DISSERTATION

SYNTHESIS AND STUDY OF BICYCLOMYCIN ANALOGS

Submitted by

Lynn K. Maruyama

Department of Chemistry

In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 1987

COLORADO STATE UNIVERSITY

Fall 1987

WE HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER OUR SUPERVISION BY LYNN K. MARUYAMA ENTITLED "SYNTHESIS AND STUDY OF BICYCLOMYCIN ANALOGS" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT

SYNTHESIS AND STUDY OF BICYCLOMYCIN ANALOGS

The synthetic utility of a key electrophilic coupling reaction developed in the total synthesis of bicyclomycin was explored in the hope that this methodology could be applied to the synthesis of homologs of this unique antibiotic. The coupling reaction was a carbon-carbon bond forming reaction which utilized an electrophilic glycine anhydride derivative and a trimethylsilylketeneacetal in the presence of a Lewis acid. A number of substituted diketopiperazines were made by this route and their elaboration to bicyclomycin homologs attempted.

Carbocyclic bicyclomycin derivatives which lacked the oxygen heteroatom in the bicyclic bridge were synthesized as a complementary series of analogs. Various [2.2.2] and [3.2.2] carbocyclic systems were made containing and lacking the structural functionalities believed necessary for biological activity. The desired structural features were based on proposed mechanisms of action for bicyclomycin. These features included: 1) an OR or SR type leaving group at the C-6 position of the piperazinedione, 2) an olefinic moiety alpha to the leaving group at C-6, 3) secondary (-NH-) amides. Methodology was developed for synthesis of these carbocycles, of particular significance was an intramolecular enolate/epoxide opening reaction which yielded both the [2.2.2] (**178**, **182**, **184**) and [3.2.2] (**179**, **183**, **185**) carbocyclic skeletons. The regiochemistry displayed by this reaction could be explained by a consideration of Baldwin's Rules for Ring Closure. Attempted

deprotonation at the bridgehead position of these carbocycles proved unsuccessful in achieving heteroatom substitution. Consequently, these bridgehead substituted bicyclic compounds (**162**, **205**) were obtained by functionalization of the C-6 position prior to cyclization. The carbocycles obtained through this synthetic work were submitted for biological testing.

Lynn K. Maruyama
Department of Chemistry
Colorado State University
Fort Collins, Colorado
Fall 1987

ACKNOWLEDGEMENTS

There are many individuals who have been a part of my life during my sojourn at CSU who have contributed to the pursuance and ultimate completion of this work.

Gail Wakayama struggled with me through the first two years of graduate school and as a roommate offered a listening ear, support, and a friendship which continues to grow. I am very grateful to Dr. and Mrs. Susumu Karaki who graciously opened up their home and their lives to me; they provided a sanctuary from the pressures of lab and lots of healthy encouragement. A thank you also goes to the members of Faith Evangelical Free Church for their support and fellowship over the years.

Numerous labmates in the Williams' group have made my stay more pleasant through the friendly comaraderie they provided as well as discussions on chemistry, chemists, and life in general. Among these people are Andy Stewart, Rob Armstrong, Dr. Jen-Sen Dung, Dr. Byung Lee, Dr. Tomasz Glinka, Paul Ehrlich, Pete Sinclair, Jim Hendrix and Weixiu Zhai. Many of these chemists freely gave of their time to answer questions and were an abundant source of knowledge and ideas.

I extend my sincere gratitude to Shelly Pinkerton who typed this dissertation on short notice. Her patience and willingness to spend time at all odd hours of the night to complete this dissertation is appreciated.

Thank you's are in order to Dr. Robert Williams for the financial support of this project, as well as for the opportunity to present a paper on this work at the

IUPAC Pacific Basin Societies meeting in Honolulu, HI. The extensive help given in studying for cumulative exams is also appreciated.

Finally, I'm deeply grateful to my parents, Take and Mary Maruyama and to my husband, Mark. My parents gave me the security of a close family and a sure knowledge of the home that is always there. Their support emotionally and financially has meant a great deal to me. Mark has been the best labmate, roommate (and husband) that anyone could ask for. He patiently proofread this dissertation and drew structures for it while also picking up the slack for the household chores that I wasn't getting done. His encouragement, support, and chemical experience were invaluable during this time.

DEDICATION

To Mom, Dad, Mark, Mike, Sandi,

Rae and Lisa

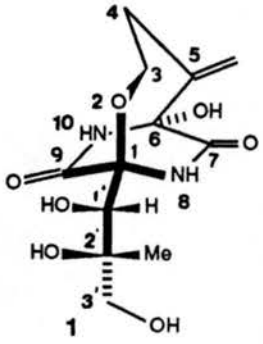
TABLE OF CONTENTS

CHAPTER 1
INTRODUCTION

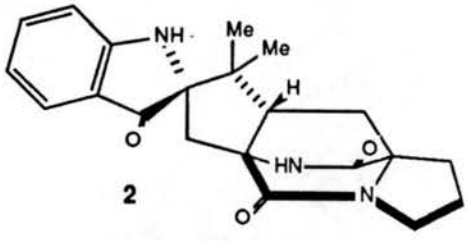
In 1972, two Japanese groups simultaneously published accounts of their research on a new and structurally unique antibiotic that had been isolated from cultures of *Streptomyces sapporonensis* and *S. aizunensis*.[1,2] The colorless, prism shaped crystals displayed an unusual spectrum of biological activity: active against such Gram-negative bacteria as *E. coli, Klebsiella, Salmonella* and *Shigella sp.*, but inactive against *Proteus, Pseudomonas sp.* and gram positive bacteria. No *in vivo* or *in vitro* cross resistance was observed between this antibiotic and commercially available antibiotics for Gram-negative organisms. Because this activity differed from that observed for known antibiotics of *Streptomyces sp.*, and because of its different molecular formula, this compound was considered to represent a new class of antibiotics.[1]

Additional studies[3,4] by workers at the Fujisawa Pharmaceutical Company revealed a curious bicyclic structure **1** (Fig. 1) for this antibiotic, hence the name bicyclomycin. While other molecules have been isolated which share with bicyclomycin the physical feature of the diketopiperazine ring such as the brevianamides[5] and the epidithiadiketopiperazines[6] (Scheme 1), the other structural differences between these classes of molecules are marked. The brevianamides are highly functionalized from the bicyclic bridge and do not have two free amides as does bicyclomycin. In turn, the epidithiadiketopiperazines are *heteroatom* fused to form the bicyclic bridge as opposed to the oxypropyl bridge on bicyclomycin.

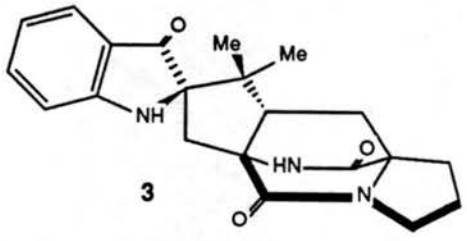
Scheme 1



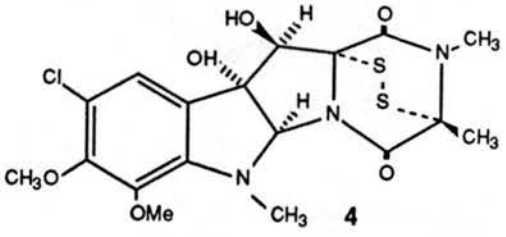
BICYCLOMYCIN



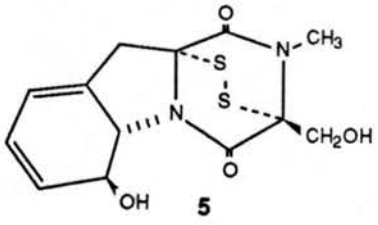
BREVIANAMIDE B



BREVIANAMIDE A



SPORIDESMINS A



GLIOTOXIN

EPIDITHIADIKETOPIPERAZINES

BIOLOGICAL AND MECHANISTIC STUDIES

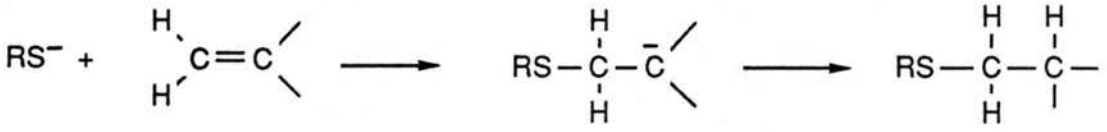
Bicyclomycin exhibits extremely low toxicity. Administration by i.v. injection into mice resulted in an acute toxicity level (LD_{50}) of 2g/kg while administration by subcutaneous, oral, and intraperitoneal methods resulted in an LD_{50} of greater that 4g/kg.[1] Early studies indicated that bicyclomycin inhibits the synthesis of envelope proteins and not that of cytoplasmic proteins. More specifically, the formation of lipoprotein found in the outer membrane was inhibited in the presence of bicyclomycin. Lipoprotein is necessary for maintaining the structural integrity of the cell wall and exists in two forms: free and bound. The bound form is covalently linked to every 10-12 diaminopimelate residues in the peptidoglycan and is the form that is primarily affected by bicyclomycin.[7] Lipoprotein inhibition cannot be the primary killing mode of action of bicyclomycin, since mutant *E. coli* lacking murein lipoprotein have been successfully grown.[8,9]

In a comparative study it was found that ^{14}C-labeled bicyclomycin bound to different proteins than did benzylpenicillin. This was determined by the differing mobilities of the two sets of proteins on SDS polyacrylamide gel electrophoresis. Benzylpenicillin bound to the penicillin binding proteins (PBP's), while bicyclomycin bound to distinct proteins; the bicyclomycin binding proteins (BBP's), or inner membrane proteins. Although the morphological effects of bicyclomycin on the cell are similar to those induced by penicillins, the mechanism of action of bicyclomycin appeared to be markedly different.[8]

Iseki and coworkers[10] published an account detailing the reaction of bicyclomycin with various thiols. It was shown that dithiothreitol and 2-mercaptoethanol inhibited the binding of ^{14}C-bicyclomycin to whole cells of *E. coli* and to the inner membrane proteins. Methanethiol was used as a model for

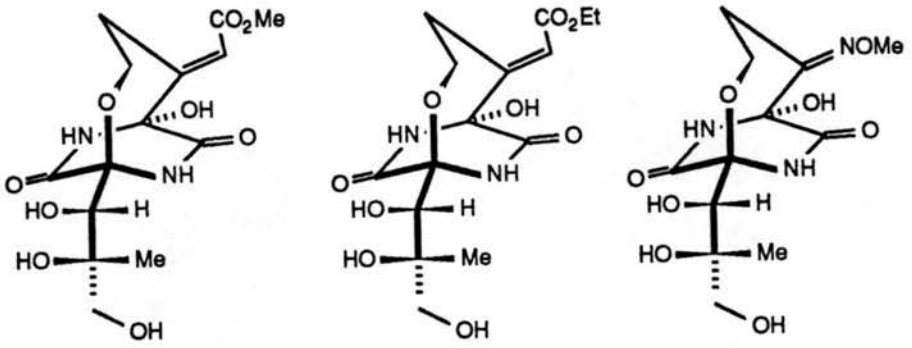
the sulfhydryl group in further reactions and was found to undergo addition to the *exo*-methylene moiety of bicyclomycin. They observed that dihydrobicyclomycin exhibits no antimicrobial activity. These results suggest that the 4,5 double bond of bicyclomycin is essential for biological activity. The authors proposed that bicyclomycin covalently binds to sulfhydryl residues on the inner membrane proteins and offered the following mechanistic scheme (Scheme 2). They gave the brief explanation that the thiol group attacks the C-5 *exo*-methylene to form an enolate anion which then undergoes protonation.

Scheme 2



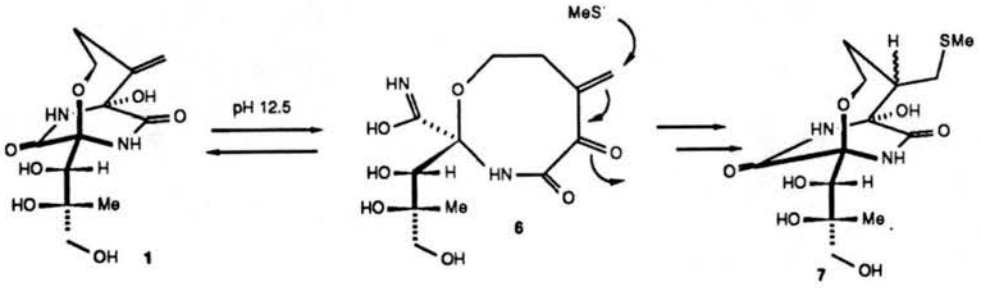
A Ciba Geigy group[11] produced a wide range of semisynthetic bicyclomycin derivatives in which the trihydroxyisobutyl side chain was altered, as was the olefinic moiety of bicyclomycin. Most of the modifications of the molecule resulted in inactive derivatives, while in a few isolated cases the derivatives displayed a broader spectrum of activity than the parent compound. Scheme 3 shows the three compounds which did display biological activity; it should be noted that in all three cases the trihydroxyisobutyl side chain and olefinic moiety were intact. Despite the extensiveness of this study, the lack of a systematic approach to the derivatives left the mechanism of action of bicyclomycin still undefined.

Scheme 3



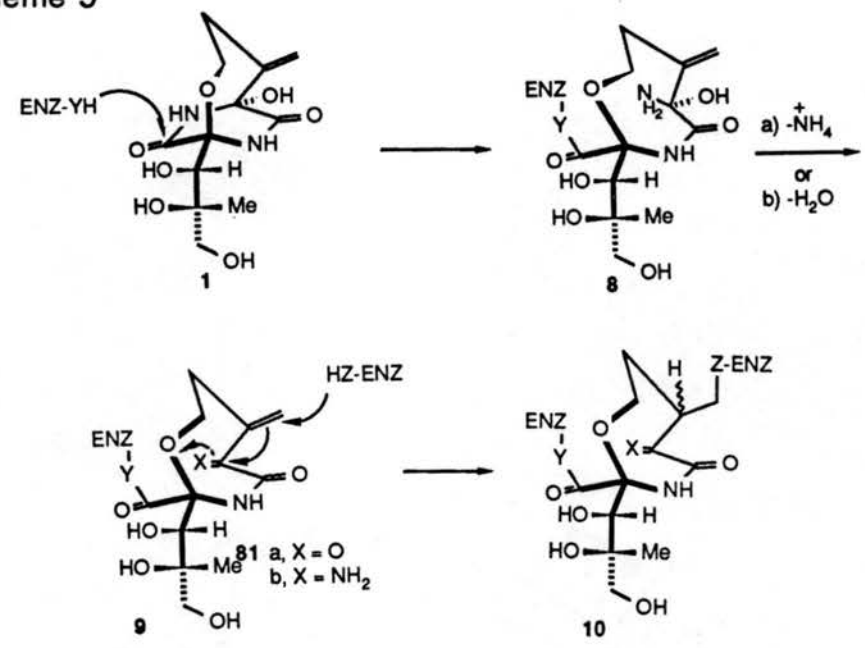
Williams and coworkers[12] expanded upon the early models of Iseki *et. al.* Williams proposed that bicyclomycin undergoes base catalyzed tautomeric ring opening to the monocyclic α,β-unsaturated ketone **6** (Scheme 4). Intermediate **6** functions as a Michael acceptor which undergoes Michael addition to the C-5 olefin to afford the adduct **7**.

Scheme 4



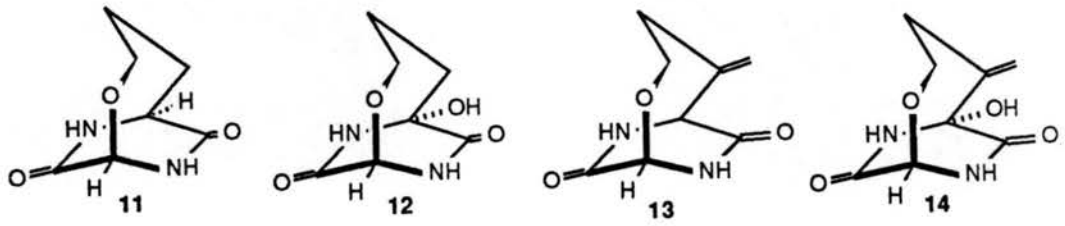
An equally interesting proposal put forth in the same paper was that bicyclomycin, because of its dipeptide nature, acts as a substrate for a protease or transpeptidase type protein which is presumably one or more of the BBP's. In this way, bicyclomycin acts as a "suicide" inhibitor by irreversibly alkylating an enzyme that is key to the synthesis of the bacterial cell wall. This is depicted in Scheme 5. The 9,10-amide bond is initially cleaved to yield acyl enzyme derivative **8**. Loss of NH^+_4 or H_2O, depending upon the pH, again yields a Michael-type acceptor. Addition to this substrate **9** affords the alkylated enzyme.

Scheme 5



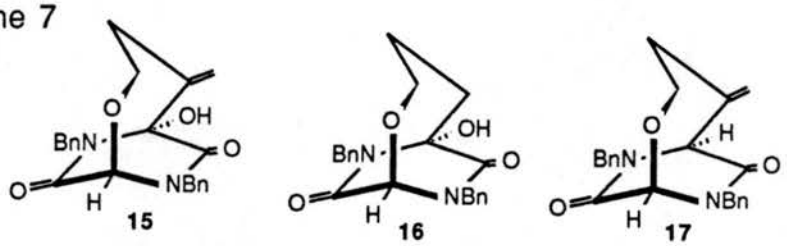
To study these hypotheses, the Williams' group synthesized analogs of bicyclomycin designed to specifically test the "obligate partnership" of the C-5 *exo*-methylene and C-6 hydroxy group. Analogs containing and lacking the following functionality were studied: 1) substitution of N-8 and N-10, 2) the C-6 hydroxyl group, 3) the C-5 *exo*-methylene, 4) the C1'-C3' trihydroxyisobutyl side chain. These analogs were subjected to a twenty microorganism screen and a few of the analogs are shown below (Scheme 6).

Scheme 6



The simple bicyclomycin nucleus **11** as expected showed no antibacterial activity. The 6-hydroxy-5-desmethylene compound, **12**, and the 6-deoxy-5-methylene derivative, **13**, also gave similar results. This lack of activity would seem to support the mechanism of action outlined earlier (Scheme 4) in which **both** the C-6 OH and C5 *exo*-methylene are required for activity. Derivative **14**, which has all of the structural features of bicyclomycin except for the C1'-C3' side chain, was not bactericidal. This would indicate that this functionality is necessary, perhaps as a site of binding or chelation. Interestingly enough, N-benzyl compound **15** (Scheme 7) exhibited weak activity but showed only Gram positive inhibition. The N-benzyl protected desmethylene compound **16** was not biologically active. Similar results were obtained for the desoxy compound **17**. This data would imply that both the C-5 *exo*-methylene and C-6 hydroxy group are necessary for biological activity. The difference in the spectrum of activity observed for bicyclomycin and for compound **15** would suggest differing modes of bactericidal action.

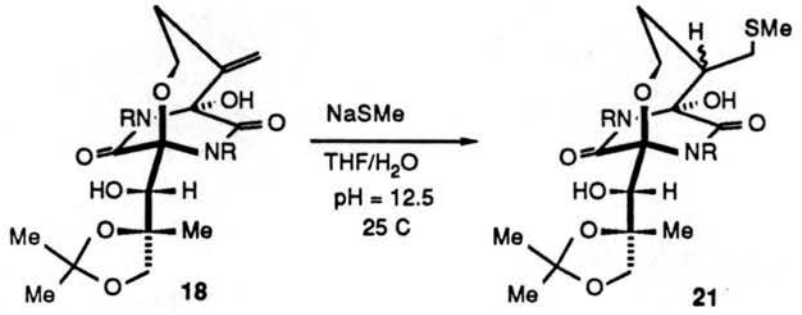
Scheme 7



More recent work by Williams and Tomizawa[13] has served to better clarify the mechanism of action of bicyclomycin.[16] Through this study they were able to determine the minimum structural requirements for thiolate addition at pH 12.5. These are: 1) the presence of **both** the C-5 *exo*-methylene and C-6 bridgehead hydroxy groups; 2) secondary or unsubstituted (NH) amide at N-10; 3) a C-1' OH to activate the C-9 carbonyl for ring opening to a reactive α,β unsaturated ketone.

o

That free amides are necessary for biological activity was demonstrated by the fact that while **18**, the acetonide derivative used as a reactivity standard, easily underwent sulfide addition to give **21**, the alkylated derivatives **19** and **20** did not:

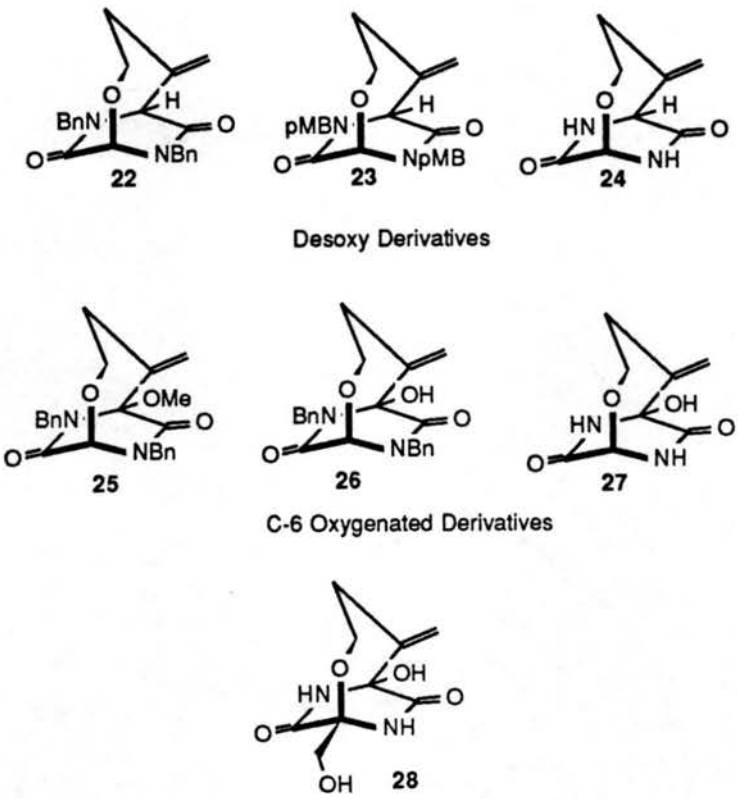


18 , R = H
19, R = CH_2Ph
20, R = CH_2Ph- p- OMe

Various C-6 desoxy derivatives and C-6 oxygenated derivatives were synthesized and their reactivity with NaSMe studied (Scheme 8). None of the desoxy derivatives, nor the C-6 oxygenated derivatives, displayed any sulfide addition. Compound **28** did, however, and it should be stressed that this was the only derivative which bore the C-1' hydroxyalkyl residue **and** also had free amides. More compound studies served to further substantiate these requirements.

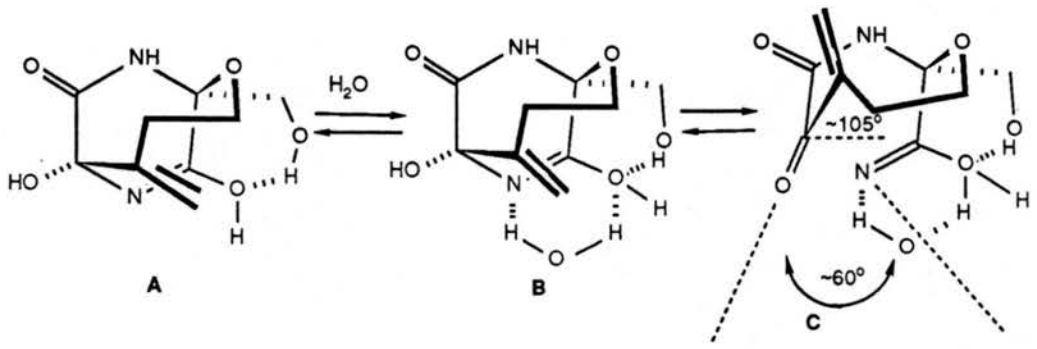
Kinetic studies on **28** for sulfide formation yielded a solvent deuterium isotope effect of K_{H_2O}/K_{D_2O} ~2.4, suggesting that the rate limiting step involves proton transfer from the solvent. ^{18}O incorporation studies on **28** provided evidence for the intermediacy of **6** (Scheme 4), the ring opened ketone.

Scheme 8



A consideration of the data regarding 1) the unreactivity of the N-alkylated derivatives to NaSMe additions, 2) the apparent need for the hydroxyalkyl moiety, 3) the evidence for a proton transfer as a rate limiting step, 4) the ^{18}O labelling studies showing the eight-membered ketone as a likely intermediate led Williams to propose that **28** suffers tautomeric ring opening to the α,β-unsaturated ketone in a step that involves proton transfer from the solvent and is rate limiting (Scheme 9).

Scheme 9



More specifically, because of the orthogonality of the C-6/N-10 bond to the C-9/N-10 amide system, the electron pair generated by the rupture of the C-6/N-10 bond breaking must be accomodated on N-10 alone. To alleviate this electronic effect N-10, as the imino alcohol tautomer has the capacity to hydrogen-bond to H_2O (structure B). This affirms the lack of reactivity of the N-alkylated derivatives since such a tautomer cannot be formed by these compounds nor is it likely that they hydrogen bond to the solvent.

NMR studies on compounds such as **18**, **19**, **20** and **28** provided evidence that the C-1' OH and C-6 OH are hydrogen bonded to the C-9 and C-7 carbonyl, respectively. Williams suggested that intramolecular hydrogen bonding of the C-1' OH to the C-9 carbonyl coupled with the proton transfer noted above catalyzes the ring opening step to the eight-membered ketone. Such an analysis is plausible, for Dreiding model studies show a vector cone for the reverse reaction (ring closure) (C ⟶ B) to be 60°; this substantially diverges from the Dunitz[14] vector of ~105°. The molecule must thus suffer considerable distortion of the ring to reclose. By the principle of microscopic reversibility, the ring opening would likewise be poor. Effects such as those noted above provide an explanation for the relative reluctance of many derivatives to undergo tautomerization.

While the structural requirements for the sulfide addition to bicyclomycin derivatives were clarified through this work, it became apparent that there is no simple correlation between thiolate susceptibility and antimicrobial activity. Compounds which readily added thiolate did not necessarily display biological activity. Such an example is compound **28**. Additionally, while compound **15** showed antimicrobial activity it was unreactive toward NaSMe.

Recent findings by Vasquez[15] would appear to support the alternate mechanistic theory of bicyclomycin as a suicide inhibitor of a protease-type enzyme. These workers observed that in *E. coli*, bicyclomycin induced an increase in the number of diaminopimelyl-diaminopimelyl (DAP-DAP) bridge units. The cleavage of these bridges in cell peptidoglycan is required for normal growth of the cell. These researchers pointed to the structural similarity between bicyclomycin and a possible structure of the DAP-DAP linkage (Fig. 1). They suggested that bicyclomycin inactivates the amidase responsible for the breakage of the DAP-DAP bond.

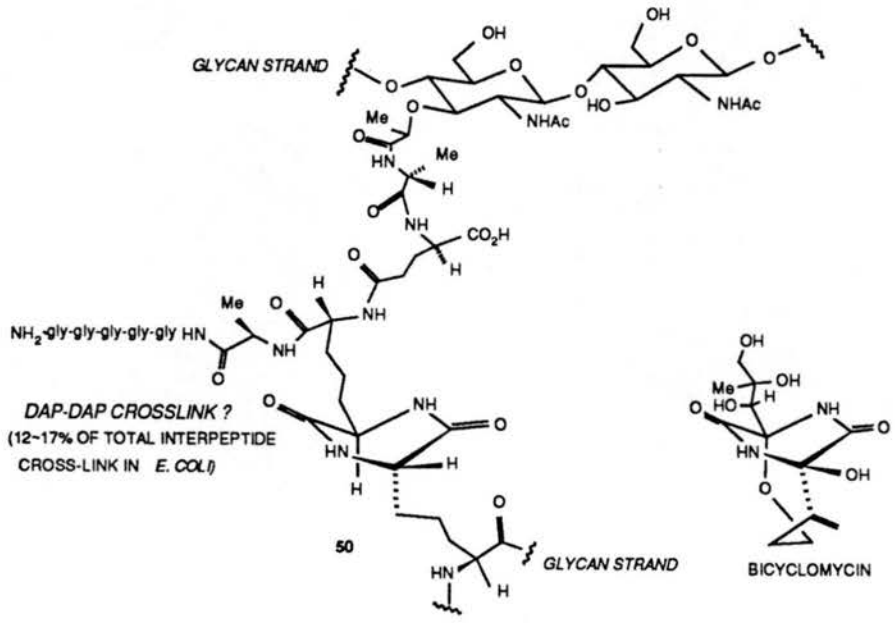


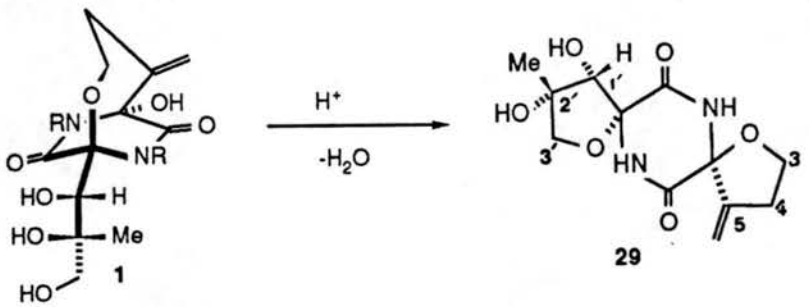
Figure 1. Comparison of the bicyclomycin structure with that of the proposed DAP-DAP crosslink in *E. coli* peptidoglycan.

SYNTHETIC STUDIES

A considerable amount of effort has been expended on the part of many researchers in the quest to synthesize bicyclomycin. These works have been thoroughly reviewed.[16,17] This particular dissertation involves the synthesis of analogs of bicyclomycin and as such, the general background on synthetic strategy toward bicyclomycin and its derivatives will be addressed. Also of interest are the total syntheses of bicyclomycin as they provide insight into the nature of the chemistry and physical properties of this molecule and molecules like it.

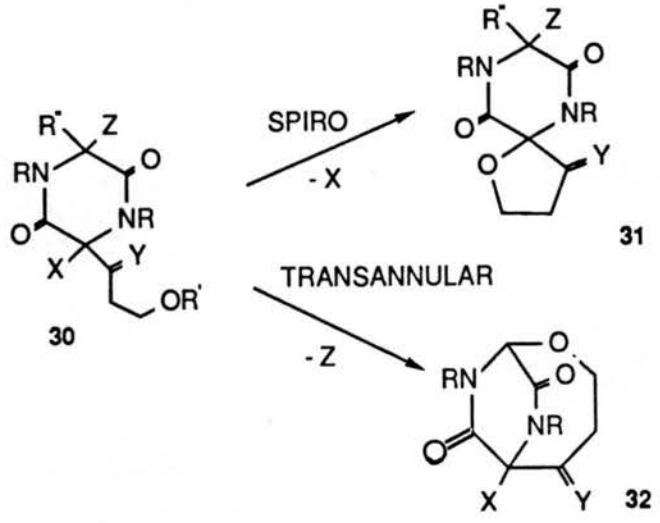
One of the earliest problems facing bicyclomycin strategists was the avoidance of the energy sink represented by spiro compound **29** derived from bicyclomycin which was first documented by Maag (Scheme 10).[18] Upon acid catalysis, the thermodynamically more stable spiro products form. From a

Scheme 10



synthetic viewpoint, most researchers' strategies led to precursors such as **30** (Scheme 11).[19] If X = Z, where X is a leaving group, the problem one is confronted with is the selective activation of C-3 over C-6 to afford the transannular compound **32** and not the energetically favored spiro ring system **31**. This apparent problem is solved in a variety of ways (*vide infra*).

Scheme 11

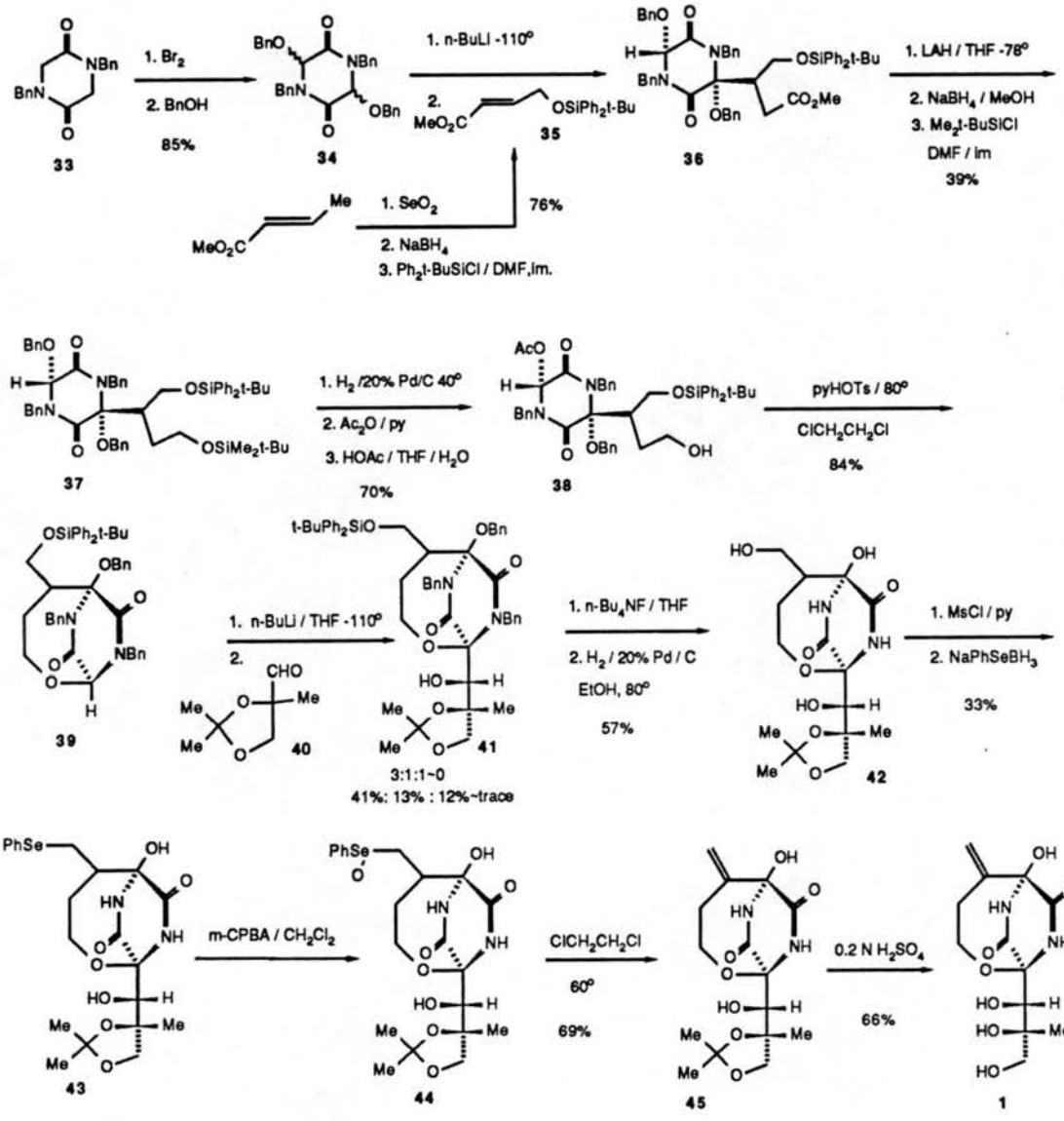


The functionality, X, is often an oxygen derivative that will be unmasked at a later stage to the C-6 OH. If the strategist changes X such that X=H to preclude formation of the spiro product, the oxygen functionalization of the C-6 position must then be introduced after the cyclization step.

In addition to the bridgehead functionalization and transannular vs. spiro ring closures, a third area requiring careful planning of a bicyclomycin synthesis is the protecting groups on nitrogen. The protecting groups must be successfully removed under conditions which do not destroy the framework of the molecule in the final stages of synthesis.

Nakatsuka and coworkers were the first to complete a total synthesis of bicyclomycin (Scheme 12).[20] They started with the N,N-dibenzyl protected diketopiperazine **33**, which was brominated to afford the dibromide. When heated with benzyl alcohol, the dibromide furnished the dibenzylether **34** in 85% yield. The 3:1 mixture of *syn* and *anti* forms could be separated by fractional crystallization but either isomer could be employed in the following step.

SCHEME 12


1. Br2
2. BnOH
85%
1. n-BuLi -110°
2.
1. SeO2
2. NaBH4
3. Ph2t-BuSiCl / DMF,Im.
76%
1. LAH / THF -78°
2. NaBH4 / MeOH
3. Me2t-BuSiCl
DMF / Im
39%
1. H2 /20% Pd/C 40°
2. Ac2O / py
3. HOAc / THF / H2O
70%
pyHOTs / 80°
ClCH2CH2Cl
84%
1. n-BuLi / THF -110°
2.
3:1:1~0
41%: 13% : 12%~trace
1. n-Bu4NF / THF
2. H2 / 20% Pd / C
EtOH, 80°
57%
1. MsCl / py
2. NaPhSeBH3
33%
m-CPBA / CH2Cl2
ClCH2CH2Cl
60°
69%
0.2 N H2SO4
66%

The side chain, methyl γ-hydroxycrotonate **35**, which would eventually form the bicyclic portion of the molecule, was prepared by selenium dioxide oxidation of methyl crotonate followed by reduction with sodium borohydride ($NaBH_4$). Protection of the hydroxy group as the diphenyl-*t*-butylsilyl (TBDPS) ether yielded γ-TBDPS-oxycrotonate **35** in 76% yield.

Dibenzylether **34** was treated with *n*-BuLi to generate the mono-anion which was subsequently quenched with the crotonate at -78°C. The reaction gave only one stereoisomer, **36**. Reduction of the ester to the aldehyde with lithium aluminum hydride ($LiAlH_4$) followed by further reduction with $NaBH_4$ yielded the primary alcohol. This alcohol was protected with *t*-butyldimethylsilylchloride to yield compound **37**.

