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MOLECULAR MODELING OF γ-LACTAM ANALOGUES OF ß-LACTAM ANTIBACTERIAL AGENTS: SYNTHESIS AND BIOLOGICAL EVALUATION OF SELECTED PENEM AND CARBAPENEM ANALOGUES

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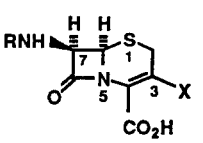
ABSTRACT - Computational chemistry made possible the prediction of the three-dimensional structures of γ-lactam analogues of penems and carbapenems before the analogues were made. Molecular superpositioning showed that these novel structures with a 7β-acylamino side-chain present the pharmacophoric groups in close spatial similarity to the groups in biologically active cephalosporin and penicillin antibiotics. This suggests that 8-oxo-7-acylamino-1-azabicyclo[3.3.0]-oct-2-ene-2-carboxylates and the 4-thia-analogues can be accommodated in the same active sites of essential bacterial penicillin-binding proteins where cephalosporins and penicillins are recognized. The syntheses of these compounds are reported. The γ-lactams exhibit low, but detectable levels of antibacterial activity and suggest promise that substantial activity can be achieved with other γ-lactams.

INTRODUCTION

The end point of a microbiological assay for minimum inhibitory concentration of an antibiotic represents the accumulated effects of many physical and biochemical events. In order for a ß-lactam antibiotic, such as a cephalosporin **1** or penicillin **2**, to prevent bacterial growth, it must be able to reach and inhibit certain target enzymes. These enzymes are the high molecular weight transpeptidases in the periplasm of a bacterial envelope.[1] The normal function of the enzymes is to form polypeptide crosslinks between glycan strands of peptidoglycan, thereby giving the cell wall its structural integrity. To reach the targets the antibiotic molecules must diffuse from the medium through the thick peptidoglycan of Gram-positive bacteria or through the outer lipid bilayer and peptidoglycan layer of Gram-negatives.[2] The rate of penetration must be sufficient to allow specific as well as nonspecific sites to be occupied and must exceed the rate at which *in situ* ß-lactamases can detoxify the inhibitors.[3-6] The antibiotic molecules that do reach the active sites must have appropriate electronic and steric properties to be



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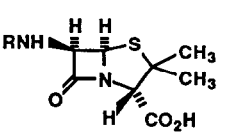

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recognized as a substrate or transition state analogue of the natural X-D-alanyl-D-alanine substrate of the enzymes.[7-9] Furthermore the electronic structure must be such that the ß-lactam ring is reactive enough that when the antibiotic molecule collides with the active site serine,[10-14] a covalent ester linkage will form. The half-life of

the acylated transpeptidases needs to be long enough that turnover of the enzyme is adversely affected, and normal bacterial autolysins can operate on the peptidoglycan without a balancing biosynthesis of new crosslinked peptidoglycan.[9,15] The net result is an aberrant cell wall which is unable to sustain the organism.

Despite the complexity of the mode of action of ß-lactam antibiotics, pharmaceutical research has made great progress in providing therapeutic agents with improved potential for treating bacterial infections. Most of the ß-lactam agents used in medical practice today can trace their essential structures to naturally occurring compounds.

Molecular modeling experiments begun in 1981 set out to test the conventional wisdom prevalent then that the ß-lactam ring was essential for antibacterial activity.[16,17] The goal was to discover new classes of compounds which would be recognized by the same active site as the ß-lactam antibiotics. Since the ß-lactam antibiotics enjoy relatively low mammalian toxicity and high potency, these are desirable compounds to emulate in the search for compounds with better pharmacokinetic properties or broader activity against resistant organisms. Among the structures considered were novel γ-lactams.

Various attempts dating back to the 1940s to enlarge the ß-lactam ring to γ-lactams had generally failed to produce compounds with interesting activity.[18-22] Hence it was not without some reservation that the γ-lactams were considered. However, recently there has been a resurgence of interest in these structures.[23-46] The work from Lilly was stimulated in part by the original computational chemistry studies. This paper describes some recent computational chemistry experiments as well as synthetic work on γ-lactam compounds.

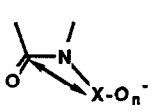
RESULTS AND DISCUSSION

Computational Chemistry. Two aspects of molecular designs which are known to be requisite for antibacterial activity can be addressed computationally. The first is the chemical reactivity of the lactam functionality: it must be reactive enough to acylate the active site serine, but not so reactive that the molecule degrades before reaching its intended target. Relative reactivities of similar molecules can be computed quantum mechanically. For example, computational experiments using the CNDO/2 molecular orbital method were used to correlate predicted chemical reactivity and *in vitro* biological activity of cephalosporins.[16,47-50]

The CNDO/2 method, although good for its intended purposes, does not predict equilibrium bond lengths and angles well. Hence instead of using molecular geometries from energy minimization, one generally uses bond lengths and angles fixed at standard values in a CNDO/2 calculation.[7,16,51] A newer molecular orbital method, such as MINDO/3,[52,53] is more appropriate for examining structures for which there is less experimental geometrical information, such as novel γ-lactams. MINDO/3 is actually superior to still newer semiempirical molecular orbital methods, such as MNDO[54] and AM1,[55] in regard to predicted equilibrium geometries of the ß-lactam ring.[56] However, MINDO/3 seriously overestimates the stability of the ß-lactam ring[56] (and other four-membered rings[54]); absolute values of heats of formation and strain energies are not well predicted. Analogous to the Transition State Energy calculations,[47-50] one can set up models in the computer using MINDO/3 to determine the electrophilicity of the lactam carbonyl carbon toward simple nucleophiles, such as H_2O or OH^-. Such computational models are useful only for ranking similar structures on a relative basis and are inappropriate for predicting absolute values of rate constants of base-catalyzed hydrolysis.

Practically speaking, the chemical reactivity should be in the same range as exhibited by biologically active cephalosporins, penicillins, and other ß-lactam antibacterial agents. In terms of hydrolysis rates at pH 10 and 35 °C, the desired reactivity range is roughly 0.04 - 6.0 hr^{-1}.[7,57-60] Although it is safe to assume that compounds with higher rates of hydrolysis will more readily acylate the active site serine, a caveat should be kept in mind. Compounds that fit into the active site poorly sterically and/or mechanistically may have to be more reactive than those that fit well. This is because compounds that lack optimum geometric and electronic requirements would spend less time reversibly bound, so that when they are presented with an opportunity to react with the serine they must be able to do so readily. This leads us to a second requirement for antibacterial activity.

Besides having the appropriate reactivity, the other key molecular property associated with activity is molecular shape.[7,61] This too can be assessed computationally. When a molecule reaches the receptor site in the transpeptidases it must present a three-dimensional pharmacophore 3 appropriate for recognition as a potential substrate or transition state analogue. Binding to the enzymes requires a separation of about 3-3.6 Å between the lactam carbonyl carbon and the center of an acidic group, such as the carboxylate at the 4-position of cephalosporins.[7,59] In the case of monobactams 4, the distance between the lactam carbonyl carbon and the sulfur of the sulfonate is about 2.8 Å,[62] but since S-O bond lengths are about 0.2 Å longer[63] than carboxylate C-O bonds, the oxygens of the acidic groups can attain similar spatial locations. More important than the location of the atomic nuclei, of course, is the spatial distribution of electron density around the oxygens.



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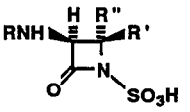

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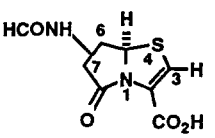
There are a number of approaches for comparing the three-dimensional structural similarity of two or more molecules. When thinking in terms of the interactions that molecules will make with a receptor site, it is best to examine the complementarity of the charge distributions.[64] A complication with this is that the charge distribution is dependent on the approximations used in arriving at the wave function. Also it is time consuming to determine a good wave function, and this can be a large undertaking when considering many conformers of a flexible molecule. Another approach is to consider atoms as spheres of van der Waals radii and to either try to maximize the overlap of selected pairs of atoms in the two molecules[65] or to minimize the united volume of the two molecules.[66] Still another approach to molecular comparison, and one that is used most often, is to do a least squares minimization of the distances between nuclei of selected pairs of atoms.[67,68] The latter method as incorporated in SYBYL[68,69] is the one used in the calculations reported here.



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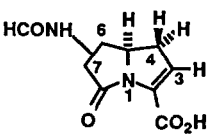

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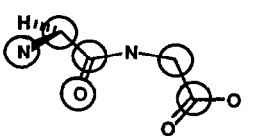

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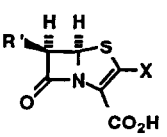

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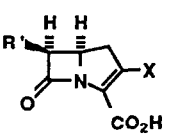

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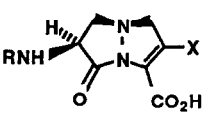

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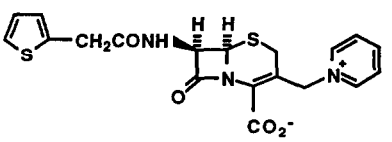

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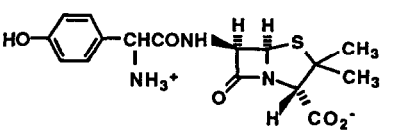

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The structures modeled are the γ-lactams of the type **5** and **6**. These are analogues of penem **7** and Δ^2-carbapenem **8**. The atomic coordinates of the γ-lactams were determined by MINDO/3 calculations using default parameters in the MOPAC program.[70] Four isomers were evaluated: formamido, which was used in all the calculations as a model acylamino side-chain in order to keep computational times reasonable, was put on the carbons α (C_7) or ß (C_6) to the lactam carbonyl and with *R* or *S* configuration. Crystalline state structures of a cephalosporin and a penicillin (in a 3α-COOH-equatorial conformation) were used as the frame of reference for fitting the MINDO/3 determined γ-lactam geometries. Evidence indicates that the COOH-equatorial conformer of penicillins is the main one responsible for biological activity.[7,58,59] The six atoms used in the least squares distance fitting are given in **9**. Atomic coordinates for cephaloridine **10**[71,72] and amoxycillin **11**[73] were retrieved from the Cambridge Crystallographic Database.[74]

The results of fitting the four isomers of **5** to the cephalosporin are typical of the overlap observed (Figures 1-4). The better overlap with the 7-(*S*) isomers in both **5** and **6** is evident in the root mean square distances (Table I) as well as in the molecular graphics. Figure 5 is a stereoview of the 7-(*S*) isomers of **5** and **6** overlapping **10** and **11**. It may be concluded from these computations that, in terms of mimicking the three-dimensional structure of known ß-lactam antibiotics, it is better for the acylamino side-chain of the γ-lactam to be on the carbon α to the lactam carbonyl. When the side-chain is on the α carbon, the chance of fitting the target receptor is greater with the *S* (ß face) stereoisomer. This prediction is consistent with the recent report that benzylhomopenicillin with the acylamino side-chain in the 6-(*R*) position does not show appreciable antibacterial activity.[75]

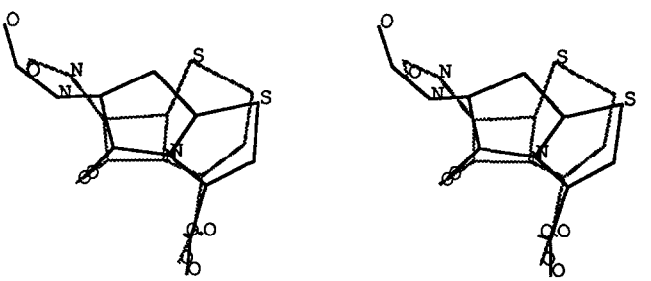


Figure 1. Stereoview of the 7-(*R*) isomer of **5** (solid) fit to cephaloridine (gray). The acylamino side-chain is on C-7. In this and subsequent figures, hydrogens and most side-chain atoms have been stripped away to make the nuclei easier to see.

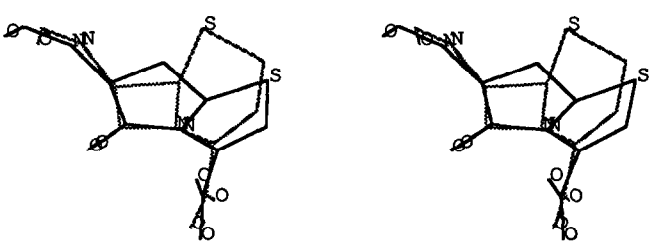


Figure 2. Stereoview of the 7-(*S*) isomer of **5** fit to cephaloridine.

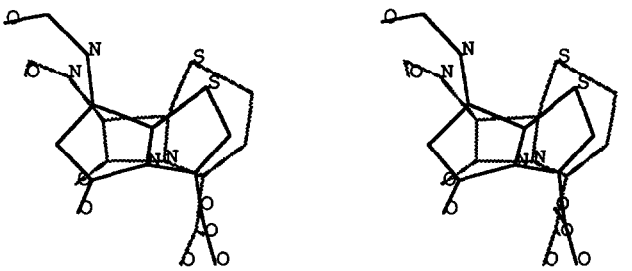


Figure 3. Stereoview of the 6-(*R*) isomer of **5** fit to cephaloridine. The acylamino side-chain of **5** is on C-6.

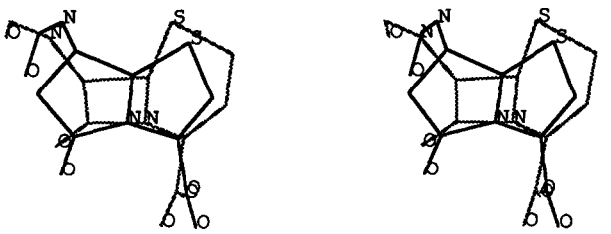


Figure 4. Stereoview of the 6-(*S*) isomer of **5** fit to cephaloridine.

