMSO-d<sub>6</sub>) 4.47 (m, 2 H), 4.97 (d, 1 H, J = 7.9 Hz, 5.12-5.32 (m, 2 H), 5.79-5.98 (m, 1 H), 6.69 (d, 1 H)2 H, J = 8.6 Hz), 7.16 (d, 2 H, J = 8.6 Hz), 7.85 (d, 1 H, J = 7.9Hz). Anal. (C<sub>12</sub>H<sub>13</sub>NO<sub>5</sub>) C, H, N.

(6S,7S)-7-[[(R)-2-(4-Hydroxyphenyl)glycyl]amino]-8oxo-3-vinyl-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (45). A solution of the trityl derivative 25 (5.60 g, 8.64 mmol) in acetone (50 mL) was cooled in an ice bath, and p-toluenesulfonic acid monohydrate (1.81 g, 1.1 equiv) was added with stirring. After being allowed to stand for 19 h, the crystals were collected, washed with a little cold acetone and ether, and then dried under high vacuum. This gave the p-toluenesulfonic acid salt of allyl (6S,7S)-7-amino-3-[2-(phenylseleno)ethyl]-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (3.60 g, 72% yield) as white crystals. This material (1.08 g, 1.87 mmol) was suspended in EtOAc (20 mL), and a stream of argon was allowed to bubble through the suspension. Then, sufficient saturated aqueous sodium bicarbonate solution was added with stirring to bring the pH of the aqueous phase to 8. The aqueous phase was removed and extracted with a little EtOAc. The combined organic phases were washed with brine and dried, and the solvent was removed. The residual oil was taken up in EtOAc (20 mL), and EEDQ (524  $\,$ mg, 1.1 equiv) followed by (R)-N-[(allyloxy)carbonyl]-2-(4hydroxyphenyl)glycine (516 mg, 1.1 equiv) was added. The resulting solution was left stirring at ambient temperature for 3 h after which it was washed with aqueous HCl  $(3 \times 4 \text{ mL}, 1 \text{ N})$ , saturated aqueous NaHCO<sub>3</sub> solution (3 mL), and water (3 mL). The organic phase was dried, and the solvent was removed. Chromatography of the residual oil afforded allyl (6S,7S)-7-[[(R)-N-[(allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycyl]amino]-3-[2-(phenylseleno)ethyl]-8-oxo-1-aza-4-oxabicyclo-[4.2.0]oct-2-ene-2-carboxylate (32) (1.10 g, 92% yield) as a foam: NMR (CDCl<sub>3</sub>)  $\delta$  3.02 (s, 4 H), 3.40 (t, 1 H, J = 10.5 Hz), 3.66 (ddd, 1 H, J = 10.5, 3.7, 3.8 Hz), 4.20 (dd, 1 H, J = 10.5, 3.7 Hz), 4.50-4.65 (m, 4 H), 5.08-5.37 (m, 6 H), 5.76-5.98 (m, 3 H), 6.15 (br s, 1 H), 6.75 (d, 2 H, J = 8.4 Hz), 6.85 (br s, 1 H), 7.10 (d, 2 Hz)H, J = 8.4 Hz), 7.18–7.48 (m, 5 H).

A solution of the selenide **32** (889 mg, 1.39 mmol) in a mixture of  $CH_2Cl_2$  (20 mL) and water (1 mL) was cooled in an ice bath. This was stirred vigorously, and pyridine (0.224 mL, 2 equiv) followed by hydrogen peroxide (0.358 mL, 30% aqueous solution, 3 equiv) was added. The bath was removed, and the reaction mixture was left stirring for 20 min. The organic phase was separated and washed with saturated aqueous NaHCO<sub>3</sub> solution (2 × 2 mL), water (3 × 2 mL), and brine (2 mL). After drying, the solvent was removed, and the residual oil was chromatographed to afford allyl (6S,7S)-7-[[(R)-N](allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycyl]amino]-8-oxo-3-vinyl-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (39) (539 mg, 81%) as a tan solid: NMR (CDCl<sub>3</sub> + D<sub>2</sub>O) 3.54 (m, 1 H), 3.84 (m, 1 H), 4.30

(m, 1 H), 4.50-4.71 (m, 5 H), 5.12-5.46 (m, 6 H), 5.75-6.04 (m, 3 H), 6.60-6.73 (m, 2 H), 7.05-7.29 (m, 3 H).