Before ring closure could take place, Goto and Nakatsuka had to differentiate the two O-benzyl groups to avoid spiro ring formation. This was accomplished by selective hydrogenation of the secondary benzyl group with 20% palladium on carbon (20% Pd/C) and pyridine in ethanol. The new secondary alcohol was then acetylated with acetic anhydride and pyridine.

The *t*-butyldimethylsilyl (TBDMS) group on the primary alcohol was selectively removed by heating in acetic acid:water:THF (1:1:2) to afford the free alcohol in 80% yield. Upon treatment of **38** with pyridinium tosylate and heating in dichloroethane, the bicyclic compound **39** was generated. Treatment of the bicyclic compound with *n*-BuLi generated the mono-anion to which (±)-2-methylglyceraldehyde acetonide **40** was added. The reaction gave four stereoisomers in the ratio of 3:1:1:trace, the major product having the same relative stereochemistry as bicyclomycin.

The major isomer of **41** was converted to the primary alcohol by use of *n*-butylammonium fluoride (*n*-Bu_4NF). At this point the N-benzyl protecting groups were removed by catalytic hydrogenation (20% Pd/C, ethanol, 80°C) to yield the

completely debenzylated product **42**. Elaboration of the primary alcohol into the *exo*-methylene then proceeded by mesylation of the alcohol followed by displacement of the mesylate with the sodium salt of phenylselenylborohydride ($NaBH_3SePh$). The selenide **43** was oxidized by treatment with *m*-chloroperbenzoic acid (m-CPBA) and the selenoxide eliminated by heating at 60°C. Finally, the acetonide was hydrolyzed with 0.2N sulfuric acid at 25°C to furnish racemic bicyclomycin.

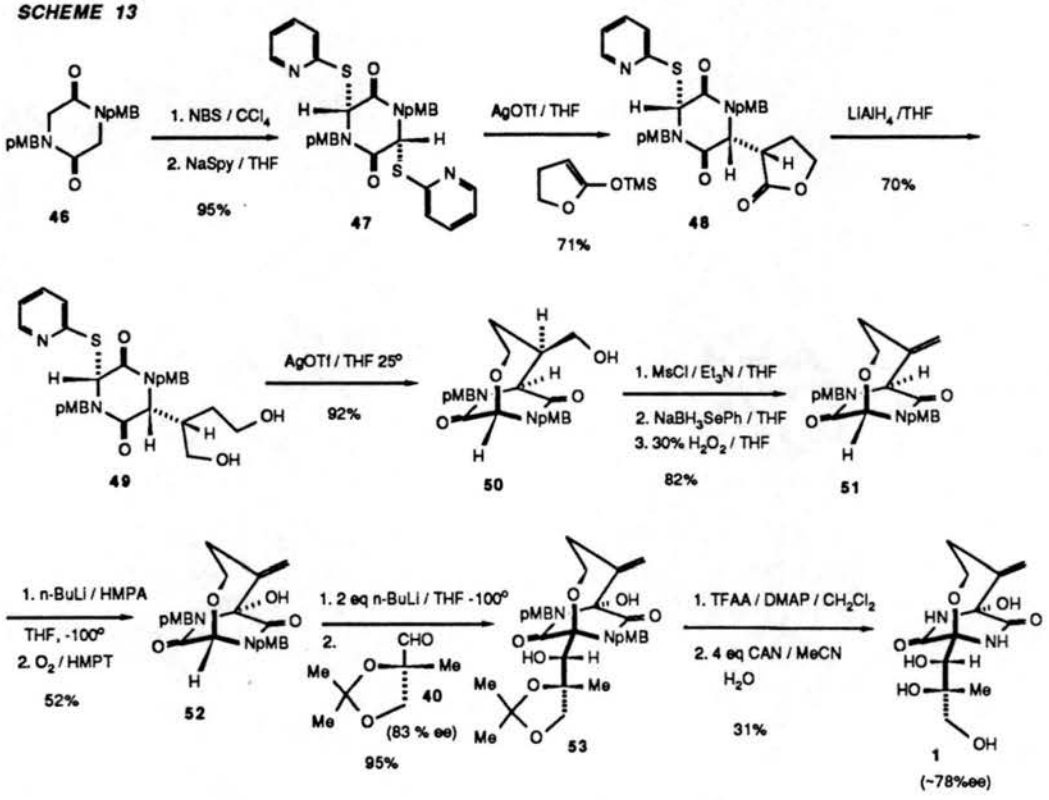
Williams, Armstrong, and Dung's[19] strategy toward bicyclomycin was rather different (Scheme 13). They began with a preformed glycine anhydride derivative **46** with nitrogens protected with the *p*-methoxybenzyl moiety. *Bis* bromination afforded the dibromide; subsequent treatment with the sodium salt of 2-mercaptopyridine (NaSpy) generated the displacement product, the disulfide **47** in 95% yield.

Whereas many of the methods to substitute diketopiperazines often utilize a *nucleophilic* enolate on the diketopiperazine ring system, Williams and coworkers used a novel *electrophilic* coupling reaction to functionalize the diketopiperazine. Silver triflate (AgOTf) mediated coupling of the silyl enol ether of γ-butyrolactone yielded only the monosubstituted piperazinedione **48** in 71% yield.

At this juncture, the 3,6-substitution of the ring system had been differentiated. The butyrolactone moiety of the molecule was then reduced with $LiAlH_4$ to give the diol **49**. Cyclization of the diol with AgOTf can give either the transannular [4.2.2.] bicyclomycin ring system or the homologous [3.2.2.] ring system. The possibility for spiro ring formation is nonexistent, however, for there is no leaving group at the C-6 position.

Mesylation of the primary alcohol afforded the mesylate which was further converted to the selenide with $NaBH_3SePh$. Subsequent oxidation and

SCHEME 13


1. NBS / CCl4
2. NaSpy / THF
95%
AgOTf / THF
71%
LiAlH4 /THF
70%
AgOTf / THF 25°
92%
1. MsCl / Et3N / THF
2. NaBH3SePh / THF
3. 30% H2O2 / THF
82%
1. n-BuLi / HMPA
THF, -100°
2. O2 / HMPT
52%
1. 2 eq n-BuLi / THF -100°
2.
(83 % ee)
95%
1. TFAA / DMAP / CH2Cl2
2. 4 eq CAN / MeCN
H2O
31%
(~78%ee)

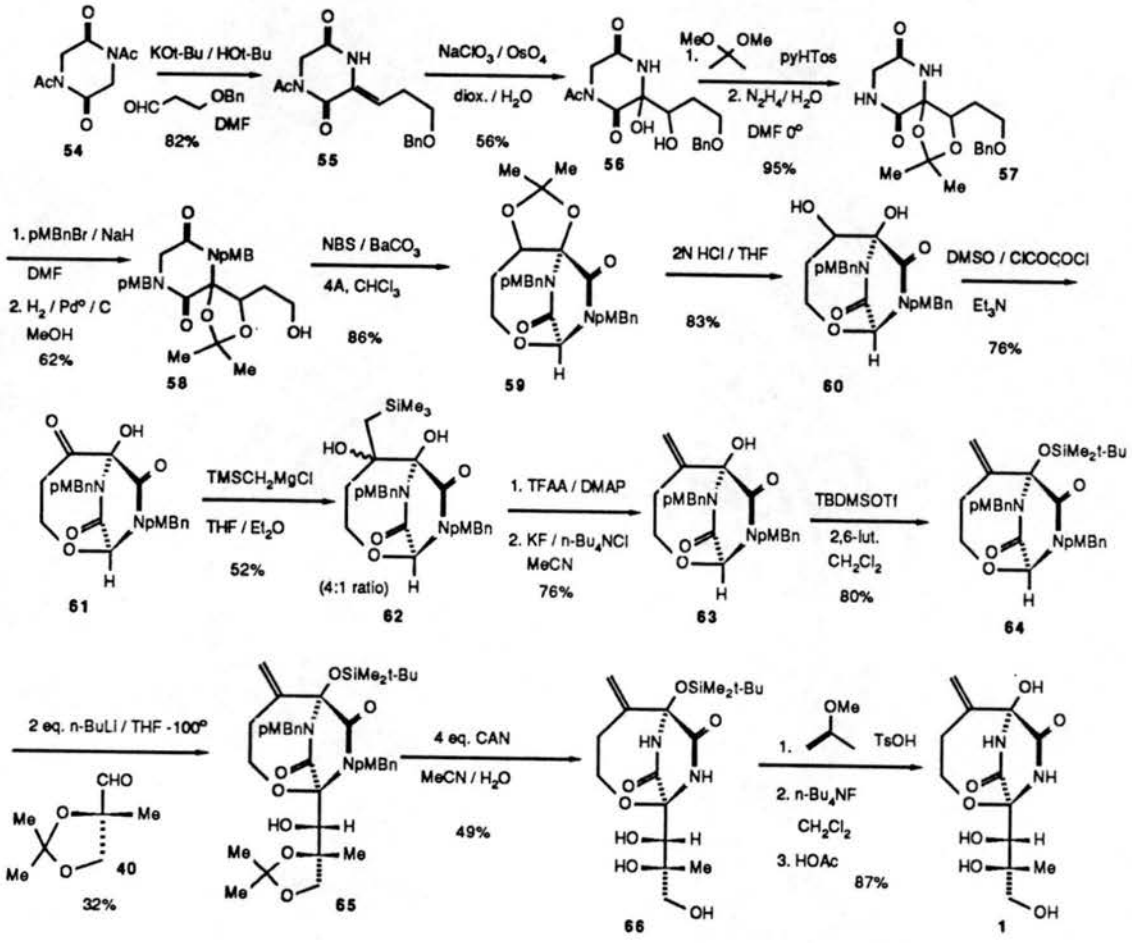
elimination afforded the *exo*-methylene functionalized bicyclic compound in 82% yield.

Since the C-6 position was not functionalized prior to the cyclization step, the bridgehead position of the bicyclic compound must therefore be substituted. This was accomplished by carbanion formation using *n*-BuLi/HMPA followed by an oxygen quench to yield the C-6 hydroxy moiety. The remaining side chain is added as the optically active acetonide through bridgehead carbanion chemistry once more to afford **53**. Selective acetylation of the C-1' OH with trifluoroacetic anhydride (TFAA) in the presence of dimethylaminopyridine (DMAP) was carried out to preclude rearrangement products[21] in the final deprotection of the amides. Subsequent treatment with ceric ammonium nitrate (CAN) directly afforded optically active bicyclomycin.

With regard to the amide deprotection step, the Williams group had initially attempted the bicyclomycin synthesis using N-benzyl derivatives. They found that these amides could not be deprotected under dissolving metal, hydrolytic, or hydrogenolytic conditions. Other protecting groups on the nitrogen such as *p*-methoxyphenyl, *p*-methoxylbenzyl could not be removed under a variety of oxidative conditions. Fortunately, they found that the *p*-methoxybenzyl moiety could be removed from the nitrogen utilizing CAN in a procedure reported by Yoshimura.[22]

Yoshimura's group had themselves[23] published a total synthesis of bicyclomycin shortly after the Williams' paper had appeared (Scheme 14). Their route initially involved the N,N-diacetylglycine anhydride derivative although they changed protecting groups on the nitrogen in the synthesis because of difficulties encountered with the cyclization step using the N-acetylated derivatives. Compound **54** was condensed with 3-benzyloxypropanal to yield the N-monoprotected Z isomer **55** in 82% yield.

SCHEME 14


KOt-Bu / HOt-Bu
DMF
82%
NaClO3 / OsO4
diox. / H2O
56%
pyHTos
2. N2H4 / H2O
DMF 0°
95%
1. pMBnBr / NaH
DMF
2. H2 / Pd° / C
MeOH
62%
NBS / BaCO3
4A, CHCl3
86%
2N HCl / THF
83%
DMSO / ClCOCOCl
Et3N
76%
TMSCH2MgCl
THF / Et2O
52%
(4:1 ratio)
1. TFAA / DMAP
2. KF / n-Bu4NCl
MeCN
76%
TBDMSOTf
2,6-lut.
CH2Cl2
80%
2 eq. n-BuLi / THF -100°
32%
4 eq. CAN
MeCN / H2O
49%
TsOH
2. n-Bu4NF
CH2Cl2
3. HOAc
87%

Oxidation of the olefin with osmium tetroxide in the presence of sodium chlorate gave the diol **56** which was then protected as the isopropylidene using 2-methoxypropene and pyridinium tosylate. Removal of the remaining acetate with hydrazine yielded the free amide system **57**.

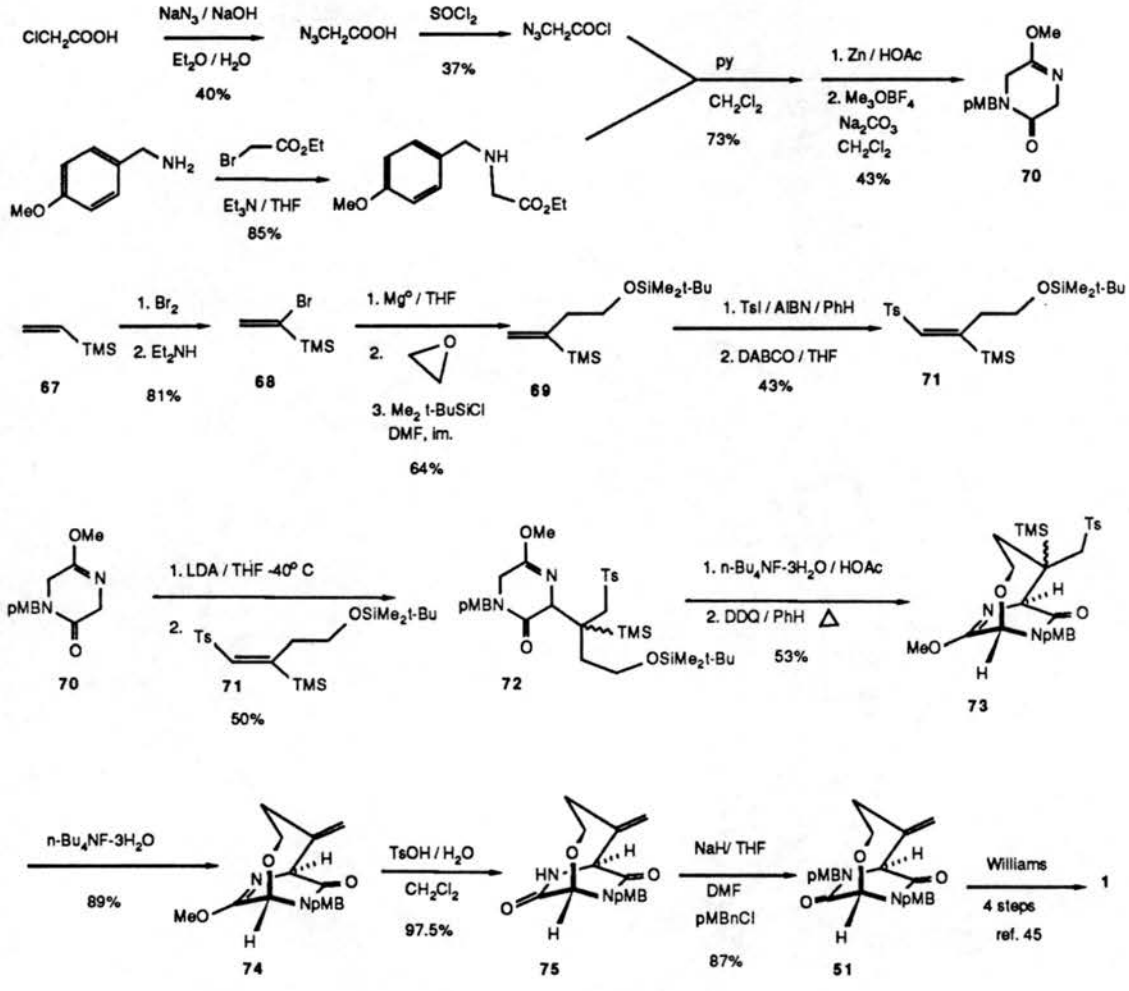
Reprotection of the amides with the *p*-methoxybenzyl group was accomplished by treatment with sodium hydride (NaH) and *p*-methoxybenzylbromide in 62% yield. Hydrogenolysis with Pd/C gave the free primary alcohol. This alcohol was then cyclized with N-bromosuccinimide (NBS) in the presence of barium carbonate to afford the bicyclic compound, **59**. The synthesis is designed such that the bridgehead functionalization is present, but masked at C-6. Spiro ring formation should not occur, but does indeed happen if barium carbonate is not used in the NBS reaction.

After cyclization, the acetonide was deprotected and now the secondary alcohol must be functionalized into the *exo*-methylene. This was brought about by Swern oxidation of the alcohol to the ketone **61** in 76% yield, followed by treatment with trimethylsilylmethylmagnesium chloride to give the addition product **62** as a 4:1 mixture of diastereomers. The secondary alcohol was converted to the acetate with TFAA; treatment with *n*-$BuNH_4F$ afforded the elimination product **63**.

The tertiary bridgehead alcohol was protected as its *t*-butyldimethylsilyl ether with the corresponding triflate reagent. Generation of the bridgehead carbanion followed by quenching with the side chain acetonide gave **65**. Ceric ammonium nitrate deprotection of the amides resulted in deisopropylidination as was seen in the Williams' synthesis. The diol was reprotected as the acetonide to preclude possible rearrangement.[25] Treatment with *n*-Bu_4NF yielded the free tertiary alcohol. This was followed by final removal of the acetonide to afford the target compound.

Another synthesis of bicyclomycin deserves mention. Samme's group[24] in England made the intermediate **51** which the Williams' group had employed in their total synthesis of bicyclomycin (Scheme 15). As mentioned earlier, the nature of the amide protecting group was always a major consideration; the approach taken by this group is novel in their use of the mono-imino ether derivative **70**. The anion of the mono-iminoether was condensed with vinyl cation synthon **70** which had been prepared as noted in Scheme 15. The Michael addition went regioselectively to yield the diastereomeric products **72** in 50% yield. Selective deprotection of the primary alcohol with *n*-Bu_4NF and acetic acid furnished the free alcohol. Oxidation with dichlorodicyano-benzoquinone (DDQ) afforded the putative iminium intermediate which then underwent cyclization to the bicyclic ether **73**. Treatment of **73** with *n*-Bu_4NF yielded **74**, the elimination product. The conversion of the mono-imino ether to the N,N-bis-*p*-methoxybenzyl protected amide was accomplished by hydrolysis of the imino ether with toluenesulfonic acid followed by alkylation with sodium hydride and *p*-methoxybenzylbromide to afford the known adduct **51**.

SCHEME 15


ClCH2COOH
NaN3 / NaOH
Et2O / H2O
40%
N3CH2COOH
SOCl2
37%
N3CH2COCl
py
CH2Cl2
73%
1. Zn / HOAc
2. Me3OBF4
Na2CO3
CH2Cl2
43%
70
MeO
NH2
Br
CO2Et
Et3N / THF
85%
NH
1. Br2
2. Et2NH
81%
TMS
67
68
1. Mg° / THF
2.
3. Me2 t-BuSiCl
DMF, im.
64%
OSiMe2t-Bu
69
1. TsI / AIBN / PhH
2. DABCO / THF
43%
Ts
71
pMBN
1. LDA / THF -40° C
2.
50%
72
1. n-Bu4NF-3H2O / HOAc
2. DDQ / PhH
53%
73
n-Bu4NF-3H2O
89%
74
TsOH / H2O
CH2Cl2
97.5%
75
NaH/ THF
DMF
pMBnCl
87%
51
Williams
4 steps
ref. 45
1

CHAPTER 2

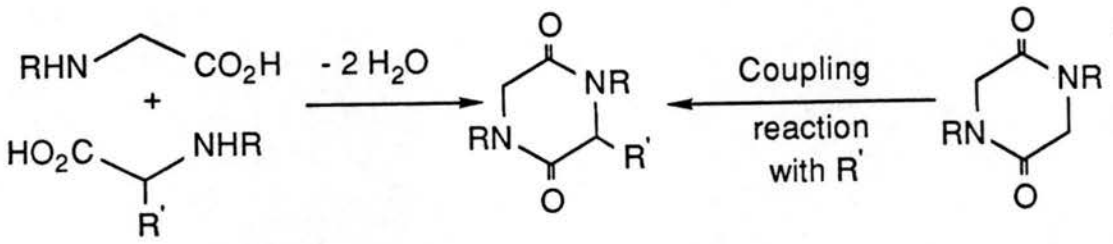
SYNTHETIC STUDIES TOWARD HETEROCYCLIC ANALOGS

The intent of the research described herein was the synthesis of analogs of bicyclomycin. In light of the ready availability of bicyclomycin itself through fermentation procedures, the chemical synthesis of this antibiotic was of dubious practical value. However, in terms of the new synthetic methodology produced and its applicability that such a synthesis realizes its full value. It was hoped that this would be the case with bicyclomycin and its analogs.

Analogs were to be prepared that could not be made directly from bicyclomycin. It was anticipated that the study of the chemical and physical properties, as well as the biological activity of these molecules would shed light on the mechanism of action of bicyclomycin. At the time that this research was initiated, little was known regarding that subject, except for the apparent need for the *exo*-methylene and C-6 OH for activity.

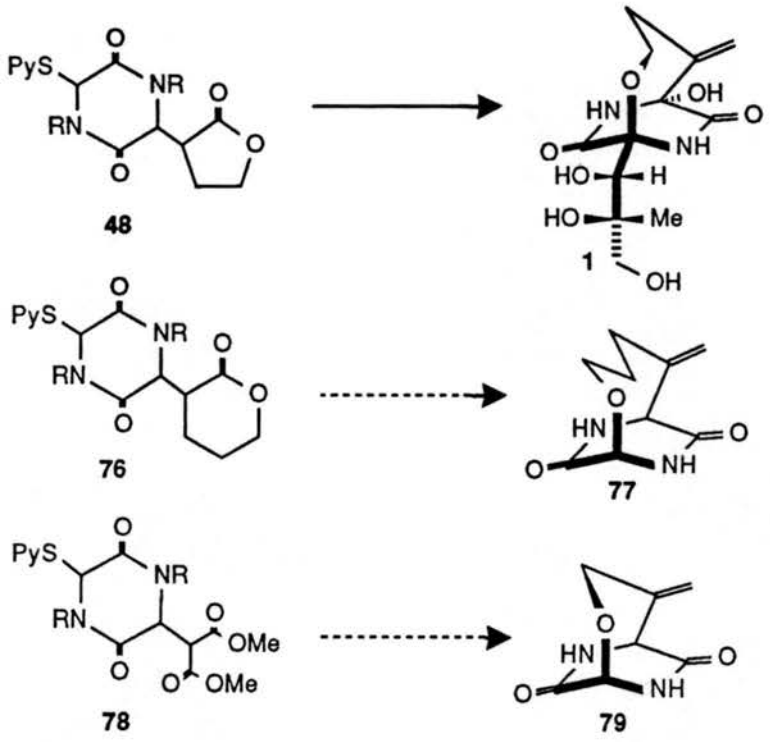
The substituted diketopiperazines that are precursors of the bicyclomycin ring system can be fashioned in a number of ways. Perhaps the two most general classifications for formation of this particular skeleton are either the dehydrative coupling of substituted peptide derivatives followed by cyclization, or the use of a preformed diketopiperazine which is then functionalized (Scheme 16). The former approach will be discussed in Chapter 3; it is the latter upon which we focus our attention now.

Scheme 16



A common procedure in functionalizing diketopiperazines, as noted earlier, is the formation of a nucleophilic enolate in the diketopiperazine ring followed by quenching with the desired electrophile. From Williams' bicyclomycin synthesis there emerged a unique reaction in which the familiar polarity of the coupling reaction was reversed; an electrophilic diketopiperazine ring was reacted with the nucleophile in the presence of a Lewis acid. We wished to capitalize on this methodology to make the one carbon smaller and one carbon larger bicyclic homologs of bicyclomycin. The thiopyridyl butyrolactone substituted diketopiperazine had been elaborated into bicyclomycin, and it was envisioned that similarly substituted derivatives could be fashioned into the homologs. The δ-valerolactone substituted diketopiperazine **76** would serve as the precursor for the [5.2.2] bicyclic analog, **77** while the malonate functionalized compound **78** would afford the corresponding [3.2.2] bicyclic analog **79** (Scheme 17).

Scheme 17

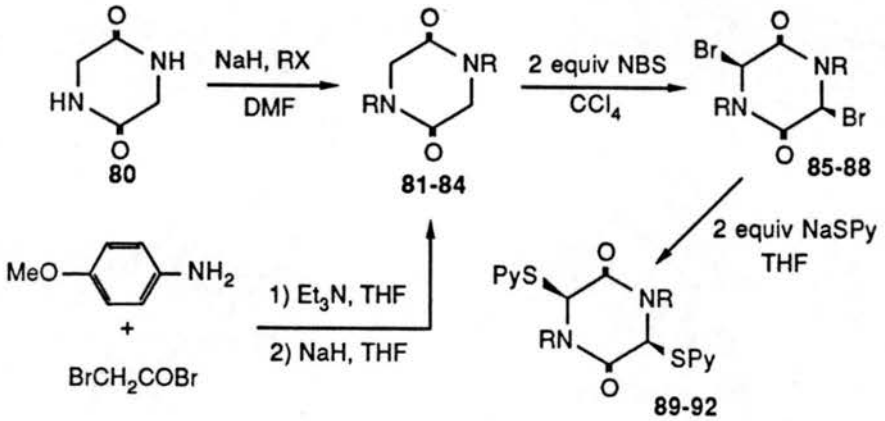


The malonate and the valerolactone coupling reactions were studied using a variety of protecting groups on nitrogen. It had not been determined yet how the nature of the protecting groups affected the stereochemistry of the coupling reactions. Early indications from the bicyclomycin synthesis were that not all of the diastereomers of the coupled product could be converted to the desired compound. In addition, the question of the removal of the protecting groups was not yet reconciled.

In order to probe these coupling reactions, the N-methyl, N-benzyl, N-*p*-methoxybenzyl and N-*p*-methoxyphenyl derivatives were employed. Generally, these derivatives were made by sodium hydride treatment of glycine anhydride at 25°C to generate the di-anion, followed by quenching with the appropriate alkyl halide (Scheme 18). The exception was the synthesis of the N-*p*-methoxyphenyl series. For these derivatives, bromoacetylbromide was

condensed with *p*-anisidine. The adduct from this reaction was then dimerized to furnish the N,N-*bis*-*p*-methoxyphenyl protected species. These substrates were brominated using N-bromosuccinimide in refluxing carbon tetrachloride. The *bis*-thiolpyridyl substituted diketopiperazine was formed by displacement of the bromides with the sodium salt of 2-mercaptopyridine.[25]

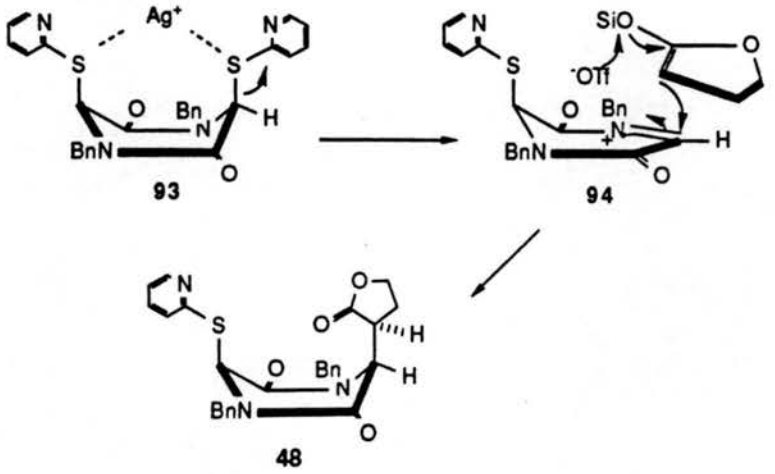
Scheme 18



The coupling reactions were relatively simple to perform. The desired *bis*-thiopyridyl substrate was dissolved in CH_2Cl_2 at 25°C and to this was added AgOTf. After ten minutes the appropriate silyl enol ether was syringed into the reaction vessel. The reaction was complete within a matter of hours, yielding only the monosubstituted product which displayed predominately *syn* stereochemistry about the diketopiperazine nucleus. Despite the addition of greater than one equivalent of AgOTf and silyl enol ether, no bis-substituted products were ever observed.

Mechanistically, it is believed that the silver ion precomplexes to the substrate as in **93** (Scheme 19). The iminium species is generated and is

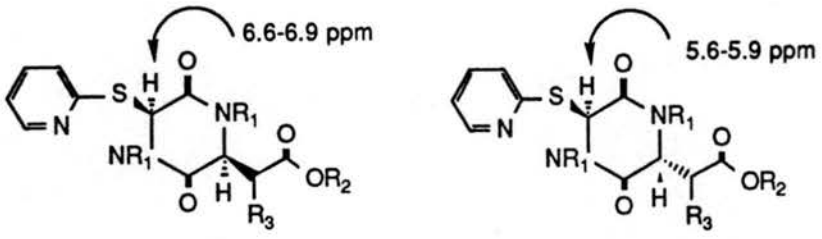
Scheme 19



subsequently approached from the top face of the diketopiperazine, as depicted for the butyrolactone species in structure **94**. Its likely the triflate counterion is attracted to the positively charged iminium ion and then assists in the Si-O bond cleavage.

An X-ray crystal structure of the butyrolactone substituted N,N-bis-*p*-methoxybenzyl derivative revealed that the diketopiperazine assumed a boat-like conformation. The C-3 and C-6 substituents adopt pseudo axial positions to minimize crowding from the alkyl groups residing on the amides. In the less favored *anti* conformation, one would assume that the substituent lying below the plane of the ring suffers a close interaction with the bulky nitrogen alkyl groups. The crystal structure on the *syn* compound, in conjunction with NMR data on the butyrolactone substituted N,N-*bis*(*p*-methoxybenzyl) compound, made possible the stereochemical assignments on other coupled products. *Syn* and *anti* designations were determined by the chemical shift of the signal produced by the methine alpha to the thiopyridyl moiety in the NMR spectrum of the molecule. In the *syn* isomers the shift of this signal was observed between

6.6-6.9 ppm, while the corresponding *anti* isomer exhibited this methine resonance between 5.6 and 5.9 ppm.

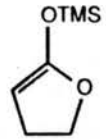
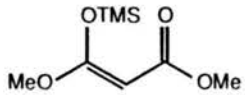
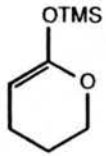


Should it be the case that only the *syn* isomer was useful to carry on in the synthesis, the *anti* isomers could be epimerized to some degree to the corresponding *syn* isomer by treatment with dilute base. That this could be done affirmed our belief that the *syn*-isomer was the thermodynamic product and the *anti*-isomer, the kinetic product.

Table 1 is a listing of all the coupling reactions attempted. Included in the data given for each reaction is the overall yield, as well as the *syn:anti* ratio of the products. The major:minor ratio describes the relative stereochemistry between the proton on C-6 of the diketopiperazine and the proton on the newly formed alpha carbon of the lactone. With the malonate products, there are no major and minor isomers.

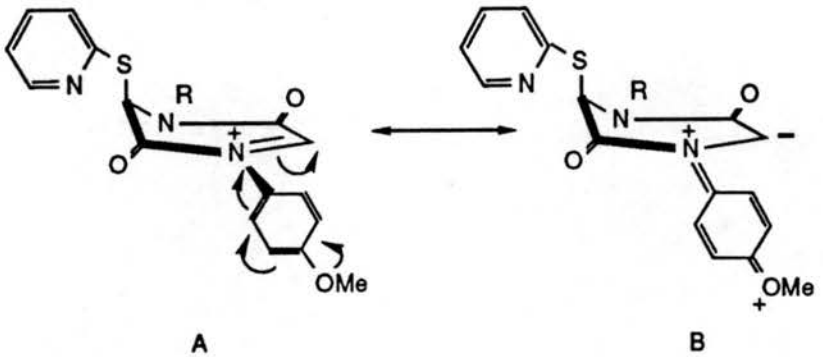
In all reactions the *syn* isomers were favored with one exception: the malonate coupling reaction with the N,N-*p*-methoxyphenyl derivative gave a 1:1 *syn:anti* ratio. In fact a rough order of the *syn* selectivity of the coupling reaction derived from this data is: N-benzyl > N-methyl > N-*p*-methoxybenzyl > N-*p*-methoxyphenyl. Rationalization of the lack of selectivity of the N-*p*-methoxyphenyl series can be attempted if one invokes resonance (Scheme 20). In this particular series, there exists a conduit which allows delocalization to

Table 1. Coupling of 81-84 with ketene trimethylsilyl acetals.

Product	Nucleophile	R_1	R_2	R_3	syn/anti ratio	major/minor ratio	Yield%
206		CH_3	$-CH_2-CH_2-$		3.8:1	3.8:1	60
*207	"	CH_2Ph			1:0	2:1	68-70
*208	"	CH_2Ph	$-p-OCH_3$		1.37:1	2.3:1	71
209		CH_3	CH_3	CO_2CH_3	5.8:1	--	76
210	"	CH_2Ph			2.4:1	--	63
211	"	CH_2Ph	$-p-OCH_3$		2:1	--	86
212	"	Ph	$-p-OCH_3$		1:1	--	66
213		CH_3	$-CH_2CH_2CH_2-$		2.5:1	1.6:1	62
*214	"	CH_2Ph			3.5:1	1.8:1	70
215	"	CH_2Ph	$-p-OCH_3$		2.9:1	2.2:1	44

* performed by Robert W. Armstrong

Scheme 20



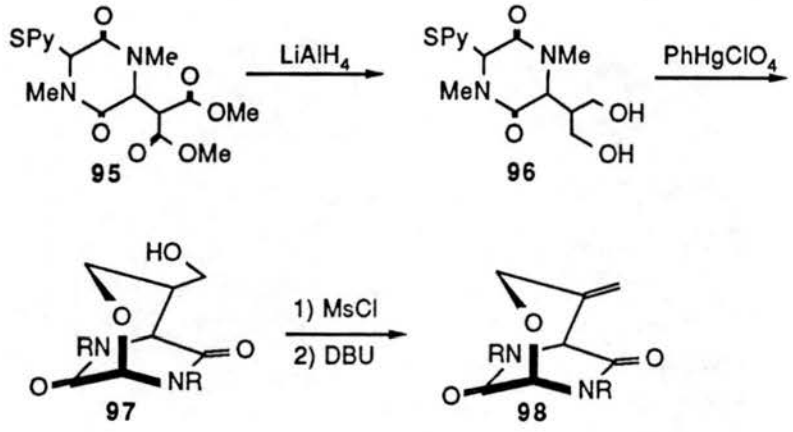
occur between the lone pair of electrons on the methoxy group and the iminium ion. Although resonance does indeed stabilize the iminium ion intermediate, resonance form B unfortunately places negative charge on the carbon that is to undergo electrophilic coupling. Assuming that canonical form B contributes to the overall structure of the iminium intermediate, then it would serve to decrease the intrinsic electrophilicity of the intermediate, perhaps making it less selective. The additional methylene in the N-*p*-methoxybenzyl series precludes such an electronic conduit between the iminium ion and the methoxy group, making a resonance form like B impossible for this series. Thus, a better selectivity is observed than in the N-*p*-methoxyphenyl derivatives. Beyond these observations it is difficult to provide a blanket rationalization that, for example, explains the difference in selectivity between the N-benzyl and N-methyl derivatives.

The proposed route for elaboration of the malonate substituted diketopiperazine to the bicyclic [3.2.2] system is outlined in Scheme 21. The coupled product was to be reduced to the diol **96**. Cyclization would directly afford the seven membered ring **97**. Mesylation, followed by DBU mediated elimination would afford the olefin **98**. This route would thus be a distinct improvement over the one that was being employed. In the bicyclomycin

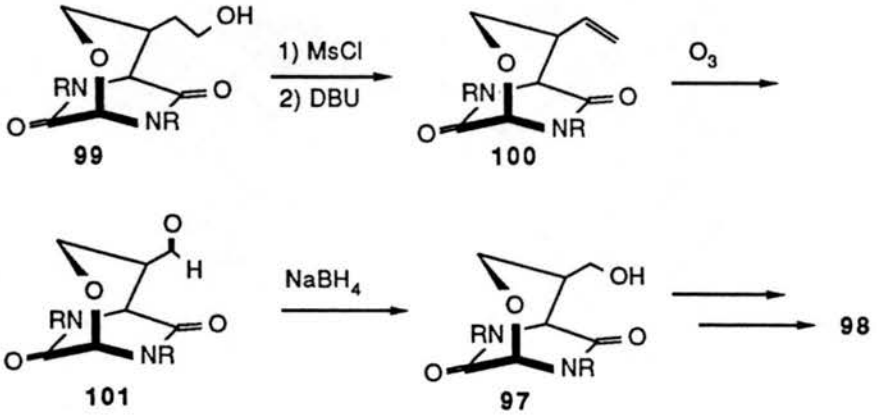
synthesis **99** was formed as a product in the cyclization step in addition to the desired [4.2.2] system. Treatment of **99** with mesyl chloride afforded the mesylate which then underwent elimination with DBU. The allyl moiety was ozonized to give the aldehyde which was converted to the alcohol by reduction with $NaBH_4$. A repeat of the mesylation, elimination procedure resulted in the desired bicyclo[3.2.2]*exo*-methylene **98**.