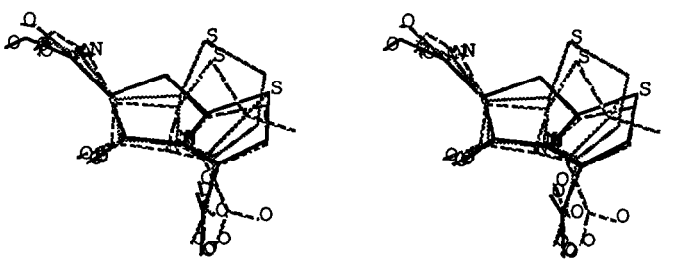


Figure 5. Stereoview of the 7-(*S*) isomers of **5** and **6** fit to cephaloridine and amoxycillin.

Table I. Root Mean Square Distances (Å) from Least Squares Distance Fitting of MINDO/3 Optimized Geometries of γ-Lactams to Cephaloridine and Amoxycillin.[a]

STRUCTURE	CEPHALORIDINE	AMOXYCILLIN
7-(*R*)-**5**	0.58	0.71
7-(*S*)-**5**	0.22	0.48
6-(*R*)-**5**	0.61	0.63
6-(*S*)-**5**	0.77	0.78
7-(*R*)-**6**	0.57	0.71
7-(*S*)-**6**	0.25	0.49
6-(*R*)-**6**	0.62	0.64
6-(*S*)-**6**	0.77	0.79

[a] By the same fitting procedure the cephalosporin and penicillin have an rms distance of 0.33 Å with respect to each other.

Qualitative Considerations. In the next section syntheses of several γ-lactams of the type **5** and **6** are described. No calculations were done in the original (1981) studies on these structures, but calculations on a closely related analogue suggested that these had a less than optimal prospect of high activity because of low chemical reactivity. The compounds that were made exhibited low but discernible activity and demonstrated promise in the concept pursuing certain γ-lactams. Much more highly active pyrazolidinone γ-lactams **12** with the requisite shape and chemical reactivities have been reported.[16,33-39,43-46] Work is in progress on still other γ-lactam structures that appeared promising in the original computational experiments.

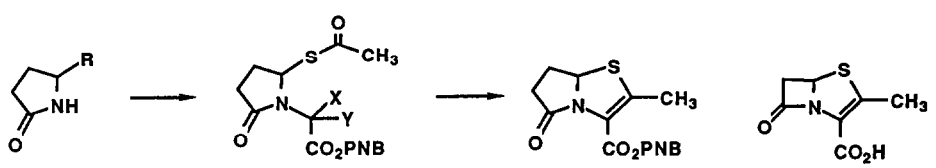
Structures with the nuclei of **5** and **6** can be selected for synthesis on the basis of the following organic chemical rationale. In the classical bicyclic ß-lactam antibiotics, the fused rings enforce a nonplanarity on the ß-lactam nitrogen which decreases amide resonance and induces the necessary chemical reactivity.[7] A γ-lactam ring is less strained than a ß-lactam, so other ways of promoting reactivity must be devised.

Cephalosporins and penicillins require an acylamino side-chain to exhibit significant antibacterial activity.[7] In contrast, certain penems and carbapenems are known to be highly active antibacterial agents without the presence of such a side-chain.[76,77] Both of the latter nuclei have a chemical reactivity that verges on the upper limit for good activity. Substitution of an acylamino side-chain on either nuclei pushes them beyond the limit and results in compounds with stability problems and poorer activity.[78,79] Hence it can be reasoned that the corresponding γ-lactam analogues of penem and carbapenem structures, while having less strained nuclei compared to a ß-lactam, would have their chemical reactivity enhanced to some unknown degree by the presence of an acylamino side-chain.

Enamine resonance promotes the reactivity of Δ^3-cephalosporins. Likewise the 3-position substituent of a cephalosporin contributes to the activation of the ß-lactam by electron withdrawal.[58] Thus the γ-lactams selected for synthesis should have unsaturation appropriate for enamine resonance and a strongly electron withdrawing group conjugatively linked to the lactam functionality. Penems and carbapenems, of course, have chemical structures consistent with these criteria.

Synthetic Chemistry. The racemic 7-unsubstituted γ-lactam penem derivative **19** was prepared[29] (Scheme I) for direct comparison with its known ß-lactam analogue **20**, which has been shown to be a potent antibiotic substance.[78] Solvolysis of 5-methoxy-2-pyrrolidinone (**13**)[80] in neat thiolacetic acid proceeded smoothly to afford the thioacetate **14** in 61% yield. The thiazoline ring was elaborated by following the conventional procedure developed by Woodward et al.[81] Condensation of **14** with p-nitrobenzyl glyoxylate in toluene afforded the hemiaminals **15** as a mixture of alcohol isomers. Treatment of this mixture with thionyl chloride and 2,6-lutidine in tetrahydrofuran gave the corresponding chlorides **16** which were converted to the phosphorane **17** with triphenylphosphine and 2,6-lutidine in dioxane. The phosphorane **17** was cyclized in toluene at 80 °C for 17 h to afford the bicyclic ester **18** in 41% overall yield from **14**. The p-nitrobenzyl ester was conveniently removed by hydrogenolysis over 5% palladium on carbon affording an 82% yield of the acid **19**.

SCHEME I



13: R = OCH_3
14: R = $SCOCH_3$

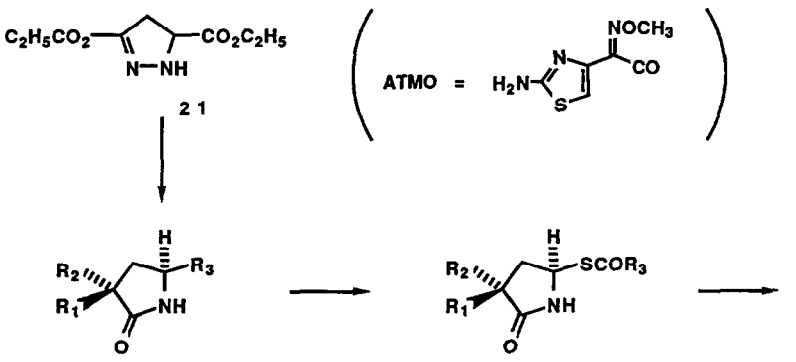
15: X = OH, Y = H
16: X = Cl, Y = H
17: X,Y = $P(C_6H_5)_3$

18: R = PNB
19: R = H

20

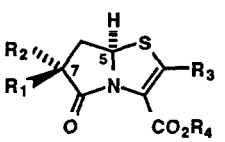
Racemic penem analogues containing an acylamino side-chain at position 7 were prepared by two different strategies. 7-Acylamino derivatives with varying substituents at position 3 were prepared (Scheme II) in an analogous fashion to the 7-unsubstituted system **19**. High pressure reductive cleavage[82] of pyrazoline **21**, prepared in 82% yield from ethyl diazoacetate and ethyl acrylate,[83] with Raney nickel at 60-115 °C gave an intermediate diamino diester which spontaneously cyclized under the reaction conditions to a mixture of aminopyrrolidinones **22**. The amine function was protected as its t-butyl carbamate **23** in 80% yield with di-t-butyl dicarbonate in methylene chloride. The esters **23** were saponified with potassium hydroxide in methanol to afford a 63% yield of a mixture of acids **24**. The acids **24** were converted to a mixture of acetates **25** with lead tetraacetate in tetrahyrofuran at 67 °C. These acetates were allowed to react with a variety of thioacids to afford the corresponding thioesters **26-28**. The

SCHEME II



22a: $R_1 = NH_2$, $R_2 = H$, $R_3 = CO_2Et$
22b: $R_1 = H$, $R_2 = NH_2$, $R_3 = CO_2Et$
23a: R_1 = BOCNH, $R_2 = H$, $R_3 = CO_2Et$
23b: $R_1 = H$, R_2 = BOCNH, $R_3 = CO_2Et$
24a: R_1 = BOCNH, $R_2 = H$, $R_3 = CO_2H$
24b: $R_1 = H$, R_2 = BOCNH, $R_3 = CO_2H$
25a: R_1 = BOCNH, $R_2 = H$, R_3 = OAc
25b: $R_1 = H$, R_2 = BOCNH, R_3 = OAc

26a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_3$
26b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_3$
27a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_2OAc$
27b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_2OAc$
28a: R_1 = BOCNH, $R_2 = H$, $R_3 = CO_2CH_3$
28b: $R_1 = H$, R_2 = BOCNH, $R_3 = CO_2CH_3$

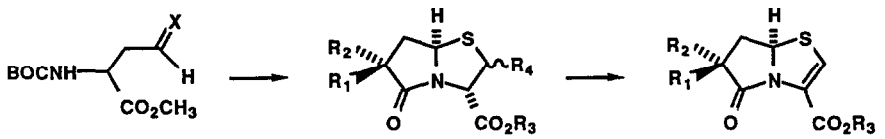


29a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_3$, R_4 = PNB
29b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_3$, R_4 = PNB
30a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_2OAc$, R_4 = PNB
30b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_2OAc$, R_4 = PNB
31a: R_1 = BOCNH, $R_2 = H$, $R_3 = CO_2CH_3$, R_4 = PNB
31b: $R_1 = H$, R_2 = BOCNH, $R_3 = CO_2CH_3$, R_4 = PNB
32a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$
32b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_3$, $R_4 = H$
33a: R_1 = BOCNH, $R_2 = H$, $R_3 = CH_2OAc$, $R_4 = H$
33b: $R_1 = H$, R_2 = BOCNH, $R_3 = CH_2OAc$, $R_4 = H$
34a: R_1 = BOCNH, $R_2 = H$, $R_3 = CO_2CH_3$, $R_4 = H$
34b: $R_1 = H$, R_2 = BOCNH, $R_3 = CO_2CH_3$, $R_4 = H$
35a: R_1 = ATMONH, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$
35b: $R_1 = H$, R_2 = ATMONH, $R_3 = CH_3$, $R_4 = H$
36a: R_1 = ATMONH, $R_2 = H$, $R_3 = CH_2OAc$, $R_4 = H$
36b: $R_1 = H$, R_2 = ATMONH, $R_3 = CH_2OAc$, $R_4 = H$
37a: R_1 = ATMONH, $R_2 = H$, $R_3 = CO_2CH_3$, $R_4 = H$
37b: $R_1 = H$, R_2 = ATMONH, $R_3 = CO_2CH_3$, $R_4 = H$

standard Wittig sequence as described above for the conversion of **14** to **18** afforded the bicyclic derivatives **29-31**. Isomer separation, protecting group removal, and acylation afforded the desired γ-lactam analogues **35-37**.

The 7-acylamino-3-unsubstituted systems **44** were prepared (Scheme III) by a route analogous to the original duVigneaud and Carpenter[18] route to the γ-lactam derivative benzylhomopenicillanic acid.[84] Racemic allyl glycine was converted to its t-butylcarbamate methyl ester **38**. Ozonolysis to the aldehyde **39** followed by condensation with (*d,l*)-cysteine in sodium acetate-acetic acid gave the bicyclic γ-lactam acids **40** as a mixture of isomers.[85] Alkylation of this mixture with p-nitrobenzyl bromide and sodium bicarbonate in dimethylformamide afforded the corresponding esters **41**. The requisite unsaturation was introduced into **41** by treatment with benzoyl peroxide in carbon tetrachloride[86] and subsequent elimination of the resultant benzoates **42** with DBU gave the bicyclic derivatives **43**. Isomer separation, followed by protecting group removal, and acylation afforded the 3-unsubstituted analogues **44**.

SCHEME III



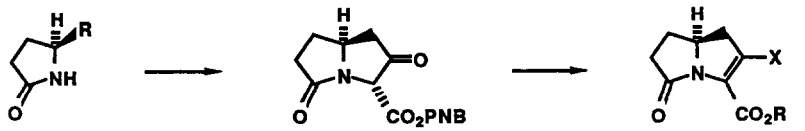
38: X = CH_2
39: X = O

40a: R_1 = BOCNH, R_2 = H, R_3 = H, R_4 = H
40b: R_1 = H, R_2 = BOCNH, R_3 = H, R_4 = H
41a: R_1 = BOCNH, R_2 = H, R_3 = PNB, R_4 = H
41b: R_1 = H, R_2 = BOCNH, R_3 = PNB, R_4 = H
42a: R_1 = BOCNH, R_2 = H, R_3 = PNB, R_4 = $O_2CC_6H_5$
42b: R_1 = H, R_2 = BOCNH, R_3 = PNB, R_4 = $O_2CC_6H_5$

43a: R_1 = BOCNH, R_2 = H, R_3 = PNB
43b: R_1 = H, R_2 = BOCNH, R_3 = PNB
44a: R_1 = ATMONH, R_2 = H, R_3 = H
44b: R_1 = H, R_2 = ATMONH, R_3 = H

Optically active γ-lactam analogues of the carbapenems were synthesized starting from derivatives of *S*-2-pyrrolidone-5-carboxylic acid (which would confer the same absolute configuration upon these analogues as that of the naturally occurring bicyclic biologically active ß-lactam antibiotics). The 7-unsubstituted γ-lactam keto ester **48** was prepared (Scheme IV) starting from *S*-2-pyrrolidinone-5-acetic acid[87,88] (**45**) using methodology developed for carbapenem syntheses.[89] Thus, treatment of **45** with carbonyldiimidazole in tetrahydrofuran followed by magnesium p-nitrobenzylmalonate afforded the keto ester **46** in 86% yield. Diazo exchange with p-carboxybenzenesulfonyl azide and triethylamine in acetonitrile gave diazo keto ester **47** in 95% yield which smoothly cyclized upon treatment with catalytic rhodium(II) acetate dimer in methylene chloride affording **48** in 85% yield. Keto ester **48** was converted to the vinyl chloride **49** in 69% yield by treatment with triphenylphosphite dichloride[90] and diisopropylethylamine in methylene chloride. Reaction of keto ester **48** with trimethylsilyl cyanide, zinc iodide, and 18-C-6/KCN complex[91] in 1,2-dichloroethane at reflux gave the TMS cyanohydrin which was immediately dehydrated by treatment with phosphorous oxychloride and pyridine[92] at 50 °C to give the vinyl nitrile **50** in 40% yield. Replacement of the chlorine in **49** by ethanethiol was accomplished by reaction with ethyl mercaptan and diisopropylethylamine in acetonitrile giving sulfide **51** in 92% yield. Sulfide **51** was oxidized to sulfone **52** in 100% yield using m-chloroperoxybenzoic acid in methylene chloride. The p-nitrobenzyl esters of compounds **49 - 52** were removed using zinc in either 1 N hydrochloric acid/dimethyl formamide or acetic acid/ tetrahydrofuran to afford acids **53 - 56**. The ethyl sulfoxide **57** was prepared in 50% yield by oxidation of **55** by peracetic acid in methylene chloride.