A mixture of the 3-vinyl compound **39** (1.71 g, 3.54 mmol), tetrakis(triphenylphosphine)palladium(0) (204 mg, 0.05 equiv) and triphenylphosphine (200 mg, 0.20 equiv) in a flask was purged with argon. Dry CH<sub>2</sub>Cl<sub>2</sub> (34 mL) followed by 2-ethylhexanoic acid (1.15 mL, 4 equiv) was added. This was left stirring for 2.25 h, during which time a precipitate formed. This was collected, washed with CH<sub>2</sub>Cl<sub>2</sub>, and dried. Reverse-phase chromatography followed by lyophilization of the appropriate fractions afforded the desired 3-vinyl-O-2-isocephem **45** (410 mg, 32%) as an off-white powder: UV (H<sub>2</sub>O) 298 ( $\epsilon$  14700), 230 nm ( $\epsilon$  12900); IR (KBr) 1760, 1695, 1550 cm<sup>-1</sup>; NMR (D<sub>2</sub>O)  $\delta$  3.51 (t, 1 H, J = 10.1 Hz), 3.95 (ddd, 1 H, J = 10.1, 3.8, 4.7 Hz), 4.32 (dd, 1 H, J = 3.8, 10.1 Hz), 5.09 (s, 1 H), 5.33 (dd, 1 H, J = 1.7, 17.3 Hz), 6.92 (dd, 1 H, J = 1.1, 17.3 Hz), 7.00 (d, 2 H, J = 8.7 Hz), 7.37 (d, 2 H, J = 8.7 Hz).

Allyl (6*S*,7*S*)-3-(Chloromethyl)-8-oxo-7-(tritylamino)-1aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (26). Similarly, by using chloroacetyl chloride, the azetidinone 10 was converted to allyl 2–[(3*S*,4*S*)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-4-chlorobutanoate (12) (95% yield):  $R_f$  0.58 (EtOAc/hexane, 1:4). Desilylation of 12 afforded allyl 2-[(3*S*,4*S*)-4-(hydroxymethyl)-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-4-chlorobutanoate (19) (77% yield):  $R_f$  0.35 (EtOAc/hexane, 1:1). Cyclization of 19 gave the 3chloromethyl derivative (26) (82% yield) as a white solid: mp 77-78 °C; IR (KBr) 3350, 1770, 1710, 1610 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  2.80 (d, 1 H, J = 5.4 Hz), 2.95–3.07 (m, 2 H), 3.56–3.68 (m, 1 H), 4.49 (q,  $\delta_A$  4.50,  $\delta_B$  4.47,  $J_{AB}$  = 11.6 Hz), 4.61–4.76 (m, 2 H), 4.81 (dd, 1 H, J = 5.4, 4.2 Hz), 5.21–5.43 (m, 2 H), 5.85–6.05 (m, 1 H), 7.20–7.39 (m, 15 H). Anal. (C<sub>30</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Cl) C, N; H: calcd, 5.29; found, 5.82.

(6S,7S)-7-[[(R)-2-(4-Hydroxyphenyl)glycyl]amino]-8oxo-3-(cis-1-propenyl)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2carboxylic Acid (46) and the 3-(trans-1-Propenyl) Isomer (47). The tritylamine 26 was converted to allyl (6S,7S)-7-[[(R)-N-[(allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycyl]amino]-3-(chloromethyl)-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2ene-2-carboxylate (33) (79% yield):  $R_f$  0.41 (two developments, EtOAc/hexane, (1:1).

A suspension of the chloride 33 (5.27 g, 10.4 mmol) and sodium iodide (2.35 g, 1.5 equiv) in acetone (50 mL) was left stirring at room temperature for 2 h. The solvent was removed, and the residual material was suspended in EtOAc. This was washed with water and dried, and the solvent was removed. A solution of this crude iodide (41) in EtOAc (25 mL) was cooled in an ice bath, and triphenylphosphine (2.72 g, 1.0 equiv) was added with stirring. After 18 h, ether (25 mL) was added, and the crude phosphonium salt (42) (7.92 g) was collected by filtration. A solution of the crude salt (2.0 g, 2.33 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was cooled in an ice bath, and then acetaldehyde (526  $\mu$ L, 4 equiv) followed by ethylene oxide<sup>14</sup> (466  $\mu$ L, 4 equiv) was added. The flask was sealed with "parafilm" and then removed from the ice bath. After 24 h at room temperature in the dark, the solvent was removed, and the residual oil was chromatographed to give a mixture of the cisand trans-propenyl isomer (43) (831 mg, 72%):  $R_f$  0.24 (Et-OAc/hexane, 1:1).

