Tetrahedron Vol. 48, No. 5, pp. 777-796, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

The Chemistry of Substituted Pyrazolidinones; Applications to the Synthesis of Bicyclic Derivatives

Robert J. Ternansky* and Susan E. Draheim

Lilly Research Laboratories, Eli Lilly and Co., Lilly Corporate Center, Indianapolis, Indiana 46285

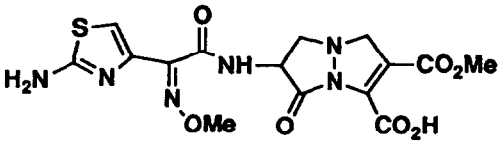
(*Received in USA* 1 *November* 1991)

Key Words: pyrazolidinones; antibacterial; gamma lactam; fused pyrazolidinones

Abstract: Methodology for the selective chemical derivatizations of substituted pyrazolidinones is described. The application of these methods to the preparation of [4.3.0] and [3.3.0] bicyclic systems is also discussed. The importance of these latter systems as nuclei of antibacterial agents with potential utility in the treatment of infectious disease provides the motivation for these investigations.

Initial reports of the antibacterial activity of pyrazolidinone-containing compounds such as LY 173013 (Figure 1)[1] prompted us to initiate a systematic study of the chemical properties of these novel heterocyclic systems. The ultimate goal of our investigation was to develop new synthetic methodologies that would provide ready access to a diverse array of structural derivatives. It was our hope that the availability of such analogues would allow us to prepare compounds having improved biological activities. This report details the results of our synthetic studies.[2,3]

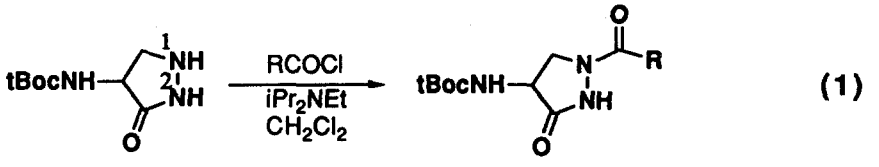
Figure 1



LY 173013

The monocyclic pyrazolidinone **1**, which served as the starting point for our chemical investigations, was readily prepared in large quantities from serine and hydrazine utilizing known methodology.[1c] For the majority of the studies reported herein, **1** was used as its racemate. The two enantiomers of **1** could be independently prepared from the appropriate D or L-serine using alternate methodology.[1f,h] Beginning with this heterocyclic building block, our initial goal was to chemically distinguish (via selective functionalization) the two nitrogens which structurally constitute the pyrazolidinone ring. It was found that the N-1 nitrogen exhibited a higher degree of nucleophilicity than N-2. Thus, selective acylation was readily accomplished at N-1 using standard conditions (eq 1). The yields in these cases were acceptable (41-88%) and no products resulting from multiple acylations were observed. It was anticipated that selective monoalkylation of N-1 would present a more difficult challenge. Indeed, when treated with allyl bromide and base in dimethylformamide, **1** was converted to a mixture of mono and di-alkylated products (eq 2). The monoalkylated product **6** was readily isolable due to the insolubility of the ylide **7** in standard organic solvents such as ethyl acetate. Although this procedure was functional, we sought alternate means to achieve the desired selective alkylation. Success was realized in the conjugate addition of **1** to activated olefins (eq 3). In these cases, high yields of the monofunctionalized

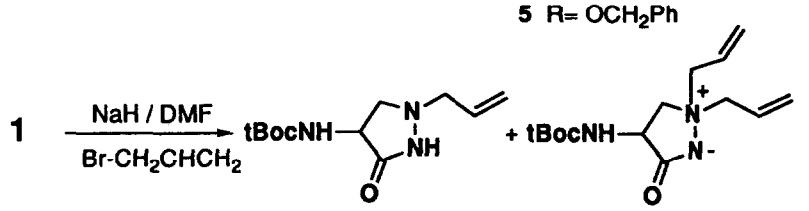
derivatives were obtained under very mild conditions. Finally, monofunctionalization at N-1 could also be realized via condensation with a ketone or aldehyde (other than formaldehyde) as previously reported by Jungheim, et. al.[1a]. The resulting ylide product could be reduced via catalytic hydrogenation or by the action of sodium cyanoborohydride. (eq 4).[4]



(1)

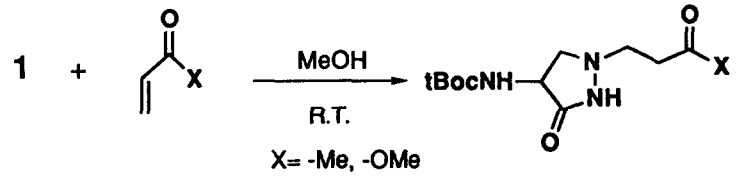
1

2 R= Me
3 R= $(CH_2)_8CH_3$
4 R= Ph
5 R= OCH_2Ph



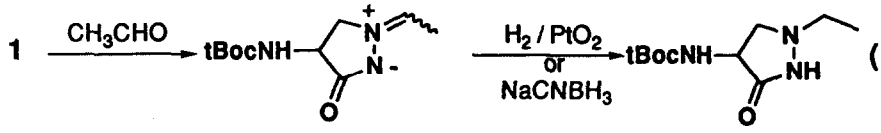
(2)

6 7



(3)

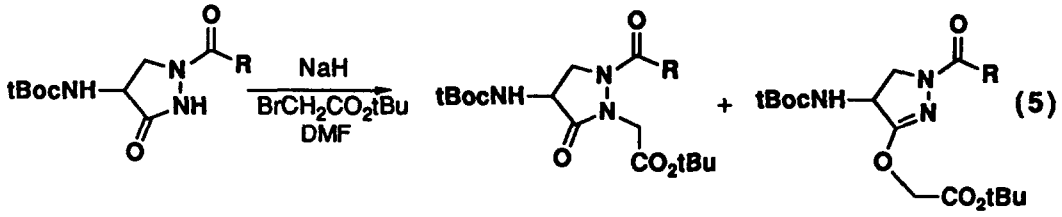
8 X= Me
9 X= OMe



(4)

10 11

The pyrazolidinones obtained from these N-1 functionalization procedures were then available for further modification via derivatization at N-2. This could be accomplished for example by reaction of the monoacylated compounds (2-5) with an alkylating agent and sodium hydride in dimethylformamide. In the case of compounds 2-4, N- and O-alkylated products were isolated in a ratio of approximately 3:1. In the case of the alkylation of 5, the products were obtained in a 12:1 ratio with N-alkylation predominating (eq 5). The two products were distinguished by examination of their proton and carbon NMR spectra as well as their IR stretching frequencies (see experimental).

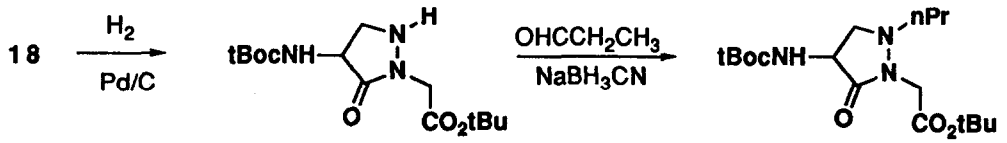


R= Me	12	13
R= $(CH_2)_8CH_3$	14	15
R= Ph	16	17
R= OCH_2Ph	18	19

Compound **18** could be further transformed via reductive removal of the CBZ group at N-1. This N-2 mono-substituted derivative (**20**) could then be further transformed by reaction at N-1 For example, acylation of **20** with benzoyl chloride provided **16**. Alkylation with 1-propionaldehyde led to **21**. (Scheme I). These procedures provided alternate means for the regiospecific appendage of functionality to the pyrazolidinone nucleus.

Having defined this repertoire of selective nitrogen functionalizations of the pyrazolidinone monocycle **1**, we were prepared to develop methodology for the construction of fused-ring systems.

Scheme I



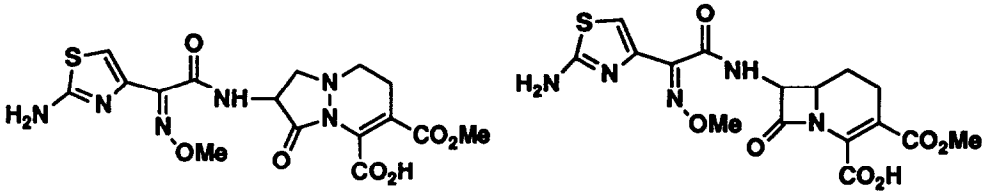
20 **21**

SYNTHESIS OF [4.3.0] RING SYSTEMS

Initially, our attention was focused on the preparation of homologues of the biologically active [3.3.0] pyrazolidinones (such as LY 173013). In particular, we directed our efforts to synthesis of [4.3.0] bicyclic pyrazolidinones (eg, **30a**). Such compounds can also be regarded as gamma-lactam analogues of the potent 1-carbacephem antibacterial agents such as **22** (LY 212280), Figure II.[5]

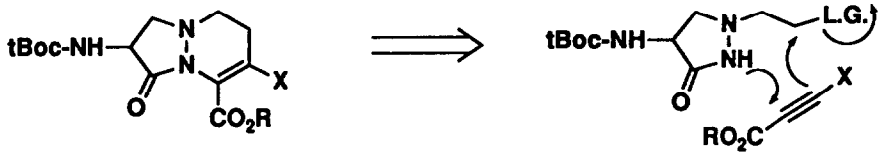
The plan for appendage of the six-membered ring to the pyrazolidinone monocycle **1** was based on the ready availability of various substituted pyrazolidinones (*vide supra*). We viewed the construction of the fused ring system as proceding via appropriate cycloaddition of an acetylene or acetylene equivalent to a suitably substituted lactam. The retrosynthesis is graphically depicted in Scheme II.

FIGURE II



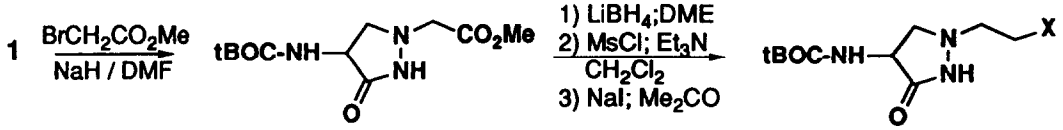
30a 22 (LY 212280)

SCHEME II



The requisite functionalized pyrazolidinone was prepared by applying the methodology previously discussed. Thus, alkylation of **1** with bromomethyl acetate provided the ester **23**. (Scheme III). Selective reduction of the ester was achieved through the action of lithium borohydride.[7] The resulting alcohol **24** was converted to the corresponding iodide **26** via the mesylate **25** (Scheme III). For the acetylenic component of our proposed cyclization, we chose the vinyl sulfoxide **27**.[6] With these two substrates in hand, the stage was now set for an attempt at ring annulation.