Scheme 21

Proposed Route:

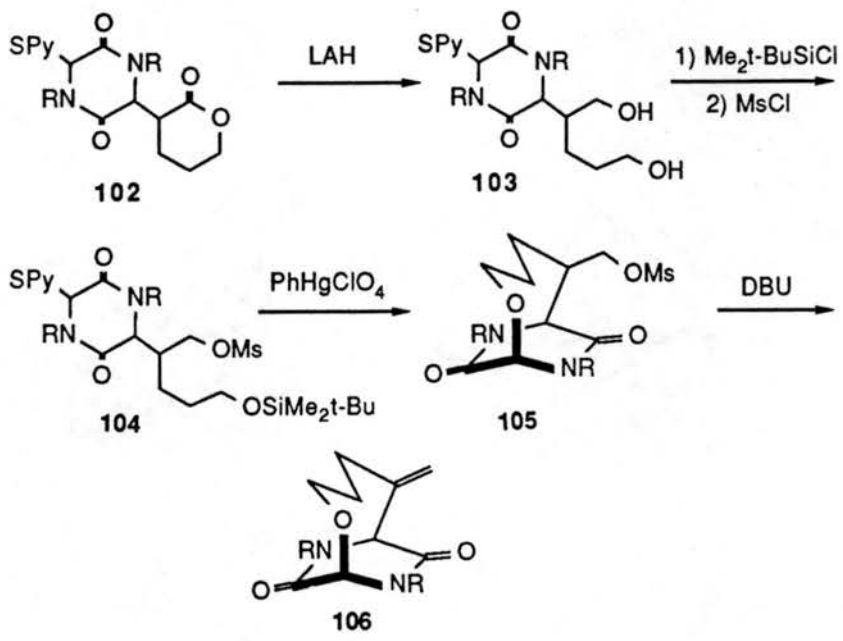


Old Route:



A similar type of synthesis of the [5.2.2] homolog was anticipated for the valerolactone substituted diketopiperazine (Scheme 22). Reduction of **102** to the diol followed by selective silylation and mesylation would afford **104**. Cyclization of **104** to the bicyclic compound with subsequent mesylation and elimination would afford the olefin **106**.

Scheme 22



Upon attempting the reduction to the diol for the malonate and valerolactone systems the situation was found to be more complex than expected. In the case of the N,N-bis-benzyl malonate, the reduction to the diol could not be effected (Table 2). Lithium aluminum hydride at 0°C and 25°C was tried in various solvents. Other reducing agents that were employed were $NaBH_4$, $LiBH_4$, DIBAL, $H_3B{\bullet}S(CH_3)_2$ and Red-Al {$[(CH_3OCH_2CH_2O)_2AlH_2]Na$}. In all cases either starting material was recovered or a complex mixture of products was produced. There are a large number of heteroatoms making up this molecule: sulfur and nitrogen on the thiolpyridyl moiety, two oxygens and

two nitrogens on the diketopiperazine, and four more oxygens on the malonate itself. It is possible that the excessive number of heteroatoms simply "tie-up" the reducing agent and prevent delivery of hydride, at least in those cases where starting material was recovered.

Table 2. Attempted Reduction of Malonate Derivative 95 to the Diol 96.

Reagent	Conditions	Result
$LiAlH_4$	4 equiv.,THF, 0°C, 2h, then 25°C, overnight	starting material
$LiAlH_4$	10 H^- equiv., THF/ether, reflux, 5h	starting material
$NaBH_4$	6 H^- equiv., isopropanol/ THF, reflux	starting material
$LiBH_4$	8 H^- equiv., THF overnight 25°C, then reflux 2h	starting material
DIBAL	4 H^- equiv., CH_2Cl_2 -78°C, 2h	decomposition products
$H_3B{\bullet}S(CH_3)_2$	4 equiv., THF, 4h, reflux	decomposition products
Red-Al	2.4 equiv., toluene 80°C, 0.5h	decomposition products

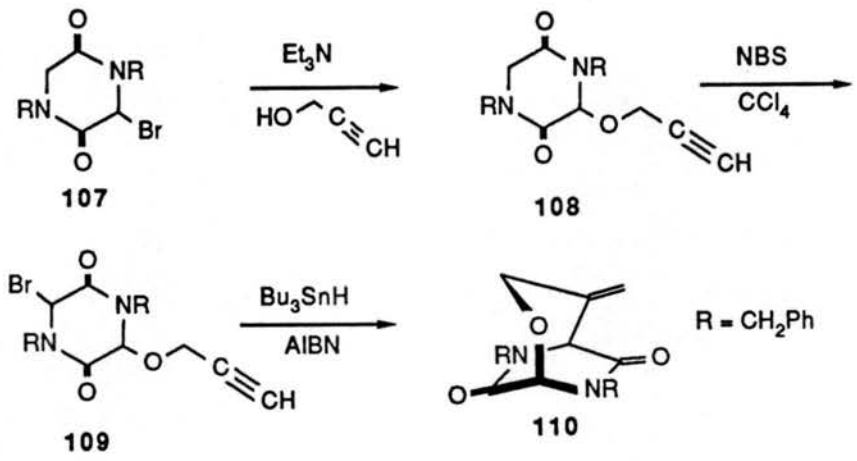
With the valerolactone substituted diketopiperazines reductions to the diol were attempted with similar results as those described for the malonates. The substrates of choice had by this time been determined to be the N-*p*-methoxybenzyl derivatives as it was known that they could be deprotected. The yield for making the coupled valerolactone N-*p*-methoxybenzyl compound was less than promising at 44%. The use of other silver salts to mediate the coupling reaction such as $AgClO_4$, $AgSbF_6$, $AgBF_4$, and $AgOSO_2C_6H_4CH_3$ had been explored in an effort to optimize this yield but with no success. Another difficulty concerning this reaction was the separation of the three diastereomeric

products. Faced with these difficulties, these bicyclomycin-like syntheses of the homologs were abandoned.

A considerable effort had been expended on the synthesis of the homologs of bicyclomycin. When our initial method of choice had not delivered results other alternatives were explored. While some of these potential routes were related to the old strategy in that they involved electrophilic diketopiperazines, other strategies that were delved into were decidedly different. We looked into other ways to form carbon-carbon bonds in order to substitute the diketopiperazines.

We were still interested in finding an efficient route to the [3.2.2] *exo*-methylene bicyclomycin homolog. One approach that we considered had, as its key step, a radical cyclization that would afford the bicyclic system **and** simultaneously generate the *exo*-methylene (Scheme 23). This type of radical cyclization chemistry had many examples in the literature.[26] The starting material, the mono-bromide, had previously been prepared in conjunction with synthetic studies on bicyclomycin. The bromide could be displaced with propargyl alcohol in the presence of triethylamine (Et_3N). This three carbon alcohol was the synthon for the bicyclic bridge. Subsequent bromination of the C-3 position would afford **109**, and then radical cyclization brought about by treatment with tributyltin hydride (Bu_3SnH) with azoisobutyronitrile (AIBN) as initiator, would directly furnish the [3.2.2] *exo*-methylene species.

Scheme 23



Much to our frustration, attempts to repeat the synthesis of the mono-bromide were unsuccessful. The conditions for the synthesis of the mono-bromide were treatment of the N-protected glycine anhydride with 0.5 equivalent of NBS in the presence of catalytic benzoyl peroxide in refluxing carbon tetrachloride for one hour. As such the yield was roughly 30%. Repeating the reaction under these conditions always yielded the *bis*(bromide) substituted product. Table 3 shows the different approaches to the mono-bromide and the results. The synthesis of **109** was also attempted from the *bis*-bromide. The *bis*-bromide was stirred with one equivalent of propargyl alcohol and Et_3N but only starting material was recovered. Reaction of the *bis*-bromide with one equivalent of NaH and propargyl alcohol consumed the starting material but yielded none of the desired product.

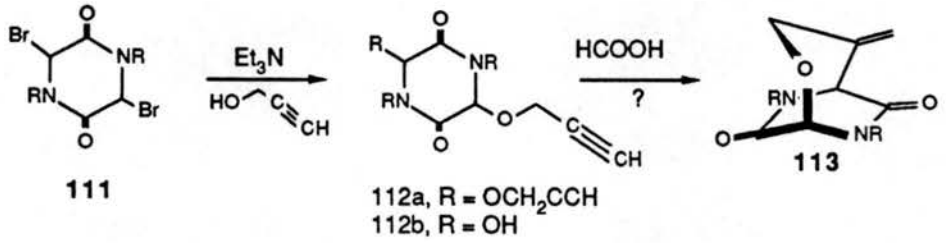
Table 3. Various Approaches to the Synthesis of 107.

Starting Material	Conditions	Result
82	NBS, benzoyl peroxide, CCl_4, 25 min.	*Bis* (bromide)
82	NBS, benzoyl peroxide, CCl_4, 8 min.	*Bis* (bromide)
82	NBS, benzoyl peroxide, CCl_4, 2 min.	*Bis* (bromide)
82	NaH, NBS	Starting material and *Bis* (bromide)
82	LDA, HMPA, NBS	decomposition products

While it appeared impossible to make **109**, the corresponding *bis*-propargyl ether diketopiperazine **112** could be made in 49% yield from the *bis*-bromide diketopiperazine treated with two equivalents of propargyl alcohol and Et_3N. We felt that there was a possibility, albeit remote, that under acidic conditions **112** could undergo cyclization to **113** (Scheme 24). Heathcock[27] had published work on π-cyclizations using butynylcyclohexenols in the presence of formic acid to give the enol formate **115**. While the propargyl ether was a much poorer leaving group than the hydroxy functionality, and the proposed system involved an iminium intermediate rather than an allyl cation, as in Heathcock's case, it was still worth a try. Surprisingly enough, treatment of **112a** with formic acid appeared to give the mono-hydroxy, mono-propargyl ether diketopiperazine **112b**. Diether **112a** was also reacted with camphorsulfonic acid (CSA) and boron trifluoride etherate [$(C_2H_5)_2O{\cdot}BF_3$]. With CSA, no reaction occurred and in the case of the $(C_2H_5)_2O{\cdot}BF_3$ reaction, similar results to those obtained upon treating **112a** with formic acid were observed. One might have expected cyclization to occur from the mono-

hydroxy, mono-propargyl ether derivative **112b** but no cyclized products were ever isolated.

Scheme 24

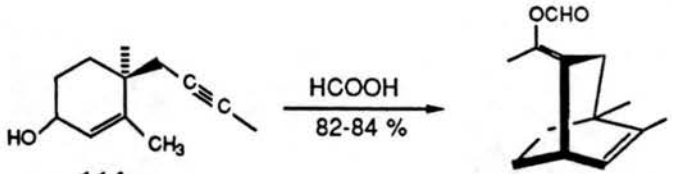


111

112a, R = OCH_2CCH
112b, R = OH

113

Heathcock:



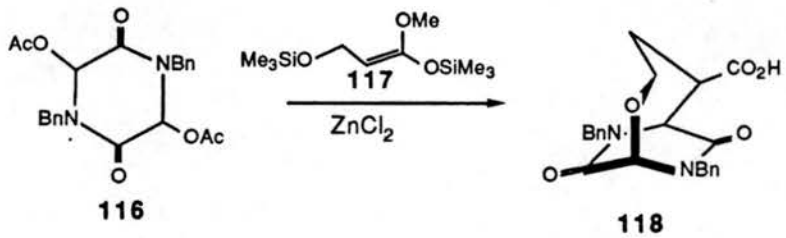
114 **115**

By all appearances, working from either the mono-bromide or the *bis*-bromide diketopiperazine toward a bicyclomycin analog synthesis was going to present a problem in view of the previously described syntheses. In looking for an alternate route, and still unwilling to totally disbelieve that the chemistry of the electrophilic *bis*-thiopyridyl ether diketopiperazines described earlier could not be used in some novel way to make these sought-after analogs, another synthesis was initiated based on using these *bis*(sulfide) derivatives in capping reactions.

In a capping reaction, as the term connotes, both ends of the functionalized bridge are simultaneously, or if necessary stepwise, attached, to the piperazinedione. An example of such chemistry was work done by Sera on the synthesis of the bicyclomycin skeleton.[28] From earlier research, these workers knew that alkoxy or acetoxy groups of 3,6-dialkoxy- or diacetoxy-2,5-piperazinediones were relatively good leaving groups that upon departure gave rise to electrophilic carbons at the C-3 and C-6 positions of the ring.

Accordingly, Sera reacted the 3,6-diacetoxy derivative **116** with the capping reagent 1,4-bis(trimethylsilyloxy)-1-methoxy-1-butene **117** in a reaction catalyzed by zinc chloride to obtain the bicyclic compound (Scheme 25). The silyl enol ether reacts first at the C-3 position and subsequent cyclization furnishes **118** in one pot. The ester can be further reduced to the alcohol, mesylated and eliminated to give the olefin.

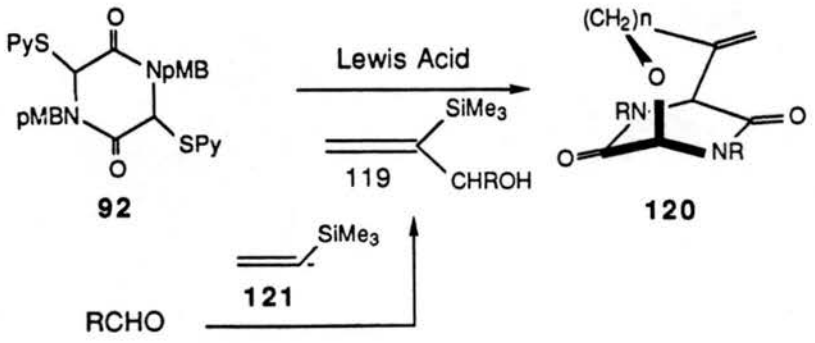
Scheme 25



116 **118**

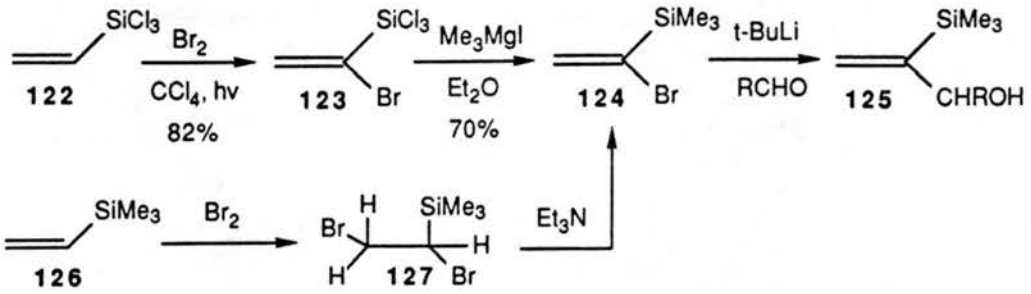
It was envisioned that vinylsilanes such as **119** (Scheme 26) in the presence of a Lewis acid would cap the diketopiperazine substrate to directly afford the homologous bicyclic *exo*-methylene skeleton. The route had the potential to be a versatile synthesis of various sized bicyclic ether systems. The capping reagent could be modified according to the desired ring size of the bicyclic compound by the reaction of the α-(trimethylsilyl)vinyl carbanion with the appropriate carbonyl compound.

Scheme 26



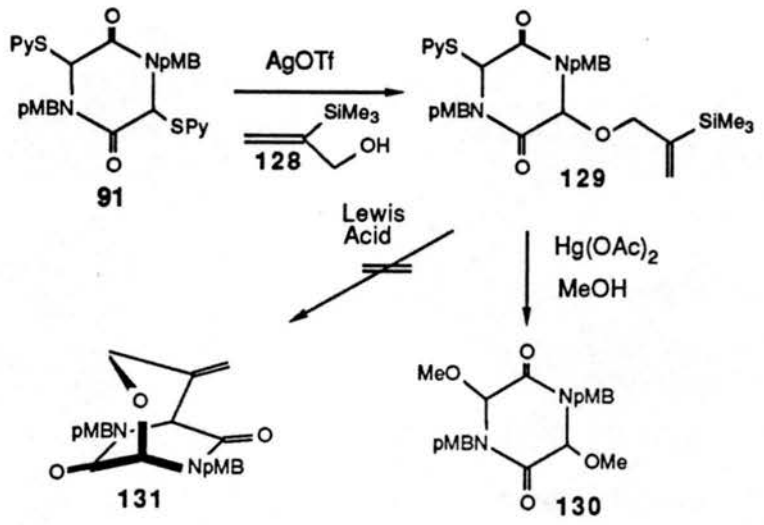
The methodology for making the α-(trimethylsilyl)vinyl compounds had been established by Chan's group.[29] The trichlorovinylsilane **122** (Scheme 28) was brominated under photolytic conditions to afford the α-bromovinyltrichlorosilane **123**. A Grignard reaction with **123** in ether yielded the α-(trimethylsilyl)vinyl compound **124**. Halogen/metal exchange with *t*-BuLi afforded the carbanion which could be quenched with the desired aldehyde. An alternate route[30] which was used to synthesize **124** is *bis*-bromination of vinyltrimethylsilane followed by diethylamine (Et_2NH) mediated elimination. The vinyltrimethylsilane reagent is quite costly, however, in comparison to the vinyltrichlorosilane. The bicyclic ether system chosen as the initial target was the [3.2.2] *exo*-methylene, and, as such, the 2-(trimethylsilyl)-2-propen-1-ol **128** was prepared by the method of Chan.

Scheme 28



The use of excess AgOTf to couple the vinylsilane **128** to the *bis*(sulfide) N,N-*p*-methoxybenzyl substrate **91** (Scheme 29) afforded the mono-coupled ether adduct **129**. The original intent had been to effect a capping reaction, however, it appeared that the reaction would have to be stepwise. Cyclization of **129** was then sought. Several Lewis acids such as $CuClO_4$, $AgClO_4$ and AgF seemed to be reasonable candidates to mediate such a ring closure. Unfortunately, these efforts met with no success, usually starting material was recovered. An attempt was made to convert the sulfide on **129** to a methoxy

Scheme 29

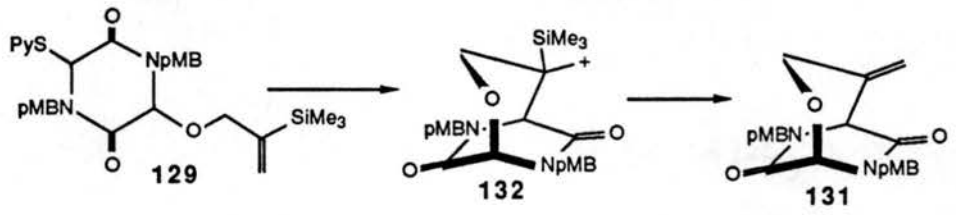


group with the purpose of using titanium tetrachloride ($TiCl_4$) to effect the ring closure. Treatment of **129** with mercuric acetate ($Hg(OAc)_2$) and methanol resulted in the isolation of only the 3,6-dimethoxy-2,5-piperazinedione **130**. The sulfide on **129** was quite labile to the mild Lewis acid conditions as expected but so was the vinylsilane ether.

It had been observed with the coupling reactions of the trimethylsilyl ketene acetals and the *bis*(sulfide) diketopiperazines that the substrate coupled only once in the presence of AgOTf. So, the fact that a capping reaction of **91** was not achieved using AgOTf was not entirely surprising. However, treatment of **129** with $Hg(OAc)_2$ in MeOH showed that under the appropriate conditions, the remaining sulfide was reactive and could definitely function as a viable leaving group. The question was then asked: why didn't cyclization occur upon treatment with $CuClO_4$ or $AgClO_4$? Consideration of the intermediate structures (Scheme 30) shows that cyclization of the iminium ion species proceeds to the bicyclic ether with formation of the presumed primary carbocation **132**. Although this carbocation is β-stabilized by silicon, the stabilization energy is

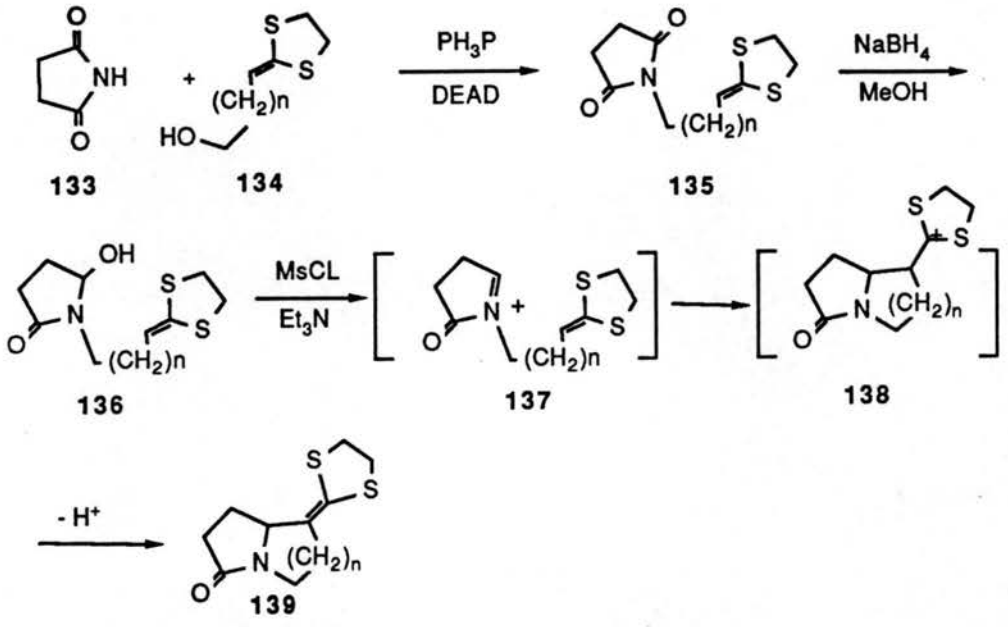
apparently not enough to drive the reaction to completion. When studying literature precedent, it was indeed found that for iminium ion/vinylsilane cyclizations the carbocations generated through the initial bond formation are generally secondary in nature.[31]

Scheme 30



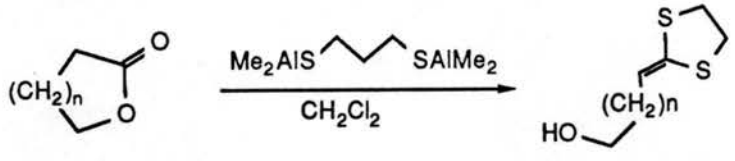
While maintaining the original concept and goal of developing capping reagents for use with the *bis*(sulfide) compounds, it was suggested that the capping reagents be modified such that, upon cyclization by the vinyl moiety, the resulting cation be stabilized by substitution. With those criteria in mind, the use of ketene dithioacetals as capping reagents appeared to be suited to meet those needs. Chamberlin,[32] in his work on the synthesis of pyrolizidine, indolizidine and quinolizidine alkaloid ring systems, had employed ketene dithioacetals to construct these ring systems. Scheme 31 is an example of this work. The ketene thioacetal is coupled with succinimide by the Mitsunobu reaction to give **135**. Reduction followed by mesylation gives the mesylate which is not isolated because it undergoes rapid elimination to the iminium ion. Cyclization then occurs, producing a sulfur-stabilized carbocation. Compound **138** suffers loss of a proton to afford **139**.

Scheme 31



The ketene thioacetal alcohols used for coupling were prepared by a modification of Corey's method[33] for protecting lactones as their 1,3 dithiolane derivatives. For obvious reasons, Chamberlin omitted the acid catalyzed cyclization step of the ketene dithioacetal to the dithioortho lactone. Treatment of the appropriate lactone with bis(dimethylaluminum)1,2-ethanedithiolate in CH_2Cl_2 furnishes the dithioacetal alcohol (Scheme 32).

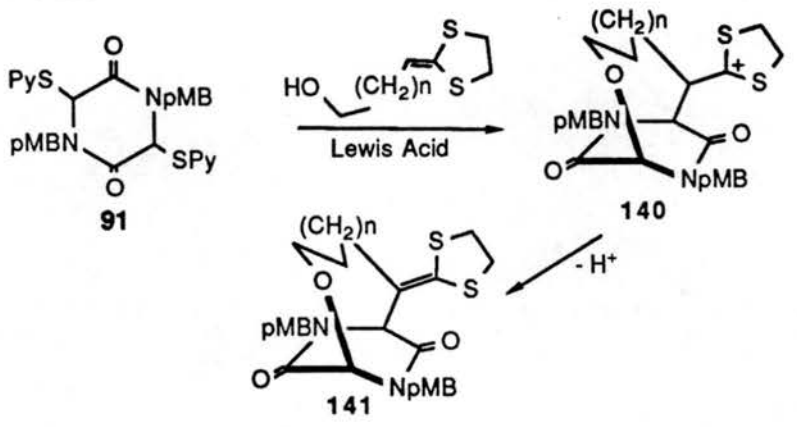
Scheme 32



The *bis*(sulfide) N,N-*p*-methoxybenzyl derivative would again serve as the substrate for the reactions with the dithioacetal alcohols (Scheme 33). The alcohol end of the reagent would be expected to couple initially followed by cyclization and the formation of the sulfur stabilized carbocation. The bicyclic ether **141** could hopefully be obtained in this fashion. Removal of the

dithioacetal could then be undertaken by one of the variety of methods existing in the literature.[33]

Scheme 33



The valerolactone derived dithioacetal (n=2) alcohol was easily synthesized by the literature procedure. This reagent, as planned, was reacted with **91** in the presence of AgOTf. The cyclization did not proceed in one pot, in fact, contrary to expectation the initial coupling to substrate appeared to be from the ketene thioacetal end of the reagent (Scheme 34). While the isolated compound was one spot by TLC, the rather complex NMR spectra revealed that two isomers were present. No olefinic resonance was observed at ~5.5 ppm as would be expected had the coupling proceeded through the alcohol end of the reagent. In addition, the IR spectra showed an OH stretch, and the mixture was quite polar on TLC. This information led to the conclusion that **142** was formed.

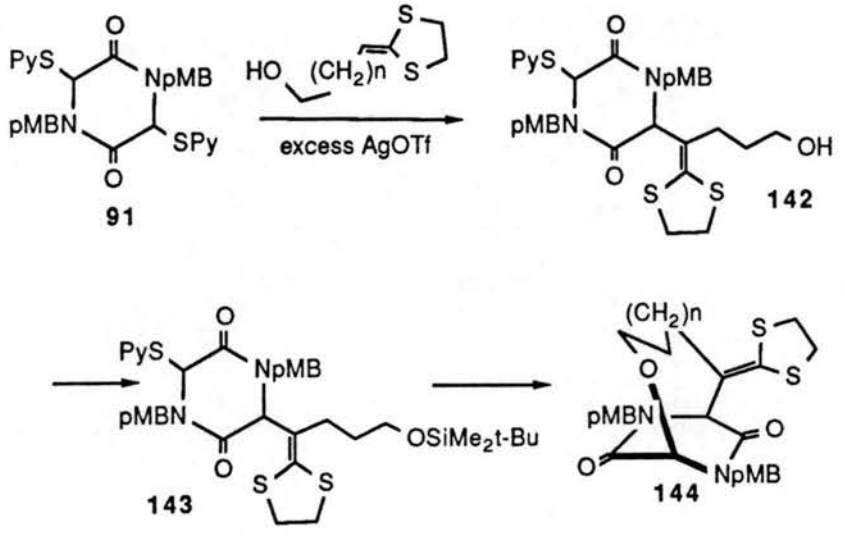
The free alcohol was silylated and was treated first with $CuClO_4$ to induce cyclization. This reaction afforded several isolable products but none that appeared to be the desired compound. Treatment with CSA in acetonitrile gave no reaction. Finally, treatment with $AgClO_4$ resulted in a product whose structure could not be determined.

As study progressed on the use of the dithioacetal alcohols other unforseen chemical problems surfaced. The coupled product **142** was found to

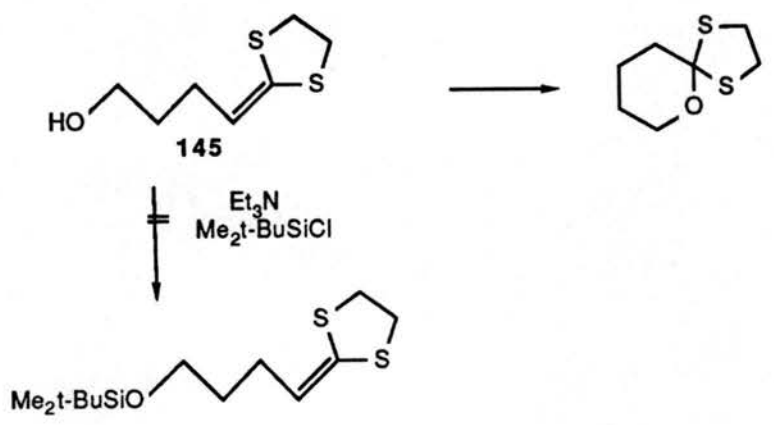
be susceptible to displacement of its C-3 and C-6 substituents. When **142** was purified by chromatography in the presence of methanol, the 3-methoxy-6-thiopyridyl diketopiperazine was isolated as was the 3,6-dimethoxy diketopiperazine. This result put into question the assigned structure of **142**. In addition, unused dithioacetal alcohols left sitting for several days would close to the spiro compound as seen for dithioacetal **145** (Scheme 35). To prevent formation of the spiro compound from the diethioacetal, an attempt was made to protect the alcohol on the dithioacetal as its *t*-butyldimethylsilyl ether. The reaction conditions (Et_3N, *t*-butyldimethyl-silylchloride) ironically resulted in spiro compound formation.

At this point, pursuit of the heterocyclic bicyclomycin analogs was set aside. While these efforts appeared to be somewhat unfruitful with regard to realizing the synthesis of these compounds, they provided a better level of understanding, knowledge, and expectations of diketopiperazine chemistry.

Scheme 34



Scheme 35



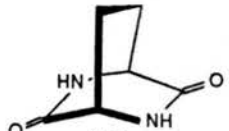
CHAPTER 3

SYNTHETIC STUDIES TOWARD CARBOCYCLIC ANALOGS

Another area of research in which work was ongoing was that of the synthesis of carbocyclic analogs of bicyclomycin. While initially not the main focus of research, these bicyclic carbocycles came to be viewed as a complementary series of analogs. Various bicyclic [2.2.2] and [3.2.2] systems were made, keeping in mind the basic structural requirements for activity. These structural features include: an olefinic moiety, an OR or SR type leaving group at the bridgehead carbon adjacent to the olefin, and free (-NH-) amides. Compounds were made both containing and lacking these functionalities. The carbocyclic analogs were of interest because of their smaller ring size; it was expected that the increased strain in the ring would impart greater reactivity to the molecule. Additionally, these analogs would not be susceptible to cleavage of the C-O bond which led to formation of the spiro adduct as had been the situation with the heterocyclic systems. This occurrence was documented by Maag (Scheme 10).

The amount of chemical literature relating to the synthesis of carbocyclic bridged diketopiperazines is rather limited. Of the reports which do address this subject, several describe the synthesis of **146** in which **147** was the immediate precursor. These syntheses were based on methodology that had appeared in

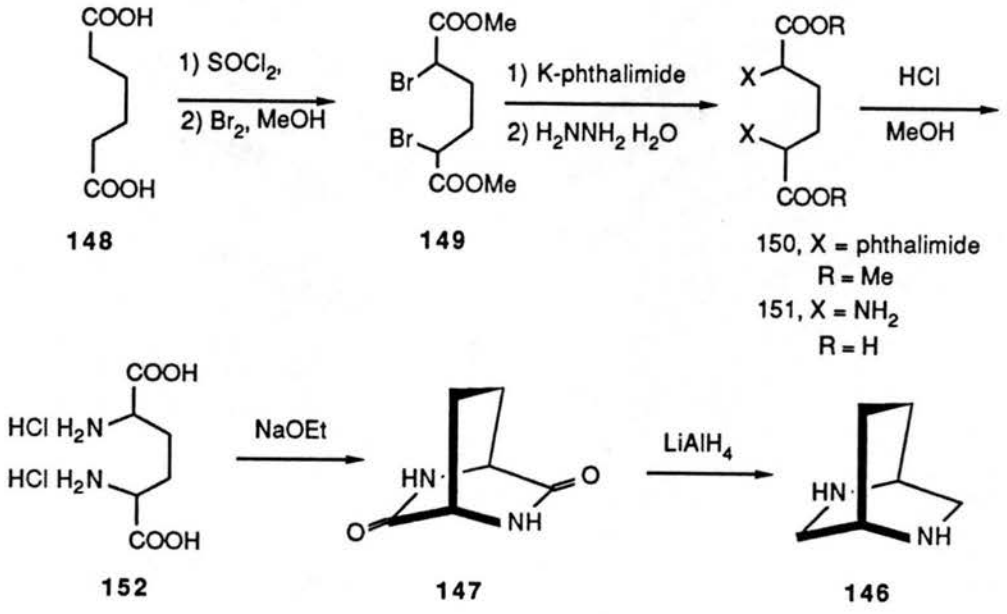
146



147

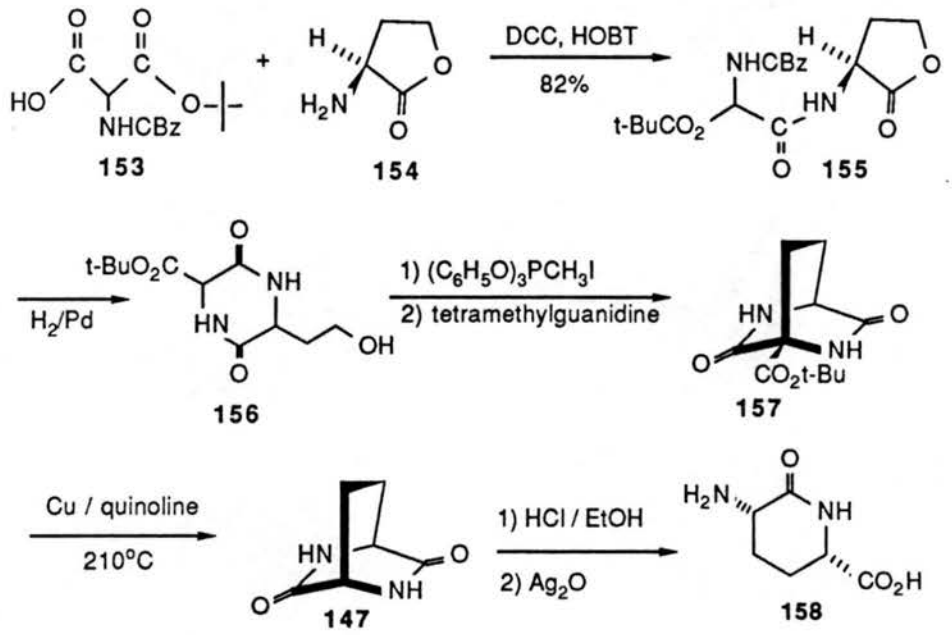
the patent literature (Scheme 36).[34] As seen, this particular route started with adipic acid **148** which was chlorinated in the presence of thionyl chloride ($SOCl_2$) to afford the dichloride. The dichloride was then converted to the dibromide by dropwise addition of Br_2 under illumination in methanol to yield the dibromoadipic acid dimethyl ester **149**. Nitrogen was introduced by treatment with potassium phthalimide in DMF. The diaminoadipic acid was obtained by reaction of **150** with 85% hydrazine hydrate. Esterification of **151** in MeOH and HCl gave the α,α-diaminoadipic acid dimethylester hydrochloride salt, **152**. The salt, **152,** was cyclized by treatment with sodium ethoxide to yield the carbocyclic diketopiperazine **147**. Compound **147** was then reduced with $LiAlH_4$ to the desired diazabicyclic species **146**. This synthesis was repeated with some minor modifications by three separate groups: Newman's, Henry's, and Eastwood's.[35] Eastwood also synthesized the corresponding [3.2.2] carbocycle from 2,6-diaminoheptanedioic acid using the same methodology.

Scheme 36



Kemp[36] synthesized **147** as an intermediate in his synthesis of LL-3-amino-2-piperidone-6-carboxylic acid **158**, an unnatural amino acid used for stabalization of β-turns in proteins (Scheme 37). The α-aminobutyrolactone **154** was condensed with **153** using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole hydrate (HOBT) to give the coupled adduct in 82% yield. Nitrogen deprotection and ring closure of **155** to the diketopiperazine skeleton **156** was afforded by treatment with H_2/Pd. Cyclization to the bicyclic compound was realized by use of the phosphite salt $(C_6H_5O)_3PCH_3I$ and base treatment with tetramethylguanidine in 79% yield. The *t*-butyl ester was removed by heating with copper in quinoline to furnish **147** in 38% yield. The diketopiperazine was then converted to the β-turn-forming amino acid **158** by treatment with HCl in ethanol.