*N*-Methylaniline<sup>13</sup> (2.18 mL, 4 equiv) was added to a stirred solution of the olefin isomers **43** (2.50 g, 5.03 mmol), tetrakis-(triphenylphosphine)palladium(0) (190 mg, 0.03 equiv), and triphenylphosphine (190 mg, 0.12 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) under Ar. After 50 min, the precipitate was collected, washed with CH<sub>2</sub>Cl<sub>2</sub>, and dried under high vacuum. Chromatography followed by lyophilization of the appropriate fractions afforded the 3-*cis*-propenyl compound **46** as a light yellow powder (455 mg, 24%): UV (H<sub>2</sub>O) 228 ( $\epsilon$  17700), 300 nm ( $\epsilon$  17500); IR (KBr disk) 3250, 1755, 1600 cm<sup>-1</sup>; NMR (D<sub>2</sub>O)  $\delta$  1.78 (dd, 3 H, J = 1.7, 7.2

<sup>(13)</sup> Excess 2-ethylhexanoic acid is generally used as the acceptor for the allyl group: Jeffrey, P. D.; McCombie, S. W. J. Org. Chem. 1982, 47, 587. We have found that this deprotection is quicker when N-methylaniline is used as the acceptor.

<sup>(14)</sup> Buddrus, J. Chem. Ber. 1974, 107, 2050.

Hz), 3.52 (t, 1 H, J = 10 Hz), 3.91 (ddd, 1 H, J = 10, 3.9, 4.7 Hz), 4.22 (dd, 1 H, J = 3.9, 10), 4.90 (s, 1 H), 5.56 (d, 1 H, J = 4.7 Hz), 5.84 (dq, 1 H, J = 11.9, 7.2 Hz), 6.18 (dd, 1 H, J = 11.9, 1.7 Hz), 6.97 (d, 2 H, J = 8.6 Hz), 7.33 (d, 2 H, J = 8.6 Hz) followed by the *trans*-propenyl isomer 47 (245 mg, 13% yield): UV (H<sub>2</sub>O) 230 ( $\epsilon$  9900), 300 nm ( $\epsilon$  11 300); IR (KBr) 3200, 1755, 1690, 1540 cm<sup>-1</sup>; NMR (D<sub>2</sub>O) 1.79 (dd, 3 H, J = 6.8, 1.5 Hz), 3.48 (t, 1 H, J = 10.5 Hz), 3.91 (ddd, 1 H, J = 4.7, 3.7, 10.5 Hz), 4.28 (dd, 1 H, J = 3.7, 10.5 Hz), 5.12 (s, 1 H), 5.59 (d, 1 H, J = 4.7 Hz), 6.26 (dq, 1 H, J = 15.4, 6.8 Hz), 6.63 (dd, 1 H, J = 15.4, 1.5 Hz), 6.99 (d, 2 H, J = 8.7 Hz), 7.35 (d, 2 H, J = 8.7 Hz).

(6S,7S)-7-[[(R)-2-(4-Hydroxyphenyl)glycyl]amino]-8oxo-3-(1-cis-3,3,3-trifluoropropenyl)-1-aza-4-oxabicyclo-[4.2.0]oct-2-ene-2-carboxylic Acid (48) and the 3-(1-trans-3,3,3-Trifluoropropenyl) Isomer (49). To a solution of the crude phosphonium salt 42 (2.25 g, 3.08 mmol) and triethylamine (0.43 mL, 1.0 equiv) in dry  $CH_2Cl_2$  (40 mL) under argon and at -78 °C was added a solution of trifluoroacetaldehyde<sup>15</sup> (4.41 mL, 2.75 g/10 mL of dry  $CH_2Cl_2$ , ca. 4 equiv), which had been cooled to -78 °C. The reaction was then placed in an ice bath and left stirring for 15 min after which it was washed with brine (5 mL) and dried, and the solvent was removed. Chromatography afforded a mixture of the olefin isomers 44 (1.16 g, 70%) as a waxy solid:  $R_f$  0.69 (EtOAc/hexane, 3:2). Deprotection as above, followed by chromatography afforded the cis olefin isomer 48 (206 mg, 23% yield) as an off-white powder [UV ( $H_2O$ ) 230 ( $\epsilon$  11 800), 308 nm ( $\epsilon$  12 800); IR (KBr) 3200, 1770, 1690, 1570 cm<sup>-1</sup>; NMR  $(D_2O) \delta 3.36 (t, 1 H, J = 10.5 Hz), 3.97 (ddd, 1 H, J = 10.5, 4.0,$ 4.8 Hz), 4.23 (dd, 1 H, J = 10.5, 4.0 Hz), 5.05 (s, 1 H), 5.62 (d, 1 H, J = 4.8 Hz), 5.83 (dq, 1 H, J = 9.3, 12.6 Hz), 6.90 (d, 1 H, J = 12.6 Hz), 6.98 (d, 1 H, J = 8.9 Hz), 7.36 (d, 1 H, J = 8.9 Hz)] and the trans olefin isomer 49 (165 mg, 18% yield) as a white powder [UV (H<sub>2</sub>O) 228 (\$\epsilon 17000), 308 nm (\$\epsilon 21000); IR (KBr) 3200, 1770, 1690, 1580 cm<sup>-1</sup>; NMR ( $D_2O + CF_3CO_2H$ ) 3.62 (t, 1 H, J = 10.4 Hz), 4.01 (ddd, 1 H, J = 10.4, 3.9, 4.9 Hz), 4.45 (dd, 1 H, J = 10.4, 3.9 Hz), 5.13 (s, 1 H), 5.64 (d, 1 H, J = 4.9 Hz), 6.42 (dq, 1 H, J = 7.1, 15.6 Hz), 6.98 (d, 2 H, J = 8.7 Hz), 7.34(d, 2 H, J = 8.7 Hz), 7.56 (dq, 1 H, J = 2.1, 15.6 Hz).