SCHEME IV



45: R = CH_2CO_2H
46: R = $CH_2COCH_2CO_2PNB$
47: R = $CH_2COCN_2CO_2PNB$

48

49: X = Cl, R = PNB
50: X = CN, R = PNB
51: X = SEt, R = PNB
52: X = SO_2Et, R = PNB
53: X = Cl, R = H
54: X = CN, R = H
55: X = SEt, R = H
56: X = SO_2Et, R = H
57: X = SOEt, R = H

The 7-acylamino γ-lactam compounds were prepared by two different routes (Scheme V). Those compounds substituted at C-3 by carbomethoxy and cyano were prepared using a [3 + 2] cyclization approach.[30] *S*-5-Hydroxymethyl-2-pyrrolidinone[88] was converted to acetonide **58** by treatment with 2,2-dimethoxypropane and p-toluenesulfonic acid in toluene at reflux. Reaction of **58** with potassium t-butoxide in tetrahydrofuran followed by n-butyl nitrite afforded oxime **59** in 58% yield. Catalytic reduction of **59** over 10% palladium on carbon at 70 psi of hydrogen followed by amine protection using di-t-butyl dicarbonate produced a single carbamate **60a** in 54% yield. Reduction of **59** by zinc/acetic acid in ethanol followed by amine protection as above gave a major carbamate (20 : 1 ratio) in 90% yield, different than that obtained from catalytic reduction, which was determined to be **60b** by x-ray crystallography. Hydrolysis of the acetonide of **60a** by acetic acid in aqueous acetonitrile afforded alcohol **61a** in 76% yield. Treatment of **61a** with methanesulfonyl chloride and triethylamine gave the mesylate which was immediately converted to iodide **62a**, in 58% overall yield, using sodium iodide in acetone. Using this sequence, the *trans*-iodomethyl derivative **62b** was prepared in 30% overall yield from **60b**.

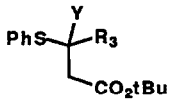
SCHEME V

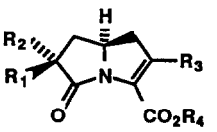
58: $R_1 = R_2 = H$
59: $R_1 = R_2 =$ NOH
60a: R_1 = BOCNH, R_2 = H
60b: R_1 = H, R_2 = BOCNH

61a: R_1 = BOCNH, R_2 = H, X = OH
61b: R_1 = H, R_2 = BOCNH, X = OH
62a: R_1 = BOCNH, R_2 = H, X = I
62b: R_1 = H, R_2 = BOCNH, X = I

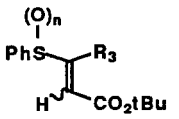
Annulating reagent **68** was prepared as follows. Alkylation of the lithium anion of methyl phenylthioacetic acid in tetrahydrofuran by t-butyl bromoacetate afforded the phenylthiosuccinate diester **63** in quantitative yield. Treatment of **63** with N-chlorosuccinimide in a mixture of carbon tetrachloride and tetrahydrofuran at reflux gave the chloride **64** which was immediately eliminated by reaction with DBU in methylene chloride to give the but-2-enedioate **67** (as a mixture of isomers) in 98% yield. Oxidation to sulfoxide **68** was accomplished in 79% yield by treatment with peracetic acid in methylene chloride. The nitrile annulating reagent **70** was prepared analogously from phenylthioacetonitrile in 13% overall yield. Treatment of the lithium anion of **62a** with sulfoxide

SCHEME V (cont.)





63: R_3 = CO_2Me, Y = H
64: R_3 = CO_2Me, Y = Cl
65: R_3 = CN, Y = H
66: R_3 = CN, Y = Cl



67: R_3 = CO_2Me, n = 0
68: R_3 = CO_2Me, n = 1
69: R_3 = CN, n = 0
70: R_3 = CN, n = 1

71a R_1 = BOCNH, R_2 = H, R_3 = CO_2Me, R_4 = t-Bu
71b R_1 = H, R_2 = BOCNH, R_3 = CO_2Me, R_4 = t-Bu
72a R_1 = BOCNH, R_2 = H, R_3 = CN R_4 = t-Bu
72b R_1 = H, R_2 = BOCNH, R_3 = CN, R_4 = t-Bu
73a R_1 = ATMONH, R_2 = H, R_3 = CO_2Me, R_4 = H
73b R_1 = H, R_2 = ATMONH, R_3 = CO_2Me, R_4 = H
74a R_1 = ATMONH, R_2 = H, R_3 = CN, R_4 = H
75 R_1 = R_2 = NOH, R_3 = SEt, R_4 = H
76a R_1 = BOCNH, R_2 = H, R_3 = SEt, R_4 = H
76b R_1 = H, R_2 = BOCNH, R_3 = SEt, R_4 = H
77a R_1 = ATMONH, R_2 = H, R_3 = SEt, R_4 = H
77b R_1 = H, R_2 = ATMONH, R_3 = SEt, R_4 = H
78a R_1 = ATMONH, R_2 = H, R_3 = SOEt, R_4 = H
78b R_1 = H, R_2 = ATMONH, R_3 = SOEt, R_4 = H
79a R_1 = ATMONH, R_2 = H, R_3 = SO_2Et, R_4 = H
79b R_1 = H, R_2 = ATMONH, R_3 = SO_2Et, R_4 = H

68 in tetrahydrofuran at -78 °C with warming to 23 °C afforded the carbomethoxy-substituted nucleus **71a** in 61% yield. Nuclei **71b**, **72a**, and **72b** were prepared analogously. Deprotection using trifluoroacetic acid followed by acylation afforded the desired γ-lactam analogues **73a**, **73b**, and **74a**.

The 7-acylamino γ-lactam compounds substituted at C-3 by sulfur (at various oxidation levels) were prepared from vinyl sulfide **55**. Treatment of **55** with 2.3 equivalents of lithium diisopropylamide in tetrahydrofuran at -78 °C followed by the addition of n-butylnitrite afforded oxime **75** in 32% yield. Reduction of **75** by zinc/acetic acid in ethanol followed by amine protection by di-t-butyl dicarbonate gave a 80% yield of carbamates **76a** and **76b** in a 3:2 ratio. Deprotection with trifluoroacetic acid and acylation afforded a 3:2 ratio of **77a** and **77b** in 43% yield. Oxidation of **77** by peracetic acid in methylene chloride gave sulfoxides **78** as a mixture of diastereomers in quantitative yield. Further oxidation of **78** by m-chloroperoxybenzoic acid gave sulfones **79a** and **79b** in 43% yield, which were separated by reverse phase chromatography.[93]

Assignment of Relative Stereochemistry of the 7-Substituted γ-Lactam Analogues. The relative *trans* configuration between H_5 and H_7 in γ-lactam analogue **30b** was unequivocally established by x-ray crystallography. We have assigned the relative configuration of H_5 and H_7 in the related isomers by a correlation of ^1H NMR chemical shifts using compound **36b** derived from **30b** as a model (Table II). The compounds designated as *trans* were assigned on the basis of a relative downfield shift of H_5 and a corresponding upfield shift of H_7 relative to the signals of those isomers designated as *cis*.[94] Due to the apparent flexibility of the γ-lactam ring with changes in 3-substitution no reliable pattern of coupling constants was observed.

The relative *trans* configuration between H_5 and H_7 in intermediate **60b** was established[30] by x-ray crystallography. The relative configuration between H_5 and H_7 in intermediate **60a** is therefore *cis*. Subsequent synthetic manipulations did not affect the C-7 stereocenter in compounds derived from **60a** and **60b**. Sulfone **79a** was assigned *cis* (Table III) by correlation of its ^1H NMR chemical shifts with the other C-3 derivatives. Compounds with the *cis* configuration exhibited a characteristic upfield shift for $H_{6'}$, and downfield shift for H_6, relative to the signals from the *trans* isomer. Additional support for this assignment is the presence of the quartet

Table II. Chemical Shifts (δ) of Selected Protons in the 360 MHz ^{1}H NMR in d_6-DMSO of γ-Lactam Analogues of the Penems.

	Compound							
Proton	**35b**	**35a**	**36b**	**36a**	**37b**	**37a**	**44b**	**44a**
H_5	6.02	5.88	6.04	5.88	6.18	5.95	6.03	5.89
H_6[a]	2.43	2.45	2.45	2.48	2.46	2.51	2.44	2.43
$H_{6'}$[b]	2.89	2.99	2.91	2.99	2.89	2.97	2.89	2.93
H_7	4.73	4.92	4.72	4.93	4.71	4.96	4.72	4.89

[a] *cis* to proton H_5; [b] *trans* to proton H_5

(J = 11 ± 1 Hz) of $H_{6'}$ (appropriate for a proton flanked by two pseudo-axial protons as well as one geminal proton with coupling constant of similar magnitude) in the spectrum of **79a** customary for the *cis* compounds.

Table III. Chemical Shifts (δ) and Coupling Constants (Hz) of Selected Protons in the ^{1}H NMR of γ-Lactam Analogues of the Carbapenems.

	Compound								
Proton	**71a**	**71b**	**72a**	**72b**	**73a**	**73b**	**74a**	**79a**	**79b**
$H_{6'}$[b]	1.80, (q, 12)	2.40	1.85, (q, 10)	2.20	2.05, (q, 11)	2.40	2.10, (q, 11)	2.25, (q, 11)	2.45
H_6[a]	3.20	2.80	3.05	2.50	2.80	2.70	2.65	2.90	2.60

[a] *cis* to proton H_5; [b] *trans* to proton H_5

Biological Activity. The γ-lactam analogues were tested for *in vitro* microbiological activity by disc-plate and agar dilution assay against a variety of microorganisms. The γ-lactam analogues of the carbapenems were generally devoid of *in vitro* microbiological activity; (compound **57** and **73a** showed trace activity at the highest concentration tested). In contrast to penem **20**, the 7-unsubstituted derivative **19** exhibited no microbiological activity. However, some of the 7-acylamino substituted penem analogues displayed low yet demonstrable levels of activity against a variety of organisms. Compounds **35a**, **35b**, **44a**, and **44b** even exhibited single digit MIC's against some sensitive organisms (Table IV). Compounds **36a**, **36b**, **37a**, and **37b** were essentially devoid of activity.

Table IV. Minimum Inhibitory Concentration (MIC - μg/ml) of Selected γ-Lactam Analogues.

	Compound			
Organism	**35a**	**35b**	**44a**	**44b**
Staphylococcus aureus (X1.1)	>128	32.0	>32	>128
Streptococcus pyogenes (C203)	64.0	4.0	8.0	64.0
S. pneumoniae (PARK)	128.0	8.0	8.0	64.0
Haemophilus influenzae (76)	>128	>128	32.0	>128
Escherichia coli (EC14)	>128	>128	32.0	>128
Klebsiella pneumoniae (X26)	>128	>128	8.0	64.0

This finding was most disappointing in light of the presence of electron-withdrawing substituents at C-3 which might have been expected to result in more reactive γ-lactams and hence increased biological activity relative to those less activated.

Preliminary studies on the mechanism of action of these γ-lactam derivatives were done by testing compounds **35a** and **35b** for activity against *S. aureus* X1 and its L-form, *S. aureus* X680 (Table V). Although activity versus *S. aureus* X1 was weak, the lack of any activity against the L-form (X680) is consistent with cell wall inhibition. Further studies to elucidate the mode of action of these and related derivatives are in progress.

Table V. In Vitro Antibacterial Activity of γ-Lactam Penem Analogues **35a** and **35b** versus *S. aureus* X1 and its L-form *S. aureus* X680.

Compound	Concentration mg/disc	Zone size (mm) X1	X680
35a	300	16	none
35b	300	11	none

This studies constitute an example of γ-lactam antibiotics as a new class of antibiotic substances.

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EXPERIMENTAL SECTION

Computational chemistry experiments were run on a VAX cluster consisting of 8800s, 8600s, and one 11/785. Modgraph GX1000 and Evans and Sutherland PS330 graphics terminals were used to run SYBYL (versions 3.5 and earlier). MOPAC (version 3.0) was run with default options independently of SYBYL. Starting geometries were derived from standard bond lengths and bond angles and with the configuration at the bridgehead set to be like that in cephalosporins and penicillins. The rotational conformations to use for the carboxylic acid and formamido side-chains were selected to be similar to the corresponding side-chains in cephalosporins, although this degree of freedom was not critical because the molecular fitting was done with atoms that are invariant to these conformational changes.