SCHEME III



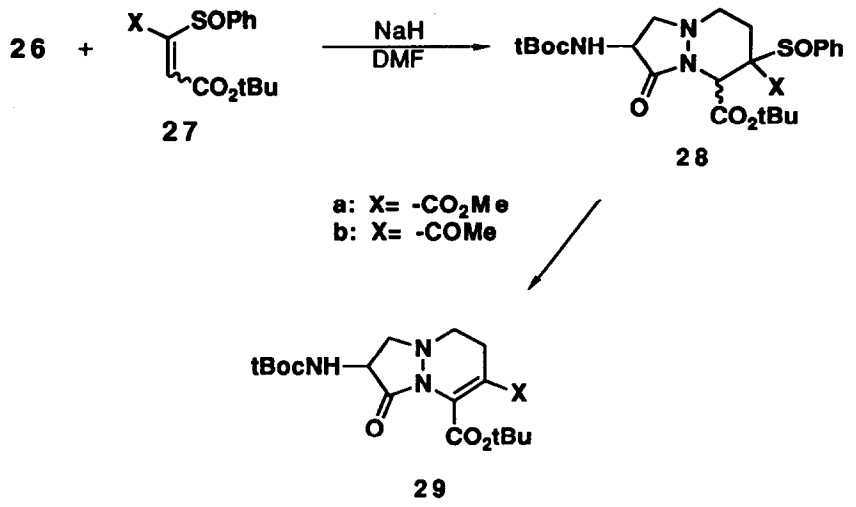
23

24 X= OH
25 X= OMs
26 X=I

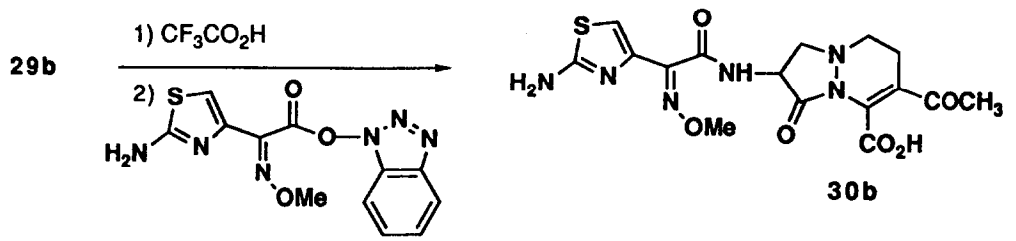
The iodide **26** was treated with sodium hydride in dimethylformamide at 0°C followed by addition of the vinyl sulfoxide **27**. After warming to room temperature, a crude mixture of two sulfoxides (**28**) was isolated via extractive workup. The mixture of sulfoxides **28** was directly treated with DBU in methylene chloride to provide the desired [4.3.0] pyrazolidinone nucleus **29** (overall yield 36%; Scheme IV). The success of this ring-appending sequence was confirmed by X-ray analysis of **29a**.[8]

The nuclei obtained in this manner (**29a,b**) were converted into derivatives suitable for biological evaluation via a deblocking-acylation procedure as depicted in Scheme V. Unlike their lower homologues, pyrazolidinones **30a** and **30b** did not exhibit antibacterial activity *in vitro*. This rather surprising result prompted us to focus our synthetic attention on the preparation of [3.3.0] fused pyrazolidinone analogues.

SCHEME IV



SCHEME V

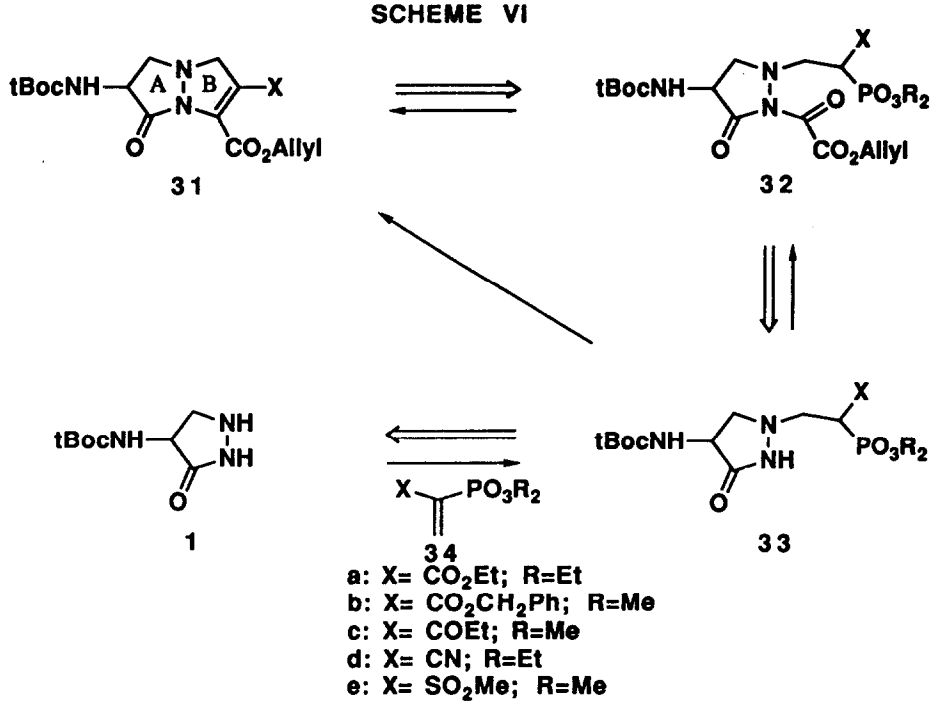


SYNTHESIS OF [3.3.0] RING SYSTEMS

Our intention for the development of a new synthetic process for the construction of [3.3.0] pyrazolidinones was to provide ready accessibility to a large number of substituted derivatives. This would allow for a detailed study of structure-activity relationships within this unique class of antibacterial agents. The proposed route, outlined in retrosynthetic fashion in Scheme VI, was viewed as desirable in terms of length, regiospecificity (in ring B construction), and flexibility (for its application to the preparation of a variety of substituted derivatives). Thus, in only a few synthetic transformations, ring B could be appended in a regiocontrolled manner by selective, stepwise functionalization of the ring nitrogens in pyrazolidinone **1** (*vide supra*). Simple variation of the group designated "X" in the vinyl phosphonate reagent **34** would provide accessibility to a variety of differentially substituted [3.3.0] systems.

In our initial investigation into the feasibility of this approach, pyrazolidinone **1** was selectively alkylated at N-1 in high yield by stirring with vinyl phosphonate **34a** in ethanol at room temperature. Removal of solvent and chromatography provided a 63% yield of **33a**. Subsequent acylation of N-2 gave rise to the functionalized pyrazolidinone **32a** in 47% yield after flash chromatography. The glyoxamide bond of **32a** was found to be

SCHEME VI



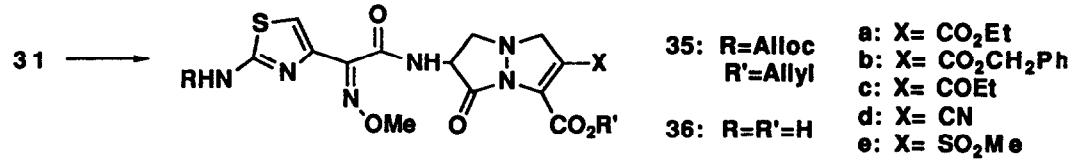
very labile to hydrolysis making isolation of pure compound problematic. Treatment of **32a** with sodium hydride in tetrahydrofuran at low temperature provided the desired bicyclic **31a** in 67.5% yield. Although the overall yield of 20% for this sequence is less than optimal, the rapidity with which the nucleus can be produced in gram quantities makes it very attractive.

A major improvement in this route to [3.3.0] fused pyrazolidinones was discovered during the preparation of the benzyl ester **31b**. Specifically, it was found to be unnecessary to isolate the sensitive intermediate **32b**. Rather, the intramolecular Wadsworth-Horner-Emmons condensation could be effected by simply adding a second equivalent of tertiary amine base to the step involving the acylation of N-2. Thus, **1** was reacted with **34b** providing **33b** in 48% yield. Treatment of **33b** with one equivalent of allyloxalyl chloride and two equivalents of *N,N*-diisopropylethyl amine in methylene chloride provided **31b** directly in 63% yield. This procedure was successfully applied to the preparation of bicyclic pyrazolidinones **31c-e**. (Scheme VI). As with the [4.3.0] pyrazolidinones, the [3.3.0] nuclei prepared in this fashion were deblocked and acylated with an appropriate sidechain providing compounds suitable for biological evaluation (Scheme VII). Much to our delight, the [3.3.0] fused pyrazolidinones (**36a-e**) exhibited impressive antibacterial activity against a broad spectrum of organisms.[10]

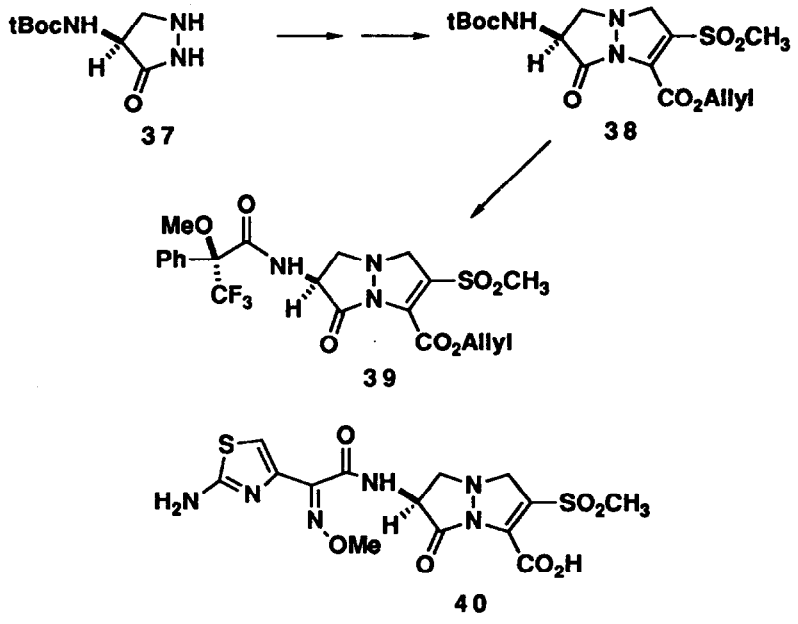
Application of this methodology to the preparation of chiral products was also successful. Thus, **37**[1h] was converted into **38** in good overall yield utilizing the methodology previously described (Scheme VIII). Preservation of the chirality present in **37** was confirmed by conversion of **38** to the functionalized derivative **39**[9] which clearly showed a 95% ee via H^1 NMR analysis of the crude product. As anticipated, antibacterial **40** (prepared from **38**) exhibited twice the antibacterial activity *in vitro* as its enantiomeric mixture (**36e**).[10] This

result supported our assumption that only one (the 7-S) isomer of the racemic pair would exhibit strong binding to the target enzyme of the bacteria contributing to biological activity.

SCHEME VII



SCHEME VIII



SUMMARY

Methodolgy has been established for the selective functionalization of substituted pyrazolidinone heterocycles. This has provided the basis for synthetic accessibility to [4.3.0] and [3.3.0] fused pyrazolidinone ring systems. The [3.3.0] pyrazolidinones have been shown to serve as nuclei for an important novel class of antibacterial agents. Further progress on the development of the medicinal chemistry of these intriguing new agents will be discussed elsewhere.

Acknowledgements: The authors gratefully acknowledge Drs. L.D. Hatfield and R.W. Burchfield for their support. We thank the physical chemistry department for providing analytical and spectral data, Dr. J.L. Ott and co-workers for microbiological evaluations, and Mr. P. Pranc for supplying quantities of **1** and **37**.