Scheme 37

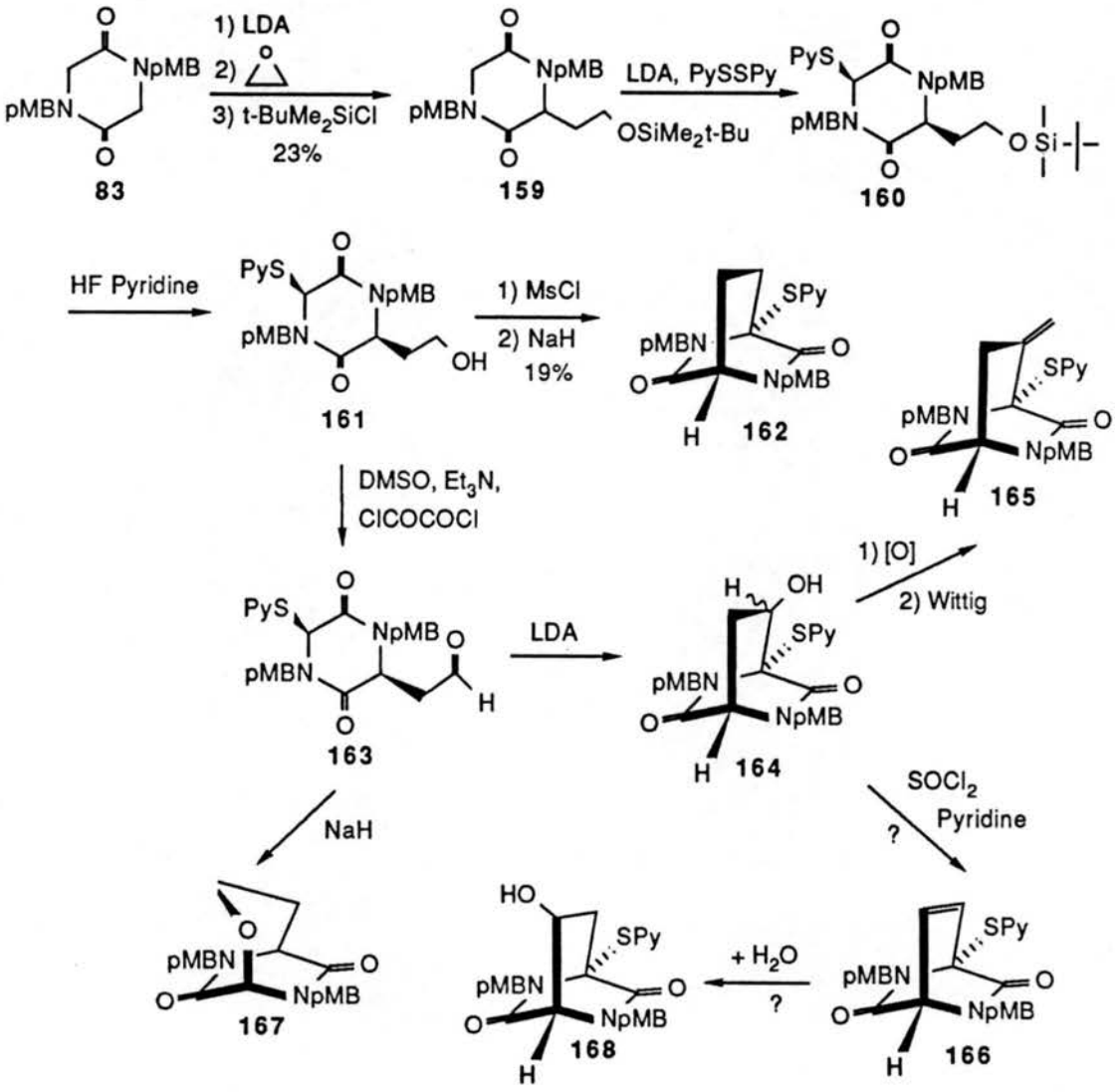


As seen, the basic framework of the bicyclic carbocycles could be made but none of these routes provided an entry into a more functionalized molecule, such as an *exo*-methylene on the bridge. It was believed that methodology for functionalizing diketopiperazine rings which had been developed within this

research group[37] could be applied with some modification to the synthesis of [2.2.2] carbocyclic *exo*-methylene derivatives as well as [2.2.2] bridgehead functionalized compounds.

The synthesis of the higher functionalized carbocyclic derivatives was undertaken as follows (Scheme 38). The N-*p*-methoxybenzyl glycine anhydride

Scheme 38



derivative was treated with LDA/HMPA at -78°C, and quenched after one hour with excess ethylene oxide followed by *t*-butyldimethylsilyl chloride to afford **159** in 23% yield. The low yield was indicative of the extremely poor solubility

of the starting substrate **83** not only in THF, but also in other polar solvents such as DMF, CH_2Cl_2, and EtOAc. This was an unexpected problem, as the original methodology had employed the readily soluble N,N-dimethyl glycine anhydride derivative. Fortunately, this problem could be overcome *(vide infra).*

Sulfenylation of the diketopiperazine by treatment with LDA and pyridyl disulfide furnished the sulfenylated product **160**. While the sulfide substituted product could be chromatographically separated from its precursor **159**, residual 2-mercaptopyridine was difficult to remove from the reaction mixture. Compound **160** was generally used in this state and deprotected with excess HF•pyridine to yield the free alcohol in a 24% two-step yield. The alcohol could be mesylated quantitatively and subsequently eliminated with NaH to afford the bridgehead substituted product **162** in unfortunately, rather low yield (19%).

Alternately, the alcohol **161** could be oxidized to the aldehyde in good yield using Swern conditions. The aldehyde was first treated with NaH to effect the ring closure to **164**. Surprisingly, the [3.2.2] heterocyclic bicyclic species **167** was isolated from the reaction in (21 %) yield. Sodium hydride is not normally known to reduce aldehydes to alcohols; however, this is the conclusion arrived at when considering this unusual result. Treatment of **163** with LDA gave the desired compound as a single stereoisomer **164** in 33% yield.

It was anticipated that the alcohol moiety of **164** could be elaborated into an *exo*-methylene group or mesylated and eliminated to furnish the internal olefin **166**. With regard to the latter, attempts to mesylate the alcohol were unsuccessful, possibly owing to the steric bulk of the sulfide on the adjacent carbon. Thionyl chloride mediated elimination of **164** resulted in what appeared by NMR and IR spectroscopy to be **166**, but it seemed to rapidly undergo re-hydration since **164** was recovered. Strangely enough, the

corresponding isomer **168** was never observed as might be expected if such a re-hydration were indeed occurring.

To synthesize the *exo*-methylene functionalized derivative **165** from **164**, it was envisioned that the alcohol could be oxidized to the corresponding ketone. A Wittig-type reaction on the ketone would be used to effect the one carbon homologation and afford the desired external olefin. Much to our disapointment, all attempts to oxidize **164** met with no success. Treatment of **164** under Swern conditions, modified Swern conditions (with SO_3•pyridine instead of oxalyl chloride) and CrO_3•py resulted in recovery of **164**. Rationale for the failed oxidations rests again on the steric bulk of the sulfide residue at the bridgehead.

Table 4 represents the results of enzyme tests conducted by Dr. Kotaro Tomizawa on compound **162**. All of the enzymes tested failed to react with the substrate. In retrospect, while the structural requirements for sulfide addition to bicyclomycin-like compounds have been delineated, it is not clear whether free amides are required for biological activity/enzyme reactivity. It is true though, that deprotection of the amides yields a compound that has a lipophobic character rather than a lipophilic one. The lipophobic compound is more likely to be compatible with protein binding. While the role of free amides as a criterion for biological activity remains uncertain, it is believed that the presence of an *exo*-methylene group is a requirement. Compound **162** lacked this functionality; this is one of the possible reasons for the observed lack of reactivity between **162** and the enzymes.

Table 4. Reaction of Selected Enzymes with 162

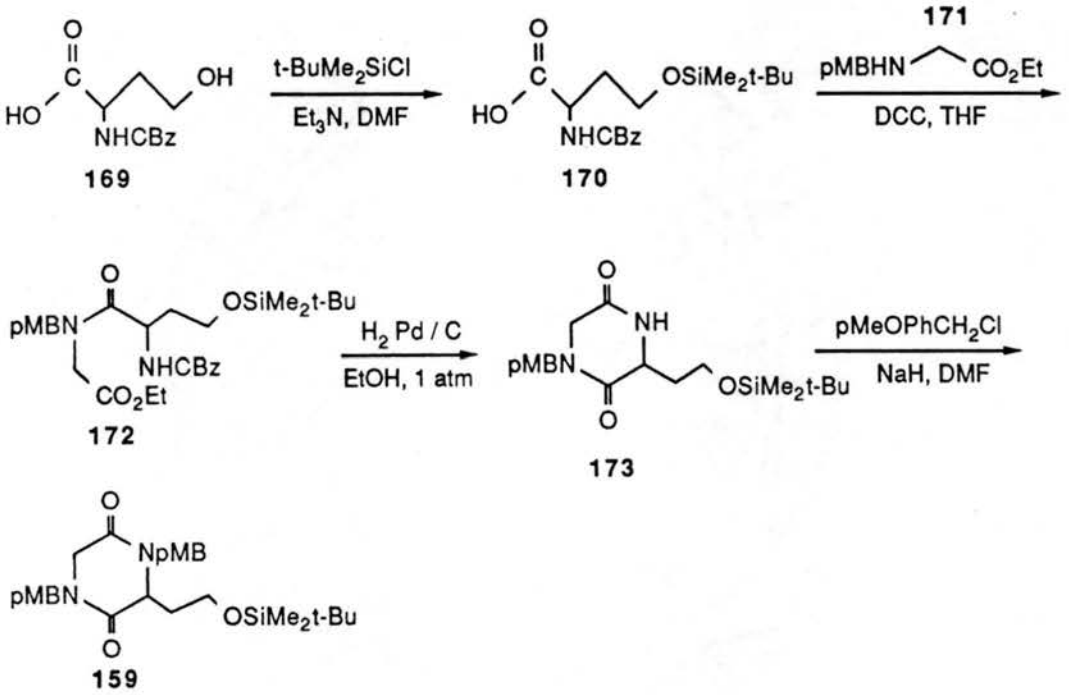
Enzyme	Duration of Reaction	Results
Penicillinase I	48 hours	rec. 70% 162
Penicillinase Type IV	48 hours	rec. 70% 162
Protease Type VII	48 hours	rec. 80% 162
Protease Type XIV	48 hours	rec. 70% 162

A drawback to the synthesis of **162** and **164** was the initial step involving the attachment of the C_2 side chain with ethylene oxide. This poor yielding step early in the synthesis made obtaining larger quantities of final product not impossible, but difficult. To preclude problems with the solubility of **83** the diketopiperazine derivative **159** could be formed from two suitably substituted peptide units. A synthesis such as this is related to those reported by Kemp, Norman and Henry in which the piperazinedione ring was assembled from amino acid derivatives instead of a pre-formed unsubstituted ring such as glycine anhydride.

As it turned out, concurrent research in our group on a possible route to Brevianamide B[38] provided an efficient synthesis of **159** that had the potential to yield multigram quantities of this important intermediate. The synthesis is depicted in Scheme 39. Readily available homoserine was protected as its carbobenzoxy derivative in 53% yield. The N-carbobenzoxy derivative **169** was then selectively silylated on the alcohol portion of the molecule to give a yellow oil. Competitive formation of the *t*-butyldimethylsilyl ester was resolved by shaking the reaction mixture with Na_2CO_3 in the workup. Compound **170** formed the cyclized butyrolactone species if left standing and was therefore

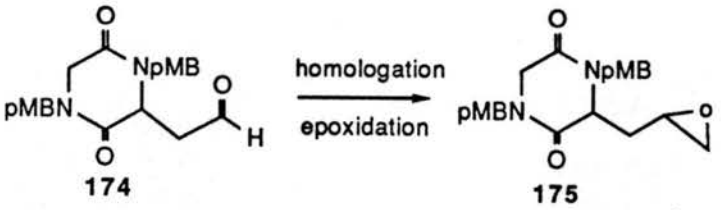
reacted immediately without purification. Condensation of **170** and **171** by DCC provided the coupled product **172** in 48% yield. Removal of the nitrogen protecting group with concomitant ring closure was accomplished by treatment of **172** with 5% Pd/C under an atmosphere of hydrogen. This reaction gave the diketopiperazine skeleton **173** in 98% yield. The remaining nitrogen was protected at this time by use of NaH and *p*-methoxybenzyl chloride to furnish **159** in 79% yield.

Scheme 39



Since appreciable quantities of intermediate **159** were now obtainable, the next step was to develop an alternate synthesis from **159** leading to the [2.2.2] *exo*-methylene. Recall that the strategy outlined earlier had been halted because of complications involving the oxidation of **164**. A different approach which would still draw from existing methodology but provide a new entry into the carbocyclic bicyclic systems, was use of epoxide **175** (Scheme 40).

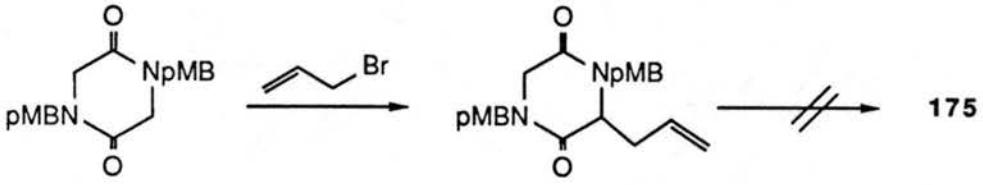
Scheme 40



174 175

The epoxide was to be synthesized from aldehyde **174** which would be made in two steps from **159**. Base catalyzed ring closure by formation of the enolate at C-6 would be attempted initially without the sulfide at C-6. Base catalyzed ring closure of **163** in the previous synthesis had been difficult to effect on such a substituted ring. A conceptually shorter method to generate epoxide **175** was reaction of allyl bromide with **83** (Scheme 41) followed by epoxidation of the olefin. This was indeed attempted. Unfortunately the alkylation reaction proceeded in low yield. Furthermore, the epoxidation of **176** could not be achieved under a variety of reaction conditions.

Scheme 41

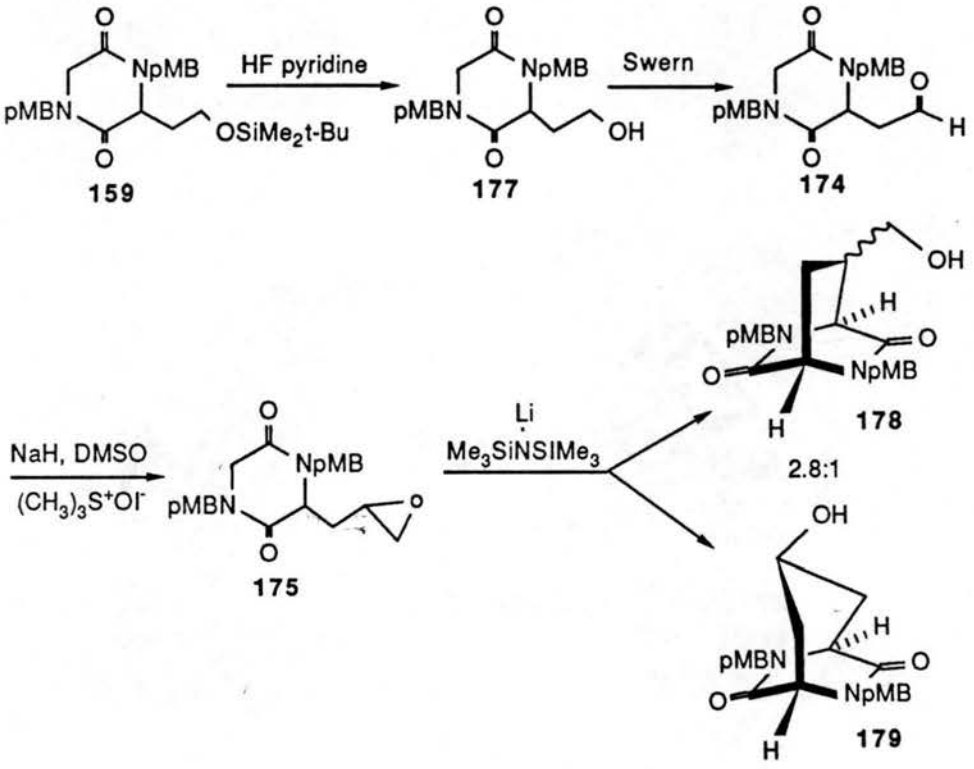


83 176

The intermediate, **159**, was treated with excess HF•pyridine complex to furnish alcohol **177** in 87% yield (Scheme 42) Swern oxidation of the alcohol easily afforded the aldehyde in 78% yield. Epoxidation of the aldehyde by the method of Corey[39] with trimethyloxosulfonium iodide and NaH in DMSO furnished the epoxide in 91% yield as a 1:1 mixture of diastereomers. Epoxide **175** was essentially pure as indicated by NMR and could be used directly. Cyclization of the epoxide was first attempted with NaH with no success.

However, it was found that the conditions of Shiozaki[40] worked fairly well. This procedure made use of the lithium salt of hexamethyldisilazane as the base at 0°C. A 2.8:1 mixture of both **178** and **179** in 61% combined yield was realized from this reaction.

Scheme 42



To confirm the structure of the compound assigned as **179**, it was oxidized to the ketone **180** by treatment with Jones reagent. It is of some interest to compare the NMR spectra of these two compounds (Figs. 2 and 3). The NMR spectrum of the ketone **180** is greatly simplified over that of the corresponding alcohol owing to the C_2 axis which is incorporated into the molecule upon oxidation of **179**. As seen, each proton of **179** gives rise to an individual signal of complex multiplicity, these signals collapse to the much simpler series of resonances recorded for the ketone as had been predicted.

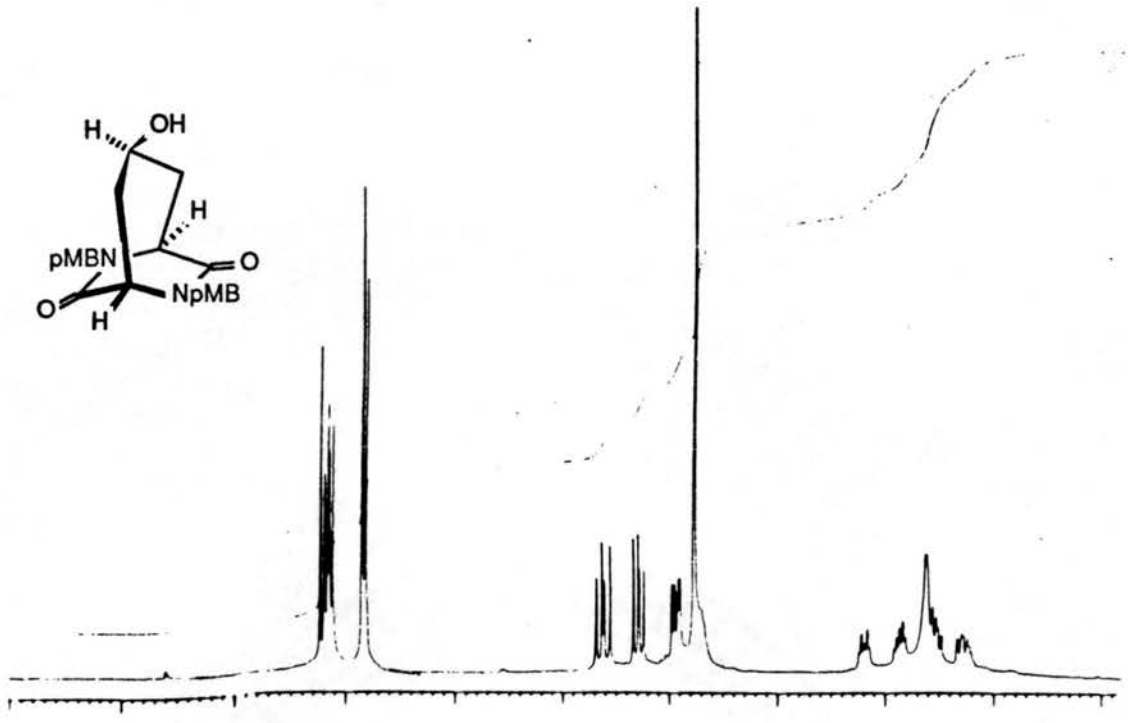
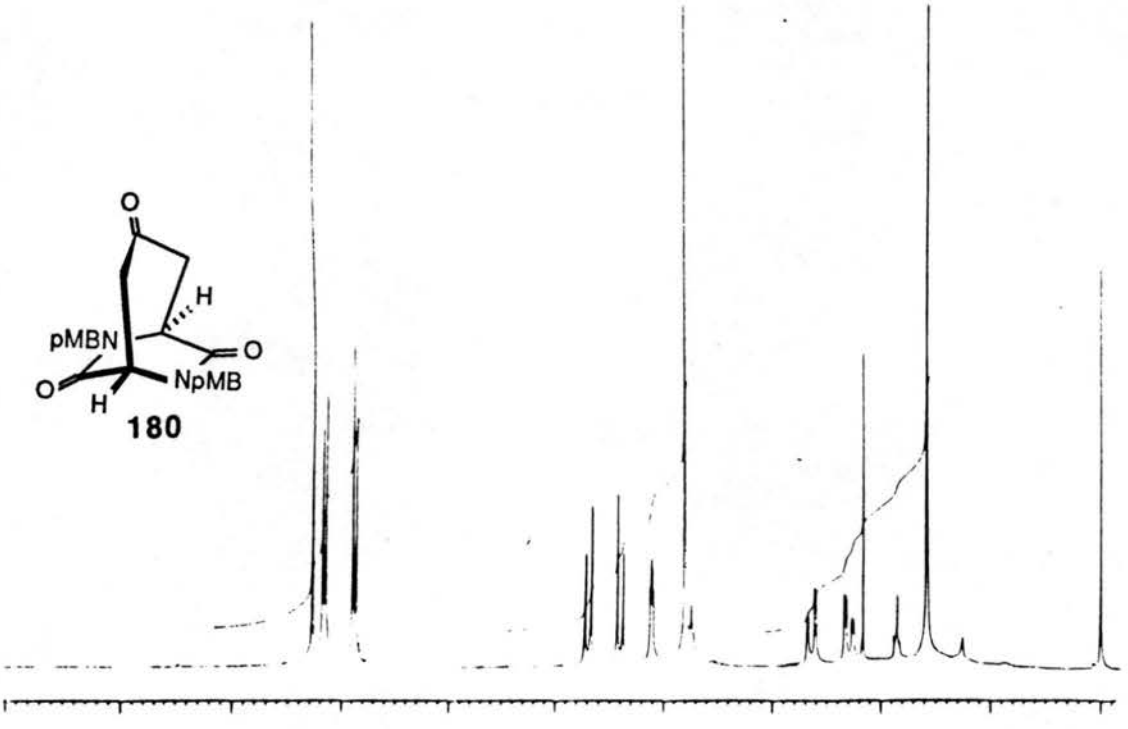


Figure 3. 270 MHz ^{1}HNMR of alcohol 179 in $CDCl_3$

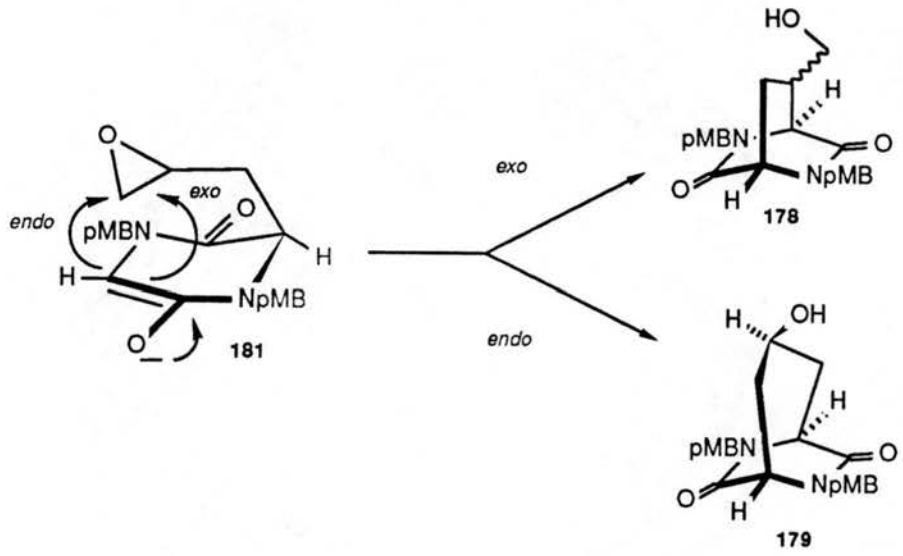


180

Figure 4. 270 MHz ^{1}HNMR of ketone 180 in $CDCl_3$

The observed regiochemistry of the base catalyzed ring opening of the epoxide to **178** and **179** is intriguing. On an intuitive level, with regard to the product ratio, one might expect formation of **179** to be favored because of a less hindered nucleophilic approach and because it should also give rise to the least strained ring system. This, however is not the case. A consideration of Baldwin's Rules[41] for ring closure nicely explains (Scheme 43) the observed experimental results. Although six and seven-membered rings are formed for **178** and **179**, these ring systems can be approximated to be four and five-

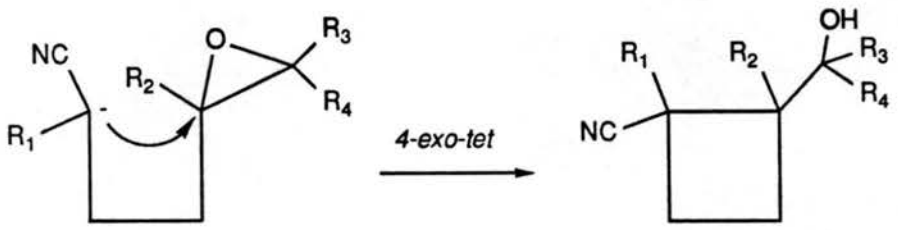
Scheme 43



membered ring closures, respectively. In this analysis, the relatively rigid dioxopiperazine ring system is taken to be geometrically equivalent to one bond. The closure of enolate **181** to form **178** is then, approximated by Baldwin's Rules, to be a *4-exo-tet* ring closure and that of **181** to **179** is correspondingly approximated to be a *5-endo-tet* ring closure. Stork[42] has reported similar results from his studies on epoxynitrile cyclizations (Scheme 44). Ring closure to the four-membered ring is favored over that to the five-

membered ring system. Indeed, Baldwin has stated with regard to opening three-membered rings to cyclic structures that the *exo*-mode is generally preferred.[41]

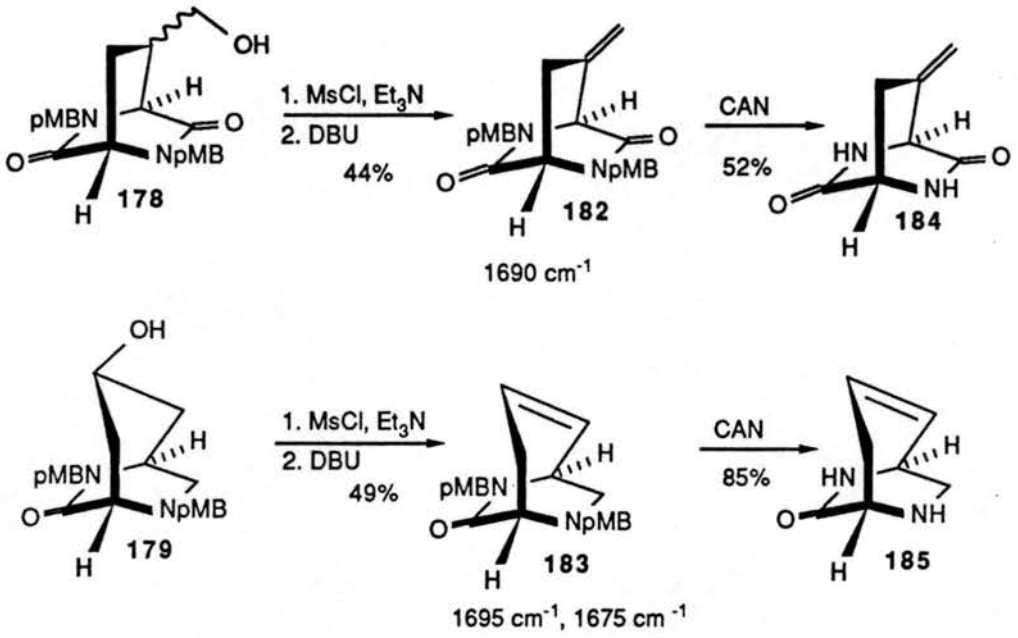
Scheme 44



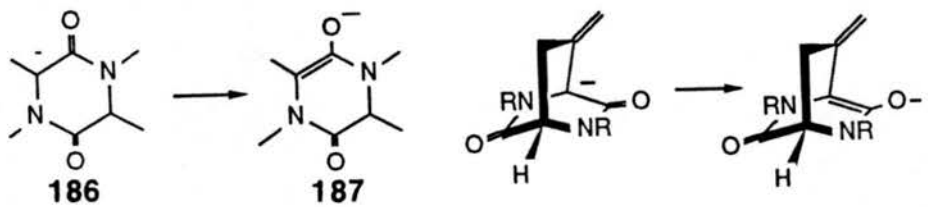
Alcohols **178** and **179** were carefully separated by silica gel chromatography. A straightforward route was now available for functionalizing the alcohols to the *exo*-methylene and internal olefin. Each alcohol was separately converted to the corresponding mesylate (Scheme 45) which was then eliminated by treatment with diazabicyclo undecene (DBU) to give the olefins **182** and **183** in 44% and 49% yield respectively. The infrared absorptions of the amide carbonyls point to the increased ring strain imposed by these geometries. For **183** these absorptions were observed at 1695 and 1675 cm^{-1} and those for **182** were at 1690 cm^{-1}.

The olefinic compounds were then deprotected by treatment with CAN in an acetonitrile:water solution to cleanly afford **185** in 85% yield and **184** in 52% yield. Both of these compounds and their respective precursors, the N-protected derivatives, have been submitted for biological testing, but proved inactive. The synthetic strategy outlined here conveniently furnished two bicyclic olefin-type systems in reasonable yields; the key feature of this synthesis was the intramolecular enolate/epoxide-opening reaction.

Scheme 45

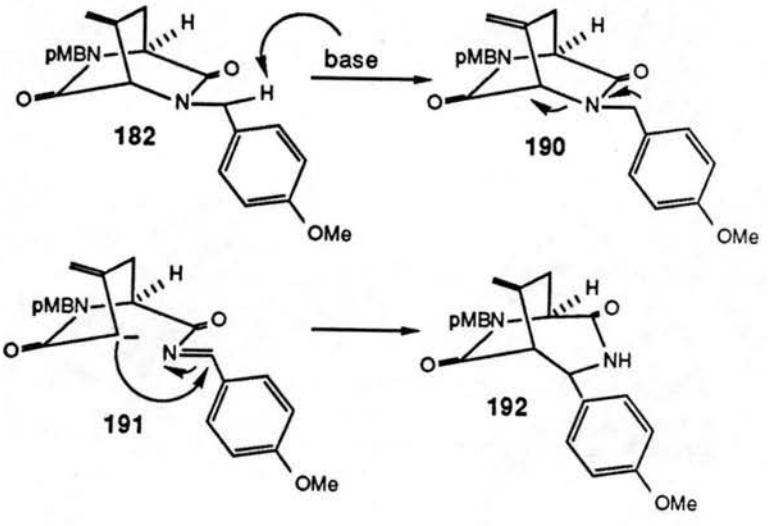


Having accomplished the synthesis of bicyclic molecules containing the olefinic moiety with free amides, the next synthetic goal was bridgehead functionalization of these molecules. As regioselective carbanion chemistry at the bridgehead position had been successfully carried out for bicyclomycin and other simple heterocyclic derivatives,[37] it was anticipated that the same methodology could be applied to these carbocycles. Bridgehead substitution on the bicyclic ring system raises some interesting questions. Whereas the monocyclic enolate is resonance stabilized (**186**◄—►**187**) through the amide carbonyl of the piperazinedione, a similar type of enolate resonance for a bridgehead carbanion would violate Bredt's Rule. Additionally, it was intriguing to consider the regioselectivity of such a reaction.



The reaction was initially carried out by treating **182** with LDA/HMPA at -78°C for 1.2 hour followed by quenching with phenyl disulfide (Scheme 46). This reaction gave predominately starting material and surprisingly a small amount of **192**, the ring expanded product. Compound **192** was presumably

Scheme 46



formed by deprotonation at the benzyl position of the nitrogen protecting group, followed by formation of the imine and attendant ring opening of the piperazinedione nucleus. Cyclization of the imine **191** then affords **192**. This result would imply that under thermodynamic conditions, benzylic anion formation is favored. The next consideration then, is the regioselectivity of anion formation under kinetic conditions.

A study was undertaken to determine the relative kinetic acidities of each of the bridgehead protons (H_a and H_b) and of the benzylic protons (H_c) (Fig. 4). The relative magnitude of the $J(^{13}C\text{-}H)$ has been correlated to the amount of s-character in the C-H bond.[43] This has been used as a rough measure of kinetic acidity on other bicyclomycin-like systems.[37] The degree of C-H coupling was

measured for the bridgehead positions of the piperazinedione and for the benzylic position on the *p*-methoxybenzyl protecting group. The coupling for C-H_a was found to be 155.5 Hz, and that of C-H_b 153.7 Hz, which reflects approximately 30-31% s character for the bridgehead positions. In turn, the C-H coupling for the benzylic position was 138.6 Hz, which translates to 27% s character. By this analysis, either of the two bridgehead protons should be slightly more kinetically acidic than a proton at one of the benzylic positions. It was possible then, under kinetic conditions that bridgehead anion formation could be achieved, and then so should bridgehead substitution.

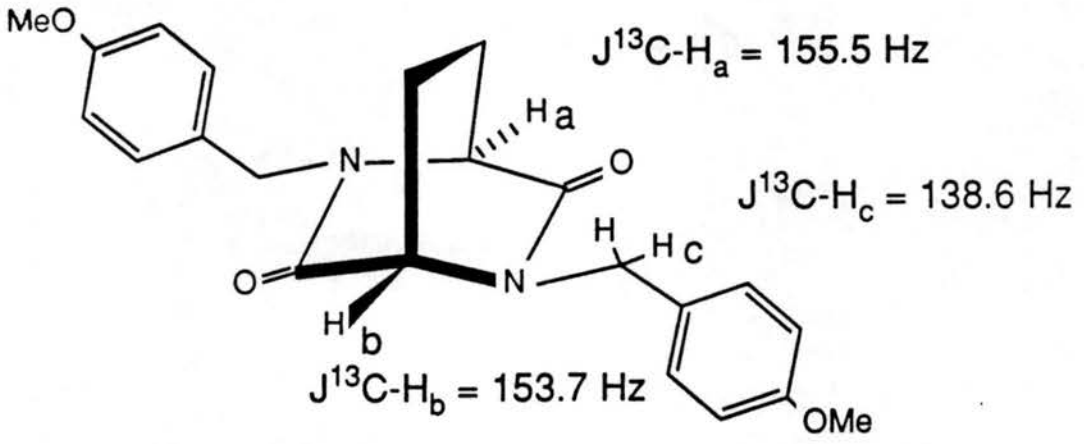


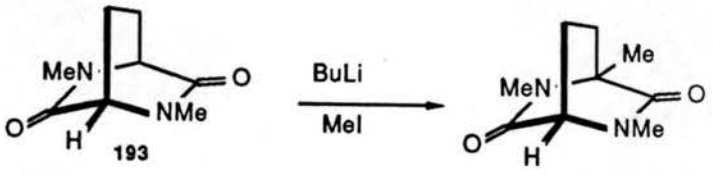
Figure 4. The $J^{13}C$-H values for the bridgehead and benzylic positions of **182**

A reaction was set up that was conducted favoring kinetic conditions (LDA, -78°C). Aliquots of the forming anion were removed 15 minutes, 30 minutes and 45 minutes after addition of base and quenched with D_2O. Upon examination of the aliquot quenched after 15 minutes, evidence of the rearranged product **192** was found. Similar results were observed for the other samples as well. The discrepancy between the theoretical data and the experimental observations may be explained by the possibility that kinetic control was never achieved in the reaction; perhaps the kinetic quench must be

done immediately after base addition. An alternate possibility is that the difference in the coupling constants of the bridgehead position and the benzylic position is too small and falls within the margin of error for such an analysis.

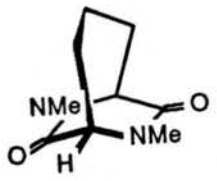
Eastwood[35c] has examined lithiation of the simple [2.2.2] carbocycle lacking the *exo*-methylene functionality (Scheme 47). Using the N,N-

Scheme 47



dimethyl carbocyclic derivative **193**, he reported monomethylation of the bridgehead position in 87% yield. To explain this result, Eastwood attributed stabilization of the bridgehead anion to a dipole effect which arose from a partial positive charge on the amide nitrogen alpha to the bridge. In addition, there was an inductive stabilization from the carbonyl residing on the other side of the bridge. A possible minor contribution to the stabalization effect was the slight overlap of the normally orthogonal p orbital of the lone pair of electrons at the bridgehead and the p_z orbital of the adjacent carbonyl. This is possible through bond distortion.

The corresponding [3.2.2] N-Me derivative shown below was also reported as capable of undergoing bridgehead methylation in 35% yield. Curiously enough, while the syntheses of the N,N-dibenzyl and N,N-dimethoxymethyl derivatives were reported, no results or discussion of lithiation studies on these compounds were given.

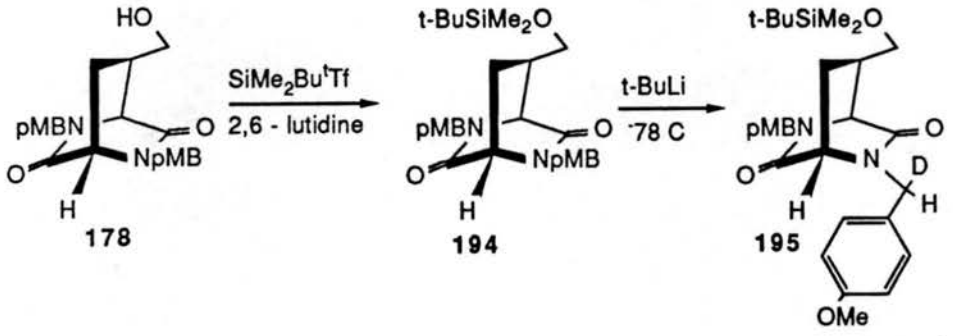


Assuming that the anion of **193** is indeed stabilized because of the inductive and dipole stabilization effects discussed earlier, then these same effects must be at work in the stabilization of the bridgehead anion of **182**, since the piperazinedione nucleus is the same in each case. The major structural differences between **193** and **182** are the N-protecting groups and the *exo*-methylene. The lack of anion formation at the bridgehead of **182** could perhaps be due to the increased rigidity of the molecule imposed by the additional sp^2 center. Bond distortion to increase p-orbital overlap (and thus stabilization through resonance) between the bridgehead lone pair of electrons and the C-7 carbonyl cannot occur. The benzylic position of the *p*-methoxybenzyl species is then favored as a site for initial deprotonation. Although Eastwood tends to disclaim the p-orbital overlap as a minimal source of stabilization, studies by Anet[44] on cyclooctatetraene have shown that delocalization of electrons can occur even when p-orbitals are misaligned by as much as 60°. In keeping with this model, the [2.2.2] olefin does not allow distortion to occur even to this extent.

Another reason for the lack of bridgehead anion formation in **182** might be the simplest one: The presence of the *exo*-methylene does actually not affect bridgehead anion formation at all and it happens that the benzylic anion is a (relatively) better anion than that of the bridgehead. Synthesis of **194** from **178** (Scheme 48) made possible the study of anion formation in a system that lacked the sp^2 center but still contained the *p*-methoxybenzyl group. Treatment of **194** with *t*-BuLi at -78°C followed by a D_2O quench after 0.5 hour furnished a

compound which displayed a distinct deuterium incorporation at one of the benzylic positions.