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 part per million (δ) relative to Me4Si or DSS as internal standard. Infrared (IR) spectra were determined on a Nicolet MX-1 FT-IR, optical rotations on a Perkin-Elmer 241 spectrometer, and ultraviolet (UV) spectra on a Cray 219. Mass spectral data (MS) were obtained on either a CEC-21-110 or a Varian MAT-731 spectrometer.

4-Thioacetoxy-2-pyrrolidinone (14). A solution of lactam **13**[81] (24.7 g, 214.8 mmol) in 35 mL distilled thiolacetic acid was stirred at room temperature for 20h. The solvent was removed *in vacuo*. The residue was dissolved in hot Et_2O , treated with activated charcoal, filtered, and crystallized to afford 20.9 g (61%) of **14** as a yellow solid: ^{1}H NMR (270 MHz, Me_2SO-d_6) δ 8.34 (s, 1H), 5.32 (dd, J = 9.5, 1.0 Hz, 1H), 2.34 (s, 3H), and 2.7-1.9 (m, 4H); IR (KBr) 3400, 1712, 1698, 1688, 1665, 1424, 1289, 1274, 1246, 1128, and 939 cm^{-1}; MS, *m/e* 160 (M^+). Anal. ($C_6H_9NO_2S$) C, H, N.

p-Nitrobenzyl 8-Oxo-4-thia-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (18). p-Nitrobenzyl glycolate hydrate (21.5 g, 94.5 mmol) was suspended in 900 mL of dry toluene and refluxed with a Dean-Stark trap for 1h. The lactam **14** (10.0 g, 62,9 mmol) was added and the mixture refluxed for 1.5h. The solvent was removed *in vacuo* to afford 23.1 g of crude hemiaminal **15** used in the next step without purification. To a solution of crude hemiaminal **15** in 300 mL dry THF at -10 °C was added dropwise 2,6-lutidine (13.5 g, 126.0 mmol) and

then thionyl chloride (15.0 g, 126.0 mmol). The mixture was stirred at -10 °C for 0.3h. The resultant tan precipitate was removed by filtration through celite. The filtrate was concentrated *in vacuo* to afford crude chloride **16** as a thick black oil. To a solution of crude chloride **16** in 300 mL of dioxane at room temperature was added 2,6-lutidine (13.5 g, 126 mmol) and then triphenylphosphine (33.0 g, 126.0 mmol). The mixture was stirred at room temperature for 0.75h then concentrated *in vacuo* to afford crude phosphorane **17** as a thick black oil. A solution of crude phosphorane **17** in 400 mL of dry toluene was stirred at 80 °C for 17h. The mixture was concentrated *in vacuo* and the residue dissolved in EtOAc, washed with H_2O and saturated brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 50.4 g of crude **18** as a black oil. HPLC on silica gel (elution with gradient $PhCH_3$/EtOAc) afforded 8.6 g (41%) of **18** as a yellow solid: ^1H NMR (270 MHz, $CDCl_3$) δ 8.24 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 5.98 (m, 1H), 5.35 (AB quartet, 2H), 2.86-2.36 (m, 4H), and 2.38 (s, 3H); IR (KBr) 1707, 1601, 1518, 1381, 1344, 1317, 1268, 1245, 1208, and 1200 cm^{-1}; UV (EtOH) λ max 265 nm (ε 13,600) and 307 nm (ε 9,100); MS *m/e* 334 (M^+). Anal. ($C_{15}H_{14}N_2$) C, H, N.

8-Oxo-4-thia-1-azabicyclo[3.3.0]octene-2-ene-2-carboxylic acid (19). A solution of **18** (1.0 g, 3.0 mmol) in 220 mL of 10:1 MeOH-THF was hydrogenated over 1.0 g of 5% palladium on carbon at 45 psi for 3.5h at room temperature. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc and extracted with saturated aqueous $NaHCO_3$. The aqueous extracts were washed with EtOAc, acidified to pH 2 with 1 N HCl, and then extracted with EtOAc. The combined EtOAc extracts were washed with H_2O and saturated brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 0.49 g (82%) of **19** as a yellow solid: ^1H NMR (270 MHz, $CDCl_3$) δ 6.90 (t, J = 6.3 Hz, 1H), 3.0-2.3 (m, 4H), and 2.40 (s, 3H); IR (KBr) 3400, 1713, 1666, 1575, 1450, 1336, 1254, 1235, 1212, 1202, and 1149 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ε 4,330) and 300 nm (ε 3,550); MS, *m/e* 199 (M^+). Anal. calcd. for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 49.79; H, 5.02; N, 6.59.

Ethyl 4,5-Dihydro-1H-pyrazole-3,5-dicarboxylate (21). Ethyl acrylate (35 g, 350 mmol) was slowly added dropwise to neat ethyl diazoacetate (40 g, 350 mmol) at 0 °C. The mixture was stirred at 0 °C for 2h, then at 40 °C for 16h. The mixture was diluted with Et_2O and the product crystallized upon cooling to afford 61.1 g (82%) of ester **21** as a white solid: ^1H NMR (270MHz, Me_2SO-d_6) δ 8.6 (br s, 1H) 4.54 (dd, J = 12.2, 6.8 Hz, 1H), 4.15 (q, J = 6.8 Hz, 2H), 3.03 (d of AB quartets, 2H), 1.22 (t, J = 6.8 Hz, 3H), and 1.20 (t, J = 6.8 Hz, 3H); IR (KBr) 3360, 2980, 1731, 1708, 1700, 1278, 1216, 1198, 1158, 1135, and 1047 cm^{-1}; UV (EtOH) λ_{max} 286 nm (ε 9,285); MS, *m/e* 214 (M^+). Anal. ($C_9H_{14}N_2O_4$) C, H, N.

Ethyl (3*R,5*S**) and (3*S**,5*S**)-3-Amino-2-pyrrolidinone-5-carboxylate (22a and 22b).** A solution of **21** (61.1 g, 285 mmol) in 427 mL of EtOH was hydrogenated over 12 g of Raney nickel at 3500 psi for 3h at 60 °C and for 3h at 115 °C. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to afford 43.0 g (88%) of a mixture of lactams **22a** and **22b** as a thick blue oil used in the next step without purification.

Ethyl (3*R,5*S**) and (3*S**,5*S**)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-oxo-2-pyrrolidine carboxylate (23a and 23b).** A solution of **22a** and **22b** (43.0 g, 250 mmol) and di-t-butyl dicarbonate (54.0 g, 250 mmol) in 700 mL of CH_2Cl_2 was stirred at room temperature for 72h. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (elution with EtOAc) to afford 54.6 g (80%) a mixture of **23a** and **23b** as a whitish-blue solid: ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.25 (s, 1H with signal at 8.20, major isomer), 8.20 (s, 1H with signal at 8.25, minor isomer), 7.10 (d, J = 6 Hz, 1H with signal at 7.06, major isomer), 7.06 (d, J = 6 Hz, 1H with signal at 7.10, minor isomer), 4.12 (overlapping quartets, J = 7 Hz, 2H), 4.03 (m, 1H), 3.35 (br s, 1H), 2.6-1.3 (m, 2H), 1.40 (s, 9H), and 1.22 (overlapping triplets, J = 7 Hz, 3H); IR ($CHCl_3$) 3440, 3018, 2985, 1719, 1501, 1372, 1206, 1201, 1163, 1120, and 1074 cm^{-1}. Anal. calcd. for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 54.09; H, 7.59; N, 7.94.

(3*S,5*S**) and (3*R**,5*S**)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-pyrrolidinone-5-carboxylic acid (24a and 24b).** To a solution of **23a** and **23b** (43.0 g, 158 mmol) in 500 mL of MeOH at room temperature was added in one portion solid potassium hydroxide (18.6 g, 332 mmol). The mixture was stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue dissolved in water, washed with EtOAc, acidified with conc. HCl, and extracted with EtOAc. The EtOAc extracts were washed with saturated brine and concentrated *in vacuo* to ~50 mL. The product crystallized upon cooling to 0 °C and was collected by filtration to afford 24.3 g (63%) of a mixture of **24a** and **24b** as a white solid: ^1H NMR (270 MHz, Me_2SO-d_6) δ 8.17 (s, 1H with signal at 8.10, major isomer), 8.10 (s, 1H with signal at 8.17, minor isomer), 7.11 (d, J = 6 Hz, 1H with signal at 7.04, major isomer), 7.04 (d, J = 6 Hz, 1H with signal at 7.11, minor isomer), 4.05 (m, 1H),

3.35 (br s, 1H), 2.6-1.7 (m, 2H), and 1.40 (s, 9H); IR ($CHCl_3$) 3365 (br), 1726, 1688, 1526, 1392, 1368, 1294, 1250, 1240, and 1166 cm^{-1}; MS, *m/e* 244 (M^+). Anal. ($C_{10}H_6N_2O_5$) C, H, N.

(3*S,5*R**) and (3*R**,5*R**)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-acetoxy-2-pyrrolidinone (25a and 25b).** To a solution of acids **24a** and **24b** (10.0 g, 41.0 mmol) in 500 mL of dry THF at room temperature was added lead tetraacetate (22.0 g, 41.0 mmol). The mixture was stirred at room temperature for 1h, then at 67 °C for 2h. The resultant yellow precipitate was removed by filtration through celite. The filtrate was concentrated *in vacuo* to afford 11.0 g of a mixture of **25a** and **25b** as a thick yellow oil used in the next step without purification: ^1H NMR (270 MHz, $CDCl_3$): δ 7.3 (br s, 1H with signal at 7.0, minor isomer), 7.0 (br s, 1H with signal at 7.3, major isomer), 5.3 (m, 1H), 5.2 (br s, 1H with signal at 5.1, major isomer), 5.1 (br s, 1H with signal at 5.2, minor isomer), 4.4 (m, 1H), 2.9 (m, 2H with signal at 2.6), 2.6 (m, 2H with signal at 2.9), 2.08 (s, 3H with signal at 2.04), 2.04 (s, 3H with signal at 2.08), 1.50 (s, 9H with signal at 1.45, minor isomer), and 1.45 (s, 9H with signal at 1.50, major isomer); MS, *m/e* 249 (M^+). Anal. calcd. for $C_{11}H_{18}N_2O_5$: C, 51.16; H, 7.03; N, 10.85. Found: C, 54.04, H, 7.91; N, 8.23.

(3*S,5*R**) and (3*R**,5*R**)-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-thioacetoxy-2-pyrrolidinone (26a and 26b).** A solution of acetates **25a** and **25b** (11.0 g, 41.0 mmol) was processed as exemplified for the conversion of **13** to **15** to afford 5.45 g (49% from **24a** and **24b**) of a mixture of **26a** and **26b** as a white solid. HPLC on silica gel (elution with gradient $PhCH_3$-EtOAc) gave pure samples of **26b** (higher RF) and **26a** (lower RF) as white solids. For **26b**: ^1H NMR (270 MHz, $CDCl_3$) δ 6.60 (br s, 1H), 5.37 (d, J = 7.5 Hz, 1H), 5.08 (m, 1H), 4.25 (m, 1H), 2.65 (m, 1H), 2.44 (m, 1H), 2.36 (s, 3H), and 1.45 (s, 9H); IR (KBr) 3389, 1722, 1708, 1681, 1667, 1521, 1294, 1269, 1173, and 1139 cm^{-1}; UV (EtOH) λ_{max} 229 nm (ε 4,325); MS, *m/e* 274 (M^+). Anal. ($C_{11}H_{18}N_2O_4S$) C, H, N. For **26a**: ^1H NMR (270 MHz, $CDCl_3$) d 6.27 (br s, 1H) 5.25 (t, J = 7 Hz, 1H), 5.10 (m, 1H), 4.20 (m, 1H), 3.02 (m, 1H), 2.36 (s, 3H), 1.95 (m, 1H), and 1.45 (s, 9H); IR (KBr) 3387, 1714, 1705, 1687, 1524, 1372, 1367, 1296, 1239, and 1165 cm^{-1}; UV (EtOH) λ_{max} 228 (ε 3,979); MS, *m/e* 274 (M^+). Anal. ($C_{11}H_{18}N_2O_4S$) C, H, N.

p-Nitrobenzyl (5*R,7*S**) and (5*R**,7*R**)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-4-thia-3-methyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (29a and 29b).** A mixture of compounds **26a** and **26b** (1.37 g, 5.0 mmol) was processed as exemplified for the conversion of **14** to **18** to afford 5.5 g of a mixture of **29a** and **29b** as a brown oil. Column chromatography on silica gel (elution with gradient hexanes-EtOAc) afforded 0.09 g (4%) of **29a** and 0.32 g (15%) of **29b** as white solids. For **29a**: ^1H NMR (270 MHz, $CDCl_3$) δ 8.22 (d, J= 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 5.80 (t, J = 5.4 Hz, 1H), 5.32 (AB quartet, 2H), 5.17 (m, 1H), 4.60 (m, 1H), 3.28 (m, 1H), 2.38 (s, 3H), 2.35 (m, 1H), and 1.45 (s, 9H); IR (KBr) 3450, 1728, 1714, 1706, 1676, 1534, 1515, 1389, 1369, 1344, and 1181 cm^{-1}; UV (EtOH) λ_{max} 312 nm (ε 9,197) and 268 nm (ε 13,431); MS, *m/e* 449 (M^+). Anal. ($C_{20}H_{23}N_3O_7S$) C, H, N. For **29b**: ^1H NMR (270 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 5.93 (dd, J = 5.5, 1.0 Hz, 1H), 5.35 (AB quartet, 2H), 5.12 (m, 1H), 4.42 (m, 1H), 2.90 (m, 1H), 2.57 (m, 1H), 2.44 (s, 3H), and 1.45 (s, 9H); IR (KBr) 3400, 1745, 1705, 1684, 1586, 1519, 1356, 1346, 1315, 1301, and 1169 cm^{-1}; UV (EtOH) λ_{max} 300 nm (ε 8,000) and 265 nm (ε 11,200); MS, *m/e* 449 (M^+). Anal. ($C_{20}H_{23}N_3O_7S$) C, H, N.