EXPERIMENTAL

All reactions described herein were performed under an inert atmosphere of dry nitrogen in flame-dried glassware unless otherwise noted. All reagents were used as supplied unless stated otherwise. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300MHz with a General Electric QE-300 instrument, at 270MHz with a Brucker W-M instrument and at 90MHz with a Joel FX-90 instrument. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane. IR spectra were recorded on a Nicolet MX-1 FT-IR, optical rotations were measured on a Perkin-Elmer 241 spectrometer, and UV spectra were obtained on a Cary 219. The mass spectral data were obtained on either a CEC-21-140 or a Varian MAT-731 spectrometer. All MPLC separations were conducted on Merck Lobar columns (LiChroprep RP-18) with the help of a Fluid Metering Inc. pump. Analytical HPLC separations were performed on a Varian chromatographic system utilizing a MicroPak MCH-5N-cap 15cmx4mm column and a variable wavelength UV detector set to record at 254nm.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-acetyl-pyrazolidin-3-one (2). To a cold (0°C), magnetically stirred suspension of **1** (10.0 g, 0.05 mol) in methylene chloride (150 mL) was added *N,N*-diisopropylethylamine (6.46 g, 0.05 mol). The resultant solution was stirred for 4 h, washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The resulting white solid was triturated with ether and filtered to provide 4.95 g (41%) of **2**: mp 149.5-153°C; IR ($CHCl_3$, cm^{-1}) 3420, 2980, 1710, 1654, 1498, 1394, 1370, 1293, 1233, 1215, 1161; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.29 (br s, 1H), 4.57 (br s, 2H), 3.78 (br s, 1H), 2.09 (s, 3H), 1.45 (s, 9H); MS m/z (M^+) 243.

Anal. Calcd for $C_{10}H_{17}N_3O_4$: C, 49.37; H, 7.04; N, 17.27. Found: C, 49.23; H, 6.79; N, 17.05.

Compounds **3-5** were prepared in a fashion similar to that described for **2**:

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-decanoyl-pyrazolidin-3-one (3) (68%): mp 154-155°C; IR ($CHCl_3$, cm^{-1}) 3410, 2930, 1710, 1649, 1497, 1394, 1370, 1294, 1215, 1162;.^{1}H NMR (270 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 5.28 (br s, 1H), 4.68-4.48 (m, 2H), 4.74 (br t, 1H), 2.28 (br t, 2H), 1.66 (br t, 4H), 1.45 (s, 9H), 1.26 (br s, 10H), 0.87 (br t, 3H); MS m/z (M^+) 355.

Anal. Calcd for $C_{18}H_{33}N_3O_4$: C, 60.82; H, 9.36; N, 11.82. Found: C, 60.96; H, 9.13; N, 11.75.

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzoyl-pyrazolidin-3-one (4). (88%): mp 185-186°C; IR ($CHCl_3$, cm^{-1}) 3420, 2990, 1711, 1642, 1497, 1394, 1370, 1293, 1233, 1207, 1162; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 7.68-7.42 (m, 5H), 5.27 (br s, 1H), 4.64 (t, J=12 Hz, 1H), 4.58-4.44 (m, 1H), 3.88 (t, J=12 Hz, 1H), 1.44 (s, 9H); MS m/z (M^+) 305.

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.93; H, 6.07; N, 13.60.

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzyloxycarbonyl-pyrazolidin-3-one (5).The product was crystallized from ethyl acetate to yield 59.65 g (71%) of a white powder: mp 154-5°C; IR ($CHCl_3$, cm^{-1}) 3440, 2980, 1712, 1499, 1394, 1370, 1326, 1294, 1290, 1215, 1162; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 7.38 (s, 5H), 5.21 (br s, 3H), 4.66 (br t, 1H), 4.55-4.35 (m, 1H), 3.63 (t, J=12 Hz, 1H), 1.45 (s, 9H); MS m/z (M^+) 335.

Anal. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.32; H, 6.32; N, 12.46.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(3-prop-1-ene)-pyrazolidin-3-one (6) and 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-3-oxo-1,1-[*bis*-(3-prop-1-ene)]-pyrazolidinium Ylide (7). To a cold (0°C), magnetically stirred suspension of sodium hydride (657 mg, 27.39 mmol) in *N,N*-dimethylformamide (20 mL) was added **1** (5.0 g, 24.9 mmol) disssolved in *N,N*-dimethylformamide (25 mL). The cold mixture was stirred for 50 min before addition of allyl bromide (3.0 g,

24.9 mmol). A brief, vigorous reaction ensued. The resulting mixture was stirred for 13 h allowing the cooling bath to warm to room temperature. The mixture was treated with xylenes (45 mL) and concentrated *in vacuo*. The crude product was dissolved in methylene chloride and washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide an oil which upon treatment with ethyl acetate formed a white solid. This solid was filtered and dried to provide 647 mg of **7**. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (elution with ethyl acetate) to provide 1.16 g (19%) of **6** as a thick yellow oil. A sample of **6** was crystallized from ethyl acetate and hexane: mp 98-100°C; IR ($CHCl_3$, cm^{-1}) 3430, 2980, 1708, 1499, 1394, 1369, 1292, 1239, 1215, 1163; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 5.95-5.77 (m, 1H), 5.38-5.10 (m, 3H), 4.64-4.44 (m, 1H), 3.81 (br t, 1H), 3.49-3.30 (m, 2H), 3.17-2.94 (m, 1H), 1.45 (s, 9H); MS (EI) m/z (M+1) 242.

Anal. Calcd for $C_{11}H_{19}N_3O_3$: C, 54.76; H, 7.94; N, 17.42. Found: C, 54.97; H, 7.88; N, 17.20.

7 : mp 163-4°C; IR ($CHCl_3$, cm^{-1}) 3410, 2985, 1703, 1623, 1486, 1368, 1284, 1215, 1165, 950; ^1H NMR (300 MHz, DMSO-d_6) δ 6.88 (d, J=9 Hz, 1H), 6.12-5.86 (m, 2H), 5.63-5.43 (m, 4H), 4.32-4.17 (m, 1H), 3.99-3.73 (m, 5H), 3.30-3.20 (m, 1H), 1.38 (s, 9H).

Anal. Calcd for $C_{14}H_{23}N_3O_3$: C, 59.77; H, 8.24; N, 14.93. Found: C, 59.37; H, 8.41; N, 14.54.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(3-oxobutyl)-pyrazolidin-3-one (8). To a cold (0°C), magnetically stirred solution of **1** (5.0 g, 24.9 mmol) in methanol (75 mL) was added methyl vinyl ketone (1.75 g, 25 mmol). The cold solution was stirred for 1.5 h. The methanol was removed *in vacuo* and the solid residue was triturated with ether and filtered to provide 5.8 g (86%) of **8** : mp 122-123.5°C; IR (KBr, cm^{-1}) 3346, 1726, 1715, 1682, 1534, 1375, 1364, 1303, 1249, 1166; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 5.60 (br d, 1H), 4.59 (br s, 1H), 3.73 (br t, 1H), 3.13 (m, 1H), 3.08 (t, J=5 Hz, 2H), 2.70 (t, J=5 Hz, 2H), 2.20 (s, 3H), 1.48 (s, 9H); MS m/z (M^+) 271.

Anal. Calcd for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.80; N, 15.49. Found: C, 53.12; H, 7.81; N, 15.51.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(3-methylproprionate)-pyrazolidin-3-one (9). To a cold (0°C), magnetically stirred solution of **1** (10.0 g, 0.05 mol) in methanol (150 mL) was added methyl acrylate (4.73 g, 0.055 mol). The solution was stirred, allowing the cooling bath to warm to room temperature. Additional 2 mL portions of methyl acrylate were added at 16.5 h and 21.5 h. The solution was stirred for a total of 40 h before it was concentrated *in vacuo* to give 13.6 g (95%) of crude **9**. The residue was crystallized from ethyl acetate-hexane, then recrystallized twice from ethyl acetate to provide a small sample of pure **9** : mp 120-123°C; IR ($CHCl_3$, cm^{-1}) 3420, 2980, 1707, 1499, 1369, 1291, 1249, 1235, 1207, 1197, 1165; ^1H NMR (270 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 5.30 (br s, 1H), 4.64-4.49 (m, 1H), 3.84-3.70 (m, 1H), 3.71 (s, 3H), 3.12 (t, J=8 Hz, 2H), 3.20-3.05 (m, 1H), 2.66 (t, J=8 Hz, 2H), 1.45 (s, 9H); MS m/z (M+) 287.

Anal. Calcd for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63. Found: C, 50.44; H, 7.63; N, 14.42.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-ethyl-pyrazolidin-3-one (11). To a magnetically stirred solution of **1** (2.01 g, 10 mmol) in methanol (20 mL) was added acetaldehyde (0.56 mL, 10 mmol) and sodium cyanoborohydride (0.63 g, 10 mmol). A few drops of bromothymol blue were added and the resulting solution stirred at room temperature maintaining an acidic pH (indicator yellow) by periodic addition of methanolic hydrochloric acid. After the pH stabilized (yellow color persisted), the reaction mixture was left to stir for 40 h. The pH was then adjusted to ca. 8 (indicator blue) with 1N sodium hydroxide and the methanol evaporated. The residue was diluted with water and extracted twice with ether. The combined extracts were dried over magnesium sulfate and concentrated to provide an oil. The oil was purified by silica gel chromatography (elution with ethyl acetate) to provide 530 mg (23%) of **11** : mp 95-97°C; IR ($CHCl_3$, cm^{-1}) 3019, 3011, 2981, 1700, 1499, 1393, 1369, 1299, 1206, 1166; ^1H NMR (90 MHz, $CDCl_3$) δ 10.12 (br s, 1H), 6.86 (br s, 1H), 4.96-4.44 (m, 1H), 3.80-3.08 (m, 2H), 2.88 (q, J=6 Hz, 2H), 1.40 (s, 9H), 1.44 (t, J=6 Hz, 3H); MS m/z (M+) 229.

Anal. Calcd for $C_{10}H_{19}N_3O_3$: C, 52.39; H, 8.35; N, 18.33. Found: C, 52.17; H, 8.12; N, 18.06.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-acetyl-2-(*tert*-butylacetate)-pyrazolidin-3-one (12) and 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-acetyl-3-[(*tert*-butylacetyl)hydroxy]-1,2-diazolid-2-ene (13). To a cold (0°C), magnetically stirred suspension of sodium hydride (240 mg, 10 mmol) in *N,N*-dimethylformamide (10 mL) under nitrogen was added **2** (2.43 g, 10 mmol) dissolved in *N,N*-dimethylformamide (10 mL) over 10 min. The cold mixture was stirred for 30 min, t-butyl bromoacetate (1.95 g, 10 mmol) was added and stirring was continued for 1.5 h allowing the cooling bath to warm to room temperature. The solvent was evaporated *in vacuo* and the residue dissolved in methylene chloride and washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The resultant products were separated by silica gel chromatography (elution with 60% ethyl acetate in toluene) to yield **12** (1.27 g, 35.5%) and **13** (470 mg, 13%).

12: mp 129-130.5°C; IR ($CHCl_3$, cm^{-1}) 3420, 2980, 1727, 1709, 1500, 1395, 1371, 1293, 1237, 1207, 1156; ^1H NMR (270 MHz, $CDCl_3$) δ 5.23 (br s, 1H), 4.76-4.21 (m, 4H), 3.90-3.76 (m, 1H), 2.18 (s, 3H), 1.45 (s, 18H); MS m/z (M^+) 357.

Anal. Calcd for $C_{16}H_{27}N_3O_6$: C, 53.77; H, 7.61; N, 11.76. Found: C, 53.70; H, 7.65; N, 11.67.