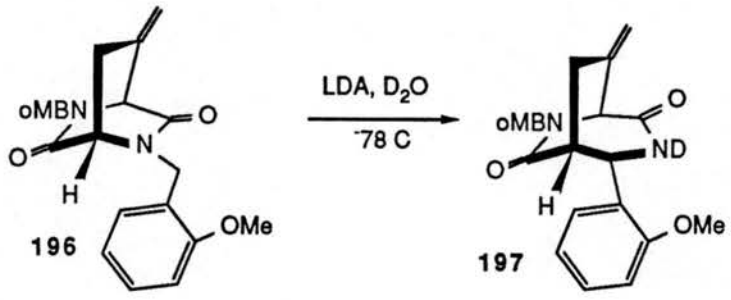
Scheme 48



The preceeding experimental result led us to consider the synthesis of carbocyclic analogs with nitrogen protecting groups that did not have an acidic proton which would be favored to deprotonate over that of the bridgehead positions. Another alternative was to sterically block the benzylic position and as such, the *o*-methoxybenzyl moiety was considered as a viable protecting group. Although it is true that inductively the methoxy group in the *ortho* position on the ring favors anion formation at the benzylic position more so than in the *p*-methoxybenzyl case, it appeared from an examination of models that a methoxy group in an *ortho* position on the ring would sterically hinder approach of the base and thus impede anion formation from occurring at the benzylic position. The use of this protecting group was also attractive as an initial starting point to solve this problem because the existing methodology to make the bicyclic analogs could be used directly with little or no changes in the synthesis. The entire synthesis employing the *o*-methoxybenzyl derivative was carried out from N,N-*p*-methoxybenzyl glycine anhydride which was initially functionalized at the C-3 position of the ring using LDA and ethylene oxide. Elaboration to **196** was accomplished as noted for the *p*-methoxybenzyl series

in Scheme 49. Treatment of **196** with LDA (Scheme XLII) followed by quenching with D_2O after 0.5 h disappointingly afforded the ring expanded product **197**.

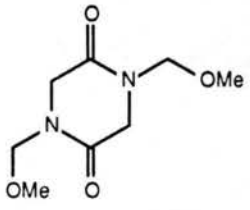
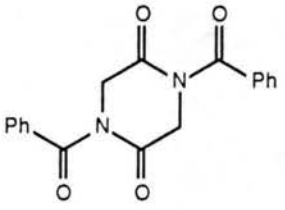
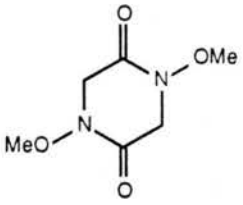
Scheme 49



The synthesis of glycine anhydride substrates totally lacking acidic protons on the nitrogen protecting groups was undertaken at this time. Table 5 summarizes the syntheses of these derivatives. Generally, it was found that if the desired glycine anhydride derivative could be synthesized in reasonable yield, the following synthesis of the C-3 functionalized compound using the LDA, ethylene oxide methodology could not be effected.

Despite efforts to vary the reaction conditions and change the nitrogen protecting groups in the synthesis, we were unable to attain bridgehead functionalization of the [2.2.2] *exo*-methylene by carbanion chemistry. We now looked at the option of functionalizing the C-6 position of the piperazinedione **before** formation of the bicyclic compound. That this could be done had been demonstrated by the synthesis of **162** and **164** (Scheme 38), these were the [2.2.2] carbocycles substituted with sulfur at the bridge. As mentioned earlier, however, the formation of the enolate alpha to the sulfide moiety and subsequent ring closure on either the mesylate or aldehyde **163** had not been readily achieved. The question then confronting us was, how would the

Table 5. Synthesis of Various Glycine Anhydride Derivatives

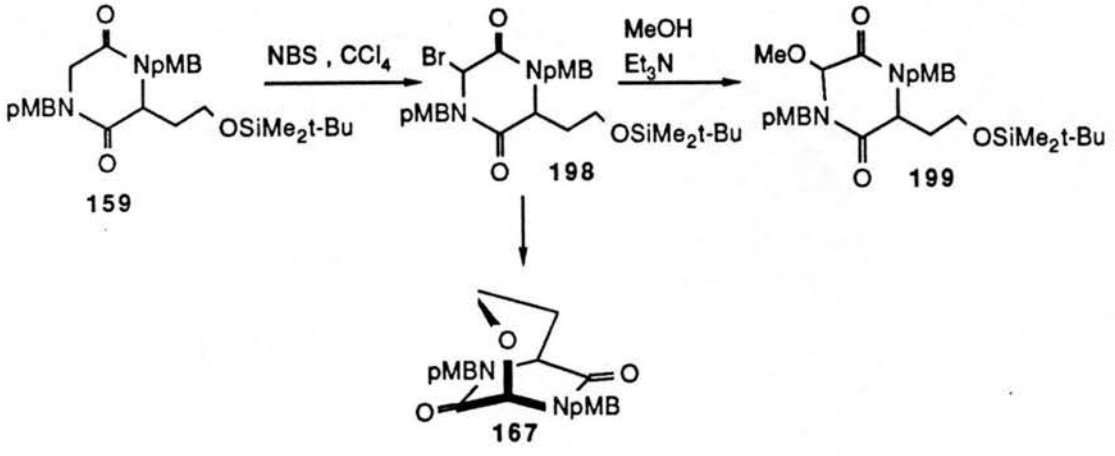
Entry	Synthesis of Glycine Anhydride Derivative and Result	Glycine Anhydride Derivative	Reaction with LDA, ethylene oxide
1	80, Bu^tO^-, Bu^tOH, $ClCH_2OMe$, 67%		N.R.
2	80, NaH, ClCOPh, 6.7%		---
3	80, NaH, $MeONHCOCH_2I$, THF, unidentifiable product. 80, Et_3N, $MeONHCOCH_2I$, THF, N.R. 80, K_2CO_3, $MeONHCOCH_2I$, acetone, N.R.		---

N.R. = no reaction

intramolecular enolate/epoxide opening reaction be affected if the enolate were substituted with a heteroatom?

The choice for the C-6 functionality was a methoxy group and it was to be coupled to the piperazinedione by bromination of the ring with NBS followed by displacement with MeOH as depicted in Scheme 50. To our dismay, treatment of **159** with NBS yielded the bicyclic heterocycle **167**. Changing the *t*-butyldimethylsilyl ether in **159** to the corresponding benzyl moiety followed by reaction with NBS afforded the same results.

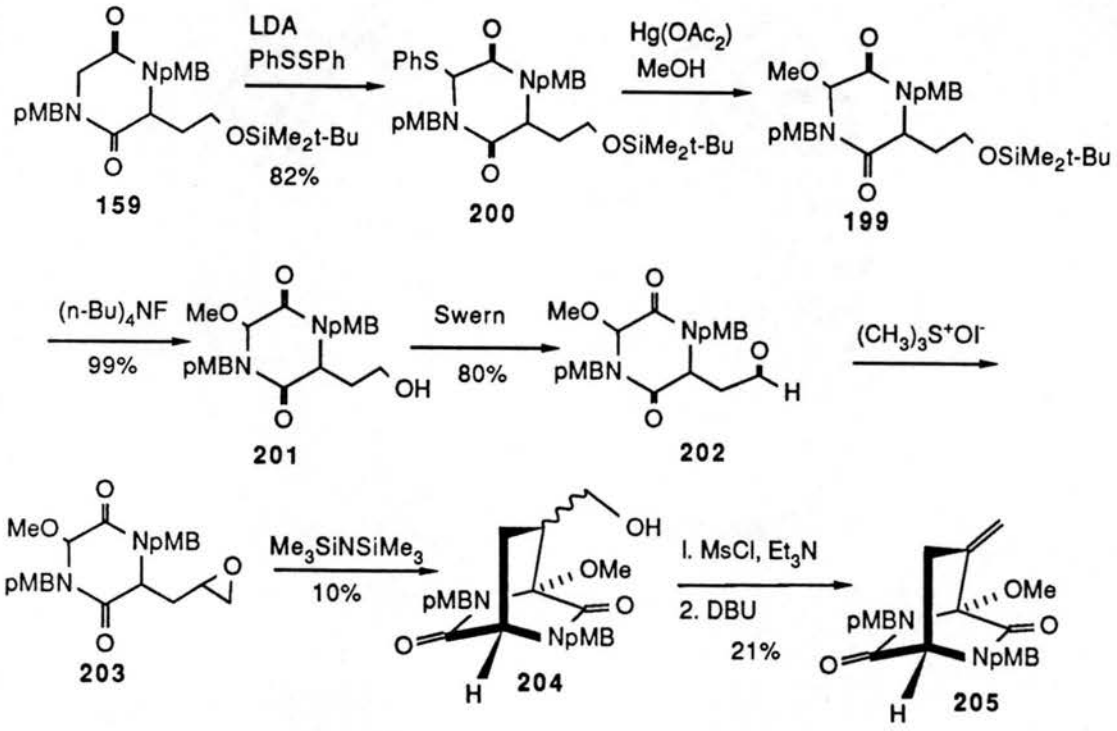
Scheme 50



Fortunately, it was found that sulfenylation at C-6 with LDA and phenyl disulfide (Scheme 51) at C-6 of compound **159**, followed by treatment with $Hg(OAc)_2$ in MeOH nicely furnished the desired compound **199** in excellent yield. Compound **199** could now be elaborated to the bicyclic compounds by the chemical methods depicted in Scheme 42. The *t*-butyldimethylsilyl ether was deprotected by use of $(n\text{-}Bu)_4NF$ to give a diastereomeric mixture of alcohols **201** in 99% yield. Use of HF•pyridine complex in this particular reaction resulted in formation of **167**, the methoxy group is apparently quite labile in the presence of a small amount of acid. The alcohols were oxidized to the aldehydes in 80% yield using the classical Swern conditions. Epoxidation

of the diastereomeric mixture of aldehydes gave the epoxide **203** as a roughly 2:1 diastereomeric mixture which were inseparable. Cyclization of the epoxide afforded the desired bicyclic [2.2.2] carbocycle that was bridgehead functionalized, but in poor yield (10%) as expected. Only one diastereomer of the [2.2.2] alcohol was isolated, formation of the [3.2.2] alcohol was not observed. Mesylation and DBU mediated elimination of the mesylate on **204** gave the final product **205** in 21% yield. The infrared of **205** exhibited amide carbonyl stretches at 1680 cm^{-1}. Figure 5 shows the ^1H NMR spectra of this compound.

Scheme 51



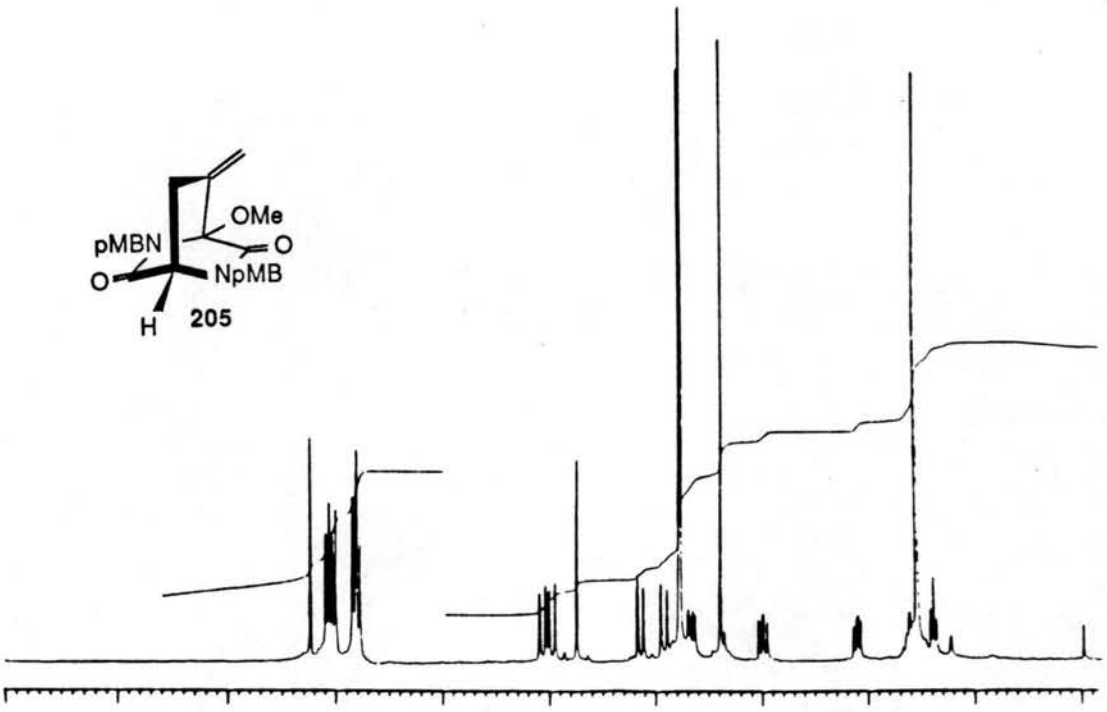


Figure 5. 270 MHz ^1H NMR of **205** in $CDCl_3$ δ $CHCl_3$

A summary of the bicyclic carbocyclic compounds which were prepared are shown in Figure 6. All of the compounds not marked by boxes were submitted for biological assay. Unfortunately, none of the compounds submitted showed any biological activity. From this result, it is apparent that the mode of action of bicyclomycin remains unclear; the salient features believed to be necessary for biological activity in these carbocycles and other analogs needs to be rescrutinized and further clarified.

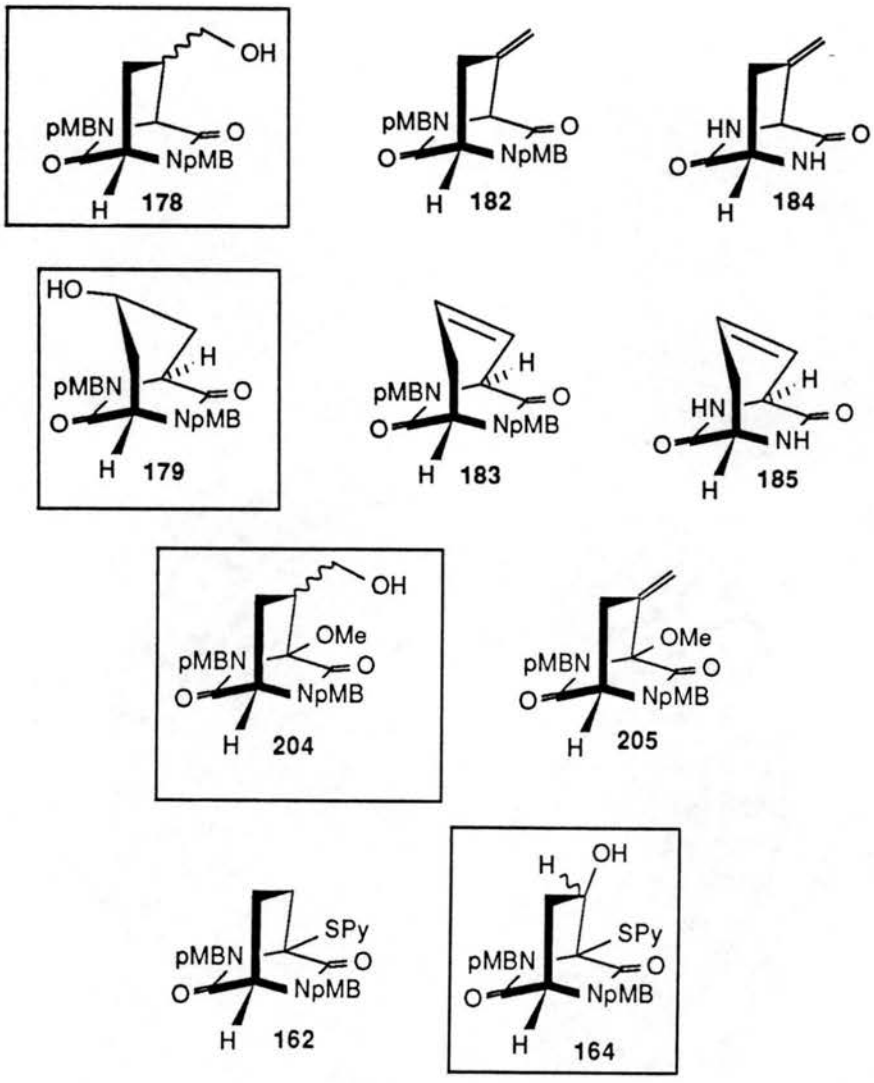


Figure 7. Carbocyclic analogs of bicyclomycin. Figures which are not boxed are compounds submitted for biological assay

CHAPTER 4

EXPERIMENTAL SECTION

General Information

Melting points were determined in open-ended capillary tubes on a "Mel-Temp" apparatus, and are uncorrected. Infrared spectra were recorded on a Beckman model 4240 spectrophotometer and were obtained on NaCl pellets. Absorptions are reported in cm^{-1}. ^1H NMR spectra were recorded on the following instruments: Varian T-60 spectrometer without lock, Brucker WP-200SY 200 MHz spectrometer with lock, or Brucker WP-270SY 270 MHz spectrometer with lock. The field strength (MHz) is indicated for each spectrum in the experimental section. Chemical shifts are reported in parts per million downfield from the internal standard, which is specifically indicated for each compound in the experimental section as δ - standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublets.

Low resolution mass spectra were obtained on a V.G. Micromass Ltd., Model 16F spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, and by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

Chromatography

Analytical thin layer chromatography was performed on E. Merck 0.25 mm or 0.50 mm silica gel 60 F-254 layers backed by glass. Visualization on

TLC was achieved with ultraviolet light, I_2 developing chamber and/or heating of TLC plates submerged in a 5% (by weight) solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column and flash chromatography were performed using Silica Woelm (32-63 μm) silica gel, in which the mixtures were preabsorbed on the silica gel. Radial chromatography was done on 1-4 mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron model 7924.

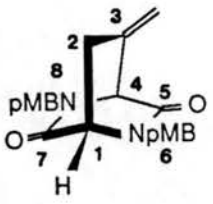
Reagents and Solvents

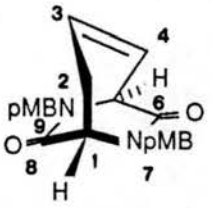
Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Triethylamine and diisopropyl amine was distilled from KOH and stored over fresh KOH. n-Butyllithium was obtained from Ventron and was titrated (diphenylacetic acid, -78°C, THF) prior to use. Lithium diisopropyl amide (LDA) was freshly prepared by dropwise addition of n-butyllithium in hexane to a stirred solution of diisopropylamide in THF, usually at -78°C except where noted. LDA solutions were transferred via cannula to the reaction vessel using N_2 pressure. Diethylether was freshly distilled from sodium benzophenone ketyl under N_2 atmosphere. Dry methylene chloride and carbon tetrachloride were obtained by distillation over P_2O_5. When required, dry DMF, DMSO, HMPA, oxalyl chloride were taken via dry syringe from storage over activated 3A or 4A sieves after distillation from an appropriate reagent. All organic intermediates were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.

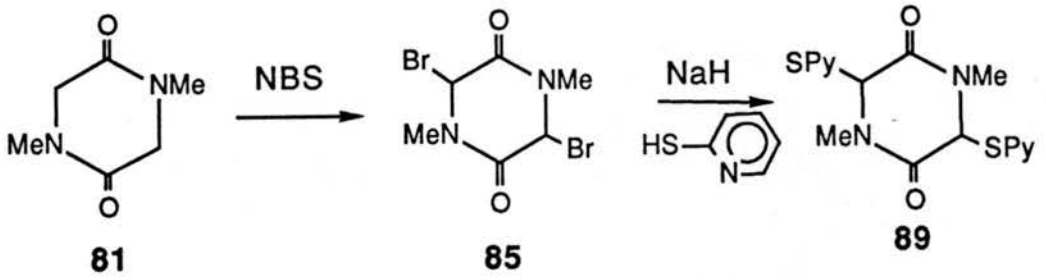
General Experimental Consideration

All moisture or oxygen sensitive reactions were conducted in glassware that was flame dried under high vacuum (0.5-2.0 mmHg) and then purged with N_2. All reactions were magnetically stirred with Teflon coated stir bars. The following low temperature baths were used: 0°C (Ice water), -78°C (acetone, dry ice). The term concentrated refers to solvent removal under the vacuum achieved by a water aspirator attached to a Buchi rotary-evaporator. Residual solvent was removed at reduced pressure (0.5-0.5 mmHg) using a vacuum pump.

Compounds were named by standard IUPAC nomenclature with exception to the carbocyclic analogs. The numbering system for bicyclomycin was used for these compounds to maintain uniformity. Examples are given below.





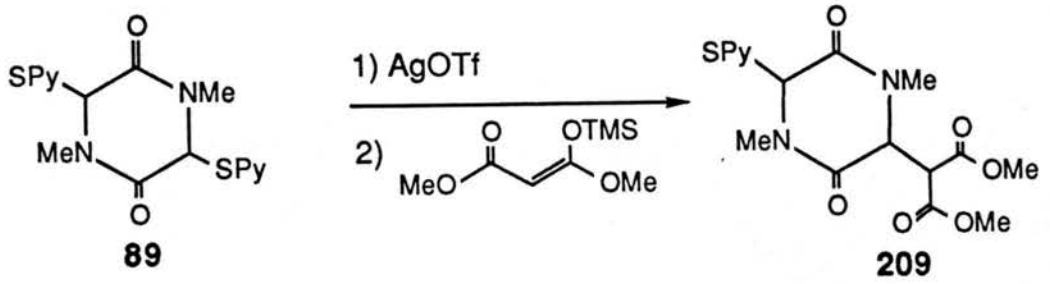


81 **85** **89**

1,4-Dimethyl-3,6-bis(2'mercaptopyridyl)-2,5-piperazinedione (89). To a stirred solution of **81** (0.500 g, 3.52 mmol, 1.0 equiv) in CCl_4 (30 mL) was added N-bromosuccinimide (1.57 g, 8.80 mmol, 2.5 equiv) and benzoyl peroxide (0.043 g, 0.176 mmol, 0.05 equiv). The solution was refluxed for 1 h, filtered, and concentrated to yield 1.04 g (3.5 mmol) of crude dibromide **85**.

To a stirred suspension of NaH (0.280 g, 7.02 mmol, 2.0 equiv) in THF (25 mL) at 0°C was added solid 2-mercaptopyridine (0.780 g, 7.02 mmol, 2.0 equiv). This stirred for 0.5 h and was then syringed into a solution of dibromide in THF (10 mL) at 0°C. After 2 h, the reaction was worked up by diluting with CH_2Cl_2, pouring into water, and thoroughly extracting with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. Product **89** was recrystallized from CH_2Cl_2/MeOH as white crystals, 0.643 g, (51% 2 step yield).

(89): mp 175-178°C dec (recrystallized CH_2Cl_2/MeOH); ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 3.08 (6 H, s), 6.66 (2 H, s), 7.11 (2 H, m), 7.27 (2 H, m), 7.58 (2 H, s), 8.51 (2 H, m); IR (KBr pellet) 1695, 1578, 1562, 1462, 1415, 1400, 1300, 1253, 1118, 1015, 770, 715, 635 cm^{-1}. Anal. ($C_{16}H_{16}N_4O_2S_2$). Calcd: C, 53.32; H, 4.47, N, 15.54; S, 17.79. Found: C, 53.13; H, 4.48; N, 15.31; S, 17.81.



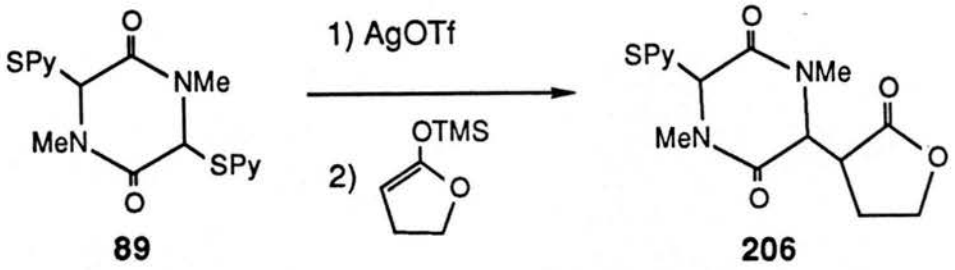
1,4-Dimethyl-3-(2'-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (209). To a stirred solution of **89** (25 mg, 0.069 mmol, 1.0 equi.) in CH_2Cl_2 (1.5 mL) at 25°C was added the AgOTf (17.8 mg, .069 mmol, 1.0 equiv). After 5 min., the silyl enol ether of dimethylmalonate[45] (0.028 mL, 0.138 mmol, 2.0 equiv) was added to the reaction mixture. This stirred for 2 h, and the crude mixture was filtered through a cotton plug. Separation by PTLC silica gel (eluted with 33% Hexanes in EtOAc) yielded 20 mg (76%) of product **209** as a 5.8:1 *syn/anti* mixture.

***Syn* Isomer (209):** mp 144.5-145°C (recrystallized EtOAc/Hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.05 (6 H, s), 3.84 (3 H, s), 3.85 (3 H, s), 4.05 (1 H, d, J = 4.7 Hz), 4.72 (1 H, d, J = 4.7 Hz), 6.87 (1 H, s), 7.05-7.10 (1 H, m), 7.24-7.28 (1 H, m), 7.52-7.59 (1 H, m), 8.45-8.47 (1 H, m); IR (NaCl, neat) 2950, 1750, 1675, 1580, 1560, 905, 730 cm^{-1}. Anal. ($C_{16}H_{19}N_3O_6S$). Calcd: C, 50.38; H, 5.02; N, 11.02; S, 8.41. Found: C, 50.15; H, 4.89; N, 10.83; S, 8.47.

***Anti* Isomer (209):** ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.02 (3 H, s), 3.09 (3 H, s), 3.79 (3 H, s), 3.83 (3 H, s), 4.15 (1 H, d, J = 3.6 Hz), 4.73 (1 H, d, J = 3.6 Hz), 5.72 (1 H, s), 7.06-7.09 (1H, m), 7.20-7.26 (1 H, m), 7.54 (1 H, m), 8.41 (1 H, m); IR (NaCl, neat) 2950, 1750, 1675, 1580, 1560, 1250, 760, 720 cm^{-1}.

Epimerization of the anti isomer to a mixture of syn/anti isomers was carried out by treatment of the anti isomer in 50% THF/MeOH with 0.1 N NaOMe

in MeOH for 2.5 h at 25°C. Evaporation of the solvent produced a 1.5:1 *syn/anti* mixture.



89 **206**

1,4-Dimethyl-3-(2'-thiopyridyl)-6-(2"-γ-butyrolactonyl)-2,5-piperazinedione (206). To a stirred solution of **89** (25 mg, 0.069 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added AgOTf (17.8 mg, 0.069 mmol, 1.0 equiv). After 5 min, the trimethylsilyl ketene acetal of γ-butyrolactone (0.16 μl, 0.1 mmol, 1.5 equiv). After 1 h, the reaction mixture was filtered through a cotton plug. Separation by PTLC silica gel afforded 14 mg (60%) of the lactone **206**, as a mixture of *syn* and *anti* diastereomers (14:6:13:1, *syn*-major: *anti*-major: *syn*-minor: *anti*-minor diastereomers) (*syn:anti*, 3.8:1).

Major *syn* (206): mp 159.5-160.5°C (recrystallized EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.19-2.28 (1 H, m), 2.43-2.51 (1 H, m), 3.04 (3 H, s), 3.13 (3 H, s), 3.74 (1 H, t, J = 6.3 Hz), 4.24-4.44 (2 H, m), 4.56 (1 H, d, J = 3.6 Hz), 6.67 (1 H, s), 7.11-7.15 (1 H, m), 7.22-7.29 (1 H, m), 7.56-7.62 (1 H, m), 8.48-8.50 (1 H, m); IR (NaCl, neat) 3050, 2980, 2930, 1770, 1670, 1575, 1560, 1025, 755 cm^{-1}. Anal. ($C_{15}H_{17}N_3O_4S$). Calcd: C, 53.72; H, 5.11; N, 12.53; S, 9.56. Found: C, 53.87; H, 5.27; N, 12.25; S, 9.67.

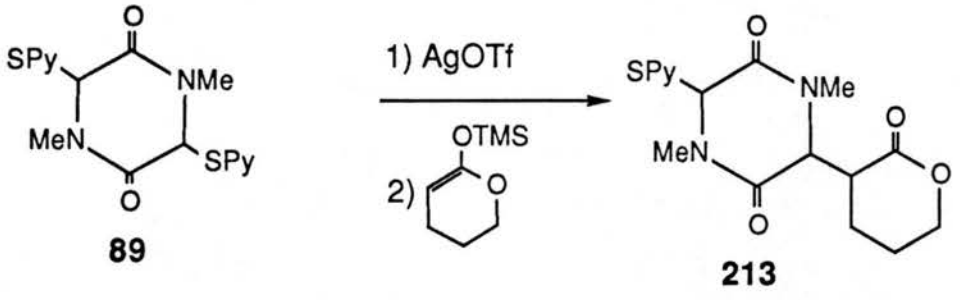
Minor *anti* (206): mp 160-161°C (recrystallized EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.14-2.28 (2 H, m), 2.92 (3 H, s), 3.05 (3 H, s), 3.68 (1 H, dd, J_1 = 10.2, J_2 = 11.5 Hz), 4.23-4.33 (1 H, m), 4.44-4.52 (1 H, m),

4.62 (1 H, s), 5.70 (1 H, s), 7.08-7.12 (1 H, m), 7.20-7.26 (1 H, m), 7.56 (1 H, dd, J = 5.08, 7.2 Hz), 8.44 (1 H, d, J = 5.00 Hz).

Minor *syn* (206): mp 148-149.5°C (recrystallized EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS (2.17-2.50 (2 H, m), 2.97 (3 H, s), 3.05 (3 H, s), 3.30-3.44 (1 H, m), 4.26-4.33 (1 H, m), 4.48-4.55 (1 H, m), 4.74 (1 H, s), 6.73 (1 H, s), 7.10-7.14 (1 H, m), 7.20-7.27 (1 H, m), 7.55-7.61 (1 H, m), 8.48-8.51 (1 H, m); IR (NaCl, neat) 3030, 2910, 2840, 1765, 1665, 1570, 1550, 1010, 750 cm^{-1}. Anal. ($C_{15}H_{17}N_3O_4S$). Calcd: C, 53,72; H, 5.11; N, 12.53; S, 9.56. Found: C, 53.89; H, 5.24; N, 12.36; S, 9.75.

Major *anti* (206): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.97-2.40 (2 H, m), 3.06 (3 H, s), 3.08 (3 H, s), 3.18-3.22 (1 H, m), 4.29-4.47 (2 H, m), 4.77 (1 H, d, J = 3.0 Hz), 5.96 (1 H, s), 7.10-7.14 (1 H, m), 7.21-7.27 (1 H, m), 7.54-7.57 (1 H, m), 8.45-8.48 (1 H, m); IR (NaCl, neat) 1770, 1675, 1580, 1560, 1300, 1025, 760 cm^{-1}.

Epimerization of the anti-minor isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25°C for 48 h resulted in a 2:1:2 ratio of *syn*-major/*anti*-major/*syn*-minor isomers.



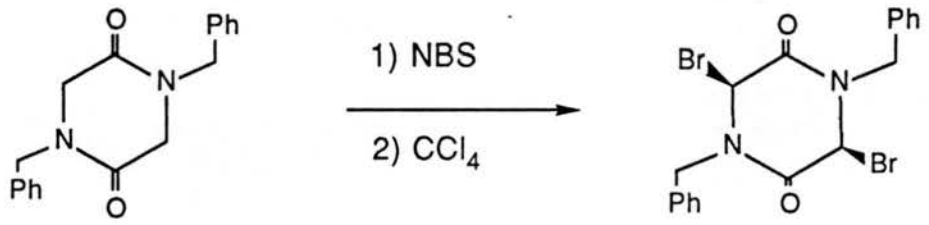
89 **213**

1,4-Dimethyl-3-(2'-thiopyridyl)-6-(2"-δ-valerolactonyl)-2,5-piperazinedione (213). To a stirred solution of **89** of (25 mg, 0.069 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 25°C was added AgOTf (17.8 mg, 0.069 mmol, 1.0 equiv) and the trimethylsilyl ketene acetal of δ-valerolactone. After 30 min,

the reaction mixture was filtered through a cotton plug. Separation by PTLC silica gel (eluted with 100% EtOAc) afforded 15 mg (62%) of the valerolactone products **213** in a 1.6:1, major:minor ratio and a 2.2:1, *syn:anti* ratio.

Major syn (213): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.80-2.19 (4 H, m), 2.95 (1 H, m), 3.04 (3 H, s), 3.10 (3 H, s), 4.27-4.50 (2 H, m), 4.94 (1 H, d, J = 3.2 Hz), 6.70 (1 H, s), 7.09-7.12 (1 H, m), 7.22-7.27 (1 H, m), 7.55-7.67 (1 H, m), 8.49 (1 H, m); IR (NaCl, neat) 1727, 1672, 1578, 1450, 1399, 1250, 1165, 1118, 754, 715 cm^{-1}.

Minor syn (213): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.03-2.10 (4 H, m), 2.98 (3 H, s), 3.05 (3 H, s), 3.20-3.31 (1 H, m), 4.31-4.37 (1 H, m), 4.42-4.50 (1 H, m), 4.97 (1 H, s), 6.78 (1 H, s), 7.08-7.18 (1 H, m), 7.20-7.38 (1 H, m), 7.54-7.65 (1 H, m), 8.47-8.49 (1 H, m); IR (NaCl, neat) 1731, 1672, 1579, 1560, 1265, 1162, 892, 728 cm^{-1}.

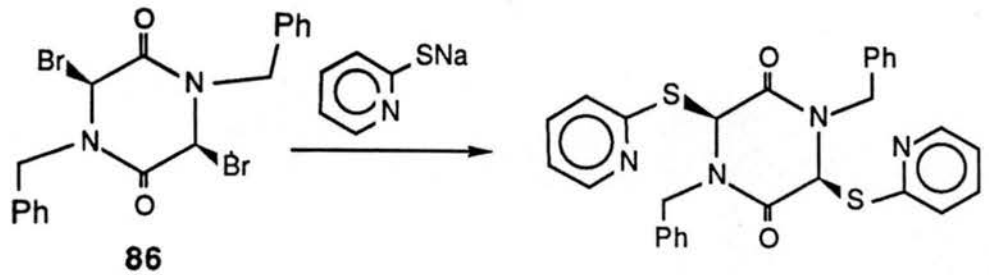


82 **86**

1,4-Dibenzyl-3,6-di-bromo-2,5-piperazinedione (86). To a stirred solution of **82** (4.36 g, 14.8 mmol, 1.0 equiv) in CCl_4 (500 mL) was added N-bromosuccinimide (6.58 g, 37 mmol, 2.5 equiv) and a catalytic amount (1 mol %) of benzoyl peroxide. The reaction mixture was refluxed for 1.5 h, cooled, filtered, and concentrated. **86** was obtained (6.35 g, 95%) by recrystallization from EtOAc/Hexanes, mp 185-186°C.

(86): ^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS: 4.04 (2 H, 1/2 ABq, J = 14.5 Hz); 5.36 (2 H, 1/2 AB, J = 14.5 Hz), 5.89 (2 H, s), 7.16-7.50 (10 H, m). IR (NaCl,

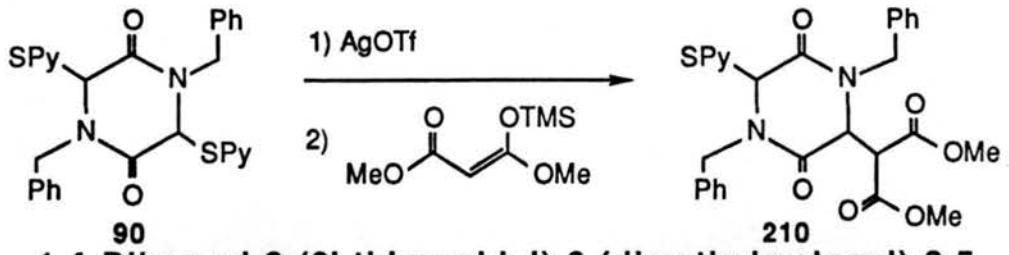
neat): 2990, 1670, 1395, 710 cm^{-1}. Mass spectrum, m/e (relative intensity): 371 (0.8), 292 (4.4), 99 (91), 56.2 (100).



86 **90**

1,4-Dibenzyl-3,6-bis(2'-thiopyridyl)-2,5-piperazinedione (90). To a stirred solution of **86** (7.2 g, 15.9 mmol, 1.0 equiv) in THF (35 mL) at 0°C was added the sodium salt of 2-mercaptopyridine. This had been prepared by addition of a solution of 2-mercaptopyridine (3.72 g, 33.5 mmol, 2.1 equiv) in THF (30 mL) to a solution of NaH (1.34 g, 33.5 mmol, 2.1 equiv) in THF (10 mL) at 0°C. After stirring for 30 min, the sodium salt of 2-mercaptopyridine was syringed into the solution of **86** and stirred at 0°C for 30 min. The reaction mixture was then diluted with CH_2Cl_2, poured into water and thoroughly extracted. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash chromatography (silica gel) eluted with 50% Hexanes/EtOAc. Recrystallization (CH_2Cl_2/Hexanes) yielded 7.67 g (94%) of **90** as a white solid mp 149-151°C.

(90): ^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 4.22 (2 H, 1/2 ABq, J = 14.6 Hz), 5.23 (2 H, 1/2 ABq, J = 14.6 Hz), 6.8 (2 H, s), 6.95-7.53 (16 H, m), 8.4 (2 H, d, J = 4.1 Hz). IR (NaCl, neat): 2910, 1670, 1450, 1150 cm^{-1}. Anal ($C_{28}H_{24}N_4O_2S_2$). Calcd: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.63; H, 4.77; N, 10.84.