(5*R,7*R**)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-4-thia-3-methyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (32b).** The ester **29b** (0.45 g, 1.0 mmol) was processed as exemplified for the conversion of **18** to **19** to afford 0.29 g (91%) of acid **32b** as a white solid: ^1H NMR (90 MHz, Me_2SO-d_6) δ 7.45 (d, J = 9 Hz, 1H), 5.90 (dd, J = 5 Hz, 1 Hz),4.30 (m, 1H), 2.9-2.0 (m, 2H), 2.39 (s, 3H), and 1.45 (s, 9H).

(5*R,7*R**)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-3-methyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (35b).** A solution of acid **32b** (0.28 g, 0.88 mmol) in 5 mL trifluoroacetic acid was stirred at room temperature for 0.3 h. The solvent was removed *in vacuo* and the residue triturated with Et_2O, then dissolved in 20 mL of 1:1 acetone-H_2O. Solid $NaHCO_3$ (0.37 g, 4.4 mmol) was added followed by the 1-hydroxybenzotriazole active ester of syn-(aminothiazolmethoximino)acetic acid (0.47 g, 1.48 mmol). The mixture was stirred at room temperature for 4h. The acetone was removed *in vacuo* and the residue diluted with EtOAc and H_2O. The aqueous layer was acidified to pH 2 with 1 N HCl and extracted with EtOAc. The EtOAc extracts were washed with H_2O and saturated brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a tan foam. Trituration with EtOAc-hexanes to remove HBT afforded 0.042 g (12%) of **35b** as a white powder: ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.4 (d, J = 8.1 Hz, 1H), 7.4 (s, 2H), 6.9 (s, 1H), 6.02 (dd, J = 6.6, 1.5 Hz, 1H), 4.73 (m,1H), 3.85 (s, 3H), 2.89 (m, 1H), 2.43 (m, 1H), and 2.35 (s, 3H); MS, *m/e* 397 (M^+).

(5*R,7*S**)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-3-methyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (35a).** The ester **32a** (0.449 g, 1.0 mmol) was processed as exemplified for the conversion of **32b** to **35b** to afford 0.153 g of a white powder: ^{1}H NMR (360 MHz, Me_2SO-d_6) δ 8.4 (d, J = 8.1 Hz, 1H), 7.4 (s, 2H), 7.15 (s, 1H), 5.88 (t, J = 6.6 Hz, 1H), 4.92 (m, 1H), 3.90 (s, 3H), 2.99 (m, 1H), 2.45 (m, 1H), and 2.3 (s, 3H); MS, *m/e* 398 (M^+ + H).

(5*R,7*S**) and (5*R**,7*R**)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-3-acetoxymethyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36a and 36b).** The acetates **25a** and **25b** (34.0 g, 133 mmol) were processed as exemplified for the conversion of **25a** and **25b** to **35a** and **35b** (substituting (acetyloxy)ethanethioic acid for thiolacetic acid) to afford 0.084 g of **36a** and 0.465 g of **36b** as white powders. For **36a**: ^{1}H NMR (360 MHz, Me_2SO-d_6) δ 8.98 (d, J = 8.1Hz, 1H), 7.23 (br s, 2H), 7.10 (s, 1H), 5.88 (dd, J = 8.1, 6.6 Hz, 1H), 5.19 (AB quartet, 2H), 4.93 (m, 1H), 3.84 (s, 3H), 2.99 (m, 1H), 2.48 (m, 1H), and 2.07 (s, 3H); MS, *m/e* 455 (M^+). Anal. ($C_{16}H_{17}N_5O_7S_2$) C, H, N. For **36b**: ^{1}H NMR (360 MHz, Me_2SO-d_6) d 9.14 (d, J = 8.0 Hz, 1H), 7.17 (br s, 2H), 6.84 (s, 1H), 6.04 (dd, J = 6.6, 1.5 Hz, 1H), 5.18 (AB quartet, 2H), 4.72 (m, 1H), 3.81 (s, 3H), 2.91 (m,1H), 2.45 (m, 1H), and 2.04 (s, 3H); MS, *m/e* 456 (M^+ + H). Anal. ($C_{16}H_{17}N_5O_7S_2$) C, H, N.

(5*R,7*S**) and (5*R**,7*R**)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-3-carbomethoxy-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acids (37a and 37b).** The acetates **25a** and **25b** (79.0 g, 305 mmol) were processed as exemplified for the conversion of **25a** and **25b** to **35a** and **35b** (substituting methyl mercaptaoxoacetate for thiolacetic acid) to afford 0.084 g of **37a** and 0.262 g of **37b** as white powders. For **37a**: ^{1}H NMR (360 MHz, Me_2SO-d_6) δ 9.05 (d, J = 8.5 Hz, 1H), 7.24 (br s, 2H), 6.98 (s, 1H), 5.95 (dd, J = 8.5, 6.1 Hz, 1H), 4.96 (m, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 2.97 (m, 1H), and 2.51 (m, 1H); MS, *m/e* 442 (M^+ + H). Anal. calcd. for $C_{15}H_{15}N_5O_7S_2$: C, 40.81; H, 3.43; N, 15.87. Found: C, 37.00; H, 3.62; N, 13.98. For **37b**: ^{1}H NMR (360 MHz, Me_2SO-d_6) d 9.34 (d, J = 7.9 Hz, 1H), 7.23 (br s, 2H), 6.71 (s, 1H), 6.18 (dd, J = 7.3, 6.7 Hz, 1H), 4.71 (m, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.89 (m, 1H), and 2.46 (m, 1H); MS, *m/e* 442 (M^+ + H). Anal. calcd. for $C_{15}H_{15}N_5O_7S_2$: C, 40.81; H, 3.43; N, 15.87. Found: C, 36.50; H, 3.12; N, 13.39.

Methyl 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-pent-3-enoate (38). To a solution of (±) allyl glycine (50.0 g, 434.0 mmol) and di-t-butyl dicarbonate (104.0 g, 476 mmol) in 400 mL of H_2O was slowly added solid sodium hydroxide in order to maintain a pH of 9.0. After 2h, the mixture was cooled to 0 °C, layered with Et_2O, and acidified to pH 2 with conc. HCl. The mixture was extracted with Et_2O and the Et_2O extracts washed with H_2O and saturated brine, dried ($MgSO_4$), filtered, and concentrated to ~1 liter in volume. Excess dicyclohexylamine was added and the resultant white precipitate collected by filtration to afford 108.6 g of a white solid. A solution of this solid and iodomethane (228.0 g, 1.6 mol) in 500 mL DMF was stirred at room temperature for 72h. The mixture was diluted with H_2O and extracted with Et_2O. The Et_2O extracts were washed with aqueous $NaHCO_3$, H_2O, and saturated brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 43.4 g (44%) of **38** as a white solid: ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.7 (m, 1H), 5.2 (m, 2H), 4.4 (m, 1H), 3.8 (s, 3H), 2.5 (m, 2H), and 1.45 (s, 9H).

p-Nitrobenzyl (2*S,5*R**,7*S**) and (2*S**,5*R**,7*R**)-7-[[(1,1-Dimethylethoxy)carbonyl]-amino]-8-oxo-4-thia-1-azabicyclo[3.3.0]octane-2-carboxylate (41a and 41b).** Ozone was passed through a solution of **38** (40.0 g, 174.7 mmol) in 500 mL of CH_2Cl_2 at -78 °C for 1h. The mixture was quenched with excess Me_2S and the solvent removed *in vacuo* to afford crude **39** as a yellow oil. A solution of crude **39**, (±) cysteine (23.3 g, 192.2 mmol), and sodium acetate (50.0 g, 609.5 mmol) in 500 mL AcOH was stirred at room temperature for 24h. The AcOH was removed *in vacuo* and the residue diluted with 1 N HCl and extracted with EtOAc. The EtOAc extracts were washed with H_2O and saturated brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 68.8 g of crude **40** as a yellow oil. A solution of crude **40**, p-nitrobenzyl bromide (49.2 g, 227.8 mmol), and $NaHCO_3$ (50.0 g, 595.2 mmol) in 500 mL of DMF was stirred at room temperature for 48h. The DMF was removed *in vacuo* and the residue dissolved in EtOAc, washed with aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated to afford 87.1 g of a thick red oil. HPLC on silica gel (elution with gradient $PhCH_3$-EtOAc) afforded 4.75 g (6%) of **41b** (higher RF) and 1.50 g (2%) of **41a** (lower RF). For **41a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 5.28 (s, 2H), 5.21 (m, 1H), 5.10 (m, 2H), 4.66 (m, 1H), 3.38 (m, 2H), 3.18 (m, 1H), 2.03 (m, 1H), and 1.44 (s, 9H); IR (KBr) 1748, 1707, 1524, 1393, 1368, 1347, 1251, 1215, and 1164 cm^{-1}; UV (EtOH) λ_{max} 263 nm (ε 8,300); MS, *m/e* 437 (M^+). Anal. calcd. for $C_{19}H_{23}N_3O_7S$: C, 52.17; H, 5.30; N, 9.61. Found: C, 52.60; H, 5.09; N, 8.20. For **41b**: ^{1}H

NMR (270 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 5.28 (s, 2H), 5.12 (m, 2H), 5.02 (br s, 1H), 4.31 (br s, 1H), 3.45 (m, 2H), 2.66 (m, 1H), 2.46 (m, 1H), and 1.46 (s, 9H); IR (KBr) 1757, 1712, 1689, 1678, 1526, 1346, 1248, 1218, 1178, and 1160 cm^{-1}; UV (EtOH) λ_{max} 263 nm (ε 8,300); MS, *m/e* 437 (M^+). Anal. ($C_{19}H_{23}N_3O_7S$) C, H, N.

p-Nitrobenzyl (2*S,3*R**,5*R**,7*R**)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-4-thia-3-benzoyloxy-1-azabicyclo[3.3.0]octane-2-carboxylate (42b).** A suspension of **41b** (4.37 g, 10.0 mmol) and benzoyl peroxide (6.05 g, 25.0 mmol) in 75 mL of CCl_4 was stirred at 77 °C for 2.5h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc, washed with aqueous $NaHCO_3$, H_2O, and saturated brine, dried ($MgSO_4$), filtered, concentrated *in vacuo*, and column chromatographed on silica gel (elution with gradient $PhCH_3$-EtOAc) to afford 1.45 g (26%) of **42b** as an orange solid: ^1H NMR (90MHz, $CDCl_3$) δ 8.1-7.5 (m, 9H), 6.70 (s, 1H), 5.67 (s, 1H), 5.42 (dd, J = 6,2 Hz, 1H), 5.32 (s, 2H), 5.26 (m, 1H), 4.30 (m, 1H), 2.70 (m, 1H), 2.32 (m, 1H), and 1.44 (s, 9H).

p-Nitrobenzyl (5R*,7R*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-4-thia-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (43b). To a solution of **42b** (1.20 g, 2.10 mmol) in 30 mL of CH_2Cl_2 at -78 °C was added DBU (0.48 g, 3.15 mmol). The mixture was stirred at -78 °C for 1.5h. The mixture was diluted with EtOAc, washed with 1 N HCl, H_2O, aqueous $NaHCO_3$, and saturated brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 0.77 g (84%) of **43b** as a yellow solid. For **43b**: 1H NMR (90 MHz, $CDCl_3$) δ 8.18 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.38 (s, 1H), 6.02 (dd, J = 6,1 Hz, 1H), 5.36 (AB quartet, 2H), 5.10 (br s, 1H), 4.46 (m, 1H), 2.92 (m, 1H), 2.66 (m, 1H), and 1.46 (s, 9H); MS, *m/e* 435 (M^+).

(5R*,7R*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (44b). The ester **43b** (0.77 g, 1.70 mmol) was processed as exemplified for the conversion of **29b** to **35b** to afford 0.045 g of **44b** as a tan powder: ^1H NMR (360 MHz, Me_2SO-d_6) δ 9.21 (d, J = 8.8 Hz, 1H), 7.24 (br s, 3H), 6.84 (s, 1H), 6.03 (dd, J = 6.6, 1.0 Hz, 1H), 4.72 (m, 1H), 3.84 (s, 3H), 2.89 (m, 1H), and 2.44 (m, 1H); MS, *m/e* 384 (M^+ + H). Anal. calcd. for $C_{13}H_{13}N_5O_5S_2$: C, 40.73, H, 3.42; N, 18.72. Found: C, 37.60; H, 3.36; N, 15.42.