Allyl (6S,7S)-8-Oxo-3-[3-(phenylseleno)propyl]-7-(tritylamino)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (27). A suspension of 4-(phenylseleno)butanoic acid<sup>16</sup> (21.7 g, 89.3 mmol) and oxalyl chloride (10.1 mL, 1.3 equiv) was left stirring for 16 h at ambient temperature. Distillation afforded 4-(phenylseleno)butyryl chloride (18.1 g, 78%) as a pale yellow liquid: bp 132 °C (0.15 mm); NMR (CDCl<sub>3</sub>)  $\delta$  2.04 (quin, 2 H, J = 7.1 Hz), 2.92 (t, 2 H, 7.1 Hz), 3.05 (t, 2 H, 7.1 Hz), 7.25-7.53 (m, 5 H).

With this acid chloride, the azetidinone 10 was converted to allyl 2- $[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-6-(phenylseleno)hexanoate (13) (76% yield): <math>R_f$  0.44 (EtOAc/hexane, 1:4).

Desilylation of 13 afforded allyl 2-[(3S,4S)-4-(hydroxymethyl)-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-6-(phenylseleno)hexanoate (20) (73% yield):  $R_f 0.1$  (EtOAc/hexane, 1:4).

Cyclization of **20** gave the O-2-isocephem (**27**) (91% yield): mp 62–63 °C; IR (KBr) 3320, 1770, 1710 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  1.87 (m, 2 H), 2.54 (m, 1 H), 2.84 (m, 6 H), 3.54 (m, 1 H), 4.56–4.78 (m, 3 H), 5.18–5.41 (m, 2 H), 5.84–6.03 (m, 1 H), 7.18–7.46 (m, 20 H). Anal. (C<sub>29</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>Se) C, H, N.

20 H). Anal.  $(C_{38}H_{36}N_2O_4Se) C$ , H, N. Allyl (6S,7S)-7-[[(R)-N-[(Allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycyl]amino]-3-<math>[3-(phenylseleno)-propyl]-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (34). By use of the aforementioned procedure, the tritylamine **27** was converted to the glycine derivative **34** (90% yield): mp 72–73 °C;  $R_f$  0.33 (EtOC/hexane, 1:1); IR (KBr) 3300, 1760, 1690 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  1.89 (m, 2 H), 2.72 (t, 2 H, J = 7.5 Hz), 2.85 (t, 2 H, J = 7.5 Hz), 3.42 (m, 1 H), 5.10 (m, 1 H), 4.22 (dd, 1 H, J = 10.9, 3.8 Hz), 4.49–4.68 (m, 4 H), 5.06–5.38 (m, 5 H), 5.75–5.98 (m, 3 H), 6.31 (br s, 1 H), 6.64 (d, 2 H, J = 11.1 Hz), 6.97 (m, 1 H), 7.09 (d, 2 H, J = 11.1 Hz), 7.19–7.47 (m, 4 H). Anal. (C<sub>31</sub>H<sub>38</sub>N<sub>3</sub>O<sub>8</sub>Se) C, N; H: calcd, 5.81; found, 5.28.