90 **210**

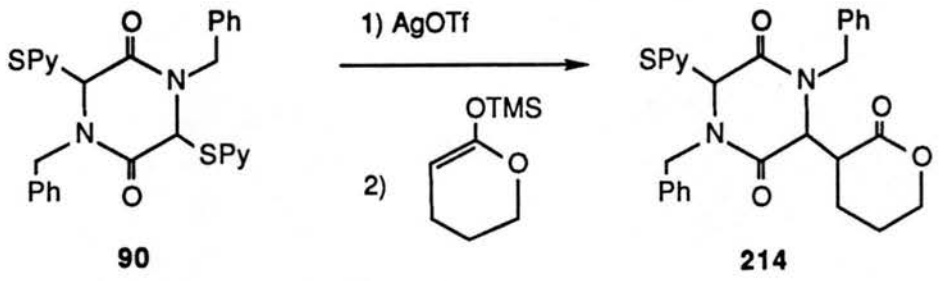
1,4-Dibenzyl-3-(2'-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (210). To a stirred solution of **90** (25 mg, 0.048 mmol, 1.0 equi.) in CH_2Cl_2 (2.0 mL) at room temperature was added AgOTf (12.5 mg, 0.048 mmol, 1.0 equiv). After 5 min., the silyl enol ether of dimethylmalonate was added. The reaction mixture stirred for 10.5 h and was then filtered through a cotton plug. Separation by PTLC silica gel (eluted with 20% EtOAc/Benzene) afforded 16.4 mg (63%) of **210** in a 2.4:1, *syn:anti* ratio.

***Syn* Isomer (210):** ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.73 (3 H, s), 3.77 (3 H, s), 3.96 (1 H, d, J = 5.2 Hz), 4.09 (1 H, 1/2 ABq, J = 14.6 Hz), 4.55 (1 H, 1/2 ABq, J = 15.4 Hz), 4.79 (1 H, d, J = 5.2 Hz), 4.82 (1 H, 1/2 ABq, J = 15.4 Hz), 5.32 (1 H, 1/2 ABq, J = 14.6 Hz), 6.81 (1 H, s), 7.05-7.09 (1 H, m), 7.21-7.34 (11 H, m), 7.52-7.59 (1 H, m), 8.39-8.41 (1 H, m); IR (NaCl, neat) 1745, 1672, 1572, 1445, 1263, 882, 725, 690 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_6S$). Calcd: C, 63.0; H, 5.10; N, 7.87; S, 6.01. Found: C, 63.15; H, 5.20; N, 8.00; S, 5.92.

***Anti* Isomer (210):** mp 150°C (dec) (recrystallized EtOAc/Hexanes): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.63 (3 H, s), 3.77 (3 H, s), 4.10 (1 H, d, J = 3.5 Hz), 4.13 (1 H, 1/2 ABq, J = 14.8 Hz), 4.34 (1 H, 1/2 ABq, J = 15.6 Hz), 4.91 (1 H, d, J = 3.5 Hz), 5.11 (1 H, 1/2 ABq, J = 15.6 Hz), 5.44 (1 H, s), 5.52 (1 H, 1/2 ABq, J = 14.8 Hz), 6.99-7.02 (1 H, m), 7.19-7.55 (12 H, m), 8.09 (1 H, d, J = 4.1 Hz); IR (NaCl, neat) 1750, 1672, 1580, 1432, 1355, 1165, 755, 725, 695 cm^{-1}.

Epimerization of the *anti* isomer to a mixture of *syn/anti* isomers was carried out by treatment of the *anti* isomer in 50% THF/MeOH with 0.1 N NaOMe

in MeOH at 25°C for 12 h. Evaporation of the solvent produced a 1.8:1 *syn/anti* mixture.



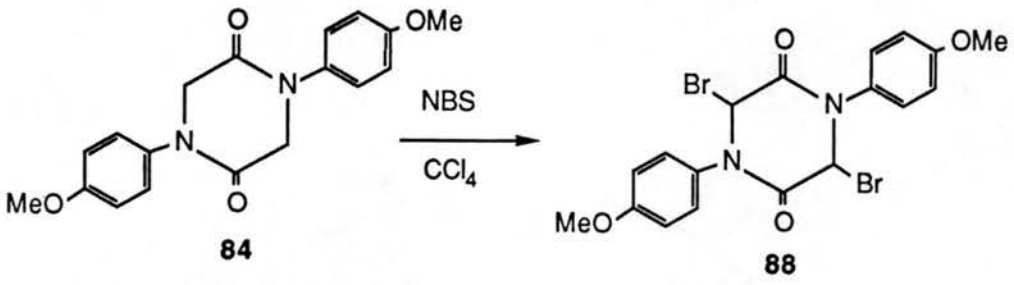
90 **214**

1,4-Dibenzyl-3-(2'-thiopyridyl)-6-(2"-δ-valerolactonyl)-2,5-piperazinedione (214). From 26 mg (0.05 mmol, 1.0 equiv) of **90**, 13 mg (0.05 mmol, 1.0 equiv) of AgOTf and 13 mg (0.076 mmol, 1.5 equiv) of the TMS enol ether of δ-valerolactone in THF (0.5 mL) was obtained 14 mg (70% based on recovered **90**)of the valerolactone product **24** as a 3.5:1 *syn/anti* mixture (1.8:1 major:minor ratio) (isolated by PTLC silica gel, eluted with 20% EtOAc in hexanes).

Major *syn* (214): mp 166-167°C (recrystallized EtOAc/hexanes): ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.40-2.15 (4 H, m), 2.89-2.95 (1 H, m), 4.05 (1 H, 1/2 ABq, J = 14.5 Hz), 4.23-4.30 (1 H, m), 4.30-4.38 (1 H, m), 4.63 (1 H, 1/2 ABq, J = 14.9 Hz), 4.81 (1H, 1/2 ABq, J = 14.9 Hz), 5.02 (1 H, d, J = 3.8 Hz), 5.30 (1 H, 1/2 ABq, J = 14.5 Hz), 6.59 (1 H, s), 7.15-7.8 (1 H, m), 7.18-7.37 (1 H, m), 7.56-7.62 (1 H, m), 8.46-8.49 (1 H, m); IR (NaCl, neat) 1730, 1665, 1450, 1260, 1160 cm^{-1}; mass spectrum, m/e 501 (M^+, 0.3), 391 (2.7), 299 (1.5), 292 (1.7), 91 (100). Anal. ($C_{28}H_{27}N_3O_4S$). Calcd: C, 67.05; H, 5.42; N, 8.37; S, 6.39. Found: C, 67.09; H, 5.46; N, 8.28; S, 6.22.

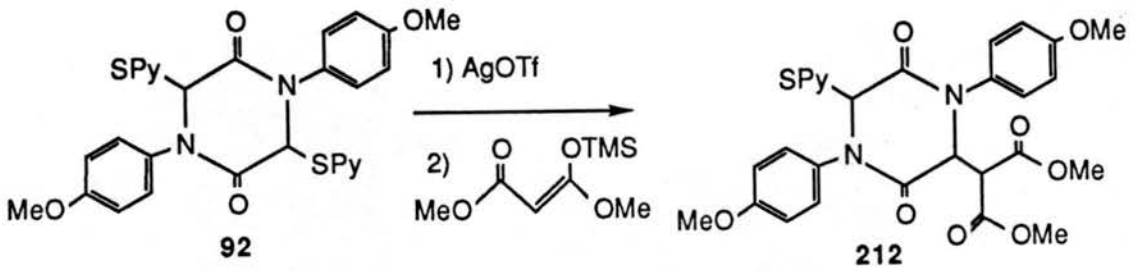
Minor *syn* (214): mp 181-183°C (recrystallized EtOAc/hexanes); ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.45-2.10 (5 H, m), 3.16-3.22 (1 H, m), 3.55-3.62 (1 H, m), 4.05 (1 H, 1/2 ABq, J = 14.3 Hz), 4.59 (1 H, 1/2 ABq, J = 15.0 Hz),

4.69 (1 H, 1/2 ABq, J = 15.0 Hz), 5.05 (1 H, d, J = 1.5 Hz), 5.29 (1 H, 1/2 ABq, J = 14.3 Hz), 6.74 (1 H, s), 7.14-7.18 (1 H, m), 7.18-7.41 (11 H, m), 7.54-7.62 (1 H, m), 8.42-8.45 (1 H, m); IR (NaCl, neat) 1730, 1665, 1450, 1260, 1160 cm^{-1}; mass spectrum, m/e 501 (M^+, 0.3), 391 (2,7), 299 (1.5), 292 (1,7), 91 (100). Anal. ($C_{28}H_{27}N_3O_4S$). Calcd: C, 67.05; H, 5.42; N, 8.37; S, 6.39. Found: C, 66.85; H, 5.31, N, 8.22; S, 6.08.



1,4-Bis(*p*-methoxyphenyl)-3,6-di-bromo-2,5-piperazinedione (88). To a stirred solution of 1,4-disubstituted 2,5-piperazinedione **84** in CCl_4 (20 mL) was added NBS (205 mg, 1.15 mmol, 2.5 equiv) and benzoyl peroxide (5 mg, 0.023 mmol, 0.05 equiv). The reaction mixture was brought to reflux temperature and stirred for 1 h. It was then cooled to ambient temperature, filtered and concentrated to afford 192 mg (86%) of crude dibromide.

(88): ^1H NMR (60 MHz) ($CDCl_3$) δ TMS: 3.87 (6 H, s), 6.33 (2 H, s), 6.97 (4 H, d, J = 9 Hz), 7.33 (4 H, d, J = 7.3 Hz). Mass spectrum, m/e (relative intensity): 484 (0.2), 405 (1.7), 403 (2.0), 377 (1.1), 375 (1.1), 364 (0.9), 324 (2.5), 296 (2.3), 163 (1.6), 149 (100), 134 (90.3), 106 (32.4), 78 (20.8).

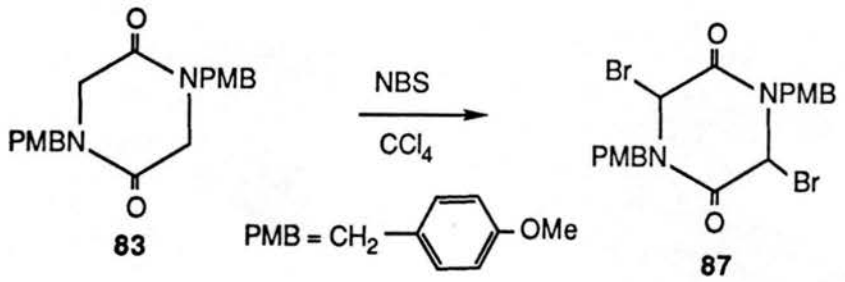


1,4-Di-*p*-methoxyphenyl-3-(2'-thiopyridyl)-6-dimethylmalonyl)-2,5-piperazinedione (212). To a stirred solution of **92** (25 mg, 0.046 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added AgOTf, (12 mg, 0.046 mmol, 1.0 equiv) Et_3N (1 µl) and the silyl enol ether of dimethylmalonate (18 mg, 0.092 mmol, 2.0 equiv). The reaction mixture stirred for 1.5 h at 25°C and was filtered over a cotton plug. Purification by PTLC silica gel (2:1 EtOAc/Hexanes) afforded 17.1 mg (66%) of product **212** as a 1.1:1, *syn:anti* mixture.

***Syn* (212):** mp 175-177°C (recrystallized, THF/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.68 (3 H, s), 3.73 (3 H, s), 3.83 (3 H, s), 3.89 (3 H, s), 3.94 (1 H, d, J = 4.7 Hz), 5.24 (1 H, d, J = 4.7 Hz), 6.79-7.39 (12 H, m), 8.20 (1 H, d, J = 4.0 Hz); IR (NaCl, neat) 1735, 1675, 1602, 1574, 1505, 1295, 1240, 1020, 820, 790, 750 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_8S$). Calcd: C, 59.46; H, 4.81; N, 7.43; S, 5.67. Found: C, 59.51; H, 5.13; N, 7.17.

***Anti* (212):** mp 164-165°C (recrystallized, EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.71 (3 H, s), 3.76 (1 H, d, J = 3.8 Hz), 3.79 (3 H, s), 3.82 (3 H, s), 5.44 (1 H, d, J = 3.8 Hz), 5.84 (1 H, s), 6.88-7.36 (10 H, m), 7.55 (1 H, m), 8.60 (1 H, d, J = 4.1 Hz); IR (NaCl, neat) 1735, 1670, 1600, 1570, 1502, 1350, 1240, 1020, 820, 790, 747, 720 cm^{-1}.

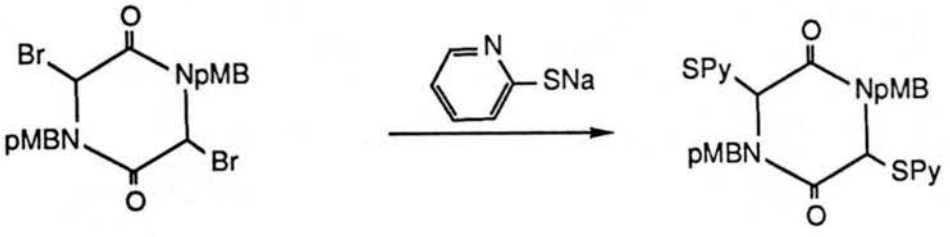
Epimerization of the *anti* isomer was carried out by treatment with 0.1 N NaOMe in 50% THF/MeOH at 25°C for 24 h. Evaporation of the solvent yielded a 1:3 *syn:anti* mixture.



83 **87**

1,4-Bis(*p*-methoxybenzyl)-3,6-(di-bromo)2,5-piperazinedione (87). To a stirred solution of **83** (5.0 g, 14.1 mmol, 1.0 equi.) in CCl_4 (3.50 mL) was aded N-bromosuccinimide (5.28 g, 29.66 mmol, 2.1 equiv) and 1 mol % benzoyl peroxide. The mixture was brought to reflux temperature for 1 h, cooled to 25°C, filtered and concentrated to give 6.72 g (93%) of **87** as pale yellow crystals. mp 164-165°C (recrystallized, EtOAc/Hexanes).

(87): ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 4.23 (6 H, s), 4.44 (2 H, 1/2 ABq, J = 13.4 Hz), 5.66 (2 H, 1/2 ABq, J = 13.4 Hz), 6.37 (2 H, s), 7.36 (4 H, 1/2 ABq, J = 8.7 Hz), 7.68 (4 H, 1/2 ABq, J = 8.7 Hz). IR (NaCl, neat) 1695, 1520 cm^{-1}.

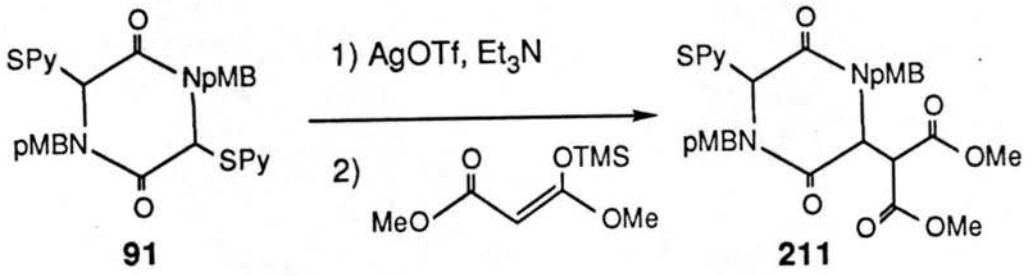


87 **91**

1,4-Bis(*p*-methoxybenzyl)-3,6-bis(2'-thiopyridyl)-2,5-piperazinedione (91). To a stirred suspension of sodium hydride, (577 mg,

14.43 mmol, 1.0 equiv) in THF (100 mL) was added 2-mercaptopyridine (1.60 g, 14.43 mmol, 2.1 equiv) over a 30 min period. The resulting solution of sodium thiolate stirred for 30 min at 25°C and was then transferred by cannula into a stirred solution of **87** (3.52 g, 6.87 mmol, 1.0 equiv) in THF (100 mL). The mixture was stirred for 30 min, poured into H_2O and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford **91** (3.81 g, 97%) as white crystals. mp 174-175°C (recrystallized EtOAc/Hexanes).

(91): ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 3.85 (6 H, s), 4.17 (2 H, 1/2 ABq, J = 14.5 Hz), 5.22 (2 H, 1/2 ABq, J = 14.5 Hz), 6.73 (2 H, s), 6.89 (4 H, 1/2 ABq, J = 8.6 Hz), 7.17 (2 H, m), 7.31 (4 H, 1/2 ABq, J = 8.6 Hz), 7.32 (2 H, m), 7.61 (2 H, m), 8.57 (2 H, d, J = 4.8 Hz). IR (NaCl, neat): 1670, 1505, 1405, 1240, 1112 cm^{-1}. Anal. ($C_{30}H_{28}N_4O_4S_2$). Calcd: C, 62.91; H, 4.93; N, 9.78; S, 11.19. Found: C, 63.21; H, 4.95; N, 9.84; S, 11.24.



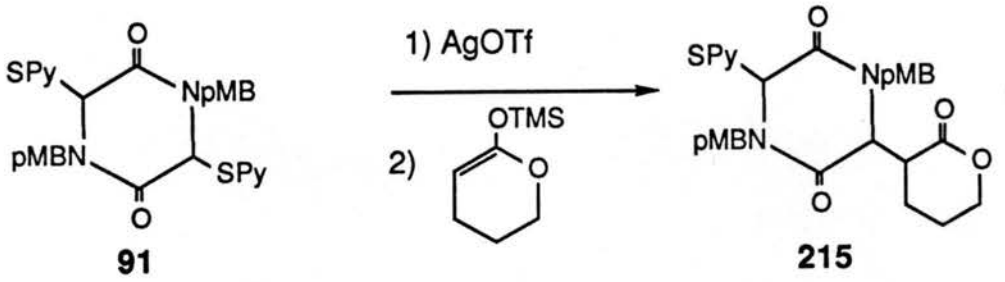
1,4-Bis(*p*-methoxybenzyl)-3-(2'-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (211). To a stirred solution of **91** in 2 mL CH_2Cl_2 at 25°C was added Et_3N (1.8 µl, 0.013 mmol, 0.15 equiv) and AgOTf (22.4 mg, 0.087 mmol, 1.0 equiv). After 5 min, the trimethylsilyl ketene acetal of dimethylmalonate (35 µl, 0.174 mmol, 2.0 equiv) was added. After 2 h, the reaction mixture was filtered through a cotton plug. Separation by PTLC silica

gel eluted with 15% EtOAc/benzene afforded 44.6 mg (86%) of product **211**, as a 2:1 *syn:anti* mixture.

***Anti* (211):** ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.66 (3 H, s), 3.78 (3 H, s), 3.79 (3 H, s), 3.82 (3 H, s), 4.04 (1 H, 1/2 ABq, J = 14.4 Hz), 4.13 (1 H, d, J = 3.8 Hz), 4.18 (1 H, 1/2 ABq, J = 15.3 Hz), 4.86 (1 H, d, J = 3.8 Hz), 5.13 (1 H, 1/2 ABq, J = 15.3 Hz), 5.39 (1 H, s), 5.46 (1 H, 1/2 ABq, J = 14.4 Hz), 6.79 (2 H, d, J = 8.6 Hz), 6.87 (2 H, d, J = 8.6 Hz), 6.95-7.01 (1 H, m), 7.16-7.21 (3 H, M), 7.36 (2 H, d, J = 8.6 Hz), 7.48-7.54 (1 H, m), 8.05-8.07 (1 H, m); IR (NaCl, neat) 1740, 1665, 1610, 1575, 1511, 1433, 1243, 1165, 1025 cm^{-1}; mass spectrum, m/e 592.9 (0.1), 481.9 (0.8), 121.0 (96.9), 111.0 (25.8).

***Syn* (211):** ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.76 (3 H, s), 3.79 (6 H, s), 3.81 (3 H, s), 4.01 (1 H, d, J = 5.1 Hz), 4.03 (1 H, 1/2 ABq, J = 14.3 Hz), 4.40 (1 H, 1/2 ABq, J = 15.0 Hz), 4.77 (1 H, d, J = 5.1 Hz), 4.85 (1 H, 1/2 ABq, J = 15.0 Hz), 5.26 (1 H, 1/2 ABq, J = 14.3 Hz), 6.78 (2 H, d, J = 8.6 Hz), 6.79 (1 H, s), 6.85 (2 H, d, J = 8.6 Hz), 7.08-7.12 (1 H, m), 7.16 (2 H, d, J = 3.2 Hz), 7.19 (2 H, d, J = 3.2 Hz), 7.29 (1 H, t, J = 7.8 Hz), 7.57 (1 H, d of t, J = 1.7, 7.8 Hz), 8.44-8.46 (1 H, m); IR (NaCl, neat) 1740, 1662, 1610, 1575, 1508, 1440, 1240, 1160, 1115, 1025, 722, 692 cm^{-1}; mass spectrum, m/e 593.2 (0.2), 482 (1.6), 111.0 (44.9), 121.1 (100.0); exact mass (M^+ - C_5H_5NS) calcd for $C_{25}H_{26}N_2O_8$ 482.16898, found 482.16893.

Epimerization of the anti isomer to a mixture of *syn/anti* isomers was carried out by treatment of the minor anti isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25°C under N_2 for 12 h. Evaporation of the solvent yielded a 5.7:1 mixture (*syn/anti*).



1,4-Bis(*p*-methoxybenzyl)-3-(2'-thiopyridyl)-6-(2"-δ-valerol-actonyl)-2,5-piperazinedione (215). To a stirred solution of **91** (25 mg, 0.043 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added AgOTf (15 mg, 0.058 mmol, 1.3 equiv) and the trimethylsilyl ketene acetal of δ-valerolactone (9.6 μl, 1.3 mmol, 0.058 mmol, 1.3 equiv). The reaction mixture stirred for 3 h and was then filtered through a cotton plug. Separation by PTLC silica gel yielded 10.7 mg (44%) of the product **215** as a mixture of diastereomers (1.7:1.0:1.2, *syn*-major:*anti*-major:*syn*-minor) (*syn:anti* = 2.9:1).

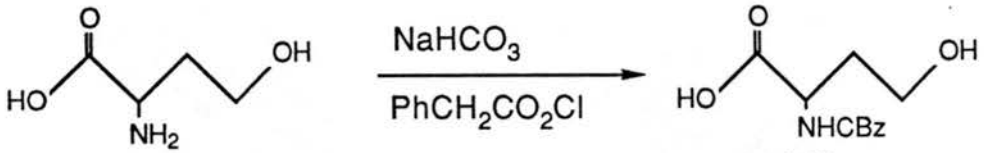
Minor *syn* (215): mp 148.5-150.5°C (recrystallized EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.85-2.01 (4 H, m), 3.17-3.24 (1 H, m), 3.58-3.65 (1 H, m), 3.80 (3 H, s), 3.81 (3 H, s), 3.98 (1 H, d, 1/2 ABq, J = 14.4 Hz), 4.20-4.24 (1 H, m), 4.54 (1 H, d, 1/2 ABq, J = 14.8 Hz), 4.61 (1 H, 1/2 ABq, J = 14.8 Hz), 5.06 (1 H, s), 5.26 (1 H, 1/2 ABq, J = 14.4 Hz), 6.72 (1 H, s), 6.80-6.86 (4 H, M), 7.12-7.36 (6 H, m), 7.57-7.64 (1 H, m), 8.49-8.50 (1 H, m); IR (NaCl, neat) 1715, 1650, 1503, 1444, 1297, 1241, 1155, 1020, 750 cm^{-1}.

Major *syn* (215): mp 158.5-159°C; ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.68-2.09 (4 H, m), 2.95 (1 H, m), 3.80 (6 H, s), 3.98 (1 H, d, 1/2 ABq, J = 14.3 Hz), 4.23-4.42 (2 H, m), 4.51 (1 H, d, 1/2 ABq, J = 14.7 Hz), 4.81 (1 H, d, 1/2 ABq, J = 14.7 Hz), 5.04 (1 H, d, J = 3.5 Hz), 5.26 (1 H, d, 1/2 ABq, J = 14.3 Hz), 6.58 (1 H, s), 6.80 (2 H, d, J = 8.6 Hz), 6.84 (2 H, d, J = 8.6 Hz), 7.13-7.31 (6 H,

m), 7.57-7.64 (1 H, m), 8.51-8.53 (1 H, m); IR (NaCl, neat) 1720, 1665, 1508, 1448, 1244, 1155, 1112, 1082, 1023, 738 cm^{-1}. Anal. ($C_{30}H_{31}N_3O_6S$). Calcd: C, 64.15; H, 5.56; N, 7.48; S, 5.71. Found: C, 63.71; H, 5.67; N, 7.30; S, 5.49.

Major *anti* (215): mp 153-155°C (recrystallized EtOAc/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 1.39-1.88 (4 H, m), 3.12 (1 H, m), 3.79 (3 H, s), 3.81 (3 H, s), 4.02 (1 H, 1/2 ABq, J = 14.4 Hz), 4.07 (1 H, 1/2 ABq, J = 15.0 Hz), 4.24-4.41 (2 H, m), 5.12 (1 H, d, J = 2.76 Hz), 5.21 (1 H, 1/2 ABq, J = 15.0 Hz), 5.34 (1 H, d, 1/2 ABq, J = 14.4 Hz), 5.71 (1 H, s), 6.79 (2 H, d, J = 8.6 Hz), 6.85 (2 H, d, J = 8.7 Hz), 6.98-7.03 (1 H, m), 7.18-7.26 (5 H, m), 7.49-7.52 (1 H, m), 8.15-8.17 (1 H, m); IR (NaCl, neat) 1715, 1655, 1503, 1410, 1297, 1242, 1170, 1080, 1020 cm^{-1}.

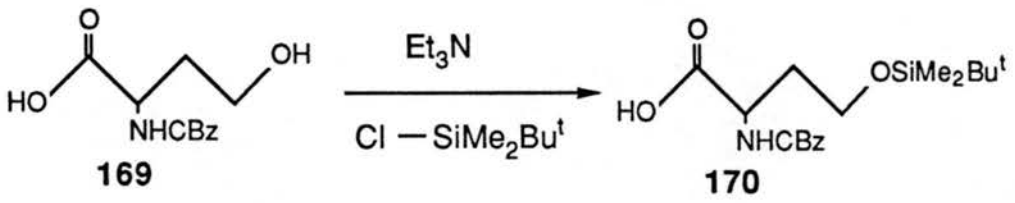
Epimerization of the anti isomer was carried out by treatment of the *anti* isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25°C under N_2 for 16 h. Evaporation of the solvent yielded the *syn* isomers.



169

d,l-N-Carbobenzyloxy homoserine (169). To homoserine **169** (20 g, 166 mmol, 1.0 equiv) in a solution of saturated aqueous $NaHCO_3$ (300 mL) was added benzylchloroformate (33.6 mL, 236 mmol, 1.4 equiv). The reaction mixture stirred for 4 h. It was then washed with 2 parts EtOAc and the water layer was concentrated. The residue was chilled and acidified with 8N HCl to pH 1.5. Crystallization was brought about by rapid stirring and agitation of the oily residue while transferring back and forth between an acetone/dry ice

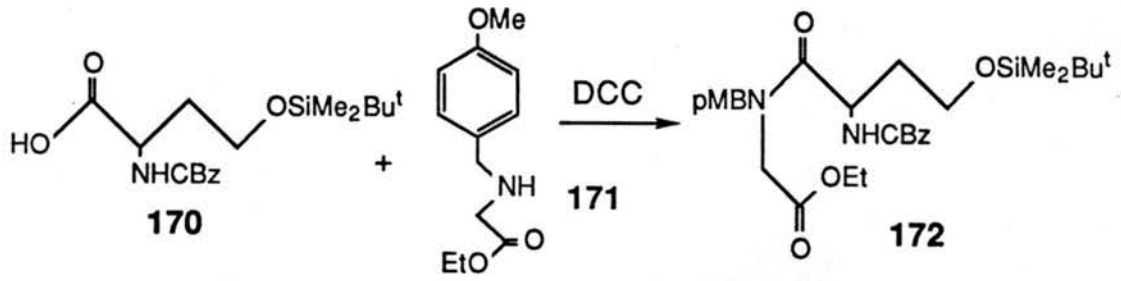
bath and a warm water bath. The product **169** was collected and dried overnight over P_2O_5 in a vacuum dessicator to yield 22.43 g, (53%) of product **169**, mp 77-80°C.



169 **170**

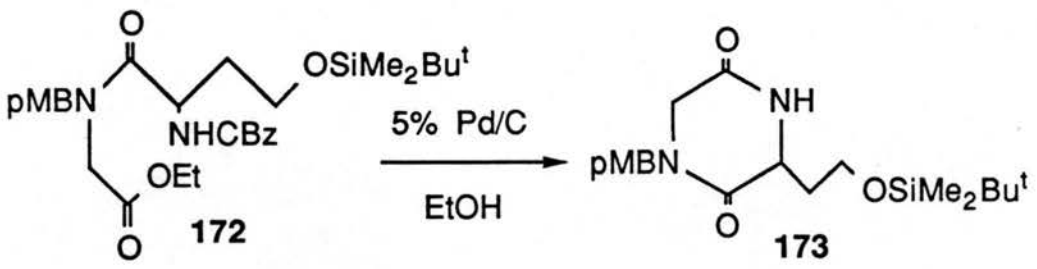
2-[(Carbobenzyloxy)amino)]-4-[(*tert*-butyldimethylsilyl)oxy)]-butanoic acid (170). To Et_3N (27.3 mL, 195 mmol, 2.2 equiv) in DMF (200 mL) at 0°C was added the N-protected homoserine (22.4 g, 88.6 mmol, 1.0 equiv). Into this mixture was cannulated a solution of *t*-butyldimethylsilylchloride (16 g, 106 mmol, 1.2 equiv) in DMF (100 mL). The ice bath was removed and the reaction stirred for 1.5 h. The reaction mixture was then poured into 1.2 L of water and solid Na_2CO_3 (35 g) was added. The water layer was washed with 0.5 L of EtOAc and then acidified to pH 1 by the slow addition of conc. HCl. This was then extracted with two portions of EtOAc; these extracts were combined and washed with water. The organic material was concentrated and dried under vacuum for 15 h to yield 22.49 g (69%) of **170** as a yellow oil. This was immediately taken on without further purification to the next step.

^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 0.02 (6 H, s), 0.86 (9 H, s), 1.90-2.33 (2 H, m), 3.62-3.82 (2 H, m), 4.34-4.50 (1 H, m), 5.10 (2 H, br.s), 6.02 (1 H, br.d, J = 17.1 Hz), 7.22-7.46 (5 H, m), 9.2 (1 H, br.s). IR (NaCl, neat): 3405, 3340, 1790, 1725, 1100, 835, 775, 690 cm^{-1}.



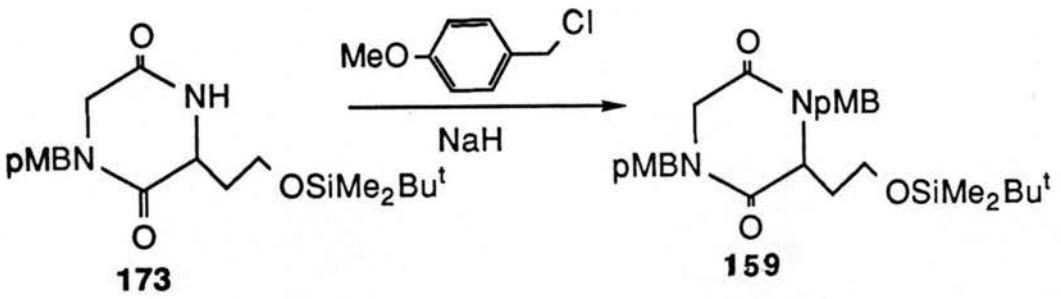
2-N-(carbobenzyloxy)amino-4-[(*tert*-butyldimethylsilyl)oxy]-N'-[(carboethoxy)methyl]-N"-(*p*-methoxybenzyl)-butyramide (172). To a stirred solution of **170** (13.19 g, 35.9 mmol, 1.0 equiv) and ( ) (8.01 g, 35.9 mmol, 1.0 equiv) in THF (100 mL) at 0°C was added DCC (7.41 g, 35.9 mmol, 1.0 equiv) in THF (100 mL) also at 0°C. The mixture was allowed to stir overnight. The reaction mixture was then filtered and the filtrate concentrated. The residue was taken up in CH_2Cl_2 and washed two times with 1 N HCl. The organic layer was concentrated and purified by flash chromatography (silica gel) (eluted 3:1 Hexanes/EtOAc) to yield 9.91 g (48%) of product, **172**.

(172): mp 80-81°C (recrystallized EtOAc/Hexanes). ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 0.0 (6 H, s), 0.87 (9 H, s), 1.22 (3 H, t, J = 7.1 Hz), 1.75-1.80 (1 H, m), 2.00-2.10 (1 H, m), 3.54 (1 H, 1/2 ABq, J = 17.2 Hz), 3.69-3.74 (2 H, m), 3.76 (3 H, s), 4.13 (2 H, q, J = 7.1 Hz), 4.32 (1 H, 1/2 ABq, J = 17.2 Hz), 4.33 (1 H, 1/2 ABq, J = 15.9 Hz), 4.91 (1 H, 1/2 ABq, J = 17.2 Hz), 5.04 (1 H, 1/2 ABq, J = 12.2 Hz), 5.14 (1 H, 1/2 ABq, J = 12.2 Hz), 5.67 (1 H, m), 6.80-7.40 (9 H, m). IR (NaCl, neat) 3295, 2955, 2930, 2855, 1741, 1718, 1650, 1510, 1452 cm^{-1}. Anal. ($C_{30}H_{44}N_2O_7Si$). Calcd: C, 62.91; H, 7.74; N, 4.89. Found: C, 63.04; H, 7.61; N, 5.03.



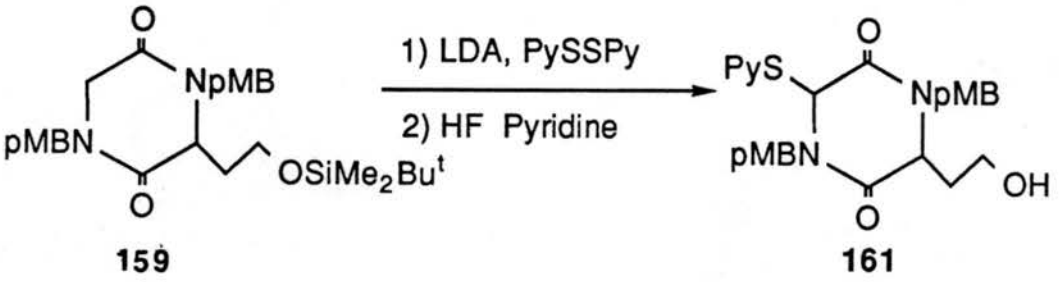
3-[2'-((*tert*-butyldimethylsilyl)oxy)ethyl]-1-(*p*-methoxybenzyl)-2,5-piperazinedione (173). A stirred solution of **172** (9.91 g, 17.3 mmol, 1.0 equiv) in 400 mL of EtOH was purged with nitrogen, 5% Pd/C (2.58 g) was added and the flask purged with hydrogen. The reaction mixture was vigorously stirred under a balloon of H_2 overnight. It was then filtered over celite and the filtrate concentrated to yield 6.64 g (98%) of a clean oil, which could be recrystallized from EtOAc to yield a white crystalline product.

(173): mp 92-94°C (recrystallized EtOAc). ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 0.01 (6 H, s), 0.83 (9 H, s), 1.80-1.99 (1 H, m), 2.29-2.44 (1 H, m), 3.72 (3 H, s), 3.74 (2 H, s), 3.72-3.94 (2 H, m), 4.09 (1 H, br.d, J = 8.6 Hz), 4.37 (1 H, 1.2 ABq, J = 14.3 Hz), 4.52 (1 H, 1/2 ABq, J = 14.3 Hz), 6.79 (2 H, d, J = 8.5 Hz), 7.12 (2 H, d, J = 8.5 Hz), 7.20 (1 H, br.s). IR (KBr) 3220, 1660, 1515, 1250, 1100, 1035, 835 cm^{-1}. Anal. ($C_{20}H_{32}N_2O_4Si$). Calcd: C, 61.18; H, 8.22; N, 7.14. Found: C, 60.97; H, 8.18; N, 7.13.



1,4-Bis(*p*-methoxybenzyl)-3-[2-((*tert*-butyldimethylsilyl)oxy)-ethyl]-2,5-piperazinedione (159). NaH (0.52 g, 10.9 mmol, 1.1 equiv, 50% oil dispersion) was washed with three portions of hexane and suspended in 50 mL of dry DMF. To this suspension was added **173**, (3.88 g, 9.87 mmol, 1.0 equiv) neat and the reaction mixture was stirred for 2 h. The reaction was then quenched with *p*-methoxybenzylchloride and stirred for an additional hour. The reaction mixture was diluted with CH_2Cl_2, poured into water and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated to yield a crude yellow oil. Purification by flash chromatography (silica gel) (eluted 1:1 EtOAc/Hexanes) afforded 4.0 g (79%) of oil which could be crystallized to a white solid.

(159): mp 133-135°C ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 0.0 (6 H, s), 0.83 (9 H, s), 1.91-1.97 (2 H, m), 3.55-3.90 (5 H, m), 3.72 (6 H, s), 3.98-4.06 (1 H, m), 4.32 (1 H, 1/2 ABq, J = 14.3 Hz), 4.51 (1 H, 1/2 ABq, J = 14.3 Hz), 5.18 (1 H, 1/2 ABq, J = 14.3 Hz), 6.74-7.16 (8 H, m). IR (NaCl, neat) 3000-2820 (broad multiplet), 1660, 1605, 1500, 1455, 1250 cm^{-1}.