13 : mp 129.5-131°C; IR ($CHCl_3$, cm^{-1}) 3440, 2980, 1745, 1720, 1642, 1502, 1478, 1371, 1240, 1215, 1156; ^1H NMR (270 MHz, $CDCl_3$) δ 5.13 (br s, 1H), 5.05-4.88 (m, 1H), 4.63 (ABq, J=16 Hz, 2H), 4.24 (t, J=12 Hz, 1H), 3.93-3.82 (m, 1H), 2.15 (s, 3H), 1.49 (s, 9H), 1.45 (s, 9H); MS m/z (M^+) 357.

Anal. Calcd for $C_{16}H_{27}N_3O_6$: C, 53.77; H, 7.61; N, 11.76. Found: C, 53.49; H, 7.40; N, 11.50.

Compounds **14-19** were prepared in a fashion similar to that described for **12/13**:

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-decanoyl-2-(*tert*-butylacetate)-pyrazolidin-3-one (14) and 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-decanoyl-3-[(*tert*-butylacetyl)-hydroxy]-1,2-diazolid-2-ene (15). Chromatography (elution with 30% ethyl acetate in toluene) yielded **14** (3.23 g, 69%) and **15** (1.06 g, 23%).

14 : mp 68-71°C; IR ($CHCl_3$, cm^{-1}) 3430, 2930, 1726, 1711, 1499, 1370, 1292, 1236, 1215, 1156; ^1H NMR (300 MHz, $CHCL_3$) δ 5.25 (br s, 1H), 4.78-4.48 (m, 3H), 4.39-4.26 (m, 1H), 3.83 (t, J=12 Hz, 1H), 2.36 (t, J=9 Hz, 2H), 1.72-1.56 (m, 4H), 1.46 (s, 9H), 1.45 (s, 9H), 1.25 (br s, 10H), 0.89 (t, J=9 Hz, 3H); MS m/z (M^+) 469.

Anal. Calcd for $C_{24}H_{43}N_3O_6$: C, 61.38; H, 9.23; N, 8.95. Found: C, 61.48; H, 9.32; N, 8.75.

15 : mp 65-69°C; IR ($CHCl_3$, cm^{-1}) 3440, 2930, 1746, 1714, 1638, 1468, 1370, 1242, 1215, 1158; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (br s, 1H), 5.04-4.88 (m, 1H), 4.63 (ABq, J=16Hz, 2H), 4.30-4.19 (m, 1H), 3.90-3.82 (m, 1H), 2.50-2.42 (m, 2H), 1.68-1.55 (m, 4H), 1.48 (s, 9H), 1.35-1.15 (m, 10H), 0.87 (t, J=9 Hz, 3H); MS m/z (M^+) 469.

Anal. Calcd for $C_{24}H_{43}N_3O_6$: C, 61.38; H, 9.23; N, 8.95. Found: C, 61.10; H, 9.25; N, 9.04.

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzoyl-2-(*tert*-butylacetate)-pyrazolidin-3-one (16) and 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzoyl-3-[(*tert*-butylacetyl)hydroxy]-1,2-diazolid-2-ene (17). Chromatography (elution with 30% ethyl acetate in toluene) yielded **16** (1.32 g, 63 %) and **17** (0.39 g, 19%).

16 : mp 85-89°C; IR ($CHCl_3$, cm-1) 3420, 2980, 1742, 1727, 1712, 1370, 1340, 1291, 1237, 1215, 1156; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68-7.40 (m, 5H), 5.25 (br s, 1H), 4.79-4.25 (m, 4H), 3.97 (t, J=12 Hz, 1H), 1.50 (s, 9H), 1.42 (s, 9H); MS m/z (M^+) 419.

Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 59.93; H, 6.85; N, 9.94.

17 : mp 147-149°C; IR ($CHCl_3$, cm^{-1}) 3440, 2980, 1745, 1719, 1626, 1497, 1463, 1371, 1243, 1215, 1157; ^1H NMR (270 MHz, $CDCl_3$) δ 7.86-7.32 (m, 5H), 5.22 br s, 1H), 5.06 (br s, 1H), 4.72-4.40 (m, 3H), 4.16-4.03 (m, 1H), 1.48 (s, 9 H), 1.43 (s, 9H); MS m/z (M+1) 420.

Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.77; N, 10.02. Found: C, 60,27; H, 7.11; N, 9.74.

4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzyloxycarbonyl-2-(*tert*-butylacetate)-pyrazolidin-3-one (18) and 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-benzyloxycarbonyl-3-[(*tert*-butylacetyl)hydroxy]-1,2-diazolid-2-ene (19). Chromatography (elution with 30% ethyl acetate in toluene) yielded **18** (64.7 g, 82%) and **19** (5.5 g, 7%).

18 : mp 111-113°C; IR (KBr, cm^{-1}) 3410, 2980, 1742, 1727, 1489, 1371, 1312, 1246, 1230, 1207, 1158, 961; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (br s, 5H), 5.34-5.12 (m, 3H), 4.84 (br t, 1H), 4.62-4.54 (m, 1H), 4.36 (ABq, J=18 Hz, 2H), 3.72 (t, J=11 Hz, 1H), 1.44 (s, 18H); MS m/z (M+1) 450.

Anal. Calcd for $C_{22}H_{31}N_3O_7$: C, 58.79; H, 6.95; N, 9.35. Found: C, 58.79; H, 6.82; N, 9.54.

19 : mp 109.5-112°C; IR (KBr, cm^{-1}) 3340, 2980, 1759, 1715, 1662, 1646, 1521, 1481, 1371, 1358, 1161, 1129; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.29 (m, 5H), 5.42-5.14 (m, 3H), 5.10-4.94 (m, 1H), 4.72 (ABq, J=14 Hz, 2H), 4.26 (t, J=11 Hz, 1H), 3.94-3.80 (m, 1H), 1.46 (s, 18H); MS m/z (M+1) 450.

Anal. Calcd for $C_{22}H_{31}N_3O_7$: C, 58.79; H, 6.95; N, 9.35. Found: C, 58.93; H, 6.82; N, 9.26.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-2-(*tert*-butylacetate)-pyrazolidin-3-one (20). **18** (3.0 g, 6.68 mmol) was dissolved in ethanol (50 mL) in a Parr bottle and a slurry of 10% palladium on carbon (300 mg) in ethanol (50 mL) was added. The reaction vessel was flushed with nitrogen and assembled on a Parr apparatus, pressurized with 30 psi hydrogen and shaken at room temperature for 1 h. The mixture was filtered through celite, concentrated *in vacuo*, and refiltered through a pad of silica gel. The solvent was removed *in vacuo* leaving a white solid which was crystallized from ethyl acetate-hexane to yield 1.54 g (73%) of a crystalline solid: mp 135-136°C; IR (KBr, cm^{-1}) 3286, 2990, 1743, 1714, 1683, 1526, 1368, 1248, 1230, 1161, 1149; ^1H NMR (270 MHz, $CDCl_3$) δ 5.10 (br s, 1H), 5.05-4.94 (m, 1H), 4.46-4.30 (m, 1H), 4.16 (ABq, J=16 Hz, 2H), 3.90-3.75 (m, 1H), 3.10 (q, J=11 Hz, 1H), 1.48 (s, 18 H); MS m/z (M^+) 315.

Anal. Calcd for $C_{14}H_{25}N_3O_5$: C, 53.32; H, 7.99; N, 13.32. Found: C, 53.58; H, 7.93; N, 13.14.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-propyl-2-(*tert*-butylacetate)-pyrazolidin-3-one (21). To a magnetically stirred solution of **20** (500 mg, 1.6 mmol) in methanol (9 mL) under nitrogen was added sodium cyanoborohydride (107.7 mg, 1.7 mmol) followed by propionaldehyde (386.4 mg, 6.65 mmol) A few drops of bromothymol blue were added and the resulting yellow solution was stirred at room temperature periodically adjusting the pH with addition of methanolic HCl to maintain the yellow color. The pH was maintained acidic for 6 h, then the reaction mixture was left to stir for an additional 12 h. The mixture was partitioned between methylene chloride and 1N sodium hydroxide. The organic portion was separated, washed with brine, dried over magnesium sulfate and concentrated to provide an oil. The oil was purified by silica gel chromatography (elution with 30% ethyl acetate in hexane) to provide 220 mg (39%) of **21**: mp 89-91°C; IR ($CHCl_3$, cm^{-1}) 3430, 2981, 1744, 1706, 1500, 1370, 1292, 1236, 1215, 1159; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (br s, 1H), 4.80-4.64 (m, 1H), 4.04 (ABq, J=16 Hz, 2H), 3.76 (br t, 1H), 3.19 (br t, 1H), 2.92-2.70 (m, 2H), 1.60-1.40 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H), 0.93 (t, J=8 Hz, 3H); MS (EI) m/z (M^+) 357.

Anal. Calcd for $C_{17}H_{31}N_3O_5$: C, 57.12; H, 8.74; N, 11.76. Found: C, 56.89; H, 8.48; N, 11.96.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-methylacetate-pyrazolidin-3-one (23). To a cold (0°C), magnetically stirred solution of **1** (150 g, 0.75 mol) in *N,N*-dimethylformamide (900 mL) was added sodium hydride (18.6 g (31 g of 60% dispersion in oil), 0.775 mol). The resulting suspension was stirred under nitrogen for 30 min at which time bromomethyl acetate (71.01 mL, 0.75 mol) was added. The mixture was stirred, allowing the bath to warm to room temperature. After 20 h, the mixture was treated with xylenes (750 mL) in portions, concentrating *in vacuo* after each addition. The semisolid that remained was treated with hexanes and methylene chloride (1 L), heated to reflux and filtered. Water was added to the filtrate and the two layers were separated. The aqueous portion was extracted three times with methylene chloride then the combined organics were dried over magnesium sulfate, filtered and concentrated to give 281 g of a yellow

solid. The solid was dissolved in hot ethyl acetate (1L) and hexane (200 mL) and upon cooling yielded 157.24 g (77%) of an off-white solid: mp 134-5°C; IR ($CHCl_3$, cm^{-1}) 3020, 1709, 1499, 1163; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 5.28 (br s, 1H), 4.54 (br s, 1H), 3.90-3.44 (m, 3H), 3.77 (s, 3H), 3.18 (br t, J=12 Hz, 1H), 1.44 (s, 9H); MS m/z (M^+) 273.

Anal. Calcd for $C_{11}H_{19}N_3O_5$: C, 48.34; H, 7.01; N, 15.38. Found: C, 48.56; H, 7.11; N, 15.46.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(2-hydroxyethyl)-pyrazolidin-3-one (24). To a mechanically stirred suspension of sodium borohydride (20.11 g, 0.53 mol) in ethylene glycol dimethyl ether (600 mL) was added lithium chloride (22.54 g, 0.53 mol) followed by ethylene glycol dimethyl ether (600 mL). The resulting slurry was refluxed for 10 min, then cooled over 50 min. Ester **23** (145.15g, 0.53 mol) was then added to the slurry over a 10 min period through a short Gooch tube. The resulting mixture was refluxed for 1.5 h, cooled and concentrated *in vacuo*. The solid residue was stirred with methylene chloride (1.5 L) for ca. 20 h and filtered through celite. The celite was washed several times with methylene chloride and the combined filtrates were concentrated *in vacuo* to yield 196.51 g of a yellow solid. The solid was dissolved in methanol (1.5 L) and the solution was refluxed for 2 h 40 min. The methanol was distilled off, first at atmospheric pressure (250 mL distilled) and the remainder *in vacuo* to yield 173.5 g. This material was purified by silica gel chromatography (prep 500 HPLC, elution with methylene chloride gradient to 75% methanol in methylene chloride) to yield 93 g (72 %) of **24** : mp 111-113°C; IR ($CHCl_3$, cm^{-1}) 3430, 3020, 2982, 1705, 1500, 1394, 1369, 1300, 1250, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (br d, J=6 Hz, 1H), 4.58-4.42 (m, 1H), 3.88-3.72 (m, 3H), 3.12-2.80 (m, 4H), 1.46 (s, 9H); MS m/z (M+) 245.