(6S,7S)-7-[[(R)-(4-Hydroxyphenyl)glycyl]amino]-8-oxo-3-(2-propenyl)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (50). A solution of the selenide 34 (1.50 g, 2.29 mmol) in a mixture of CHCl<sub>3</sub> (30 mL) and 1,1,1-trichloroethane (120 mL) was cooled to -15 °C, and *m*-chloroperbenzoic acid (496 mg, 80%, 1 equiv) was added with stirring. After 0.5 h, pyridine (0.74 mL, 4 equiv) followed by dihydropyran (8.36 mL, 40 equiv) was added, and the reaction was placed in an oil bath (130 °C). After being heated at reflux for 1.5 h, the reaction mixture was allowed to cool to room temperature. It was diluted with  $CH_2Cl_2$  (100 mL) and washed with an aqueous HCl solution  $(3 \times 10 \text{ mL}, 1\text{N})$ , a saturated aqueous NaHCO<sub>3</sub> solution ( $3 \times 15$  mL), and brine (2  $\times$  5 mL). Drying followed by removal of the solvents left an oil, which was chromatographed to give ally (6S,7S)-7-[[(R)-N-[(allyloxy)carbonyl]-2-(4-hydroxyphenyl)glycyl]amino]-3-(2propenyl-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (40) (998 mg, 88% yield) as a foam:  $R_f 0.33$  (EtOAc/hexane, 1:1); NMR (CDCl<sub>3</sub>)  $\delta$  3.37 (d, 2 H, J = 6.1 Hz), 3.56 (m, 1 H), 3.72 (m, 1 H), 4.23 (m, 1 H), 4.47 (m, 2 H), 4.65 (m, 2 H), 5.02-5.47 (m, 8 H), 5.65–6.00 (m, 3 H), 6.55 (d, 2 H, J = 7.2 Hz), 7.04 (d, 2 H, J = 7.2 Hz).

Palladium-catalyzed deprotection of the 3-propenyl derivative **40** gave the final product **50** (64% yield) as an off-white powder: UV (H<sub>2</sub>O) 270 nm ( $\epsilon$  10000); IR (KBr) 1750, 1700, 1630 cm<sup>-1</sup>; NMR (D<sub>2</sub>O)  $\delta$  3.36 (m, 2 H), 3.48 (t, 1 H, J = 10.2 Hz), 3.89 (ddd, 1 H, J = 10.2, 3.9, 4.7 Hz), 4.21 (dd, 1 H, J = 10.2, 3.9 Hz), 5.09 (s, 1 H), 5.13 (m, 1 H), 5.57 (d, 1 H, J = 4.7 Hz), 5.78–5.92 (m, 1 H), 6.99 (d, 2 H, J = 8.7 Hz), 7.36 (d, 2 H, J = 8.7 Hz).

Allyl (6S,7S)-8-Oxo-7-(tritylamino)-1-aza-4-oxabicyclo-[4.2.0]oct-2-ene-2-carboxylate (28). With use of acetic formic anhydride,<sup>17</sup> the azetidinone 10 was converted to allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxopropanoate (14) (86% yield):  $R_f$  0.63 (EtOAc/hexane, 1:4).

Desilylation of 14 gave allyl 2-[(3S,4S)-4-(hydroxymethyl)-2oxo-3-(tritylamino)-1-azetidinyl]-3-oxopropanoate (21) (89% yield):  $R_f$  0.25 (EtOAc/hexane, 19:1).

Cyclization of 21 gave the O-2-isocephem 28 (39% yield):  $R_f$  0.55 (EtOAc/hexane, 1:4); mp 126–129 °C;  $[\alpha]^{21}_D$ –12° (c 1.0, CHCl<sub>3</sub>); IR (KBr disk) 3460, 1760, 1715, 1680, 1650 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  2.95 (m, 2 H), 3.54 (m, 1 H), 4.66 (m, 2 H), 4.81 (d, 1 H, J = 4.3 Hz), 5.17–6.00 (m, 3 H), 7.20–7.38 (m, 16 H). Anal. (C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>·H<sub>2</sub>O) C, H, N.

Allyl (6*S*,7*S*)-[[(*R*)-*N*-[(Allyloxy)carbonyl]-2-(4hydroxyphenyl)glycyl]amino]-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (35). The tritylamine 28 was converted to the glycyl derivative 35 (63% yield):  $R_f$  0.44 (EtOAc: hexane, 3:1); mp 107–109 °C; [ $\alpha$ ]<sup>21</sup><sub>D</sub> 63° (c 1.0, CHCl<sub>3</sub>); IR (KBr disk) 3320, 1770, 1700, 1620 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  3.53–4.22 (m, 3 H), 4.50–4.65 (m, 4 H), 5.10–5.48 (m, 4 H), 5.76–5.96 (m, 2 H), 6.58–7.10 (m, 5 H). Anal. (C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>8</sub>) C, H; N: calcd, 9.19; found, 8.52.