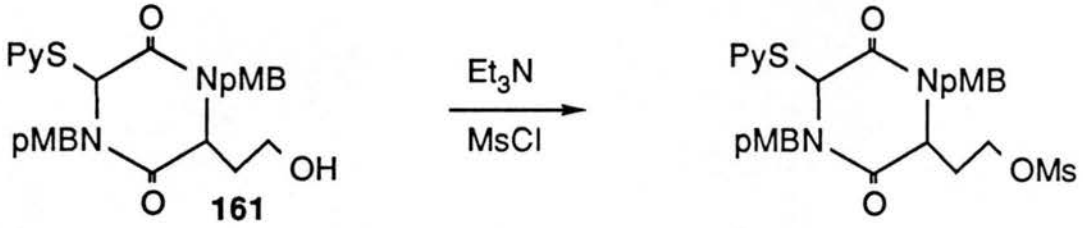


159 **161**

1,4-Bis(*p*-methoxybenzyl)-3-(2'-thiopyridyl)-6-(2-hydroxy-ethyl)-2,5-piperazinedione (161). LDA was generated by adding *n*-BuLi (1.6 mL, 2.8 mmol, 1.2 equiv) to a solution of diisopropylamine (0.392 mL, 2.8 mmol, 1.2 equiv) in THF (10 mL) at -78°C. After 30 min, LDA was added to a solution of **159** (1.2 g, 2.3 mmol, 1.0 equiv) in THF (20 mL) at -78°C. This stirred for 1 h and was then cannulated into a solution of the disulfide (0.76 g, 3.4 mmol, 1.5 equiv). The reaction mixture stirred at -78°C for 0.5 h and was then warmed to 25°C. It was subsequently diluted with CH_2Cl_2, poured into water and extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Separation by flash chromatography (silica gel) eluted with 2:1 Hexanes/EtOAc afforded sulfenylated product contaminated with inseparable 2-mercaptopyridine. The crude product was redissolved in THF and treated with excess HF•pyridine complex. This was allowed to stir for 1 h and was then diluted with CH_2Cl_2 and poured into 0.1 N NaOH. After extracting three times with CH_2Cl_2, the extracts were combined and dried over Na_2SO_4, filtered and concentrated. Separation by PTLC (silica gel) (eluted 2:1 EtOAc/Hexanes) yielded 273 mg (24% two step yield) of *syn* alcohol **160**.

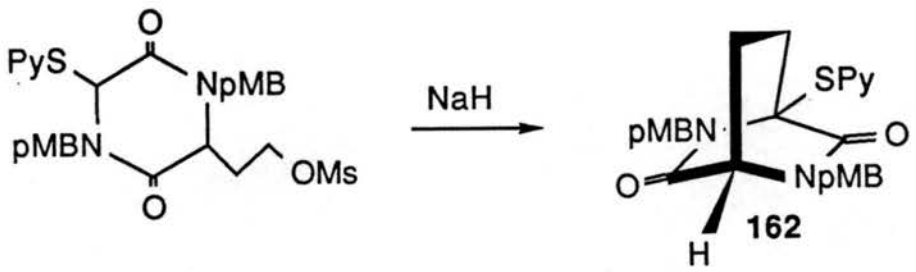
***Syn* (160):** mp 110.5-112°C (recrystallized EtOAc/Hexanes). ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.94-2.10 (1 H, m), 2.15-2.24 (1 H, m), 3.78 (6 H, s), 4.02 (1 H, 1/2 ABq, J = 14.5 Hz), 4.03 (1 H, 1/2 ABq, J = 14.7 Hz), 4.10-4.16

(3 H, m), 5.05 (1 H, 1/2 ABq, J = 14.7 Hz), 5.13 (1 H, 1/2 ABq, J = 14.5 Hz), 6.56 (1 H, s), 6.77-6.83 (4 H, m), 7.09-7.23 (6 H, m), 7.52-7.59 (1 H, m), 8.47-8.49 (1 H, m). IR (NaCl, neat) 2920, 2825, 1670, 1610, 1572, 1510, 1450, 1242 cm^{-1}. Mass spectrum, m/e (relative intensity) (CI, NH_3) 507 (M^+, 0.3), 396 (2.4), 112 (42.5), 35 (100, NH_3 + 18).



1,4-Bis(*p*-methoxybenzyl)-3-(2'-thiopyridyl)-6-(methane-sulfonyloxy-ethyl)-2,5-piperazinedione. To a stirred solution of the alcohol **161** (349 mg, 0.689 mmol, 1.0 equiv) in THF (6 mL) at 0°C was added MsCl (80 µl, 1.03 mmol, 1.5 equiv) and Et_3N (290 µl, 2.067 mmol, 3.0 equiv). This stirred overnight and was then diluted with CH_2Cl_2, poured into distilled water, and extracted with CH_2Cl_2 three times. The combined extracts were dried over Na_2SO_4, and then filtered and concentrated. NMR of the crude indicated an essentially quantitative conversion.

^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 2.16-2.37 (2 H, m), 3.03 (3 H, s), 3.79 (6 H, s), 3.98 (1 H, 1/2 ABq, J = 14.8 Hz), 4.02 (1 H, m), 4.04 (1 H, 1/2 ABq, J = 15.5 Hz), 4.38 (2 H, m), 5.06 (1 H, 1/2 ABq, J = 15.5 Hz), 5.12 (1 H, 1/2 ABq, J = 14.8 Hz), 6.53 (1 H, s), 6.78-6.85 (5 H, m), 7.10-7.24 (5 H, m), 7.54-7.60 (1 H, m), 8.48-8.50 (1 H, m). IR (NaCl, neat) 2920, 2825, 1670, 1610, 1572, 1570, 1450, 1350, 1242, 1170, 1024 cm^{-1}.



6,8-Bis(*p*-methoxybenzyl)-4-(2'-thiopyridyl)-6,8-diazabicyclo-[2.2.2]-octane-5,7-dione (162). NaH (33 mg, 0.83 mmol, 1.2 equiv) was washed with three portions of hexane. To this was added a solution of mesylate (393 mg, 0.69 mmol, 1.0 equiv) in THF (6 mL). Over a period of 24 h, an additional 58 mg of NaH was added. The crude was separated without workup by PTLC (silica gel) (eluted 1:1 EtOAc/Hexanes) to afford 64 mg (19%) of product **162**.

(162): mp 94-95°C (recrystallized Methanol, Hexanes, Ether). ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.65-1.96 (3 H, m), 2.50-2.58 (1 H, m), 3.77 (3 H, s), 3.78 (3 H, s), 4.06 (1 H, s), 4.36 (1 H, 1/2 ABq, J = 14.5 Hz), 4.67 (1 H, 1/2 ABq, J = 14.5 Hz), 4.74 (1 H, 1/2 ABq, J = 15.4 Hz), 5.02 (1 H, 1/2 ABq, J = 15.4 Hz), 6.75-7.38 (10 H, m), 7.54-7.60 (1 H, m), 8.45-8.46 (1 H, m). IR (NaCl, neat) 2930, 2830, 1682, 1610, 1570, 1510, 1242, 1170, 1025 cm^{-1}. Anal. ($C_{27}H_{27}N_3O_4S$). Calcd: C, 66.24; H, 5.56; N, 8.58; S, 6.55. Found: C, 66.34; H, 5.63; N, 8.38; S, 6.50.

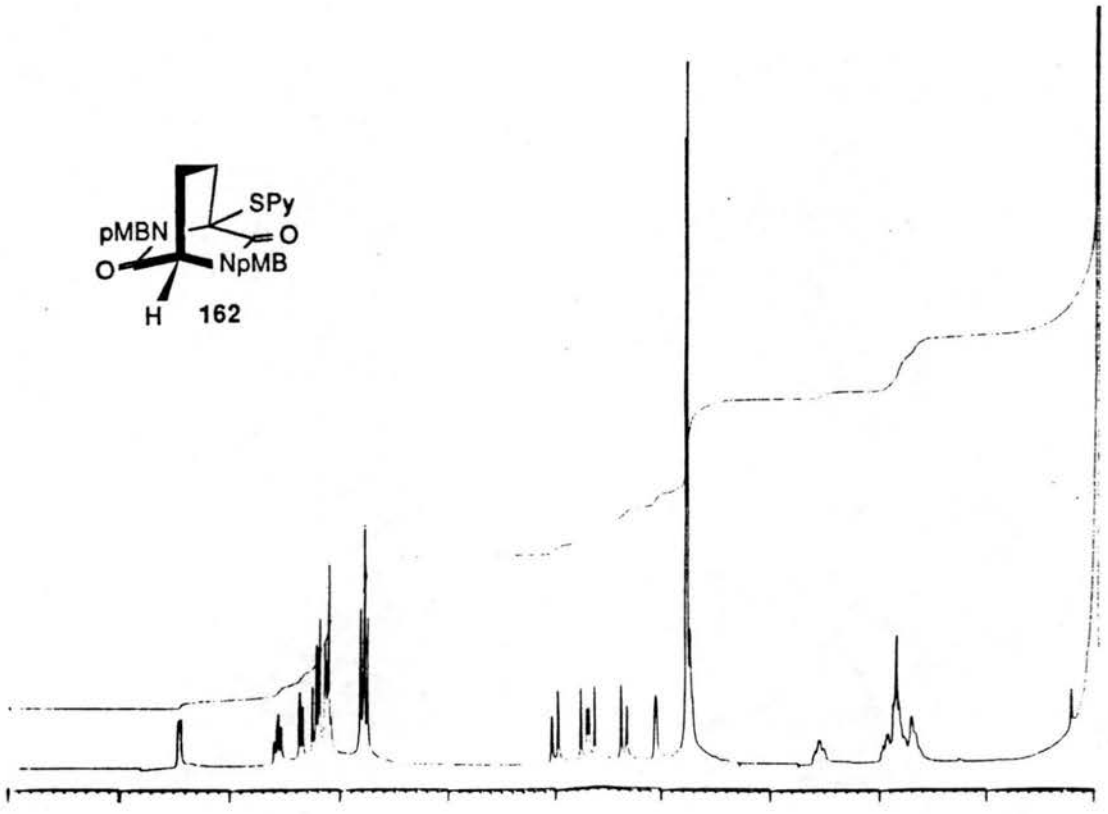
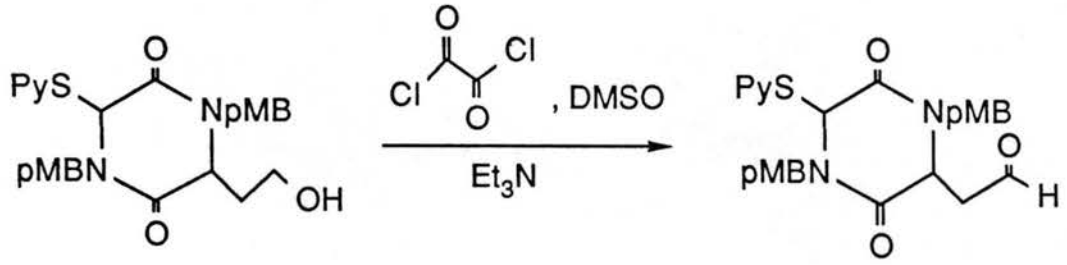


Figure 7. 270 MHz ^1H NMR of **162** in $CDCl_3$.

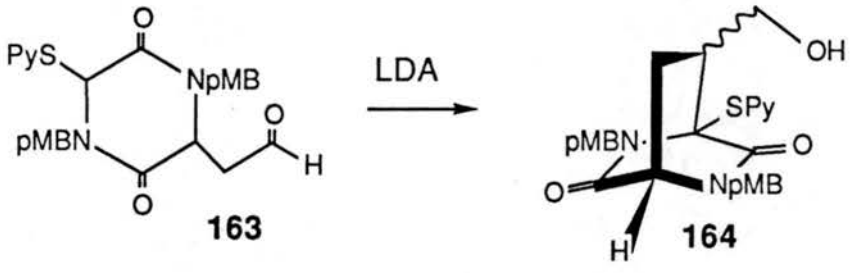


161 **163**

1,4-Bis-(*p*-methoxybenzyl)-3-)2'thiopyridyl)-6-(formylmethyl)-2,5-piperazinedione (163). To a stirred solution of oxalyl chloride (0.153 mL, 1.77 mmol, 1.5 equiv) in CH_2Cl_2 (15 mL) at -78°C was added DMSO (0.27 mL, 3.5 mmol, 3.0 equiv). This stirred for 25 min at which time the alcohol (600

mg, 1.18 mmol, 1.0 equiv) in CH_2Cl_2 (14 mL) was added. One hour later, Et_3N was added and the ice bath was removed. Stirring continued at 25°C for 3.5 h. The solvent was removed and the residue redissolved in THF, and the insoluble Et_3N•HCl salt filtered off. Separation was achieved by PTLC (silica gel) with 1:1 Hexane/EtOAc to afford 380 mg (64%) of product.

(163): ^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 3.02-3.04 (2 H, m), 3.81 (6 H, s), 4.02 (1 H, 1/2 ABq, J = 14.5 Hz), 4.29 (1 H, 1/2 ABq, J = 14.7 Hz), 4.57 (1 H, t, J = 5.8 Hz), 4.84 (1 H, 1/2 ABq, J = 14.7 Hz), 5.17 (1 H, 1/2 Abq, J = 14.5 Hz), 6.57 (1 H, s), 6.81-7.29 (10 H, m), 7.56-7.61 (1 H, m), 8.49-8.51 (1 H, m), 9.68 (1 H, s). IR (NaCl, neat) 2940, 2840, 1778, 1675, 1615, 1578, 1518, 1453, 1418, 1246, 1030 cm^{-1}. Mass spectrum, m/e (relative intensity): 505 (M^+, 1.1), 395 (11.8), 273 (9.0), 135 (9.2).



163 **164**

6,8-Bis(*p*-methoxybenzyl)-4-(2'-thiopyridyl)-3-hydroxy-6,8-diazabicyclo[2.2.20octane-5,7-dione (164). To a stirred solution of diisopropylamine (3 µl, .021 mmol, 1.2 equiv) in THF (0.5 mL) at -78°C was added *n*-BuLi (12.3 µl, .021 mmol, 1.2 equi., 1.7 M in hexane). The LDA formed over a period of 10 min and was then syringed into a solution of the aldehyde **163** (9 mg, .018 mmol, 1.0 equiv.) in 1 mL THF at -78°C. This was warmed to 25°C and stirred for 4.5 h. The reaction mixture was diluted with CH_2Cl_2, poured into water and exhaustively extracted with CH_2Cl_2. The extracts were combined and dried over Na_2SO_4. After filtering and concentrating, the

material was separated by PTLC (silica gel) eluted with 2:1 EtOAc/Hexanes to afford 3.3 mg of product (36%).

(164): ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 2.30-2.42 (2 H, m), 3.77 (3 H, s), 3.79 (3 H, s), 3.95 (1 H, m), 4.46 (1 H, 1/2 ABq, J = 14.5 Hz), 4.50 (1 H, m), 4.67 (1 H, 1/2 ABq, J = 15.6 Hz), 4.74 (1 H, 1/2 ABq, J = 14.5 Hz), 4.88 (1 H, 1/2 ABq, J = 15.6 Hz), 6.73-7.19 (9 H, m), 7.44-7.48 (1 H, m), 7.57-7.64 (1 H, m), 8.48-8.50 (1 H, m). IR (NaCl, neat) 2920, 1682, 1505, 1240, 1170, 1022 cm^{-1}. Mass spectrum, m/e (relative intensity) (CI, NH_3) 505 (M^+, 0.9), 473 (3.2), 136 (11.4), 112 (28.6), 35 (NH_3 + 18).

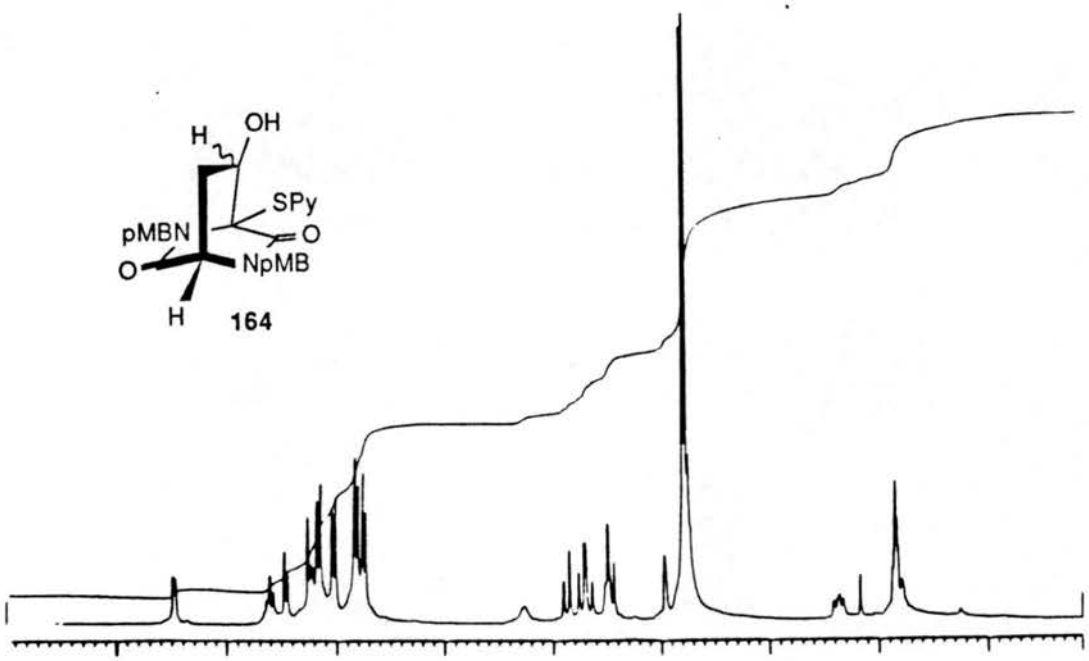
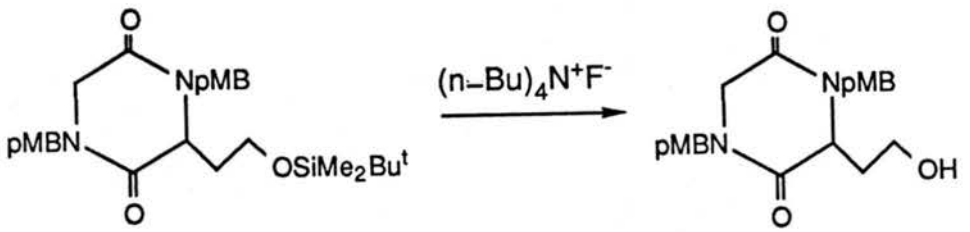


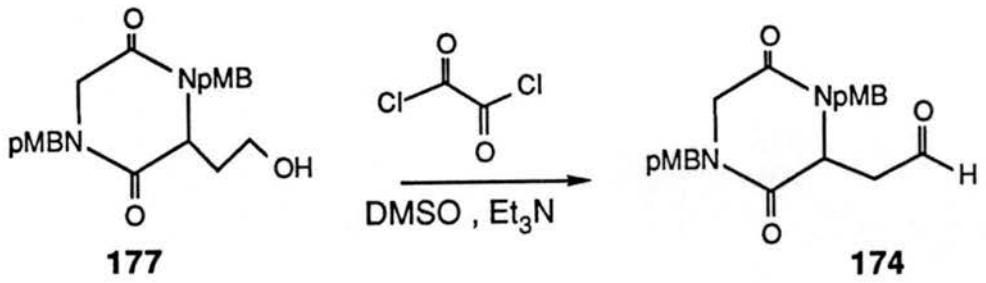
Figure 8. 270 MHz ^{1}H NMR of **164** in $CDCl_3$.



159 **177**

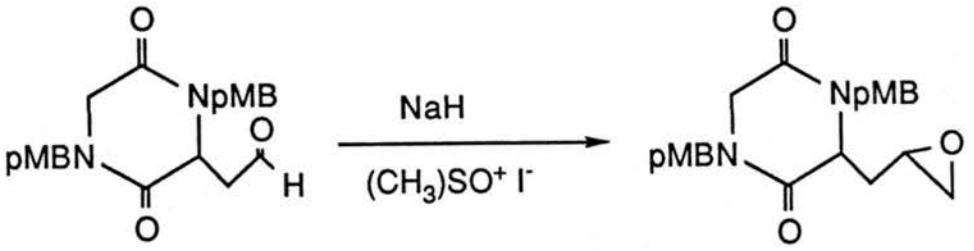
1,4-Bis(*p*-methoxybenzyl)-3-(2-hydroxyethyl)-2,5-piperazinedione (177). To the silyl ether **159** (4.0 g, 7.8 mmol, 1.0 equiv) in THF (45 mL) was added excess HF pyridine complex. After being stirred for 1 h at 25°C, the reaction mixture was poured into 0.1 N NaOH and extracted 3 times with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by flash chromatography (eluted with EtOAc) to afford 2.7 g (87%) of the alcohol.

(177): mp 131-132°C (recrystallized from EtOAc/hexanes). ^1H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$. 1.78-1.90 (1 H, m), 2.03-2.15 (1 H, m), 2.74 (1 H, s), 3.64 (2 H, m), 3.76 (6 H, s), 3.80-3.95 (3 H, m), 4.00-4.09 (1 H, m), 4.24 (1 H, 1/2 ABq, J = 14.32 Hz), 4.67 (1 H, 1/2 ABq, J = 14.32 Hz), 5.14 (1 H, 1/2 ABq, J = 14.68 Hz), 6.80-7.16 (8 H, m). IR (NaCl, neat): 3420, 3025, 2940, 1660, 1615, 1465, 1170 cm^{-1}. Anal. ($C_{22}H_{26}N_2O_5$) Calcd: C, 66.31; H, 6.58; N, 7.08. Found: C, 66.03; H, 6.44; N, 6.88.



1,4-Bis(*p*-methoxybenzyl)-3-(formylmethyl)-2,5-piperazine-dione (174). To a stirred solution of oxalyl chloride (0.89 mL, 10.2 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL) at -78°C was added DMSO (1.45 mL, 20.4 mmol, 3.0 equi.). After 30 min, the alcohol **177** (2.70 g, 6.8 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added at -78°C. After 1 h Et_3N (4.76 mL, 34.0 mmol, 5.0 equiv) was added and the cooling bath was removed. The reaction mixture was stirred for 15 min, concentrated, and redissolved in THF. The insoluble Et_3N•HCl salt was filtered off and the crude residue purified by flash chromatography (silica gel) (eluted 100% EtOAc) to yield 2.1 g (78%) of aldehyde **174**.

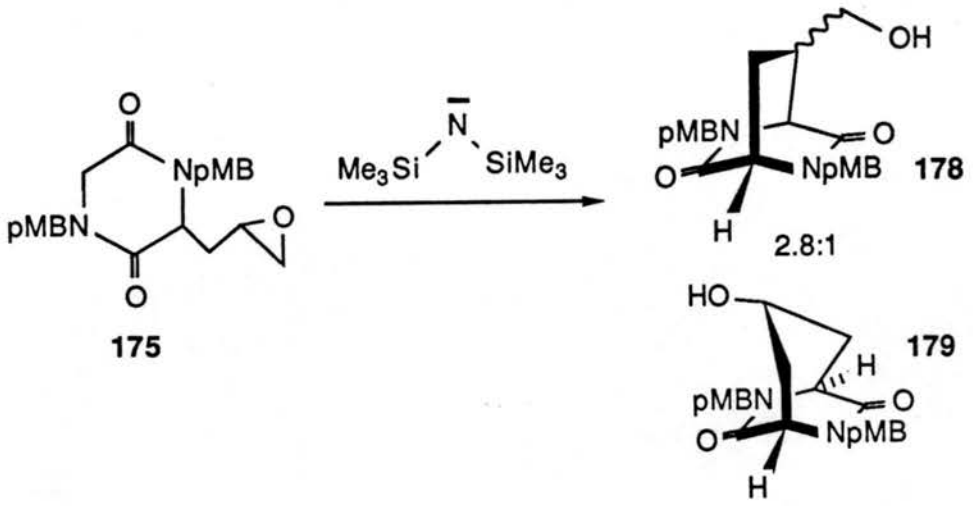
(174): mp 100-104°C (recrystallized from EtOAc/hexanes). ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 2.88-3.12 (3 H, m), 3.75 (3 H, s), 3.76 (3 H, s), 3.82 (1 H, 1/2 ABq, J = 17.15 Hz), 4.14 (1 H, s), 4.23 (1 H, 1/2 ABq, J = 14.94 Hz), 4.38 (1 H, 1/2 ABq, J = 14.38 Hz), 4.62 (1 H, 1/2 ABq, J = 14.38 Hz), 4.79 (1 H, 1/2 ABq, J = 14.94 Hz), 6.79-6.86 (4 H, m), 7.08-7.16 (4 H, m), 9.49 (1 H, s). IR (NaCl, neat): 1665, 1615, 1515, 1215, 750 cm^{-1}. Anal. ($C_{22}H_{24}N_2O_5$) Calcd: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.82; H, 6.20; N, 7.17.



174 **175**

1,4-Bis(*p*-methoxybenzyl)-3-(2',3'-epoxypropyl)-2,5-piperazinedione (175). NaH (15.4 mg, 0.320 mol, 1.2 equiv) was washed several times with hexane. To this was added trimethylsulfoxonium iodide (70.5 mg, 0.320 mmol, 1.2 equiv) and then DMSO (2 mL). After 20 min, the aldehyde **174** (106 mg, 0.267 mmol, 1.0 equiv) in DMSO (2.6 mL) was added to the ylide. The reaction mixture was stirred for 1 h and was then diluted with EtOAc and poured into water. After extracting several times with EtOAc, the combined organic extracts were washed with water two times and dried over $MgSO_4$. Filtration and concentration of the material yielded 100 mg (91%) of oil, which by ^1H NMR proved to be a clean, 1:1 mixture of diastereomeric epoxides **175**.

(175): ^1H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$: 1.80-1.89 (2 H, m), 2.03-2.12 (2 H, m), 2.33-2.36 (1 H, m), 2.39-2.42 (1 H, m), 2.59-2.62 (1 H, m), 2.69-2.73 (1 H, m), 2.78-2.86 (2 H, m), 3.76 (12 H, s), 3.79-4.09 (8 H, m), 4.19 (1 H, 1/2 ABq, J = 14.23 Hz), 4.36 (1 H, 1/2 ABq, J = 14.34 Hz), 4.60 (1 H, 1/2 ABq, J = 14.34 Hz), 4.78 (1 H, 1/2 ABq, J = 14.23 Hz), 5.10 (1 H, 1/2 ABq, J = 14.74 Hz), 5.18 (1 H, 1/2 ABq, J = 14.74 Hz), 6.80-7.18 (16 H, m). IR: 2930, 2835, 1665, 1610, 1583, 1510, 1460, 1240, 1170, 1025 cm^{-1}. Mass spectrum, m/e (relative intensity): 410 (M^+, 3.7), 354 (2.3), 289 (2.1), 121 (100).



6,8-Bis(*p*-methoxybenzyl)-3-(hydroxymethyl)-6,8-diaza-bicyclo[2.2.2]octane-5,7-dione (178) and 7,9-Bis(*p*-methoxybenzyl)-3-hydroxy-7,9-diazabicyclo[3.2.2]nonane-6,8-dione (179). To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.155 mL, 0.735 mmol, 5.5 equiv) at 0°C in THF (2.5 mL) was added *n*-BuLi (0.345 mL, 0.805 mmol, 6.0 equiv). After 20 min an aliquot of the lithium base (0.6 mL, 0.147 mmol, 1.1 equiv) was added to a solution of epoxides **175** (55 mg, 0.134 mmol, 1.0 equiv) in THF (1.0 mL) at 0°C. The reaction mixture was stirred at 0°C for 20 min and then at 25°C for an additional 2 h. The reaction mixture was then diluted with CH_2Cl_2, poured into water, and extracted with CH_2Cl_2 three times. The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by PTLC (silica gel) (eluted 2:1 EtOAc/hexanes) to afford **178** (24.6 mg of diastereomeric mixture) and **179** (8.9 mg), bicyclic alcohols, in a 2.8:1 ratio (combined yield 61%).

178 (single isomer of unassigned relative stereochemistry). mp: 98-100°C (diastereomeric mixture) (recrystallized from EtOAc/hexanes). ^{1}H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$: 1.82-1.91 (1 H, m), 2.13-2.18 (1 H, m), 3.15-3.21 (2 H, m), 3.35-3.39 (1 H, m), 3.72 (3 H, s), 3.74 (3 H, s), 3.92 (1 H, s), 4.09 (1 H, m),

4.24 (1 H, 1/2 ABq, J = 14.59 Hz), 4.42 (2 H, s), 4.48 (1 H, 1/2 ABq, J = 14.59 Hz), 6.76-7.16 (8 H, m). IR (NaCl, neat): 3410, 2925, 2830, 1655, 1580, 1480, 1210, 993 cm^{-1}. Anal. ($C_{23}H_{26}N_2O_5$) Calcd: C, 67.30; H, 6.39; N, 6.83. Found: C, 67.39; H, 6.20; N, 6.75.

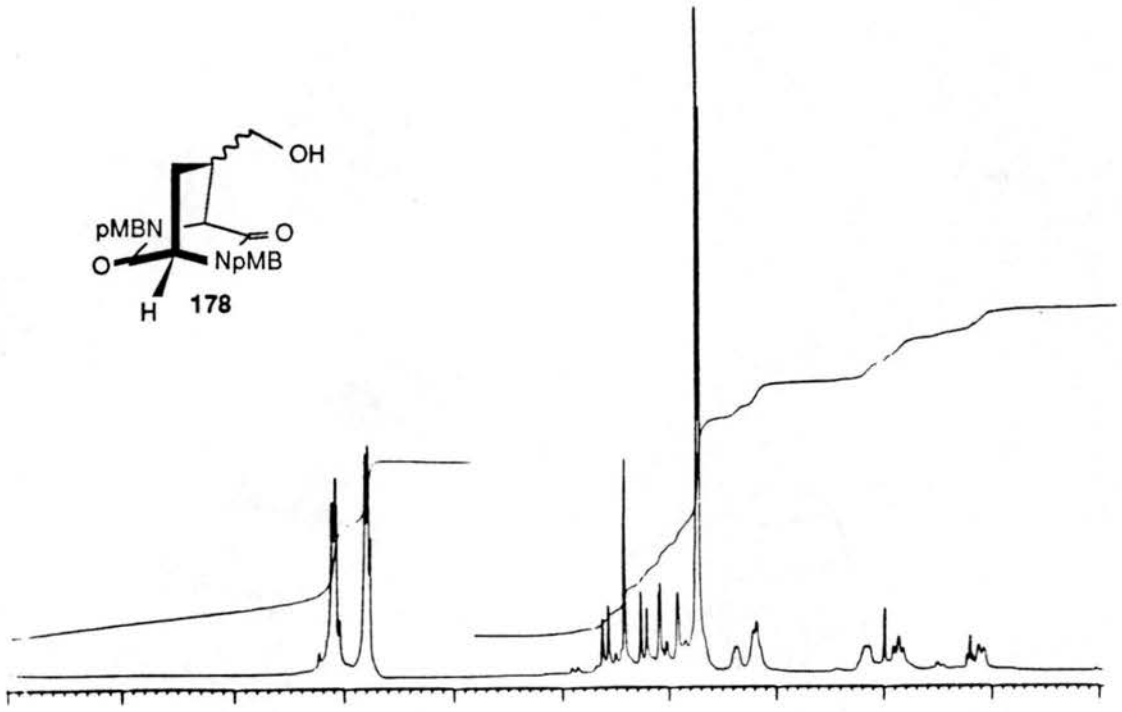


Figure 9. 270 MHz ^1H NMR of **178** (single isomer of unassigned relative stereochemistry) in $CDCl_3$, δ $CHCl_3$.

(179): mp: 145-147°C (recrystallized from EtOAc/hexanes). ^1H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$: 1.32-1.36 (1 H, m), 1.48-1.56 (1 H, m), 1.78-1.89 (1 H, m), 2.14-2.19 (1 H, m), 3.63-3.71 (1 H, m), 3.75 (6 H, s), 3.81-3.89 (1 H, m), 3.92-3.95 (1 H, m), 4.22 (1 H, 1/2 ABq, J = 14.66 Hz), 4.30 (1 H, 1/2 ABq, J = 14.38 Hz), 4.58 (1 H, 1/2 ABq, J = 14.66 Hz), 4.62 (1 H, 1/2 ABq, J = 14.66 Hz), 6.78-7.17 (8 H, m). IR (NaCl, neat): 3410, 2923, 1665, 1245 cm^{-1}. Anal. ($C_{23}H_{26}N_2O_5$) Calcd: C, 67.30; H, 6.39; N, 6.83. Found: C, 67.05; H, 6.37; N, 6.67.

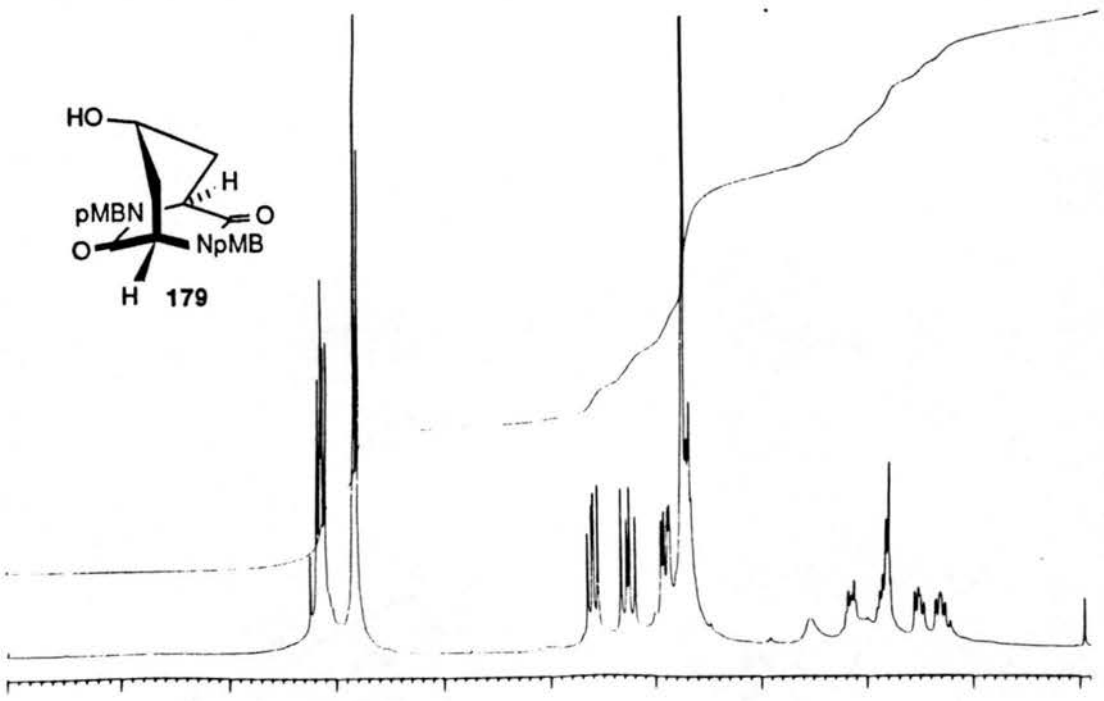
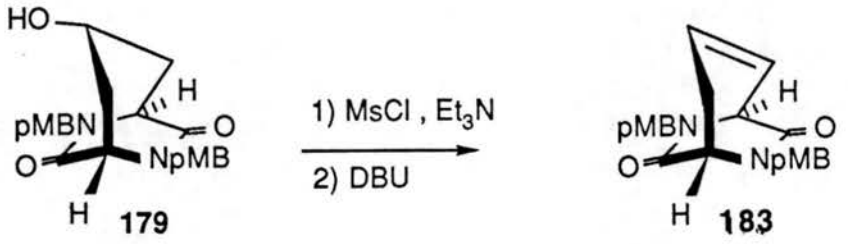


Figure 10. 270 MHz ^{1}H NMR of **179** in $CDCl_3$, δ $CHCl_3$



7,9-Bis(*p*-methoxybenzyl)-7,9-diazabicyclo[3.2.2]non-3-ene-6,8-dione (183). To a stirred solution of alcohol **179** (0.064 g, 0.157 mmol, 1.0 equiv) in THF (2.0 mL) at 0°C was added Et_3N (0.110 mL, 0.785 mmol, 5.0 equiv) and MsCl (0.024 mL, 0.314 mmol, 2.0 equiv). After 14 h the reaction mixture was filtered and washed with cold THF. After concentration and redissolution in toluene (5.0 mL), DBU (0.143 mL, 0.955 mmol, 5.0 equiv.) was added and the reaction mixture refluxed for 5 h. The mixture was then diluted

with CH_2Cl_2, poured into 0.1 N HCl, and exhaustively extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by PTLC silica gel (eluted EtOAc) yielded 30 mg (48.7% two-step yield) of olefin.

(183): mp 147-148°C (recrystallized from EtOAc/hexanes). ^1H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$: 1.98 (1 H, d, J = 19.34 Hz), 2.41 (1 H, d, J = 19.34 Hz), 3.76 (6 H, s), 3.96 (1 H, s), 3.98 (1 H, s), 4.38 (1 H, 1/2 ABq, J = 14.67 Hz), 4.40 (1 H, 1/2 ABq, J = 14.61 Hz), 4.55 (1 H, 1/2 ABq, J = 14.61 Hz), 4.65 (1 H, 1/2 ABq, J = 14.67 Hz), 5.51-5.55 (1 H, m), 5.86-5.94 (1 H, m), 6.80-7.15 (8 H, m). IR (NaCl, neat): 3048, 2935, 1695, 1675, 1615, 1510, 1452 cm^{-1}. Anal. ($C_{23}H_{24}N_2O_4$) Calcd: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.09; H, 6.28; N, 7.02.