(5R*,7S*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-4-thia-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (44a). The ester **41a** (1.50 g, 3.40 mmol) was processed as exemplified for the conversion of **41b** to **44b** to afford 0.013 g of **44a** as a tan powder: ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.94 (d, J = 8.5 Hz, 1H), 7.25 (s, 2H), 7.19 (s, 1H), 6.58 (s, 1H), 5.89 (t, J = 6.7 Hz, 1H), 4.89 (m, 1H), 3.84 (s, 3H), 2.93 (m, 1H), and 2.43 (m, 1H); MS, *m/e* 406 (M^+ + Na).

p-Nitrobenzyl (*S*)-ß,5-Dioxo-2-pyrrolidinebutanoate (46). To a suspension of acid **45**[87] (4.02 g, 28.1 mmol) in 125 mL of THF was added 1,1'-carbonyldiimidazole (5.27 g, 32.5 mmol) and was stirred at room temperature for 4h. Magnesium p-nitrobenzylmalonate was added in one portion and the suspension was stirred 18h at room temperature. The mixture was poured into 1 N HCl and and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and evaporated. The residue was taken up in warm CH_2Cl_2 and Et_2O was added. The solid was collected and dried *in vacuo* to afford 7.72 g (86%) of **46** as a light yellow solid: ^1H NMR (270 MHz, $CDCl_3$) δ 8.35 (d, J = 10 Hz, 2H), 7.55 (d, J = 10 Hz, 2H), 6.00 (bs, 1H), 5.30 (s, 2H), 4.05 (bs, 1H), 3.57 (s, 2H), 2.9 (dd, J = 21, 5 Hz, 1H), 2.70 (dd, J = 21, 11 Hz, 1H), 2.3 - 2.5 (m, 3H), and 1.7 (m, 1H); IR ($CHCl_3$) 3440, 3020, 1748, 1696, 1526, 1350, and 1165 cm^{-1}; $[\alpha]_D$ = +16.8° (c = 0.5 in EtOH); Anal. ($C_{15}H_{16}N_2O_6$) C, H, N.

p-Nitrobenzyl (*S*)-α-Diazo-ß,5-dioxo-2-pyrrolidinebutanoate (47). To a suspension of keto-ester **46** (4.03 g, 12.6 mmol) and 4-carboxyphenylsulfonylazide (2.94 g, 12.9 mmol) in 65 mL of CH_3CN at 0 °C was added 9.0 mL of Et_3N dropwise over 5 min. After stirring an additional hour, the suspension was allowed to warm to 23 °C and stirred an additional 2h. The mixture was filtered, precipitate washed with 100 mL of CH_3CN, and the combined filtrates evaporated. The residue was taken up in CH_2Cl_2 and washed with aqueous $NaHCO_3$, water, dried ($MgSO_4$), filtered and evaporated. Trituration with Et_2O, filtering and drying *in vacuo* afforded 4.16 g (95%) of **47** as a yellow solid: ^1H NMR (270 MHz, $CDCl_3$) δ 8.25 (d, J = 10 Hz, 2H), 7.55 (d, J = 10 Hz, 2H), 6.10 (bs, 1H), 5.35 (s, 2H), 4.05 (m, 1H), 3.22 (dd, J = 21, 4 Hz, 1H), 2.90 (dd, J = 21, 10 Hz, 1H), 2.25 - 2.45 (m, 3H), and 1.8 (m, 1H); IR ($CHCl_3$) 3440, 3020, 2146, 1718, 1697, 1653, 1527, 1350, 1295, and 1015 cm^{-1}; MS, *m/e* 318 (M^+ - N_2); [a]$_D$ = +37.6° (c = 0.5 in EtOH); Anal. ($C_{15}H_{14}N_4O_6$) C, H, N.

p-Nitrobenzyl (2*R*,5*S*)-3,8-Dioxo-1-azabicyclo[3.3.0]octane-2-carboxylate (48). A solution of diazoketone **47** (4.07 g, 11.75 mmol) and rhodium (II) acetate dimer (23 mg, 0.05 mmol) in 60 mL of CH_2Cl_2 was stirred 3 days at room temperature. The mixture was diluted with CH_2Cl_2 and washed with water, brine, and

dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed, triturated with Et_2O, and dried *in vacuo* to afford 3.18 g (85%) of **48** as an off-white solid: ^1H NMR (270 MHz, $CDCl_3$) δ 8.25 (d, J = 11 Hz, 2H), 7.55 (d, J = 11 Hz, 2H), 5.3 (AB, J = 16 Hz, 2H), 4.85 (m, 1H), 4.40 (m, 1H), 3.95 - 2.25 (m, 5H), and 1.95 (m, 1H); IR ($CHCl_3$) 3020, 1776, 1749, 1701, 1525, 1421, 1350, 1333, 1215, 1182, and 1176 cm^{-1}; MS, *m/e* 318 (M^+); $[a]_D$ = +242.7° (c = 0.5 in EtOH); Anal. ($C_{15}H_{14}N_2O_6$) C, H, N.

p-Nitrobenzyl (5*S*)-3-Chloro-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (49). To a solution of ketone **48** (0.50 g, 1.58 mmol) in 6 mL of CH_2Cl_2 at -20 °C was added 1.8 mL of triphenylphosphite dichloride (1.1 M in CH_2Cl_2, 2.0 mmol) and then diisopropylethylamine (0.41 mL, 2.35 mmol). The solution was allowed to warm to room temperature and stirred 2h. The mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), filtered and evaporated. Column chromatography on silica gel (elution with Et_2O) afforded 0.37 g (69%) of **49** as a hard yellow foam: ^1H NMR (90 MHz, $CDCl_3$) δ 8.20 (d, J = 11 Hz, 2H), 7.60 (d, J = 11 Hz, 2H), 5.4 (AB, J = 16 Hz, 2H), 4.60 (m, 1H), 2.9 - 2.35 (m, 5H), and 2.0 (m, 1H); IR (KBr) 2980, 1722, 1689, 1517, 1390, 1341, 1251, 1184, and 1174 cm^{-1}; MS, *m/e* 336 (M^+), 338 ($M^+ + 2$).

p-Nitrobenzyl (5*S*)-3-Cyano-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (50). A solution of ketone **48** (11.4 g, 35.9 mmol), ZnI_2 (0.1 g, 0.31 mmol), TMSCN (12 mL, 89.8 mmol), and 18-crown-6/KCN complex[91] in 40 mL of 1,2-dichloroethane was heated to reflux for 3h. Upon cooling to room temperature, 80 mL of pyridine and $POCl_3$ (10 mL, 107 mmol) were added and the mixture heated to 50 °C for 16h. Upon cooling, the mixture was poured onto 300 mL of ice in 150 mL of 3 N HCl. This was extracted with CH_2Cl_2, and the combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered and evaporated. Column chromatography on silica gel (elution with 10% hexane/EtOAc) followed by crystallization afforded 4.7 g (40%) of **50** as amber crystals: ^1H NMR (270 MHz, $CDCl_3$) δ 8.25 (d, J = 10 Hz, 2H), 7.65 (d, J = 10 Hz, 2H), 5.45 (AB, J = 11 Hz, 2H), 4.70 (m, 1H), 3.05 (dd, J = 9, 16 Hz, 1H), 2.95 - 2.75 (m, 2H), 2.65 - 2.45 (m, 2H), and 2.00 (m, 1H); IR ($CHCl_3$) 3020, 2220, 1733, 1610, 1526, 1395, 1348, and 1191 cm^{-1}; MS, *m/e* 327 (M^+); Anal. ($C_{16}H_{13}N_3O_5$) C, H, N.

p-Nitrobenzyl (5*S*)-3-Ethylthio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (51). A solution of chloride **49** (154 mg, 0.46 mmol), diisopropylethylamine (0.32 mL, 1.84 mmol), and ethanethiol (0.27 mL, 3.7 mmol) in 3 mL of CH_3CN was stirred for 24h at room temperature. The mixture was evaporated and column chromatography on silica gel (elution with 25% hexane/EtOAc) afforded 152 mg (92%) of **51** as a yellow foam: ^1H NMR (90 MHz, $CDCl_3$) δ 8.20 (d, J = 11 Hz, 2H), 7.65 (d, J = 11 Hz, 2H), 5.4 (AB, J = 18 Hz, 2H), 4.55 (m, 1H), 3.2 - 1.9 (m, 8H), and 1.3 (t, J = 9 Hz, 3H); IR (KBr) 2970, 1695, 1550, 1514, 1374, 1341, 1331, and 1173 cm^{-1}; MS, *m/e* 362 (M^+).

p-Nitrobenzyl (5*S*)-3-Ethylsulfonyl-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylate (52). To a stirred solution of sulfide **51** (50 mg, 0.14 mmol) in 3 mL of CH_2Cl_2 at -30 °C was added m-chloroperoxybenzoic acid (66 mg, 0.31 mmol) and the mixture was allowed to warm to room temperature over 1h. After 3h, the mixture was diluted with CH_2Cl_2, aqueous $Na_2S_2O_3$, and aqueous $NaHCO_3$. The phases were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give 54 mg (100%) of **52** as a white foam: ^1H NMR (90 MHz, $CDCl_3$) δ 8.20 (d, J = 10 Hz, 2H), 7.60 (d, J = 10 Hz, 2H), 5.40 (s, 2H), 4.70 (m, 1H), 3.40 - 2.40 (m, 7H), 2.1 (m, 1H), and 1.35 (t, J = 10 Hz, 3H); IR (neat) 2900, 1710, 1600, 1515, 1380, 1340, 1305, 1180 and 1130 cm^{-1}; MS, *m/e* 394 (M^+).

(5*S*)-3-Chloro-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (53). To a solution of ester **49** (43 mg, 0.13 mmol) in 2.6 mL of DMF and 1.3 mL of 1 N HCl was added zinc dust (14 mg, 0.21 mmol) in three equal portions over 3 h with stirring at room temperature. The mixture was diluted with EtOAc and extracted with 5% aqueous $NaHCO_3$. These aqueous extracts were combined, acidified and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Crystallization afforded 8 mg (31%) of **53** as a white powder: ^1H NMR (90 MHz, $CDCl_3$) δ 4.65 (ddd, J = 8, 11, 27 Hz, 1H) and 2.95 - 1.90 (m, 6H); IR (KBr) 3440, 2920, 1707, 1700, 1685, 1624, 1618, 1609, and 1412 cm^{-1}; MS, *m/e* 201 (M^+).

(5*S*)-3-Cyano-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (54). The ester **50** (100 mg, 0.31 mmol) was processed as exemplified for the conversion of **49** to **53** (THF - HOAc solvent) to afford 28 mg (48%) of **54** as a white solid: ^1H NMR (90 MHz, $CDCl_3$) δ 4.80 (m, 1H) and 3.20 - 2.00 (m, 6H); IR ($CHCl_3$) 2900, 2500 (br), 2220, 1750, 1630, 1460, 1410, 1355, and 1150 cm^{-1}; MS, *m/e* 192 (M^+).

(5*S*)-3-Ethylthio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (55). The ester **51** (31 mg, 0.086 mmol) was processed as exemplified for the conversion of **49** to **53** to afford 8 mg (41%) of **55** as a white powder: ^1H NMR (270 MHz, $CDCl_3$) δ 14.2 (bs, 1H), 4.60 (m, 1H), 3.10 - 2.60 (m, 6H), 2.45 (m, 1H),

2.1 (m, 1H), and 1.3 (t, J = 7 Hz, 3H); IR (KBr) 3400, 3000, 1698, 1594, 1553, 1496, 1438, 1421, 1350, 1217, 1192, and 961 cm^{-1}; MS, *m/e* 227 (M^+); Anal. ($C_{10}H_{13}NO_3S$) C, H, N.

(5*S*)-3-Ethylsulfonyl-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (56). The ester **52** (54 mg, 0.14 mmol) was processed as exemplified for the conversion of **49** to **53** to afford 12 mg (34%) of **56** as a white powder: ^1H NMR (90 MHz, Me_2CO-d_6) δ 4.70 (m, 1H), 3.40 - 1.90 (m, 8H), and 1.3 (t, J = 8 Hz, 3H); MS, *m/e* 259 (M^+).

(5*S*)-3-Ethylsulfinyl-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (57). To a solution of sulfide **55** (10 mg, 0.044 mmol) in 2 mL of CH_2Cl_2 at -30 °C was added 0.1 mL of peracetic acid (0.6 M in CH_2Cl_2, 0.06 mmol) and the mixture allowed to warm to 23 °C over 1h. After 2h, the solution was diluted with CH_2Cl_2, aqueous $Na_2S_2O_3$, and aqueous $NaHCO_3$. This mixture was extracted with EtOAc, and the aqueous layer was acidified (pH = 2) and concentrated *in vacuo*. The residue was taken up in 25% HOAc/EtOAc and column chromatography (elution with same solvent) afforded 5 mg (50%) of **57**, a mixture of diastereomers, as a white powder: ^1H NMR (90 MHz, $CDCl_3$) δ 4.6 (m, 1H), 3.40 - 1.90 (m, 8H), and 1.40 (2t, J = 10 Hz, 3H); IR (KBr) 3420, 2980, 1717, 1698, 1612, 1415, 1392, 1377, 1052, and 972 cm^{-1}; MS, *m/e* 243 (M^+).

(5*S*)-2,2-Dimethyl-8-oxo-1-aza-3-oxa-bicyclo[3.3.0]octane (58). A solution of *S*-5-hydroxymethyl-2-pyrrolidinone[88] (88 g, 0.77 mol), 2,2-dimethoxypropane (200 mL, 1.63 mol), and p-toluenesulfonic acid (6.66 g, 35 mmol) in 550 mL of toluene was heated to reflux for 1.5h, at which time 160 mL of solvent was removed by distillation. Toluene (50 mL) and 50 mL of 2,2-dimethoxypropane (0.41 mol) were added and reflux continued for 40 min at which time 50 mL of solvent was removed by distillation. Upon cooling, the mixture was evaporated, residue suspended in saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford 77.5 g (65%) of **58** as a colorless liquid: ^1H NMR (90 MHz, $CDCl_3$) δ 4.40 - 4.00 (m, 2H), 3.40 (dd, J = 7, 9 Hz, 1H), 3.00 - 1.80 (m, 4H), 1.65 (s, 3H), and 1.45 (s, 3H).