(6S,7S)-7-[[(R)-2-(4-Hydroxyphenyl)glycyl]amino]-1aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (51). Deprotection of 35 afforded the product 51 (60% yield): IR (KBr) 1765, 1690, 1620 cm<sup>-1</sup>; UV (H<sub>2</sub>O) 264 ( $\epsilon$  6900), 232 nm ( $\epsilon$  9000); NMR (D<sub>2</sub>O)  $\delta$  3.42 (t, 1 H, J = 10.3 Hz), 3.89 (ddd, 1 H, J = 10.3, 3.9 Hz, 4.8 Hz), 4.23 (dd, 1 H, J = 10.3, 3.9 Hz), 5.11 (s, 1 H), 5.62 (d, 1 H, J = 4.8 Hz), 6.98 (d, 2 H, J = 8.7 Hz), 7.07 (s, 1 H), 7.36 (d, 2 H, J = 8.7 Hz).

Allyl (6S,7S)-3-Methyl-8-oxo-7-(tritylamino)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (29). With use of acetyl chloride, the azetidinone 10 was converted to allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxobutanoate (15) (87% yield):  $R_f$  0.49 (Et-OAc/hexane, 1:4).

<sup>(15)</sup> Trifluoroacetaldehyde was generated from the commercially available ethyl hemiacetal. An equal volume of concentrated H<sub>2</sub>SO<sub>4</sub> was added to the hemiacetal under an Ar atmosphere. The resulting mixture was heated to 100 °C, and slightly impure aldehyde was collected in a receiver, which had been cooled to -78 °C. This was redistilled to give pure material (<sup>1</sup>H NMR).

<sup>(16)</sup> The acid was prepared according to a literature procedure: Scarborough, R. M.; Smith, A. B. *Tetrahedron Lett.* 1977, 4361. It was obtained as a yellow solid: bp 170-172 °C (0.25 mm); NMR (CDCl<sub>3</sub>) δ 1.99 (quin, 2 H, J = 7.1 Hz), 2.50 (t, 2 H, J = 7.1 Hz), 2.94 (t, 2 H, J = 7.1 Hz), 7.21-7.51 (m, 5 H).

<sup>(17)</sup> Krimen, L. I. Org. Synth. 1970, 50, 1.

Desilylation of 15 gave allyl 2- $[(3S,4S)-4-(hydroxymethyl)-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxobutanoate (22) (95% yield): <math>R_f 0.23$  (EtOAc/hexane, 1:4).

Cyclization of **22** gave the 3-methyl-O-2-isocephem **29** (95% yield):  $R_f 0.58$  (EtOAc/hexane, 1:4); mp 88–89 °C;  $[\alpha]_D +90^\circ$  (c 0.5, CHCl<sub>3</sub>); IR (KBr) 3340, 1760, 1710, 1610 cm<sup>-1</sup>; NMR (C<sub>6</sub>H<sub>6</sub> + D<sub>2</sub>O)  $\delta$  2.23 (s, 3 H), 2.36 (dt, 1 H, J = 9.8, 4.1 Hz), 2.53 (dd, 1 H, J = 9.8, 4.1 Hz), 2.53 (dd, 1 H, J = 9.8 Hz), 4.29 (d, 1 H, J = 4.1 Hz), 4.36–6.02 (m, 5 H), 6.89–7.29 (m, 15 H, arom). Anal. (C<sub>30</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

(6S,7S)-7-[[(R)-2-(4-Hydroxyphenyl)glycyl]amino]-3methyl-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (52). The 7 $\beta$ -tritylamine 29 was converted to the protected glycyl derivative 36 (58% yield):  $R_f$  0.51 (EtOAc/hexane, 3:2); mp 141–143 °C; [ $\alpha$ ]<sup>22</sup><sub>D</sub> +72° (c 1.0, CHCl<sub>3</sub>); IR (KBr) 3320, 1720, 1680, 1620 cm<sup>-1</sup>.

Deprotection gave the product **52** (44% yield) as a white powder: UV (H<sub>2</sub>O) 266 ( $\epsilon$  9200), 232 nm ( $\epsilon$  10500); IR (KBr) 3200, 1760, 1690, 1600 cm<sup>-1</sup>; NMR (D<sub>2</sub>O)  $\delta$  2.04 (s, 3 H), 3.44 (t, 1 H, J = 10.3 Hz), 3.86 (ddd, 1 H, J = 10.3, 4.6, 3.8 Hz), 4.19 (dd, 1 H, J = 10.3, 3.8 Hz), 5.11 (s, 1 H), 5.54 (d, 1 H, J = 4.6 Hz), 6.98 (d, 2 H, J = 8.6 Hz), 7.34 (d, 2 H, J = 8.6 Hz).