Anal. Calcd for $C_{10}H_{19}N_3O_4$: C, 48.97; H, 7.81; N, 17.13. Found: C, 49.27; H, 7.56; N, 16.85.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(2-methanesulfonyloxyethyl)-pyrazolidin-3-one (25). A magnetically stirred suspension of **24** (1.0 g, 4.08 mmol) in methylene chloride (50 mL) was warmed to effect dissolution. The colorless solution was cooled to room temperature and treated with triethylamine (0.57 mL, 4.08 mmol). Mesyl chloride (0.32 mL, 4.04 mmol) was dissolved in methylene chloride (4 mL) and added slowly to the reaction solution (addition via syringe pump over a 35 min period). The solution was stirred for an additional 15 min and concentrated *in vacuo* providing a solid. The solid was partitioned between methylene chloride and water. The layers were separated and the aqueous portion was extracted an additional 3 times with methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a foam which was crystallized from ethyl acetate-hexanes to provide 500 mg (38 %) of **25** as yellow crystals: mp 134-5°C; IR (KBr, cm^{-1}) 3370, 1718, 1691, 1532, 1368, 1344, 1331, 1308, 1180, 920, 527; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.80 (m, 1H), 5.10 (br s, 1H), 4.64-4.50 (m, 1H), 4.48-4.28 (m, 2H), 3.88-3.72 (m, 1H), 3.23-3.11 (m, 3H), 3.11 (s, 3H), 1.44 (s, 9H); MS m/z (M+) 323.

Anal. Calcd for $C_{11}H_{21}N_3O_6S$: C, 40.86; H, 6.55; N, 12.99. Found: C, 41.03; H, 6.32; N, 12.79.

Preparation of 4-(*R,S*)-[(*tert*-Butoxycarbonyl)amino]-1-(2-iodoethyl)-pyrazolidin-3-one (26). To a magnetically stirred solution of **25** (29.31 g, 90.7 mmol) in acetone (1.2 L) was added sodium iodide (54.4 g, 362.8 mmol). The solution was refluxed for 4 h during which time a solid precipitated. The solid was removed by filtration and discarded. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (elution with ethyl acetate). The resulting solid was stirred with acetone and filtered to yield 28.28 g (88%) of the iodide **26** : mp 186-9°C; IR ($CHCl_3$, cm^{-1}) 3377, 1731, 1690, 1528, 1367, 1360, 1276, 1167; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.54 (m, 1H), 5.13-5.03 (m, 1H), 4.64-4.50 (m, 1H), 3.87-3.74 (m, 1H), 3.32-3.06 (m, 5H), 1.45 (s, 9H); MS m/z (M+) 355.

Anal. Calcd for $C_{10}H_{18}N_3O_3I$: C, 33.82; H, 5.11; N, 11.83. Found: C, 34.05; H, 5.00; N, 11.93.

Preparation of *tert*-Butyl-[8-(*R,S*)-(*tert*-Butoxy-carbonylamino)-3-methoxycarbonyl-3-phenylsulfinyl]-9-oxo-1,6-diazabicyclo[4.3.0]nonane-2-carboxylate (28a) and *tert*-Butyl-[8-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-methoxycarbonyl]-9-oxo-1,6-diazabicyclo[4.3.0]non-2-

ene-2-carboxylate (29a). To a cold (0°C) magnetically stirred suspension of sodium hydride (240 mg, 10 mmol) in *N,N*-dimethylformamide (50 mL) under nitrogen was added **26** (3.55 g, 10 mmol) dissolved in *N,N*-dimethylformamide (100 mL) in a dropwise manner over 10 min. The mixture was stirred for 25 min resulting in a homogeneous solution. To this solution was added **27**[6] (3.1 g, 10 mmol) dissolved in *N,N*-dimethylformamide (50 mL). The resulting solution was stirred for 1 h 45 min while allowing the cooling bath to warm to room temperature. A saturated solution of ammonium chloride was added and the solid that precipitated was filtered and discarded. The filtrate was concentrated *in vacuo* and the residue purified by silica gel chromatography (elution with 50% ethyl acetate in hexanes) to yield 4.67 g (87%) of a mixture of isomers of **28a** : mp (isomer 1) 136-40°C; mp (isomer 2) 97-100°C; MS (isomer 1 and isomer 2) m/z (M+) 537.

To a cold (0°C), magnetically stirred solution of **28a** (4.52 g, 8.4mmol) in methylene chloride (200 mL) under nitrogen was added 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU) (1.26 mL, 8.4 mmol). The solution was stirred for 2 h 15 min while allowing the cooling bath to warm to room temperature. The solution was cooled to 0°C, a second portion of DBU (0.63 mL, 4.2 mmol) was added, and stirring was continued for an additional 4 h. Similarly, a third portion of DBU (0.63 mL, 4.2mmol) was added followed by 5 h of additional stirring. The final solution was washed with water and the organic portion dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography (elution with 50% ethyl acetate in hexanes) to yield 1.36 g (39%) of **29a** : mp 142-5°C; IR ($CHCl_3$, cm^{-1}) 3018, 1730, 1711, 1395, 1369, 1293, 1241, 1159; ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (br s, 1H), 4.62-4.50 (m, 1H), 4.12-4.00 (m, 1H), 3.76 (s, 3H), 3.36-3.26 (m, 1H), 2.76-2.60 (m, 4H), 1.60 (s, 9H), 1.44 (s, 9H); MS m/z (M+) 411; UV (EtOH) 309 nm (ε=14335).

Anal. Calcd for $C_{19}H_{29}N_3O_7$: C, 55.46; H, 7.10; N, 10.21. Found: C, 55.46; H, 6.85; N, 10.08.

Compounds **28b-29b** were prepared in a fashion similar to that described for **28a-29a**:

***tert*-Butyl-[8-(*R,S*)-(*tert*-Butoxy-carbonylamino)-3-methylcarbonyl-3-phenylsulfinyl]-9-oxo-1,6-diazabicyclo[4.3.0]nonane-2-carboxylate (28b) and *tert*-Butyl-[8-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-methylcarbonyl]-9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate (29b).** Purification by silica gel chromatography (elution with 50% ethyl acetate in hexanes) yielded 1.45 g (63%) of **28b** as a mixture of isomers: MS m/z (M^+) 521.

Purification by silica gel chromatography (elution with 50% ethyl acetate in hexanes) provided 530 mg (61%) of **29b** : mp 181-2°C; IR (KBr, cm^{-1}) 3370, 2980, 1749, 1712, 1569, 1394, 1369, 1249, 1168; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18-5.06 (m, 1H), 4.61-4.46 (m, 1H), 4.14-3.99 (m, 1H), 3.40-3.28 (m, 1H), 2.86-2.66 (m, 3H), 2.66-2.54 (m, 1H), 2.26 (s, 3H), 1.61 (s, 9H), 1.44 (s, 9H); MS m/z (M^+) 395; UV (EtOH) 328 nm (ε=11799).

Anal. Calcd for $C_{19}H_{29}N_3O_6$: C, 57.71; H, 7.39; N, 10.63. Found: C, 57.87; H, 7.53; N, 10.37.

Conversion of 29a into 30a. A solution of **29a** (870 mg, 2.1 mmol) in ethanol (25 mL) was treated with *p*-toluenesulfonic acid (443.6 mg, 2.3 mmol) and the mixture warmed slightly. The resulting solution was concentrated *in vacuo* (ca. 40°C). The addition of ethanol followed by concentration was repeated three times. An additional amount of *p*-toluenesulfonic acid (112 mg, 0.6 mmol) and ethanol (25 mL) were added and the solution once more concentrated *in vacuo*. The addition of ethanol followed by concentration was repeated two additional times. Finally, the residue was partitioned between methylene chloride and water and the layers separated. The aqueous layer was adjusted to pH 8 with solid sodium bicarbonate and extracted with methylene chloride (three times). The combined organics were dried over magnesium sulfate, filtered and concentrated to provide 450 mg (68%) of *tert*-Butyl-[8-(*R,S*)-amino-3-methoxycarbonyl]-9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate which was crystallized from ether: mp 129-132°C; IR ($CHCl_3$, cm^{-1}) 3020, 1734, 1704, 1614, 1396, 1384, 1274, 1245, 1157; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90-3.70 (m, 2H), 3.74 (s, 3H), 3.30-3.20 (m, 1H), 2.80-2.60 (m, 4H), 1.60 (s, 9H); MS m/z (M^+) 311; UV (EtOH) 310 nm (ε=13336).

Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 53.77; H, 6.51; N, 13.33.

The *tert*-Butyl-[8-(*R,S*)-amino-3-methoxycarbonyl]-9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate (400 mg, 1.29 mmol) was mixed with 2-(2-aminothiazole-4-yl)-2-methoxyiminoacetic acid-hydroxybenztriazole active ester[11] (409 mg, 1.29 mmol) and *N,N*-diisopropylethylamine (166.24 mg, 0.224 mL, 1.29 mmol) in acetonitrile (40 mL). The reaction was stirred at room temperature overnight. The resulting slurry was filtered and the filtrate concentrated *in vacuo*. The solid was crystallized from 5% methanol in ethyl acetate to provide 101 mg (16%) of *tert*-Butyl-8-(*R,S*)-[2-(2-aminothiazole-4-yl)-2-methoxyiminoacetylamino]-3-methoxycarbonyl-9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate: mp 196-200°C(d); IR (KBr, cm^{-1}) 3450, 3270, 1744, 1721, 1702, 1539, 1395, 1368, 1303, 1279, 1248, 1127; ^1H NMR (300 MHz, DMSO-d_6) δ 9.12 (d, J=9 Hz, 1H), 7.24 (s, 2H), 6.90 (s, 1H), 4.94 (q, J=9 Hz, 1H), 4.10 (ABq, J=6 Hz, 1H), 3.92-3.84 (m, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.17 (d, J=6 Hz, 2H), 2.94 (t, J=10 Hz, 1H), 2.76-2.64 (m, 1H), 1.50 (s, 9H); MS m/z (M+1) 495; UV (EtOH) 305 nm (ε=19725), 230 nm (ε=17846).

Anal. Calcd for $C_{20}H_{26}N_6O_7S \cdot 1/2H_2O$: C, 47.71; H, 5.40; N, 16.69. Found: C, 47.75; H, 5.00; N, 16.22.

tert-Butyl-8-(*R,S*)-[2-(2-aminothiazole-4-yl)-2-methoxyiminoacetylamino]-3-methoxycarbonyl-9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate (50 mg, 0.1 mmol) was stirred at room temperature with trifluoroacetic acid (5 mL) for 30 min. The reaction was concentrated and the residue triturated with ether to provide **30a** as a cream-colored solid: mp >225°C; IR (KBr, cm^{-1}) 3330, 1734, 1671, 1403, 1290, 1236, 1194, 1134, 1045; ^1H NMR (300 MHz, DMSO-d_6) δ 9.18 (d, J=9 Hz, 1H), 7.60-7.30 (br s, 2H), 6.92 (s, 1H), 4.98-4.84 (br q, J=9Hz, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 4.00-3.40 (m, 3H), 3.44-3.30 (m, 2H), 2.94 (t, J=9 Hz, 1H), 2.74-2.60 (m, 1H); MS m/z (M+1) 439; HRMS (FAB) m/z (M+1) calcd 439.1036, obs 439.1052; UV (EtOH) 304 nm (ε=15997), 230 nm (ε=13808).