(5*S*)-2,2-Dimethyl-7-oximino-8-oxo-1-aza-3-oxa-bicyclo[3.3.0]octane (59). A solution of lactam **58** (10.0 g, 64.5 mmol) and KOt-Bu (19.5 g, 174 mmol) in 85 mL of THF and 45 mL t-BuOH was stirred with warming from 0 °C to room temperature over 1h. n-Butylnitrite (38 mL, 323 mmol) was added and mixture stirred 1.5h. The suspension was poured into 500 mL of 0.1 M pH 7.0 phosphate buffer and extracted with $CHCl_3$. The aqueous layer was acidified to pH 7 and extracted with 20% isopropanol/$CHCl_3$, the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Trituration with Et_2O afforded 6.9 g (58%) of **59** as a light tan solid: ^1H NMR (270 MHz, $CDCl_3$) δ 9.40 (bs, 1H), 4.20 (m, 2H), 3.40 (m, 1H), 3.15 (dd, J = 6, 19 Hz, 1H), 2.50 (dd, J = 5, 19 Hz, 1H), 1.70 (s, 3H), and 1.55 (s, 3H); IR (KBr) 3230, 1696, 1664, 1431, 1430, 1368, 1289, 1019, and 822 cm^{-1}; MS, *m/e* 184 (M^+); $[a]_D$ = +122.2° (c = 1.0 in MeOH); Anal. ($C_8H_{12}N_2O_3$) C, H, N.

(5*S*,7*S*)-2,2-Dimethyl-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-1-aza-3-oxa-bicyclo[3.3.0]octane (60a). A solution of oxime **59** (14.1 g, 76.5 mmol) in 200 mL of MeOH and 30 mL of EtOH was hydrogenated over 10% Pd/C (1.5 g) at 70 psi of H_2 for 16h at room temperature. The mixture was filtered and evaporated. The residue was taken up in 100 mL of saturated aqueous $NaHCO_3$, 1.0 N NaOH added to adjust to pH 10, and treated with di-t-butyl dicarbonate (25 g, 115 mmol) for 16h. The mixture was extracted with $CHCl_3$, the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Trituration with Et_2O afforded 11.2 g (54%) of **60a** as a white solid: ^1H NMR (270 MHz, $CDCl_3$) δ 5.15 (bs, 1H), 4.50 (m, 1H), 4.15 (dd, J = 6, 7 Hz, 1H), 4.05 (m, 1H), 3.45 (t, J = 7 Hz, 1H), 2.85 (m, 1H), 1.65 (s, 3H), 1.60 (m, 1H), 1.50 (s, 3H), and 1.47 (s, 9H); IR ($CHCl_3$) 3420, 2985, 1702, 1499, 1412, 1379, 1298, 1253, 1238, and 1164 cm^{-1}; MS, *m/e* 271 (M^+ + H); Anal. ($C_{13}H_{22}N_2O_4$) C, H, N.

(5*S*,7*R*)-2,2-Dimethyl-7-[[(1,1-dimethylethoxy)carbonyl]amino]-8-oxo-1-aza-3-oxa-bicyclo[3.3.0]octane (60b). To a solution of oxime **59** (10.0 g, 54.4 mmol) in 50% HOAc/EtOH was added Zn (14.0 g, 214 mmol) and stirred 2h at room temperature. The mixture was filtered and evaporated. The residue was suspended in 500 mL of saturated aqueous $NaHCO_3$, 1.0 N NaOH added to adjust to pH 10, and treated with di-t-butyl dicarbonate (15 g, 69 mmol) for 70h at room temperature. The mixture was extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Crystallization afforded 13.3 g (90%) of **60b** as a white solid: ^1H NMR (90 MHz, $CDCl_3$) δ 5.10 (m, 1H), 4.40 - 4.00 (m, 3H), 3.40 (dd, J = 10, 7 Hz, 1H), 2.30 - 2.10 (m, 2H), 1.65 (s, 3H), 1.5 (m, 1H), 1.50 (s, 3H), and 1.47 (s, 9H).

(5*S*,7*S*)-5-Hydroxymethyl-3-[[(1,1-dimethylethoxy)carbonyl]amino]pyrrolidin-2-one (61a). A solution of acetonide **60a** (11.2 g, 41.5 mmol) in 96 mL of HOAc, 18 mL of CH_3CN, and 6 mL of water was stirred 20h at 23 °C. Upon evaporation, the residue was suspended in 100 mL of saturated $NaHCO_3$,

and extracted with 20% isopropanol/$CHCl_3$. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford 7.3 g (76%) of **61a** as a white solid: ^1H NMR (270 MHz, $CDCl_3$) δ 7.0 (s, 1H), 5.35 (bs, 1H), 4.20 (m, 1H), 3.70 (m, 2H), 3.40 (m, 1H), 2.60 (m, 1H), 2.30 (bs, 1H), 1.55 (m, 1H), and 1.45 (s, 9H); IR ($CHCl_3$) 3440, 3019, 1706, 1505, 1394, 1369, 1297, 1250, and 1164 cm^{-1}; MS, *m/e* 231 (M^+ + H); Anal. ($C_{10}H_{18}N_2O_4$) C, H, N.

(5*S*,7*S*)-5-Iodomethyl-3-[[(1,1-dimethylethoxy)carbonyl]amino]pyrrolidin-2-one (62a). To a solution of alcohol **61a** (2.54 g, 10.2 mmol) and Et_3N (8 mL, 57 mmol) in 20 mL of $CHCl_3$ at 0 °C was added methanesulfonyl chloride (3 mL, 38.8 mmol) and the mixture was allowed to warm to room temperature with stirring. After 2h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated to afford 2.9 g (93%) of the crude mesylate used without purification. A solution of the mesylate (2.9 g, 9.4 mmol) and sodium iodide (4.2 g, 28.2 mmol) in 35 mL of acetone was refluxed for 16h. Upon cooling, the mixture was evaporated and the residue suspended in CH_2Cl_2, filtered and the filtrate was washed with water, dried ($MgSO_4$), filtered and evaporated. Column chromatography on silica gel (elution with 25% EtOAc/hexane) afforded 2.0 g (62%) of **62a** as a white solid: ^1H NMR (270 MHz, $CDCl_3$) δ 6.4 (bs, 1H), 5.15 (bd, J = 5 Hz, 1H), 4.25 (m, 1H), 3.75 (m, 1H), 3.30 (dd, J = 5, 16 Hz, 1H), 3.15 (dd, J = 7, 16 Hz, 1H) 2.90 (m, 1H), 1.60 (m, 1H), and 1.45 (s, 9H); IR ($CHCl_3$) 3440, 3000, 1710, 1502, 1369, 1295, 1278, 1251, 1235, and 1164 cm^{-1}; MS, *m/e* 284 (M^+ - C_4H_8); Anal. ($C_{10}H_{17}N_2O_3I$) C, H, N.

(5*S*,7*R*)-5-Hydroxymethyl-3-[[(1,1-dimethylethoxy)carbonyl]amino]pyrrolidin-2-one (61b). The acetonide **60b** (1.93 g, 7.3 mmol) was processed as exemplified for the conversion of **60a** to **61a** to afford 1.56 g (92%) of **61b** as a white solid: ^1H NMR (90 MHz, Me_2CO-d_6) δ 6.90 (bs, 1H), 5.80 (bd, J = 6 Hz, 1H), 4.20 (m, 1H), 3.70 (m, 1H), 3.00 (m, 2H), 2.70 (bs, 1H), 1.70 (m, 2H), and 1.00 (s, 9H).

(5*S*,7*R*)-5-Iodomethyl-3-[[(1,1-dimethylethoxy)carbonyl]amino]pyrrolidin-2-one (62b). The alcohol **61b** (1.57 g, 6.8 mmol) was processed as exemplified for the conversion of **61a** to **62a** to afford 1.27 g (92%) of the crude mesylate as a tan solid. The mesylate (1.00 g, 3.2 mmol) was processed as above to afford 0.60 g (55%) of **62b** as a white solid: ^1H NMR (90 MHz, $CDCl_3$) δ 6.40 (bs, 1H), 5.00 (bd, J = 4 Hz, 1H), 4.20 (dt, J = 9, 5 Hz, 1H), 3.90 (m, 1H), 3.20 (m, 2H), 2.60 - 2.00 (m, 2H), and 1.40 (s, 9H); IR ($CHCl_3$) 3440, 3000, 1710, 1502, 1369, 1295, 1278, 1251, 1235, and 1164 cm^{-1}; MS, *m/e* 341 (M^+ + H); Anal. ($C_{10}H_{17}N_2O_3I$) C, H, N.

1-Methyl-4-t-butyl (±)-2-Phenylthiosuccinate (63). To a solution of methyl phenylthioacetate (3.7 g, 20.3 mmol) in 20 mL of THF at -50 °C was added lithium hexamethyldisilazane (20.5 mL of a 1.0 M solution, 20.5 mmol) and stirred for 15 min. t-Butyl bromoacetate (3.35 mL, 20.8 mmol) was added and the mixture allowed to warm 0 °C over 1h. After an additional 1h, the mixture was poured into 1 N HCl and extracted with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and evaporated to afford 6.1 g (100%) of **63** as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.00 (dd, J = 7, 9 Hz, 1H), 3.70 (s, 3H), 3.00 - 2.50 (m, 2H), and 1.40 (s, 9H).

t-Butyl 3-Cyano-3-phenylthiopropanoate (65). Phenylthioacetonitrile (50 g, 335 mmol) was processed as exemplified for the conversion of methyl phenylthioacetate to **63** to afford 18.1 g (20%) of **65** as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.70 - 7.30 (m, 5H), 4.05 (t, J = 7 Hz, 1H), 2.70 (dd, J = 7, 1 Hz, 2H), and 1.45 (s, 9H).

1-Methyl-4-t-butyl (E,Z)-2-Phenylthiobut-2-enedioate (67). A solution of sulfide **63** (1.95 g, 6.6 mmol) and N-chlorosuccinimide (0.93 g, 6.9 mmol) in 10 mL of THF and 40 mL of CCl_4 was refluxed for 12h. Upon cooling, the mixture was evaporated. The residue was suspended in hexane, filtered, and the filtrate evaporated to afford 2.0 g (92%) of crude chloride **64** as a light yellow oil used without purification. To a solution of chloride **64** (5.7 g, 17.2 mmol) in 50 mL of CH_2Cl_2 at -78 °C was added DBU (2.8 mL, 18.7 mmol) and the mixture allowed to warm to 0 °C over 0.5h. The mixture was diluted with CH_2Cl_2 and washed with 0.2 N HCl, dried ($MgSO_4$), filtered and evaporated to afford 5.0 g (98%) of **67**, 60 : 40 isomer ratio, as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.30 & 5.50 (s, 1H), 3.65 & 3.30 (s, 3H), and 1.50 & 1.40 (s, 9H).

1-Methyl-4-t-butyl (E,Z)-2-Phenylsulfinylbut-2-enedioate (68). To a solution of sulfide **67** (2.32 g, 7.95 mmol) in 75 mL of CH_2Cl_2 at -42 °C was added peracetic acid (1.67 mL of a 5.2 M solution, 8.75 mmol) and the mixture was allowed to warm to room temperature over 1h. After an additional 1h, 2.0 mL of Me_2S was added and stirred 30 min. The solution was flushed through silica gel (elution with CH_2Cl_2 changing to Et_2O once residual **67** had eluted) to afford 1.95 g (79%) of **68** as a pale yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.70 -

7.10 (m, 5H), 7.20 & 6.90 (s, 1H), 3.70 & 3.60 (s, 3H), and 1.60 & 1.50 (s, 9H); IR ($CHCl_3$) 3011, 1721, 1445, 1371, 1259, 1153, and 1052 cm^{-1}; MS, *m/e* 310 (M^+).

t-Butyl (E,Z)-3-Cyano-3-phenylthiopropenoate (69). Sulfide **65** (12.3 g, 46.7 mmol) was processed as exemplified for the conversion of **63** to **67** to afford 12.2 g (88%) of crude chloride **66** as a light yellow oil used without purification. Chloride **66** (12.2 g, 41.1 mmol) was processed as above to afford 9.7 g (90%) of **69** as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.40 (s, 5H), 6.20 & 4.80 (s, 1H), and 1.55 & 1.20 (s, 9H); MS, *m/e* 261 (M^+).

t-Butyl (E,Z)-3-Cyano-3-phenylsulfinylpropenoate (70). Sulfide **69** (5.59 g, 21.4 mmol) was processed as exemplified for the conversion of **67** to **68** to afford 4.94 g (83%) of **70** as a light yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.90 - 7.40 (m, 5H), 6.80 & 6.70 (s, 1H), and 1.40 & 1.39 (s, 9H); IR ($CHCl_3$) 2985, 2240 (w), 1713, 1446, 1373, 1233, 1151 and 1059 cm^{-1}; MS, *m/e* 277 (M^+).

t-Butyl (5*S*,7*S*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-3-carbomethoxy-1-aza-bicyclo[3.3.0]oct-2-ene-2-carboxylate (71a). To a solution of iodide **62a** (595 mg, 1.75 mmol) in 7 mL of THF at -78 °C was added lithium hexamethyldisilazane (1.9 mL of a 1.0 M solution, 1.9 mmol) and stirred for 20 min. Sulfoxide **68** (650 mg, 2.09 mmol) in 4 mL of cold THF was added dropwise and the mixture allowed to warm to room temperature over 3h. The mixture was poured into aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. Crystallization afforded 420 mg (61%) of **71a** as a light yellow solid: ^1H NMR (90 MHz, $CDCl_3$) δ 5.10 (bd, J = 7 Hz, 1H), 4.70 - 4.10 (m, 2H), 3.70 (s, 3H), 3.20 - 2.50 (m, 3H), 1.80 (q, J = 12 Hz, 1H), 1.55 (s, 9H), and 1.40 (s, 9H); IR (KBr) 3381, 1727, 1703, 1693, 1529, 1406, 1394, 1337, 1254 and 1155 cm^{-1}; MS, *m/e* 396 (M^+).