Allyl (6S,7S)-3-Propyl-8-oxo-7-(tritylamino)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (30). With use of butyryl chloride, the azetidinone 10 was converted to allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)- $1-azetidinyl]-3-oxohexanoate (16) (90% yield): <math>R_f$  0.53 (Et-OAc/hexane, 1:4).

Desilylation of 16 gave allyl 2-[(3S,4S)-4-(hydroxymethyl)-2oxo-3-(tritylamino)-1-azetidinyl]-3-oxohexanoate (23) (95% yield):  $R_f$  0.26 (EtOAc/hexane, 1:4).

Cyclization of 23 gave the 3-propyl-O-2-isocephem 30 (81% yield):  $R_f 0.54$  (EtOAc/hexane, 1:4); mp 154–156 °C;  $[\alpha]_D + 104^\circ$  (c 1.0, CHCl<sub>3</sub>); IR (KBr) 3430, 1770, 1705, 1600 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  0.86 (t, 3 H, J = 7.4 Hz), 1.50 (m, 2 H), 2.45 (m, 2 H), 2.94 (m, 2 H), 3.56 (m, 1 H), 4.57–6.01 (m, 6 H), 7.21–7.38 (m, 15 H). Anal. ( $C_{32}H_{32}N_2O_4$ ) C, H, N.

(6*S*,7*S*)-7-[[( $\overline{R}$ )-2-(4-Hydroxyphenyl)glycyl]amino]-3propyl-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (53). The 7 $\beta$ -tritylamine 30 was converted to the glycyl derivative 37 (78% yield): [ $\alpha$ ]<sub>D</sub>+61° (c 1.0, CHCl<sub>3</sub>); mp 92–95 °C; IR (KBr) 3320, 1760, 1720, 1680, 1620 cm<sup>-1</sup>.

Deprotection of 37 gave the product 53 (33% yield): UV (H<sub>2</sub>O) 203 ( $\epsilon$  11 500), 266 nm ( $\epsilon$  10 300); IR (KBr) 3200, 1760, 1690, 1600 cm<sup>1</sup>; NMR (D<sub>2</sub>O)  $\delta$  0.84 (t, 3 H, J = 7.4 Hz), 1.48 (m, 2 H), 2.32 (dt, 1 H, J = 13.9, 7.0 Hz), 2.65 (dt, 1 H, J = 13.9, 7.0 Hz), 3.45 (t, 1 H, J = 10.2 Hz), 3.87 (ddd, 1 H, J = 10.2, 3.8, 4.6 Hz), 4.20 (dd, 1 H, J = 10.2, 3.8 Hz), 5.12 (s, 1 H), 5.56 (d, 1 H, J = 4.6 Hz), 6.99 (d, 2 H, J = 8.7 Hz), 7.36 (d, 2 H, J = 8.7 Hz).

Allyl (6S,7S)-7-[[(R)-N-[(Allyloxy)carbonyl]-2-(4hydroxyphenyl)glycyl]amino]-3-cyclopropyl-8-oxo-1-aza-4oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (38). With use of cyclopropanecarboxylic acid chloride, the azetidinone 10 was converted to allyl 2-[(3S,4S)-4-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-3-cyclopropylpropanoate (17) (95% yield):  $R_f$  0.55 (EtOAc/hexane, 1:4). Desilylation of 17 gave allyl 2-[(2S,4S)-4-(hydroxymethyl)-2-

oxo-3-(tritylamino)-1-azetidinyl]-3-oxo-3-cyclopropylpropanoate (24) (95% yield):  $R_f$  0.24 (EtOAc/hexane 1:4).

Cyclization of 24 gave allyl (6S,7S)-3-cyclopropyl-8-oxo-7-(tritylamino)-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (31) (95% yield) as a white solid:  $R_f$  0.31 (EtOAc/hexane, 3:17); mp 141–143 °C) [ $\alpha$ ]<sup>21</sup><sub>D</sub> 59° (c 1.0, CHCl<sub>3</sub>); IR (KBr) 3340, 1750, 1690, 1590 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  0.63–0.92 (m, 4 H), 2.77–2.91 (m, 4 H), 3.53 (m, 1 H), 4.60–4.83 (m, 3 H), 5.19–5.43 (m, 2 H), 5.87–6.07 (m, 1 H), 7.20–7.37 (m, 15 H).