Conversion of 29b into 30b. Compound **30b** was prepared following a procedure similar to that described above for the preparation of **30a**. For **30b**: mp 192-4°C(d); IR (KBr, cm^{-1}) 3430, 1743, 1644, 1583, 1560, 1397, 1354, 1284, 1216, 1177, 1039; ^1H NMR (300 MHz, DMSO-d_6) δ 9.14 (d, J=6Hz, 1H) 7.24 (s, 2H), 6.90 (s, 1H), 4.96-4.80 (m, 1H), 3.90-3.80 (m, 1H), 3.84 (s, 3H), 3.50-3.10 (m, 2H), 3.00-2.88 (m, 1H), 2.76-2.54 (m, 2H), 2.22 (s, 3H); MS m/z (M+1) 423; HRMS (FAB) m/z (M+1) calcd 423.1087, obs 423.1114; UV (EtOH) 314 nm (ε=15144), 232 nm (ε=15268).

Preparation of Allyl-[7-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-ethoxycarbonyl]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (31a). To a suspension of paraformaldehyde (9.0 g, 0.3 mol) in ethanol (250 mL) was added pyrrolidine (2.13 g, 0.03 mol). The magnetically stirred mixture was heated to reflux under nitrogen. After 1.5 h, the cloudy solution was cooled to room temperature and ethyl 2-(diethylphosphonato)acetate (50 g, 0.223 mol) was added. The mixture was refluxed for 8.5 h. The solvent was removed *in vacuo*. To the oil that remained was added 86% phosphoric acid (2.5 mL) and the solution was distilled *in vacuo* through a vigreux column. A clear liquid was collected at 120-25°C yielding 22.74 g of ethyl-2-(diethylphosphonato)prop-2-enoate, **34a**: ^1H NMR (90 MHz, $CDCl_3$) δ 6.96 (dd, J = 41 Hz, 1H), 6.72 (dd, J = 20 Hz, 1H), 4.40-4.00 (m, 6H), 1.32 (t, J = 5.4 Hz, 9H).

1 (5.0 g, 24.9 mmol) was dissolved in ethanol (50 mL) with heating, then cooled in an ice bath under nitrogen. The vinyl phosphonate **34a** (5.87 g, 24.9 mmol) was added neat and the resulting solution was stirred 15 h, allowing the ice to melt. The solvent was evaporated *in vacuo* and the product was purified by silica gel chromatography (elution with 5% methanol in ethyl acetate) to give 6.9 g (63%) **33a** as a yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ 8.60-8.16 (br d, 1H), 5.36-5.08 (br t, J = 5.4 Hz, 1H), 4.40-3.00 (m, 12H), 1,36 (s, 9H), 1.32-1.20 (m, 9H).

To a cold (-78°C), magnetically stirred solution of **33a** (6.5 g, 14.9 mmol) in methylene chloride (50 mL) was added allyl oxalyl chloride (2.21 g, 14.9 mmol) dissolved in methylene chloride (5 mL) followed immediately by *N,N*-diisopropylethylamine (1.93 g, 14.9 mmol). The solution was stirred at -78°C for 2 h 40 min, at which time the cooling bath was removed and stirring was continued for 1 h 15 min. The solution was washed with water, dried over magnesium sulfate, filtered, and evaporated in vacuo to give an oil which was

purified by silica gel chromatography (elution with ethyl acetate) to give 3.87 g of **32a** as a golden oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.40-5.64 (m, 1H), 5.52-5.12 (m, 2H), 4.88-4.60 (br d, J = 5.4 Hz, 2H), 4.40-3.20 (m, 13H), 1.40 (s, 9H), 1.36-1.20 (m, 9H).

To a cold (0°C), magnetically stirred solution of **32a** (3.75 g, 6.83 mmol) in tetrahydrofuran (100 mL) under nitrogen was added sodium hydride (546.5 mg of a 60% dispersion in oil, 13.66 mmol). Additional tetrahydrofuran (200 mL) was added and the cooling bath removed resulting in dissolution of the suspended solid. The solution was stirred 16 h at room temperature and treated with methylene chloride (100 mL) followed by cautious addition of a saturated ammonium chloride solution (30 mL) (vigorous gas evolution). The mixture was transferred to a separatory funnel and methylene chloride and water were added. The organic layer was separated and the aqueous layer was extracted with an additional portion of methylene chloride. The combined organics were dried over magnesium sulfate, filtered and concentrated *in vacuo* leaving an oil which was purified by silica gel chromatography (elution with 50% ethyl acetate in hexanes). The oil crystallized on standing to give 1.82 g (67.5%) of **31a**: mp 118-121°C; IR ($CHCl_3$, cm-1) 3021, 2980, 1750, 1707, 1393, 1370, 1283, 1233, 1207, 1163; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06-5.90 (m, 1H), 5.44 (d, J = 18 Hz, 1H), 5.32 (d, J = 9 Hz, 1H), 5.08 (br s, 1H), 4.92-4.66 (m, 3H), 4.21 (q, J = 6 Hz, 2H) 4.12-4.02 (m, 1H), 4.36,3.91 (ABq, J = 12 Hz, 2H), 2.84 (m, 1H), 1.46 (s, 9H),1.26 (t, J = 6 Hz, 3H); MS m/z (M+) 395; UV (EtOH) 345 nm (ε=8825).

Anal. Calcd for $C_{18}H_{25}N_3O_7$: C, 54.68; H, 6.37; N, 10.63. Found: C, 54.99; H, 6.55; N, 10.36.

Preparation of Allyl-[7-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-benzyloxycarbonyl]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (31b). To a suspension of paraformaldehyde (0.8 g, 27.0 mmol) in benzene (40 mL) under nitrogen was added acetic acid (20 mL) and pyrrolidine (0.22 mL, 5.3 mmol). The magnetically stirred mixture was heated at reflux for 30 min, then cooled in an ice bath. Benzyl 2-(dimethylphosphonato)acetate (5.15 g, 20 mmol) was added and the resulting solution was fitted with a Dean-Stark apparatus and refluxed for 1.5 h. Additional paraformaldehyde (0.8 g, 27 mmol) was added and the mixture was heated at reflux for 30 min without the Dean-Stark apparatus, then for an additional 1 h with the Dean-Stark apparatus in place. Another portion of paraformaldehyde (0.8 g, 27 mmol) was added and refluxed as above. The resulting solution was concentrated *in vacuo*, then purified by silica gel chromatography (elution with 5% methanol in ethyl acetate) yielding 2.58 g of **34b**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.26 (s, 5H), 7.00 (dd, J = 42.3 Hz and 1.8 Hz, 1H), 6.70 (dd, J = 25.2 Hz and 1.8 Hz, 1H), 5.18 (s, 2H), 3.70 (d, J = 10.8 Hz, 6H).

To a cold (0°C), magnetically stirred solution of **1** (1.12 g, 5.6 mmol) in methanol (25 mL) was added the vinyl phosphonate **34b** (1.6 g, 5.9 mmol) in one portion. The resulting solution was stirred for 2 h under nitrogen, allowing the ice to melt. The methanol was removed *in vacuo* and the oil that remained was purified by silica gel chromatography (elution with 1% methanol in ethyl acetate, followed by 4% methanol in ethyl acetate) to give 1.8 g (64% yield).of **33b**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.26 (s, 5H), 5.44-4.96 (m, 1H), 5.13 (s, 2H), 4.70-4.10 (m, 1H), 3.62 (d, J = 10.8 Hz, 6H), 3.88-2.60 (m, 6H), 1.40 (s, 9H).

To a cold (0°C), magnetically stirred solution of **33b** (1.79 g, 3.8 mmol) in methylene chloride (10 ml) under nitrogen was added allyl oxalyl chloride (564 mg, 3.8 mmol) followed by *N,N*-diisopropylethylamine (1.3 mL, 7.6 mmol). The resulting solution was stirred for 1.5 h, allowing the ice in the bath to melt. Additional allyl oxalyl chloride (30 mg) was added and the solution was stirred for another 1.5 h. The solution was washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (elution with 50% ethyl acetate in hexane) to yield 1.09 g (63% yield) of **31b**: IR ($CHCl_3$, cm^{-1}) 3020, 1750, 1724, 1500, 1385, 1370, 1280, 1167; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5 H), 5.92-5.76 (m, 1H), 5.38-5.12 (m, 5H), 5.07 (br s, 1H), 4.80-4.54 (m, 3H), 4.39, 3.92 (ABq, J = 12 Hz, 2H), 2.94-2.74 (m, 1H),1.45 (s, 9H); MS m/z (M+) 457; UV (EtOH) 345 nm (ε=5600).

Anal. Calcd for $C_{23}H_{27}N_3O_7$: C, 60.39; H, 5.95; N, 9.19. Found: C, 60.68; H, 6.10; N, 8.93.

Compounds **31c-31e** were prepared in a fashion similar to that described for **31b**:

Allyl-[7-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-ethylcarbonyl]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (31c).

34c: ^{1}H NMR (90 MHz, CDCl3) d 7.18-6.46 (m, 2H), 3.76 (d, J=10.8 Hz, 6H), 2.74 (q, J=7.2 Hz, 2H), 1.08 (t, J=7.2 Hz, 3H).

33c (purified by silica gel chromatography;50% ethyl acetate in hexane): ^{1}H NMR (90 MHz, CDCl3) δ 5.30 (br s, 1H), 3.74 (d, J=11.7 Hz, 6H), 4.82-2.50 (m, 8H), 1.44 (s, 9H), 1.07 (t, J=7.2 Hz, 3H).

31c (6% yield from phosphonate; crystallized from diethyl ether/ hexane): mp129-30°C; IR (CHCl3, cm^{-1}) 3021, 1716, 1503, 1418, 1380, 1354, 1272, 1207, 1161; ^{1}H NMR (90 MHz, CDCl3) δ 7.26-6.16 (m, 1H), 5.62-5.26 (m, 2H), 5.24-4.54 (m, 4H), 4.16-3.94 (m, 1H), 4.38 and 3.90 (ABq, J=10.8 Hz, 2H),2.83 (dd, J=9 and 10.8 Hz, 1H), 2.68-2.40 (m, 2H), 1.42 (s, 9H), 1.06 (t, J=7.2 Hz, 3H); MS m/z (M^+) 379; UV (EtOH) 224 nm (ε=7600), 364 nm (ε=8100).

Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08. Found: C, 56.73; H, 6.89; N, 11.01.

Allyl-[7-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-cyano]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (31d).

34d: ^{1}H NMR (90 MHz, CDCl3) d 7.00-6.36 (m, 2H), 4.60-3.88 (m, 4H), 1.44 (t, J=7 Hz, 6H).

33d (purified by silica gel chromatography; 5% methanol in ethyl acetate): IR (CHCl3, cm^{-1}) 3021, 2250, 1712, 1264, 1023; ^{1}H NMR (90 MHz, CDCl3) δ 8.72 (br s, 1H), 5.34 (br s, 1H), 4.80-3.08 (m, 10H), 1.36 (s, 9H), 1.40-1.16(m, 6H); MS m/z (M+1) 391.