t-Butyl (5*S*,7*R*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-carbomethoxy-8-oxo-1-aza-bicyclo[3.3.0]oct-2-ene-2-carboxylate (71b). Iodide **62b** (255 mg, 0.75 mmol) and sulfoxide **68** (300 mg, 0.97 mmol) were processed as exemplified for the conversion of **62a** to **71a** to afford 150 mg (50%) of **71b** as a light cream foam: ^1H NMR (90 MHz, $CDCl_3$) δ 5.20 (d, J = 7 Hz, 1H), 4.80 (m, 1H), 4.30 (m, 1H), 3.70 (s, 3H), 2.80 (m, 2H), 2.40 (m, 2H), 1.60 (s, 9H), and 1.40 (s, 9H); IR ($CHCl_3$) 3019, 1709, 1408, 1394, 1369, 1298, 1248, 1225, and 1157 cm^{-1}; MS, *m/e* 396 (M^+).

t-Butyl (5*S*,7*S*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-3-cyano-1-azabicyclo-[3.3.0]oct-2-ene-2-carboxylate (72a). Iodide **62a** (2.86 g, 8.4 mmol) and sulfoxide **70** (2.53 g, 9.12 mmol) were processed as exemplified for the conversion of **62a** to **71a** to afford 2.2 g (72%) of **72a** as a white solid: ^1H NMR (270 MHz, $CDCl_3$) δ 5.10 (bs, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 3.10 (dd, J = 10, 19 Hz, 1H), 3.05 (m, 1H), 2.75 (dd, J = 11, 19 Hz, 1H), 1.85 (q, J = 10 Hz, 1H), 1.55 (s, 9H), and 1.45 (s, 9H); IR ($CHCl_3$) 3019, 2240 (w), 1740, 1705, 1372, 1359, 1342, 1307, 1252, and 1158 cm^{-1}; MS, *m/e* 363 (M^+); Anal. ($C_{18}H_{25}N_3O_5$) C, H, N.

t-Butyl (5*S*,7*R*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-3-cyano-1-azabicyclo-[3.3.0]oct-2-ene-2-carboxylate (72b). Iodide **72b** (290 mg, 0.85 mmol) and sulfoxide **70** (400 mg, 1.44 mmol) were processed as exemplified for the conversion of **62a** to **72a** to afford 55 mg (18%) of **72b** as a white solid: ^1H NMR (360 MHz, $CDCl_3$) δ 5.25 (bs, 1H), 4.85 (m, 1H), 4.30 (m, 1H), 3.05 (dd, J = 9, 15 Hz, 1H), 2.70 (dd, J = 12, 15 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.55 (s, 9H), and 1.45 (s, 9H); IR ($CHCl_3$) 3019, 2240 (w), 1704, 1371, 1355, 1313, 1252, and 1159 cm^{-1}; MS, *m/e* 363 (M^+); Anal. ($C_{18}H_{25}N_3O_5$) C, H, N.

(5*S*,7*S*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-3-carbo-methoxy-1-aza-bicyclo[3.3.0]oct-2-ene-2-carboxylic acid (73a). A solution of carbamate **71a** (106 mg, 0.27 mmol) in 3 mL of TFA was stirred 3h at room temperature. The solution was evaporated and residual TFA removed by azeotropic distillation *in vacuo* with CH_3CN. The resulting solid was suspended in 20 mL of 1:1 acetone/10% aqueous $NaHCO_3$ and treated with the hydroxybenzotriazole active ester of syn-(2-amino-4-thiazolyl)-(methoximino)acetic acid (172 mg, 0.54 mmol). After stirring 16h, the mixture was diluted with water and extracted with CH_2Cl_2. The aqueous layer was acidified to pH 4 and extracted with CH_2Cl_2 then $CHCl_3$. The aqueous layer was evaporated, the residue suspended in CH_3CN, filtered and evaporated. Crystallization afforded 38 mg (34%) of **73a** as a white solid: ^1H NMR (90 MHz, D_2O) δ 7.10 (s, 1H), 5.00 (m, 1H), 4.40 (m, 1H), 3.90 (s, 3H), 3.65 (s, 3H), 2.80 (m, 3H), and 2.05 (q, J = 11 Hz, 1H); IR (KBr) 3380, 2820 br, 1728, 1700, 1686, 1671, 1667, 1652, 1631, 1414, and 1244 cm^{-1}; MS, *m/e* 423 (M^+).

(5*S*,7*R*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-3-carbo-methoxy-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (73b). Carbamate **71b** (100 mg, 0.25 mmol) and was processed as exemplified for the conversion of **71a** to **73a** to afford 28 mg (26%) of **73b** as a white solid:

^{1}H NMR (90 MHz, D_2O) δ 6.95 (s, 1H), 5.00 - 4.20 (m, 2H), 3.95 (s, 3H), 3.65 (s, 3H), 2.75 (m, 2H), and 2.40 (m, 2H); IR (KBr) 2997, 1721, 1694, 1683, 1632, 1549, 1416, 1302, and 1048 cm^{-1}; MS, *m/e* 423 (M^+).

(5*S*,7*S*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-3-cyano-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (74a). Carbamate **72a** (100 mg, 0.25 mmol) and was processed as exemplified for the conversion of **71a** to **73a** to afford 16 mg (15%) of **74a** as a white solid: ^{1}H NMR (270 MHz, Me_2SO-d_6) δ 8.95 (d, J = 7 Hz, 1H), 7.20 (bs, 2H), 7.00 (s, 1H), 4.90 (m, 1H), 4.50 (m, 1H), 3.80 (s, 3H), 3.05 (dd, J = 10, 18 Hz, 1H), 2.75 (dd, J = 11, 18 Hz, 1H), 2.65 (m, 1H), 2.10 (q, J = 11 Hz, 1H), 1.55 (s, 9H), and 1.45 (s, 9H); IR (KBr) 3345, 3340, 2240 (w), 1716, 1655, 1614, 1535, 1373, 1345, and 1036 cm^{-1}; MS, *m/e* 390 (M^+).

(5*S*)-3-Ethylthio-7-oximino-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (75). To a solution of LDA (2.12 mmol) in 6 mL of THF and 1.25 mL of DMPU at -78 °C was added a THF solution of acid **55** (205 mg, 0.90 mmol). After 0.3h, n-butylnitrite (0.4 mL, 3.5 mmol) was added and the mixture warmed to -20 °C and stirred 0.3h The suspension was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The aqueous layer was acidified to pH 1 and extracted with EtOAc and CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. Trituration with EtOAc and column chromatography (elution with 9:9:2 EtOAc/CH_2Cl_2/HOAc) afforded 74 mg (32%) of **75** as a white solid. Silylation with BSTFA aided in its characterization: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.40 - 2.50 (m, 6H), 1.35 (t, J = 7 Hz, 3H), 0.40 (s, 9H), and 0.30 (s, 9H).

(5*S*,7*S*) and (5*S*,7*R*)-7-[[(1,1-Dimethylethoxy)carbonyl]amino]-8-oxo-3-ethylthio-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (76a, 76b). To a suspension of oxime **75** (74 mg, 0.29 mmol) in 5 mL of EtOH and 5 mL HOAc was added Zn (115 mg, 1.76 mmol) in two portions over 1.5h with stirring. After 4h, the mixture was filtered and evaporated. The residue was suspended in 8 mL of 10% aqueous $NaHCO_3$, pH adjusted to 10 with 1 N NaOH, and 4 mL p-dioxane was added followed by di-t-butyl dicarbonate (0.5 mL, 2.1 mmol). The mixture was stirred 16h, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The aqueous layer was acidified to pH 4, extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford 80 mg (80%) of **76a** and **76b**, a 60:40 mixture of diastereomers, as a white solid: ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.30 (m, 1H), 4.9 - 4.0 (m, 2H), 3.20 - 1.80 (m, 6H), 1.45 & 1.43 (s, 9H), and 1.30 (t, J = 7 Hz, 3H).

(5*S*,7*S*) and (5*S*,7*R*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-3-ethylthio-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (77a, 77b). A solution of acids **76a** and **76b** (89 mg, 0.26 mmol) and 4 mL of TFA was stirred 0.25h at room temperature and then evaporated. The residue was taken up in 5 ml of water and 5 mL of acetone, pH adjusted to 8 using $NaHCO_3$, and the hydroxybenzotriazole active ester of syn-(2-amino-4-thiazolyl)(methoximino)acetic acid (172 mg, 0.54 mmol) was added. The mixture was stirred 0.5h maintaining the pH at 8 using $NaHCO_3$. Water was added, the aqueous layer extracted with CH_2Cl_2, and the aqueous layer was acidified to pH 4 and further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Crystallization afforded 47 mg (43%) of **77a** and **77b**, a 60:40 mixture of diastereomers, as a white solid: ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.80 & 8.30 (d, J = 8 Hz, 1H), 6.90 & 6.75 (s, 1H), 5.80 (bs, 1H), 5.00 - 4.10 (m, 2H), 3.80 (s, 3H), 3.00 - 1.70 (m, 6H), and 1.10 (t, J = 7 Hz, 3H); IR (KBr) 3375, 3320, 1673, 1614, 1538, 1467, 1450, 1379, and 1046 cm^{-1}; MS, *m/e* 425 (M^+).

(5*S*,7*S*) and (5*S*,7*R*)-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-3-ethylsulfinyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (78a and 78b). A solution of acids **77a** & **77b** (20 mg, 0.047 mmol) and peracetic acid (0.16 mL of a 0.3 M CH_2Cl_2 solution, 0.048 mmol) in 4 mL of $CDCl_3$ and 0.5 mL of HOAc was stirred at -40 °C for 15 min then allowed to warm to 0 °C over 1h. Me_2S (1 mL) was added and the mixture stirred for 1h at 23 °C. The solution was filtered through Na_2SO_4, evaporated and the removal of DMSO was affected by azeotropic distillation with toluene *in vacuo* to afford 21 mg (100%) of **78a** & **78b**, a mixture of diastereomers, as a cream colored solid: ^{1}H NMR (90 MHz, $CDCl_3$-Me_2SO-d_6) δ 9.0 - 8.0 (m, 1H), 6.9 - 6.4 (s, 1H), 5.8 (bs, 1H), 5.0 - 4.0 (m, 2H), 3.7 (s, 3H), 3.2 - 1.8 (m, 6H), 1.10 (m, 3H).

(5*S*,7*S*) and (5*S*,7*R*)-3-syn-7-[2-(2-Aminothiazol-4-yl)-2-methoximinoacetamido]-8-oxo-ethylsulfonyl-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (79a and 79b). A solution of acids **78a** and **78b** (4 mg, 0.01 mmol) and MCPBA (6 mg, 0.03 mmol - added in 3 equal portions over 24h) in 1.4 mL of 1:1 HOAc/$CDCl_3$ was stirred at room temperature for 30h. Me_2S (0.3 mL) was added and the mixture stirred for 16h at room temperature. The mixture was evaporated and column chromatography on HP20-SS (elution with 2 - 4% CH_3CN/H_2O) afforded 1.7 mg (41%) of **79a** and **79b**, a mixture of diastereomers, as a white solid. HPLC

on μ-Bondapak (elution with 5% CH_3CN/0.5% NH_4OAc/H_2O) separated the major (ß-side-chain) **79a**: ^1H NMR (300 MHz, D_2O) δ 7.15 (s, 1H), 5.15 (m, 1H), 4.6 (m, 1H), 4.10 (s, 3H), 3.35 (m, 2H), 3.15 (dd, J = 9, 14 Hz, 1H), 2.90 (m, 2H), 2.25 (q, J = 11 Hz, 1H), and 1.35 (t, J = 7 Hz, 3H); IR (KBr) 3073, 3046, 3004, 1726, 1661, 1632, 1403, 1305, 1133, and 1046 cm^{-1}; MS, *m/e* 458 (M^+ + H).
The minor (α-side-chain) **79b**: ^1H NMR (300 MHz, D_2O) δ 7.05 (s, 1H), 5.00 (m, 1H), 4.6 (m, 1H), 4.05 (s, 3H), 3.35 (m, 2H), 3.10 (dd, J = 10, 16 Hz, 1H), 2.90 (dd, J = 10, 12 Hz, 1H), 2.60 (m, 1H), 2.45 (m, 1H), and 1.35 (t, J =7 Hz, 3H); IR (KBr) 3159, 3147, 3048, 1717, 1655, 1635, 1406, and 1134 cm^{-1}; MS, *m/e* 457 (M^+).

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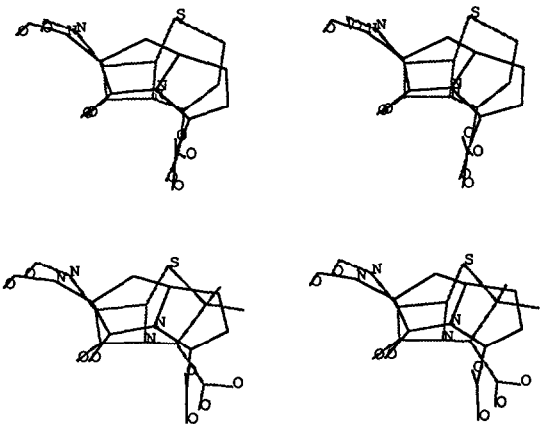

(94) Difference NOE measurements (although not obtainable on all derivatives) were consistent with these assignments.