The tritylamine **31** was converted to the glycine derivative **38** (78% yield):  $[\alpha]^{21}_{D}$  9.8 (c 1.0, CHCl<sub>3</sub>); mp 110–115 °C; IR (KBr) 3100, 1770, 1690, 1600 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub> + D<sub>2</sub>O)  $\delta$  0.71–0.99 (m, 4 H), 2.81 (m, 1 H), 3.43 (m, 1 H), 3.71 (m, 1 H), 4.11 (m, 1 H), 4.41–4.77 (m, 4 H), 5.14–5.40 (m, 6 H), 5.75–6.07 (m, 2 H), 6.60 (m, 2 H), 7.06 (m, 2 H). Anal. (C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>) C, H, N.

(6S,7S)-3-Cyclopropyl-7-[[ $(\bar{R})$ -2-(4-hydroxyphenyl)glycyl]amino]-8-oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2carboxylic Acid (54). Deprotection of 38 gave the product 54 (37% yield) as a white powder: IR (KBr) 3200, 1740, 1680, 1610 cm<sup>-1</sup>; UV (H<sub>2</sub>O) 274 ( $\epsilon$  10 000), 232 nm ( $\epsilon$  11 000); NMR (D<sub>2</sub>O + CF<sub>3</sub>CO<sub>2</sub>H)  $\delta$  0.75-1.04 (m, 4 H), 2.65 (m, 1 H), 3.48 (t, 1 H, J = 10.3 Hz), 3.88 (ddd, 1 H, J = 10.3, 4.6, 3.9 Hz), 4.26 (dd, 1 H, J = 10.3, 3.9 Hz), 5.11 (s, 1 H), 5.56 (d, 1 H, J = 4.6 Hz), 6.97 (d, 2 H, J = 8.6 Hz), 7.32 (d, 2 H, J = 8.6 Hz).

Acknowledgment. We are grateful to P. Lapointe and S. Plamondon for their technical assistance.

Registry No. 5, 86299-41-4; 6, 86334-63-6; 7 (disilylated), 113627-36-4; 8, 113599-60-3; 9 (detritylated), 113599-59-0; 10, 113599-63-6; 12, 113599-64-7; 13, 113599-65-8; 14, 113599-66-9; 15, 113599-67-0; 16, 113599-68-1; 17, 113599-69-2; 18, 113599-70-5; 19, 113599-71-6; 20, 113599-72-7; 21, 113599-73-8; 22, 113599-74-9; 23, 113599-75-0; 24, 113599-76-1; 25, 113599-77-2; 26, 113599-78-3; 27, 113599-79-4; 28, 113599-80-7; 29, 113599-81-8; 30, 113627-35-3; 31, 113599-82-9; 32, 113599-83-0; 33, 113599-84-1; 34, 113599-85-2; 35, 113599-86-3; 36, 113599-87-4; 37, 113599-88-5; 38, 113599-89-6;**39**, 113599-90-9; **40**, 113599-91-0; **41**, 113599-92-1; **42**, 113599-93-2; trans-43, 113599-94-3; cis-43, 113666-83-4; trans-44, 113599-95-4; *cis*-44, 113666-84-5; 45, 113599-96-5; 46, 113599-97-6; 47, 113666-85-6; 48, 113599-98-7; 49, 113666-86-7; 50, 113599-99-8; **51**, 113600-00-3; **52**, 113600-01-4; **53**, 113600-02-5; **54**, 113600-03-6; allyl 2-bromoacetate, 40630-84-0; 3-(phenylseleno)propionic acid, 16599-78-3; 3-(phenylseleno)propionyl chloride, 113600-04-7; (R)-2-(4-hydroxyphenyl)glycine, 22818-40-2; (R)-[N-(allyloxycarbonyl)]-2-(4-hydroxyphenyl)glycine, 84792-41-6; allyl (6S, 7S)-7-amino-3-[2-(phenylseleno)ethyl]-8-oxo-1-aza-4-oxabicyclo-[4.2.3]oct-2-ene-2-carboxylate (p-toluenesulfonic acid salt), 113666-87-8; allyl (6S, 7S)-7-amino-3-[2-(phenylseleno)ethyl]-8oxo-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate, 113600-05-8; chloroacetyl chloride, 79-04-9; acetaldehyde, 75-07-0; trifluoroacetaldehyde, 75-90-1; 4-(phenylseleno)butanoic acid, 23768-06-1; 4-(phenylseleno)butyryl chloride, 104680-44-6; cyclopropanecarboxylic acid chloride, 4023-34-1.