31d (28%) (yellow crystals): mp 158-60°C; IR (CHCl3, cm^{-1}) 3040, 2990, 2220, 1753, 1742, 1716, 1501, 1407, 1370, 1160; ^{1}H NMR (300 MHz, CDCl3) δ 5.47 (d, J=15 Hz, 1H), 5.36 (d, J=12 Hz, 1H), 5.13 (br s, 1H), 4.96-4.78 (m, 2H), 4.77-4.62 (m, 1H), 4.10 (ABq, J=12 Hz, 2H), 4.09 (br t, J=9 Hz, 1H), 2.93 (dd, J=9 Hz and 12Hz, 1H), 1.47 (s, 9H); MS m/z (M^+) 348; UV (EtOH) 212 nm (ε=8400), 365 nm (ε= 5300).

Anal. Calcd for $C_{16}H_{20}N_4O_5$: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.46; H, 5.56; N, 15.95.

Allyl-[7-(*R,S*)-(*tert*-Butoxycarbonylamino)-3-methylsulfonyl]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (31e).

34e: ^{1}H NMR (90 MHz, CDCl3) δ 7.00 (d, J=36 HZ, 1H), 6.80 (d, J=18 Hz, 1H), 3.80 (d, J=13 Hz, 6H), 3.08 (s, 3H).

33e: mp 141-143°C; IR (KBr, cm^{-1}) 3310, 3190, 1710, 1696, 1525, 1232, 1165, 1142, 1052, 1043; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.70 (br d, J=6 Hz, 1H), 7.20 (br d, J=12 Hz, 1H), 4.54-4.20 (m, 2H), 3.80-3.66 (m, 6H), 3.20 (s, 3H), 3.66-3.10 (m, 3H), 3.00-2.80 (m, 1H), 1.40 (s, 9H); MS m/z (M+) 415.

Anal. Calcd for $C_{13}H_{26}N_3O_8SP$: C, 37.59; H, 6.31; N, 10.12. Found: C, 37.85; H, 6.30; N, 9.99..

31e (purified by flash chromatography on silica gel;75% ethyl acetate in hexane; yellow crystals) (35%): mp 80°C; IR (CHCl3, cm^{-1}) 3021, 1741, 1717, 1326, 1142; ^{1}H NMR (90 MHz, CDCl3) δ 6.18-5.68 (m, 1H), 5.54-5.18 (m, 2H), 5.18-4.96 (br d, J=5 Hz, 1H), 4.49,3.97 (ABq, J=12.5 Hz, 2H), 4.90-3.86 (m, 4H), 3.10 (s, 3H), 2.94 (dd, J=11 Hz,11 Hz, 1H), 1.44 (s, 9H); MS m/z (M+) 401; UV (EtOH) 329 nm (ε=6037).

Anal. Calcd for $C_{16}H_{23}N_3O_7S$: C, 47.87; H, 5.78; N, 10.47. Found: C, 47.75; H, 5.74; N, 10.55.

Preparation of 3-Methylsulfonyl-7-(R,S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36e). To 100 mL of 3M hydrochloric acid in glacial acetic acid at 0°C was added solid **31e** (3.8 g, 9.5 mmol). The mixture was stirred while allowing it to warm to room temperature until complete dissolution of occured (ca. 2 min). The reaction was then evaporated to dryness *in vacuo*. The residue was further processed by treating with methylene chloride and evaporating. This procedure was repeated several times. The residue was used immediately in the next reaction.

To a suspension of 2-[2'-(allyloxycarbonylamino)thiazol-4'-yl]-2-(Z)-methoxyiminoacetic acid (2.7 g, 9.5 mmol) in methylene chloride (100 mL) at 0°C. was added 2-chloro-4,6-dimethoxy-1,3,5-triazine[12] (1.7 g, 9.5 mmol) and *N*-methylmorpholine (1.0 mL, 9.5 mmol) and the reaction stirred at 0°C for 45 min. The crude material from the acid treatment (above) was then added followed by additional *N*-methylmorpholine (1.0 mL, 9.5 mmol). The resultant mixture was stirred overnight, allowing the reaction to warm slowly to room temperature. The following day, the reaction was concentrated and the residue dissolved in ethyl acetate and 0.1N hydrochloric acid. The layers were separated and the organic layer washed with saturated sodium bicarbonate solution, brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (100% ethyl acetate) to yield 1.27 g (24%) of **35e**: IR ($CHCl_3$, cm^{-1}) 3240, 3019, 1748, 1732, 1704, 1554, 1423, 1321, 1144; ^1H NMR (300 MHz, DMSO-d_6) δ 12.20 (s, 1H), 9.31 (d, J=6 Hz, 1H), 7.43 (s, 1H), 6.06-5.86 (m, 2H), 5.54-5.20 (m, 4H), 5.20-5.04 (m, 1H), 4.92-4.60 (m, 4H), 4.42 and 4.23 (ABq, J=12 Hz, 2H), 3.90 (s, 3H), 3.96-3.80 (m, 1H), 3.30-3.20 (m, 1H), 3.26 (s, 3H); MS m/z (M+1) 569; UV (EtOH) 206 nm (ε=22059), 264 nm (ε=13351).

Anal. Calcd for $C_{21}H_{24}N_6O_9S_2$: C, 44.36; H, 4.25; N, 14.78. Found: C, 44.56; H, 4.25; N, 14.50.

A solution of palladium (II) acetate (54 mg, 0.24 mmol) in acetone (13 mL) was treated with triphenylphosphine (316 mg, 1.2 mmol). The resulting suspension was stirred at room temperature for 30 min. **35e** (1.23 g, 2.17 mmol) was dissolved in acetone (85 mL) and added in one portion to the above suspension. The resulting solution was stirred at room temperature for 40 min and at -10°C for 10 min. Tributyltin hydride (1.26 g, 4.34 mmol, 1.17 mL) was then added and the resulting suspension stirred for 75 min at -10°C and 1.75 h at room temperature. After recooling to -10°C, 1N hydrochloric acid (4.34 mL, 2 mmol) was added and the suspension stirred for 10 min at -10°C and 10 min at room temperature. The reaction was filtered and the yellow solid washed with water (400 mL). The combined filtrates were washed with hexanes (4x150 mL) and ether (2x200 mL) and the aqueous layer lyophilized to provide 1.0 g of a yellow solid. The crude product was purified via MPLC chromatography (2% methanol, 0.5% acetic acid in water) to provide 300 mg (31%) of **36e**: mp >200°C; IR (KBr, cm^{-1}) 3340, 1721, 1644, 1534, 1403, 1304, 1134, 1047; ^1H NMR (300 MHz, DMSO-d_6) δ 9.18 (d, J=9 Hz, 1H), 7.24 (br s, 2H), 6.94 (s, 1H), 5.10-4.94 (m, 1H), 4.34 and 4.12 (AB_q, J=12 Hz, 2H), 3.84 (s, 3H), 4.04-3.70 (m, 1H), 3.22 (s, 3H), 3.26-3.00 (m, 1H); MS m/z (M+1) 445; UV (EtOH) 303 nm (ε=11495), 232 nm (ε=14681).

Anal. Calcd for $C_{13}H_{16}N_6O_7S_2$: C, 37.83; H, 3.63; N, 18.91. Found: C, 37.57; H, 3.73; N, 18.68.

Preparation of 3-Ethoxycarbonyl-7-(R,S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyminoacetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36a). The title compound was prepared from **31a** (via **35a**) in a manner similar to that described for the conversion of **31e** to **36e**.

35a: mp 204-207°C (d); IR ($CHCl_3$, cm^{-1}) 3021, 1750, 1730, 1701, 1554, 1226; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 8.08 (br s, 1H), 7.28 (s, 1H), 6.08-5.90 (m, 2H), 5.52-5.28 (m, 5H), 4.92-4.70 (m, 4H), 4.23 (q, J=6 Hz, 2H), 4.14 (t, J=9 Hz, 1H), 4.41 and 3.97 (AB_q, J=12 Hz, 2H), 3.99 (s, 3H), 3.07 (dd, J=6 and 12 Hz, 1H), 1.27 (t, J=6 Hz, 3H); MS m/z (M+) 562; UV (EtOH) 343 nm (ε=9105), 264 nm (ε=13970), 209 nm (ε=24594).

Anal. Calcd for $C_{23}H_{26}N_6O_9S$: C, 49.11; H, 4.66; N, 14.94. Found: C, 49.33; H, 4.64; N, 14.90.

36a: mp >168°C (d); IR (KBr, cm^{-1}) 3210, 1720, 1682, 1621, 1538, 1389, 1279, 1262; ^1H NMR (300 MHz, DMSO-d_6) δ 9.14 (d, J=9 Hz, 1H), 7.60-7.10 (m, 2H), 7.03 (s, 1H), 5.00-4.85 (m, 1H), 4.06-4.00 (m, 2H), 3.85-3.20 (m, 3H), 3.80 (s, 3H), 2.93 (dd, J=9 and 12 Hz, 1H), 1.13 (t, J=7.5 Hz, 3H); MS m/z (M+1) 439; UV (EtOH) 326 nm (ε=10781), 233 nm (ε=15001).

HRMS (FAB) m/z (M+1) Calcd for $C_{16}H_{19}N_6O_7S$: 439.106960, obs: 439.105260.

Preparation of 3-Benzyloxycarbonyl-7-(R,S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36b). The title

compound was prepared from **31b** (via **35b**) in a manner similar to that described for the conversion of **31e** to **36e**.

35b: IR ($CHCl_3$, cm^{-1}) 3025, 1731, 1704, 1557, 1386, 1369, 1277; ^1H NMR (90 MHz, $CDCl_3$) δ 9.38 (br s, 1H), 8.09 (br d, 1H), 7.28 (br s, 5H), 7.10 (s, 1H), 6.16-5.50 (m, 2H), 5.42 (d, J=10.8 Hz, 2H), 5.23 (d, J=9 Hz, 2H), 5.16 (s, 2H), 4.92-4.56 (m, 4H), 4.28-3.88 (m, 2H), 4.43 and 3.99 (AB_q, J= 12.6 Hz, 2H), 3.96 (s, 3H), 3.08 (dd, J= 10.8 and 10.8 Hz, 1H); MS m/z (M+1) 625; UV (EtOH) 338 nm (ε=6493), 264 nm (ε=10926).

Anal. Calcd for $C_{28}H_{28}N_6O_9S$: C, 53.84; H, 4.52; N, 13.54. Found: C, 53.68; H, 4.59; N, 13.21.

36b: mp>160°C (d); IR (KBr, cm^{-1}) 3417, 1696, 1662, 1617, 1521, 1442, 1396, 1380, 1331, 1272; ^1H NMR (90 MHz, DMSO-d_6) δ 9.01 (br d, J=7 Hz, 1H), 7.24 (br s, 5H), 7.12 (br s, 2H), 5.04 (s, 2H), 5.20-4.64 (m, 2H), 3.76 (s, 3H), 4.14-2.60 (m, 5H); MS m/z (M+1) 501; UV (EtOH) 329 nm (ε=11296), 231 nm (ε=15547).

HRMS (FAB) m/z (M+1) Calcd for $C_{21}H_{21}N_6O_7S$: 501.1192, obs: 501.1173.

Preparation of 3-Ethylcarbonyl-7-(R,S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36c). The title compound was prepared from **31c** (via **35c**) in a manner similar to that described for the conversion of **31e** to **36e**.

35c: mp 183-186°C; IR ($CHCl_3$, cm^{-1}) 3230, 1733, 1679, 1554, 1423, 1377, 1353, 1044; ^1H NMR (90 MHz, $CDCl_3$) δ 9.55 (br s, 1H), 8.28 (br d, J=7.2 Hz, 1H), 7.09 (s, 1H), 6.22-5.72 (m, 2H), 5.68-5.16 (m, 4H), 4.96-4.60 (m, 4H), 4.42 (1/2ABq, J=12.5 Hz, 1H), 4.24-3.80 (m, 3H), 3.95 (s, 3H), 3.09 (dd, J=9 and 11.7 Hz, 1H), 2.79-2.39 (m, 2H), 1.11 (t, J=7.2 Hz), 3H); MS m/z (M+1) 547; UV (EtOH) 365 nm (e=8122), 261 nm (ε=13612), 228 nm (ε=22084), 208 (ε=21522).

Anal. Calcd for $C_{23}H_{26}N_6O_8S$: C, 50.54; H, 4.80; N, 15.38. Found: C, 50.28, H, 4.82; N, 15.43.

36c: mp >260°C; IR (KBr, cm^{-1}) 3310, 1716, 1636, 1534, 1414, 1380, 1257, 1050; ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (d, J=9 Hz, 1H), 7.24 (br s, 2H), 7.03 (s, 1H), 5.06-4.92 (m, 1H), 4.20-3.00 (m, 3H), 3.83 (s, 3H), 2.48-2.46 (m, 2H), 2.97 (dd, J=6 and 12 Hz, 1H), 0.92 (t, J=6 Hz, 3H); MS m/z (M+1) 423; UV (EtOH) 350 nm (ε=9801), 300 nm (ε=6987), 233 nm (e=15992).

HRMS (FAB) m/z (M+1) Calcd for $C_{16}H_{19}N_6O_6S$: 423.1087, obs: 423.1105.

Preparation of 3-Cyano-7-(R,S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (36d). The title compound was prepared from **31d** (via **35d**) in a manner similar to that described for the conversion of **31e** to **36e**.

35d: IR ($CHCl_3$, cm^{-1}) 3020, 3000, 2230, 1733, 1681, 1554, 1411, 1371, 1276, 1044; ^1H NMR (300 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.29 (d, J=6 Hz, 1H), 7.44 (s, 1H), 6.04-5.86 (m, 2H), 5.52-5.22 (m, 4H), 5.15-5.02 (m, 1H), 4.85 (d, J=6 Hz, 2H), 4.70 (d, J=6 Hz, 2H), 4.41 and 4.13 (AB_q, J=15 Hz, 2H), 3.88 (s, 3H), 3.94-3.82 (m, 1H), 3.20 (dd J= 12 and 12 Hz, 1H); MS m/z (M+) 515; UV (EtOH) 363 nm (ε=5800), 263 nm (ε=14291), 227 nm (ε=21822), 209 nm (ε=22387).

Anal. Calcd for $C_{21}H_{21}N_7O_7S$: C, 48.93; H, 4.11; N, 19.02. Found: C, 49.14; H, 4.23; N, 18.77.

36d: mp >225°C (d); IR (KBr, cm^{-1}) 3320, 2220, 1724, 1649, 1534, 1398, 1046; ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (d, J=9 Hz, 1H), 7.24 (br s, 2H), 6.98 (s, 1H), 5.06-4.92 (m, 1H), 4.27 (1/2AB_q, J=12 Hz, 1H), 3.96 (d, J=12 Hz, 1H), 3.84 (s, 3H), 3.09 (dd, J=9 and 12 Hz, 1H), 4.00-3.00 (m, 1H); MS m/z (M+1) 392; UV (EtOH) 302 nm (ε=9726), 227 nm (ε=16225).

HRMS (FAB) m/z (M+1) Calcd for $C_{14}H_{14}N_7O_5S$: 392.07769, obs: 392.07610.

Preparation of Allyl-[7-(S)-(*tert*-Butoxycarbonylamino)-3-methylsulfonyl]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylate (38). To a cold (0°C), magnetically stirred solution of **37** (20.1 g, 100 mmol) in methanol (250 mL) was added 1-(diethylphosphonato)-1-(methanesulfonyl)ethylene (prepared as described for **34e**) (100 mmol) in one portion. The resulting solution was stirred under nitrogen for

five min. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (elution with ethyl acetate followed by 5% methanol in ethyl acetate) to provide a semi-solid which was slurried with ether to give 37.0 g (56%) of the vinyl phosphonate adduct as a white solid: mp 111-112°C; IR (KBr, cm^{-1}) 3310, 2980, 2920, 1709, 1701, 1532, 1391, 1368, 1320, 1307, 1286, 1254, 1230, 1166, 1140, 1057, 1031, 977, 941; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 5.15-5.04 (m, 1H), 4.60-4.40 (m, 1H), 4.27 (q, J=9 Hz, 4H), 3.93-3.75 (m, 1H), 3.75-3.40 (m, 3H), 3.18-3.06 (m, 1H), 3.26 (s, 3H), 1.46 (s, 9H), 1.40 (t, J=9 Hz, 6H); MS m/z (M^+) 443; $[\alpha]^{25}_{365}$ -254.47° (c=0.256, DMSO).

Anal. Calcd for $C_{15}H_{30}N_3O_8SP$: C, 40.63; H, 6.82; N, 9.48. Found: C, 40.90; H, 7.00; N, 9.36.

To a cold (-78°C), magnetically stirred suspension of the vinyl phosphonate adduct (73.7 g, 166 mmol) in methylene chloride (400 mL) under nitrogen was added allyl oxalyl chloride (24.6 g, 166 mmol) followed immediately by *N,N*-diisopropylethylamine (57.8 mL, 332 mmol). The cooling bath was removed and the reaction was stirred for 18 h during which time the solid dissolved and the solution became yellow. The solution was concentrated and the residue was purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexane) to yield 15.5 g (23%) of **38** as a yellow solid: mp 50-60°C; IR (KBr, cm^{-1}) 3390, 2980, 1746, 1718, 1522, 1457, 1447, 1395, 1369, 1317, 1275, 1250, 1187, 1162, 1139, 1097, 957; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06-5.91 (m, 1H), 5.50-5.31 (m, 2H), 5.16-5.06 (m, 1H), 4.90-4.83 (m, 2H), 4.80-4.64 (m, 1H), 4.27 (ABq, J=12 Hz, 2H), 4.15-4.00 (m, 1H), 3.14 (s, 3H), 3.03-2.90 (m, 1H), 1.46 (s, 9H); MS m/z (M^+) 401; UV (EtOH) 329 nm (ε=12398); $[\alpha]^{25}_{589}$= -142.86 (c=0.23, DMSO).

Anal. Calcd for $C_{16}H_{23}N_3O_7S$: C, 47.87; H, 5.78; N, 10.47. Found: C, 47.73; H, 5.84; N, 10.25.

Preparation of 3-Methylsulfonyl-7-(S)-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (40). The title compound was prepared in a fashion analogous to that described above for compounds **36a-e**.

40: mp >200°C (d); IR (KBr, cm^{-1}) 3320, 1722, 1652, 1534, 1402, 1383, 1304, 1133, 1046; ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (d, J=9 Hz, 1H), 7.23 (br s, 2H), 6.95 (s, 1H), 5.05-4.93 (m, 1H), 4.37 and 4.00 (AB_q, J=12 Hz, 2H), 3.85 (s, 3H), 3.90-3.74 (m, 1H), 3.20 (s, 3H), 3.13 (dd, J=9 and 12 Hz, 1H); MS m/z (M+1) 445; UV (EtOH) 302 nm (ε=11022), 229 nm (ε=17163); $[\alpha]^{25}_{589}$ -88.84° (c=0.215, DMSO).

Anal. Calcd for $C_{14}H_{16}N_6O_7S_2$+(1/2)H_2O: C, 37.08; H, 3.78; N, 18.53. Found: C, 37.00; H, 3.64; N, 18.31.

REFERENCES AND NOTES

1. (a) Jungheim, L.N.; Sigmund, S.K.; Fisher, J.W. *Tetrahedron Lett.* **1987**, *28*, 285. (b) Jungheim, L.N.; Sigmund, S.K.; Jones, N.D.; Swartzendruber, J.K. *Tetrahedron Lett.* **1987**, *28*, 289. (c) Jungheim, L.N.; Sigmund, S.K. *J. Org. Chem.* **1987**, *52*, 4007. (d) Jungheim, L.N.; Barnett, C.J.; Gray, J.E.; Horcher, L.H.; Shepherd, T.A.; Sigmund, S.K. *Tetrahedron* **1988**, *44*, 3119. (e) Allen, N.E.; Hobbs, J.N. Jr.; Preston, D.A.; Turner, J.R.; Wu, C.Y.E. *J. Antibiotics* **1990**, *43*, 92. (f) Jungheim, L.N.; Sigmund, S.K.; Holmes, R.E.; Barnett, C.J.; Ternansky, R.J. Eur. Patent Appl. **1986**, EP 202,046; US Patent Appl. **1985**, 729,021. (g) Jungheim, L.N.; Ternansky, R.J.; Holmes, R.E. *Drugs of the Future* **1990**, *15*, 149. (h) Holmes, R.E.; Neel, D.A. *Tetrahedron Lett.* **1990**, *31*, 5567.

2. Preliminary accounts of this work have been reported: Ternansky, R.J.; Draheim, S.E. *Tetrahedron Lett.* **1988**, *29*, 6569. Ternansky, R.J.; Draheim, S.E. *Tetrahedron Lett.* **1990**, *31*, 2805.

3. Pirrung, F.O.H.; Rutjes, F.P.J.T.; Heimstra, H.; Speckamp, W.N. *Tetrahedron Lett.* **1990**, *31*, 5365.

4. Jungheim, L.N. personal communication. Dorn, H.; Otto, A. *Angew. Chem. Int. Ed. Eng.* **1968**, *7*, 214. Dorn, H.; Otto, A.; *Chem. Ber.* **1968**, *101*, 3287. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc* **1971**, *93*, 2897.

5. (a) Cook, G.K.; Hornback, W.J.; Jordan, C.L.; McDonald III, J.H.; Munroe, J.E. *J. Org. Chem.* **1989**, *54*, 5828. (b) Blaszczak, L.C.; Brown, R.F.; Cook, G.K.; Hornback, W.J.; Hoying, R.C.; Indelicato, J.M.; Jordan, C.L.; Katner, A.S.; Kinnick, M.D.; McDonald III, J.H.; Morin Jr., J.M.; Munroe, J.E.; Pasini, C.E. *J. Med. Chem.* **1990**, *33*, 1656.

6. Boyd, D.B.; Foster, B.J.; Hatfield, L.D.; Hornback, W.J.; Jones, N.D.; Munroe, J.E.; Swartzendruber, J.K. *Tetrahedron Lett.* **1986**, *27*, 3457.

7. Brown, H.C.; Subba Rao, B.C. *J. Org. Chem.* **1957**, *22*, 1136.

8. The X-ray analysis was performed by N.D. Jones, J.K. Swartzendruber and J.B. Deeter of The Lilly Research Laboratories.

9. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

10. MIC (ug/ml): *Haemophilus influenzae* (76): **40**; 0.5 **36e**; 1.0
Escherichia coli (TEM): **40**; 0.125 **36e**; 0.25
Strep. pneumoniae (ParkI): **40**; 0.125 **36e**; 0.25

11. Newall, C.E. in *Recent Advances in the Chemistry of Beta-Lactam Antibiotics, Third International Symposium*, Brown, A.G. and Roberts, S.M. ed. **1984**.

12. Kaminski, Z.J. *Tetrahedron Lett.* **1985**, 26, 2901.