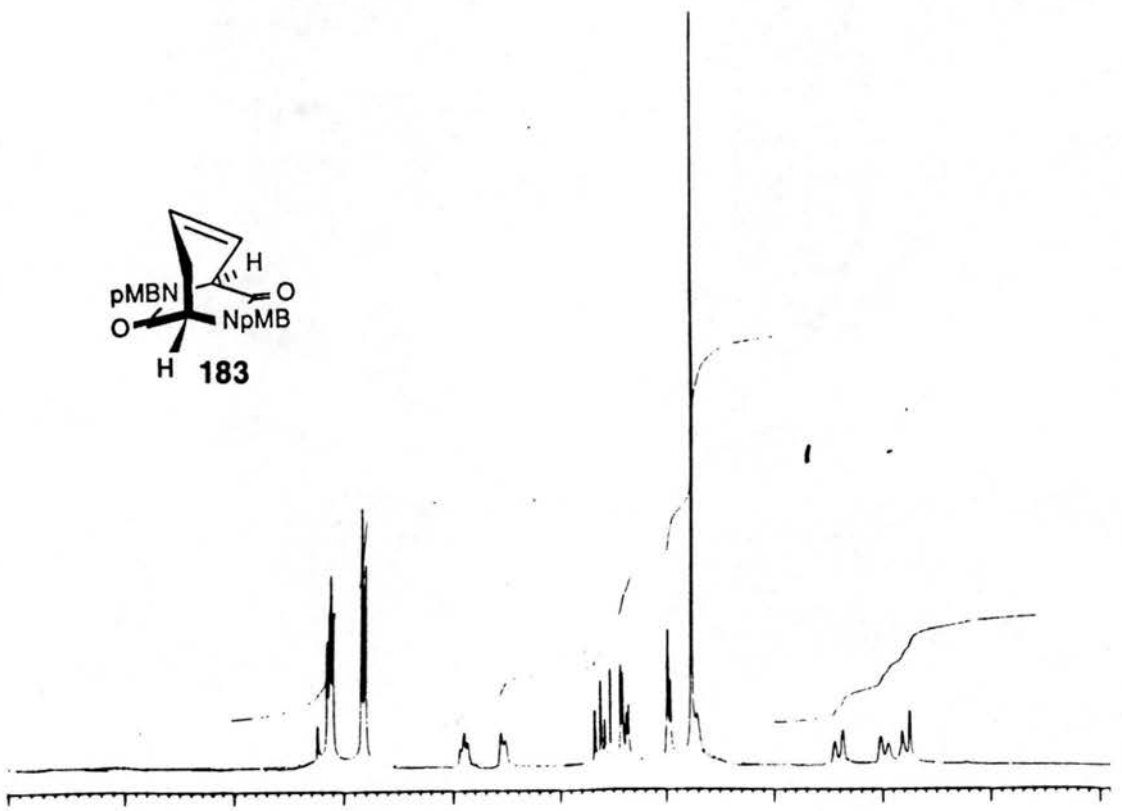


Figure 11. 270 MHz ^1H NMR of **183** in $CDCl_3$, δ $CHCl_3$

6,8-Bis(*p*-methoxybenzyl)-3-methylene-6,8-diazabicyclo-[2.2.2]octane-5,7-dione (182). To a stirred solution of alcohols **178** (0.260 g, 0.633 mmol, 1.0 equiv) in THF (10 mL) at 0°C was added Et_3N (0.354 mL, 2.53 mmol, 4.0 equiv) and then MsCl (0.098 mL, 1.27 mmol, 2.0 equiv). After 2 h the reaction was filtered and washed with cold THF. After concentration and redissolution in toluene (6.0 mL), DBU (0.283 mL, 1.90 mmol, 5.0 equiv) was added and the reaction mixture refluxed for 17 h. The mixture was then diluted with CH_2Cl_2, poured into 0.1 N HCl, and exhaustively extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (silica gel) (eluted with 2:1 EtOAc/hexanes) yielded 110 mg of olefin **182** (44% two-step yield).

(182): mp 117-118°C (recrystallized from ETOAc/hexanes). ^1H NMR (270 MHz, $CDCl_3$) δ $CHCl_3$: 2.22-2.47 (2 H, m), 3.73 (3 H, s), 3.74 (3 H, s), 3.96 (1 H, s), 4.18 (1 H, s), 4.23 (1 H, 1/2 ABq, J = 14.62 Hz), 4.44 (2 H, s), 14.60 (1 H, 1/2 ABq, J = 14.62 Hz), 4.87 (1 H, s), 4.99 (1 H, s), 6.77-7.13 (8 H, m). IR (NaCl, neat): 2923, 2825, 1690, 1605, 1503, 1437, 1240, 1021 cm^{-1}. Anal. ($C_{23}H_{24}N_2O_4$) Calcd: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.21; H, 5.87; N, 7.09.

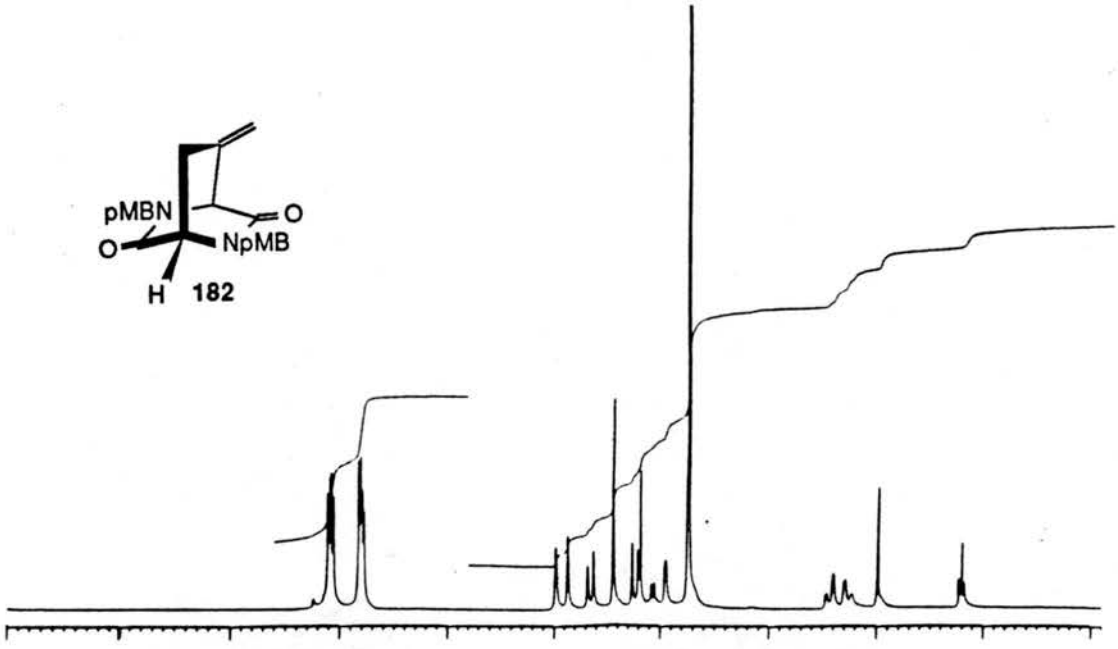
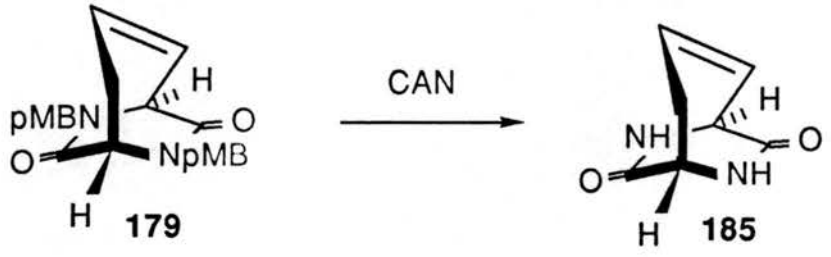


Figure 12. 270 MHz ^1H NMR of **182** in $CDCl_3$, δ $CHCl_3$



7,9-Diazabicyclo[3.2.2]non-3-ene-6,8-dione. **185** (30 mg, .076 mmol, 1.0 equiv) was dissolved in a 10:1 solution of acetonitrile/water (220 μl). To this was added $(NH_4)_2Ce(NO_3)_6$ (168 mg, 0.306 mmol, 4.0 equiv) and the reaction mixture was stirred for 2 h at 25°C. The reaction mixture was diluted with methanol and separated by PTLC (silica gel) eluted with 20% MeOH/$CHCl_3$ to afford 10 mg (87%) of **185**.

(185): mp 245°C (dec) (recrystallized from EtOH). ^1H NMR (270 MHz) (D_2O) (DSS as external ref.) 2.45-2.67 (2 H, m), 3.72 (1 H, t, J = 6.5 Hz), 4.00-4.08 (1 H, m), 5.84-5.91 (1 H, m), 6.17-6.26 (1 H, m); IR (KBr): 3240, 2400,

1670. Anal. ($C_7H_8N_2O_2$). Calcd: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.50; H, 5.59; N, 18.52.

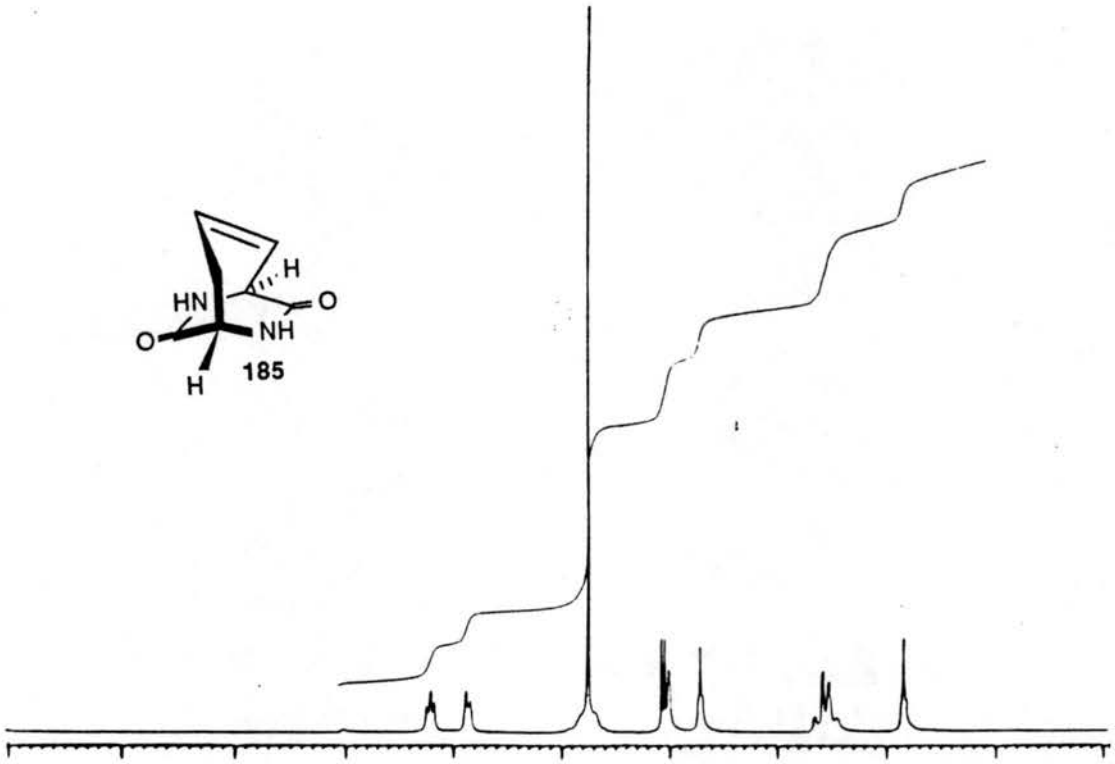
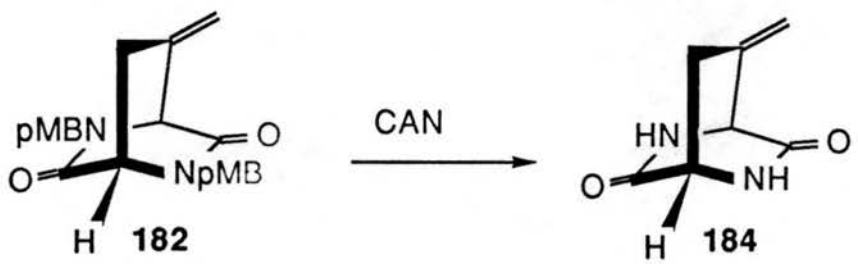


Figure 13. 270 MHz ^{1}H NMR of **185** in D_2O, DSS as external reference



3-Methylene-6,8-diazabicyclo-[2.2.2]octane-5,7-dione (184). **182** (82 mg, 0.209 mmol, 1.0 equiv) was dissolved in an acetonitrile/water solution (2:1, 600 µl). To this was added $(NH_4)_2Ce(NO_3)_6$ (458 mg, 0.836 mmol, 4.0 equiv) and the reaction mixture stirred for 2.5 h at 25°C. The reaction

mixture was diluted with methanol and purified by PTLC (silica gel) eluted with 25% MeOH/$CHCl_3$ to afford 16.4 mg (52%) of **184**.

(184): ^1H NMR (270 MHz) (D_2O) δ DSS: 2.63-2.85 (2 H, m), 4.19 (1 H, br.s), 4.44 (1 H, s), 5.23 (1 H, m), 5.42 (1 H, m); IR (KBr) 3420, 3230, 1685 cm^{-1}. Mass spectrum, m/e (relative intensity) 152 (M=, 23.2), 109 (41), 80 (100), 28 (57).

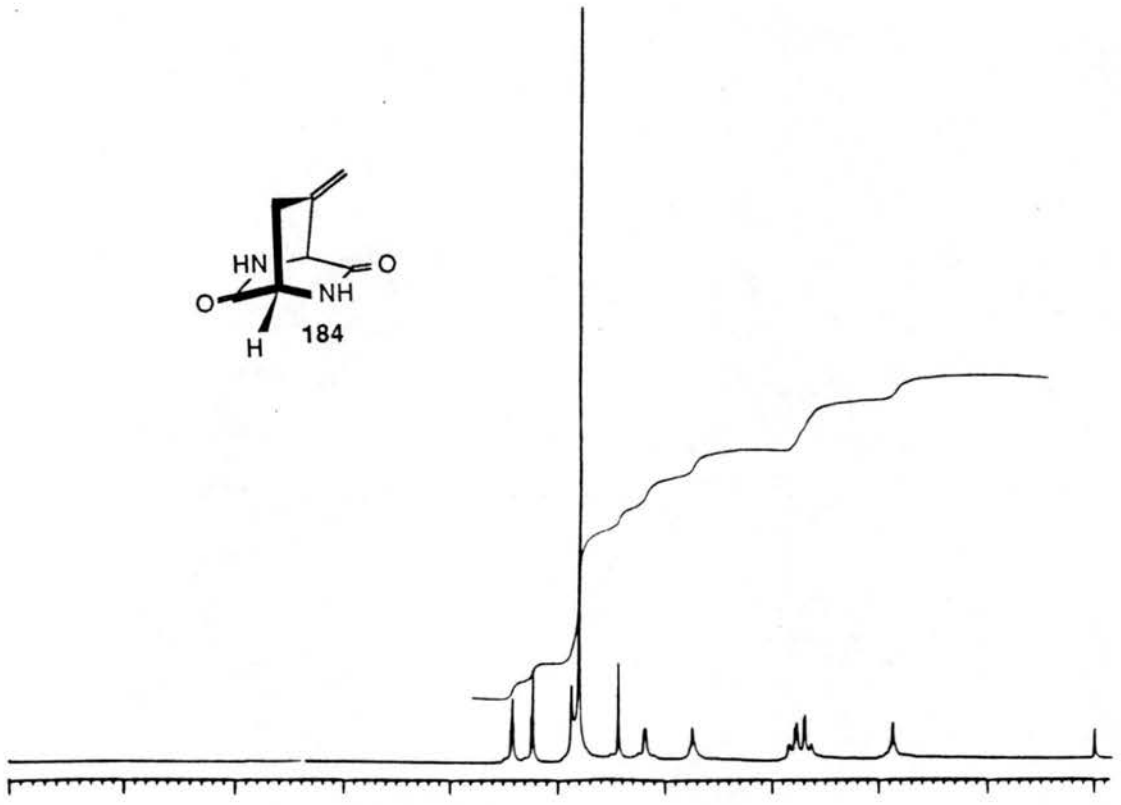
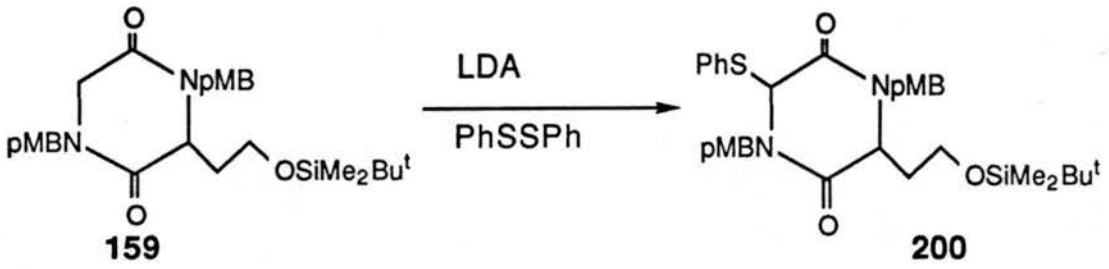


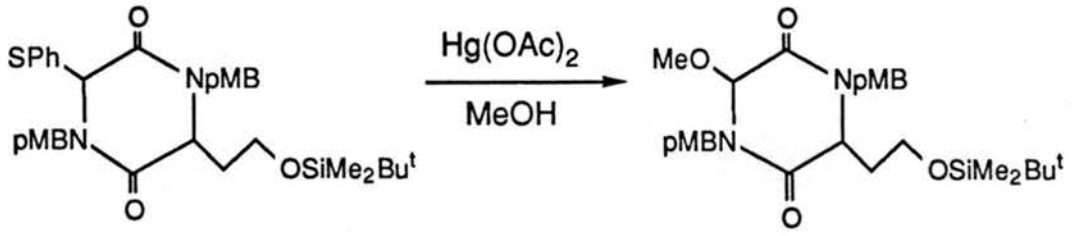
Figure 14. 270 MHz ^1H NMR of **184** in D_2O, δ DSS



159 **200**

1,4-*Bis*(*p*-methoxybenzyl)-3-(2'-thiophenyl)-6-[2-((*tert*-butyldimethylsilyl)oxy)ethyl]-2,5-piperazinedione (200). LDA was generated by adding *n*-BuLi (14.4 mL, 24.8 mmol, 1.1 equiv) to a solution of diisopropylamine (3.5 mL, 24.8 mmol, 1.1 equiv) in THF (125 mL) at -78°C. After 30 min, the LDA was added to a solution of **159** (11.54 g, 22.5 mmol, 1.0 equiv) in THF (250 mL) at -78°C. This stirred for 2 h and was then added to a solution of diphenyldisulphide (6.4 g, 29.2 mmol, 1.3 equiv) in THF (150 mL) at -78°C. The reaction mixture was stirred at -78°C for 45 min and then at 25°C for an additional 45 min. It was then diluted with CH_2Cl_2, poured into water and extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was separated by silica gel flash chromatography (eluted 2:1 Hexanes/EtOAc) to yield 10.9 g (82%) of product **200**.

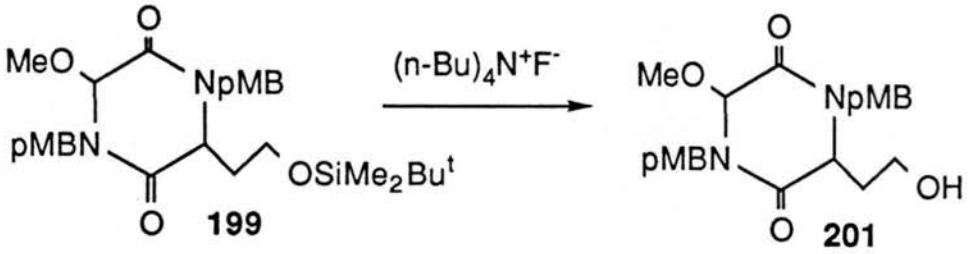
(200): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 0.17 (6 H, s), 0.99 (9 H, s), 2.05 (2 H, m), 3.81 (3 H, s), 3.85 (3 H, s), 3.93-3.98 (3 H, m), 4.04 (1 H, 1/2 ABq, J = 14.5 Hz), 4.19 (1 H, t, J = 6.6 Hz), 4.97 (1 H, s), 5.24 (1 H, 1/2 ABq, J = 14.5 Hz), 5.37 (1 H, 1/2 ABq, J = 14.5 Hz), 6.74-7.68 (13 H, m). IR (NaCl, neat) 3030-2815 bm, 1675, 1510, 1450 cm^{-1}. Mass spectrum, m/e (relative intensity) (CI NH_3): 620 (M^+, 2.4), 512 (43.3), 121 (36.1), 35 (100).



200 **199**

1,4-*Bis*(*p*-methoxybenzyl)-3-(2'-oxymethyl)-6-{2-[(*tert*-butyldimethylsilyl)-oxy]ethyl}-2,5-piperazinedione, (199). To a solution of **200** (48 mg, 0.081 mmol, 1.0 equiv) in methanol (2 mL) was added mercuric acetate (25.8 mg. 0.081 mmol, 1.0 equiv). The reaction mixture stirred for 1.5 h at 25°C and was then concentrated. The residue was redissolved in CH_2Cl_2 and separated by PTLC (silica gel) eluted 2:1 Hexanes/EtOAc to yield 36 mg (86%) of product **199**. mp 79.5-80°C (recrystallized THF/Hexanes)

(199): ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 0.02 (6 H, s), 0.88 (9 H, s), 2.00-2.27 (2 H, m), 3.35 (3 H, s), 3.58-3.70 (2 H, m), 3.81 (6 H, s), 3.87 (1 H, 1/2 ABq, J = 14.7 Hz), 4.08 (1 H, 1/2 ABq, J = 14.0 Hz), 4.08 (1 H, m), 4.85 (1 H, s), 5.20 (1 H, 1/2 ABq, J = 14.0 Hz), 5.50 (1 H, 1/2 ABq, J = 14.7 Hz), 6.85-7.31 (8 H, m). IR (neat) 2830-2995, 1663, 1512, 1244 cm^{-1}. Anal. ($C_{29}H_{42}N_2O_6Si$). Calcd: C, 64.17; H, 7.80; N, 5.16. Found: C, 64.15; H, 7.70; N, 5.21.



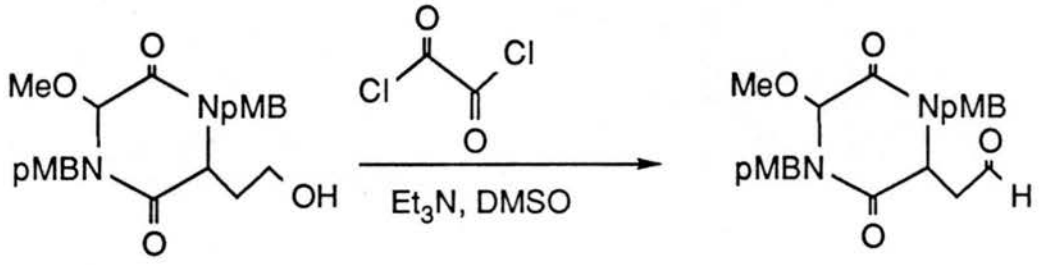
199 **201**

1,4-*Bis*(*p*-methoxybenzyl)-3-(2'-oxymethyl)-6-(2-hydroxyethyl)-2,5-piperazinedione (201). To a stirred solution of **199** (123 mg,

0.239 mmol, 1.0 equiv) in THF (8.0 mL) was added *tetra*-butylammonium fluoride (83 mg, 0.263 mmol, 1.1 equiv). The reaction mixture stirred for 2 h at 25°C. It was then diluted with CH_2Cl_2, poured into water and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. Separation by PTLC (silica gel) (eluted 2:1 EtOAc/Hexanes) afforded two diastereomeric alcohols (120 mg, 99%).

(201) Isomer A: mp 125-128°C (recrystallized EtOAc/Hexanes) ^{1}H NMR (200 MHz) ($CDCl_3$) δ TMS: 1.97-2.07 (1 H, m), 2.29-2.35 (1 H, m), 3.35 (3 H, s), 3.63 (2 H, br.s), 3.78 (3 H, s), 3.80 (1 H, m), 3.80 (3 H, s), 4.03 (1 H, 1/2 ABq, J = 14.0 Hz), 4.06 (1 H, br.s), 4.83 (1 H, s), 5.22 (1 H, 1/2 ABq, J = 14.0 Hz), 5.44 (1 H, 1/2 ABq, J = 14.7 Hz), 6.84-7.29 (8 H, m). IR (KBr): 3440, 2938, 2838, 1653, 1513, 1240 cm^{-1}. Anal. ($C_{23}H_{28}N_2O_6$). Calcd: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.28; H, 6.42; N, 6.61.

(201) Isomer B: ^{1}H NMR (200 MHz) ($CDCl_3$) δ TMS: 1.99-2.30 (2 H, m), 3.50 (3 H, s), 4.73 (2 H, br.s), 3.80 (3 H, s), 3.81 (3 H, s), 3.96 (1 H, 1/2 ABq, J = 14.5 Hz), 4.03-4.10 (1 H, m), 4.17 (1 H, 1/2 ABq, J = 14.6 Hz), 4.61 (1 H, s), 5.01 (1 H, 1/2 ABq, J = 14.5 Hz), 5.11 (1 H, 1/2 ABq, J = 14.6 Hz), 6.83-7.28 (8 H, m). IR (NaCl, neat): 3440, 2925, 2825, 1665, 1503, 1452, 1242 cm^{-1}. Mass spectrum, m/e (relative intensity): 396 (10.1), 121 (100), 32 (66.4), 28 (100).



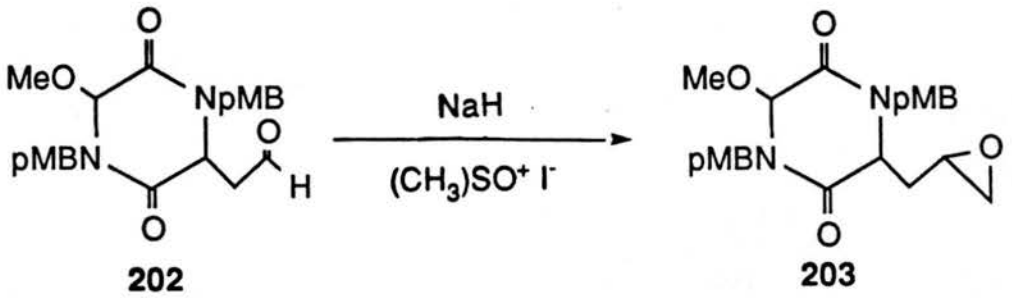
201 **202**

1,4-*Bis*(*p*-methoxybenzyl)-3-(2'-oxymethyl)-6-(formylmethyl-2,5-piperazinedione (202). To a stirred solution of DMSO (0.912 mL, 12.8

mmol, 5.0 equiv) in CH_2Cl_2 (40 mL) at -78°C was added oxalyl chloride (0.379 mL, 4.36 mmol, 1.7 equiv). This stirred for 0.5 h and then diastereomeric alcohols (1.10 g, 2.57 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) were added at -78°C by cannula. After 3 h, Et_3N was added to the reaction mixture and the cold bath removed. The reaction mixture was stirred for an additional 1.5 h at 25°C and then concentrated. The residue was taken up in THF and filtered. Separation by PTLC (silica gel) (eluted 1:1 EtOAc/Hexanes) yielded 0.877 g (80%) of aldehyde as a mixture of diastereomers which could be separated by recrystallization from CH_2Cl_2/Hexanes.

(202) Isomer A: (solid) mp 133-135°C (recrystallized CH_2Cl_2/Hexanes) ^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.99-3.23 (2 H, m), 3.44 (3 H, s), 3.79 (3 H, s), 3.80 (3 H, s), 4.07 (1 H, 1/2 ABq, J = 15.6 Hz), 4.13 (1 H, 1/2 ABq, J = 14.5 Hz), 4.26 (1 H, br.s), 4.88 (1 H, s), 5.10 (1 H, 1/2 ABq, J = 15.6 Hz), 5.19 (1 H, 1/2 ABq, J = 14.5 Hz), 6.84-7.26 (8 H, m), 9.54 (1 H, s). IR (NaCl, neat): 1740, 1667, 1575, 1450, 1245 cm^{-1}. Anal. ($C_{23}H_{26}N_2O_6$). Calcd: C, 64.79; H, 6.14; N, 6.57. Found: C, 64.52; H, 5.95; N, 6.55.

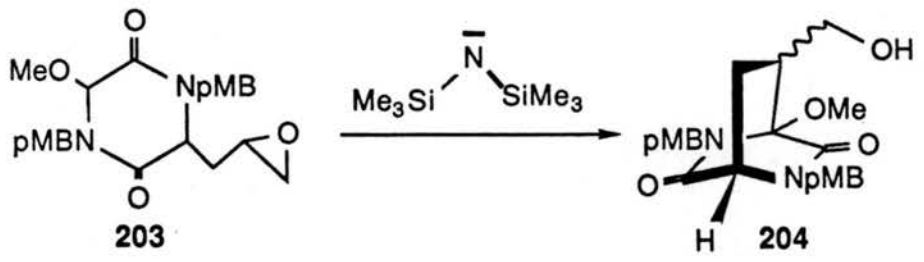
(202) Isomer B: (oil) ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 2.98 (2 H, d, J = 6.1 Hz), 3.44 (3 H, s), 3.77 (3 H, s), 3.78 (3 H, s), 4.07 (1 H, 1/2 ABq, J = 14.7 Hz), 4.10 (1 H, 1/2 ABq, J = 14.6 Hz), 4.48 (1 H, t, J = 6.1 Hz), 4.57 (1 H, s), 4.94 (1 H, 1/2 ABq, J = 14.7 Hz), 4.98 (1 H, 1/2 ABq, J = 14.6 Hz), 6.82-7.17 (8 H, m), 9.68 (1 H, s). IR (NaCl, neat): 1728, 1674, 1515, 1244 cm^{-1}. Mass spectrum, m/e (relative intensity) (CI, NH_3): 427 (M^+ + 1, 4.9), 394 (5.9), 121 (12), 35 (100), 32 (30.6).



202 **203**

1,4-Bis(*p*-methoxybenzyl)-3-(2'-oxymethyl)-6-(2,3-epoxypropyl)-2,5-piperazinedione (203). NaH (69 mg, 1.43 mmol, 1.2 equiv) was washed with three portions of hexane. To this was added trimethylsulfoxonium iodide (314 mg, 1.43 mmol, 1.2 equiv) and DMSO (8 mL). After 30 min, a single diastereomer of the aldehyde ( ) (510 mg, 1.19 mmol, 1.0 equiv) in DMSO (11 mL) was added by cannula to the ylide. The reaction mixture was stirred for 1.2 h then diluted with EtOAc and poured into water. The organic layer was washed three times with water and then dried over $MgSO_4$, filtered, and concentrated. Purification by PTLC (silica gel) afforded a roughly 2:1 diastereomeric mixture (by NMR) of epoxides which were inseparable (215 mg, 41%).

(203): ^1H NMR (270 MHz) ($CDCl_3$) δ TMS: (Major isomer only) 2.13 (1 H, d, J = 6.1 Hz), 2.15 (1 H, d, J = 6.5 Hz), 2.48-2.51 (1 H, m), 2.77-2.82 (1 H, m), 3.03-3.08 (1 H, m), 3.45 (3 H, s), 3.77 (3 H, s), 3.78 (3 H, s), 3.93 (1 H, 1/2 ABq, J = 14.8 Hz), 3.97 (1 H, m), 4.12 (1 H, 1/2 ABq, J = 14.6 Hz), 4.58 (1 H, s), 5.00 (1 H, 1/2 ABq, J = 14.6 Hz), 5.20 (1 H, 1/2 ABq, J = 14.8 Hz), 6.81-7.15 (8 H, m). IR (NaCl, neat): 1667, 1503, 1451, 1242 cm^{-1}. Mass spectrum, m/e (relative intensity) (CI, NH_3): 440 (M^+, 11.3), 121 (20.2), 35 (100), 32 (25.7).



6,8-Bis(*p*-methoxybenzyl)-1-(oxymethyl)-3-(hydroxymethyl)-6,8-diazabicyclo[2.2.2]oxtane-5,7-dione (204). To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.081 mL, 0.389 mmol, 1.1 equiv) in THF (3.5 mL) at 0°C was added *n*-BuLi (0.247 mL, 0.425 mmol, 1.2 equiv). After 25 min, the lithium base was added to a solution of epoxides **203** (156 mg, 0.354 mmol, 1.0 equiv) at 0°C in THF (5.0 mL). The reaction mixture stirred at 0°C for 1.5 h and was worked up without warming to room temperature. The reaction mixture was diluted with CH_2Cl_2, poured into water and thoroughly extracted with CH_2Cl_2. The organic extracts were combined and dried over Na_2SO_4, filtered and concentrated. Separation by PTLC (silica gel) (eluted 2:1 EtOAc/Hexanes) afforded 14 mg (10%) of a single diastereomeric alcohol **204**.

(204): ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.20-1.25 (1 H, m), 1.59-1.69 (1 H, m), 1.98-2.04 (1 H, m), 2.95-2.98 (1 H, m), 3.13-3.21 (1 H, m), 3.44 (3 H, s), 3.76 (3 H, s), 3.78 (3 H, s), 3.85 (1 H, 1/2 ABq, J = 15.5 Hz), 4.21 (1 H, 1/2 ABq, J = 14.8 Hz), 4.86 (1 H, s), 5.00 (1 H, 1/2 ABq, J = 14.8 Hz), 5.17 (1 H, 1/2 ABq, J = 15.5 Hz), 6.76-7.16 (8 H, m). IR (NaCl, neat): 1675, 1512, 1452, 1410, 1248, 1025. Mass spectrum, m/e (relative intensity) (CI, NH_3): 440 (M^+, 3.9), 408 (16.8), 121 (47.3), 35 (100), 32 (25.6).

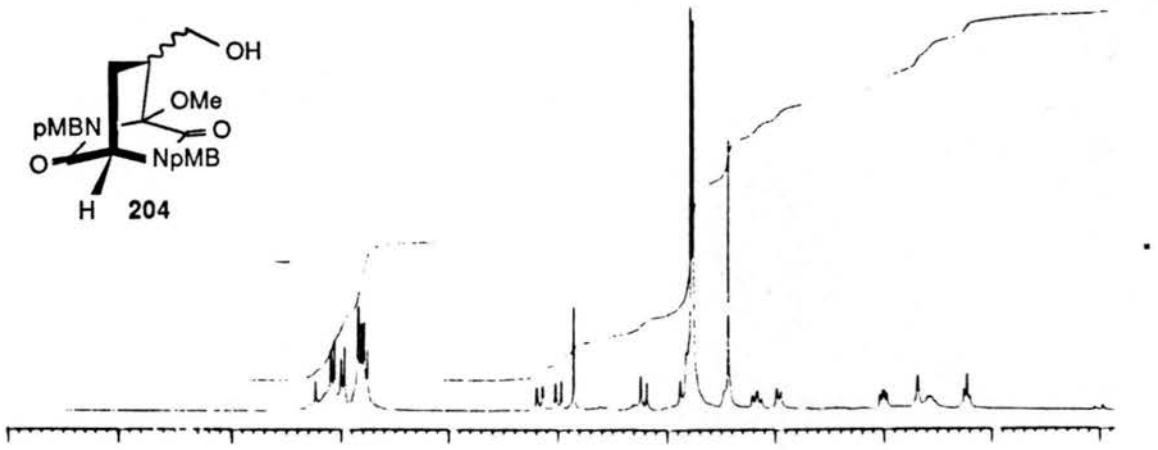
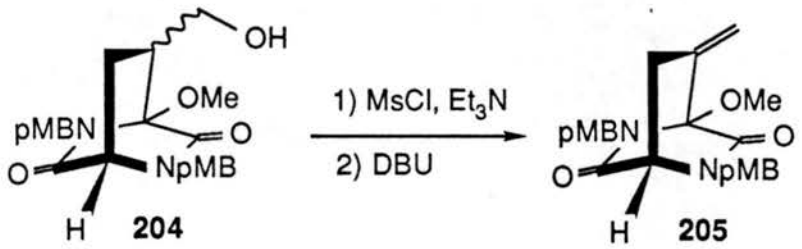


Figure 13. 270 MHz ^1H NMR of **204** in $CDCl_3$, δ $CHCl_3$



6,8-Bis(*p*-methoxybenzyl)-1-(oxymethyl)-3-methylene-6,8-diazabicyclo-[2.2.2]octane-5,7-dione (205). To a stirred solution of alcohol **204** (14 mg, 0.034 mmol, 1.0 equiv) in THF (1 mL) at 0°C was added Et_3N (0.019 mL, 0.136 mmol, 4.0 equiv) and MsCl (0.005 mL, 0.068 mmol, 2.0 equiv). After 2 h the reaction was filtered and washed with cold THF. After concentration and redissolution in toluene (1.0 mL) DBU (0.025 mL, 0.170 mmol, 5.0 equiv) was added and the reaction mixture was refluxed for 4 h. The reaction mixture was then concentrated and the residue redissolved in CH_2Cl_2. Separation by PTLC (silica gel) (eluted 2:1 Hexanes/EtOAc) afforded 3 mg (21%) of olefin **205**.

(205): ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.39 (1 H, t, J = 7.1 Hz), 2.11 (1 H, dd, J = 9.5 Hz, J_2 = 7.1 Hz), 2.99 (1 H, dd, J_1 = 11.8 Hz, J_2 = 9.5 Hz), 3.39 (3 H, s), 3.66 (1 H, dd, J_1 = 11.8 Hz, J_2 = 5.8 Hz), 3.77 (3 H, s), 3.78 (3 H, s), 3.92 (1 H, 1/2 ABq, J = 15.3 Hz), 4.15 (1 H, 1/2 ABq, J = 14.8 Hz), 4.75 (1 H, s), 4.98 (1 H, 1/2 ABq, J = 14.8 Hz), 5.07 (1 H, 1/2 ABq, J = 15.3 Hz), 6.78-7.10 (8 H, m). IR (NaCl, neat): 2930, 2835, 1680, 1615, 1515, 1247. Mass spectrum, m/e (relative intensity): 422 (M^+, 2.5), 121 (66.5), 32 (34.4), 28 (100).

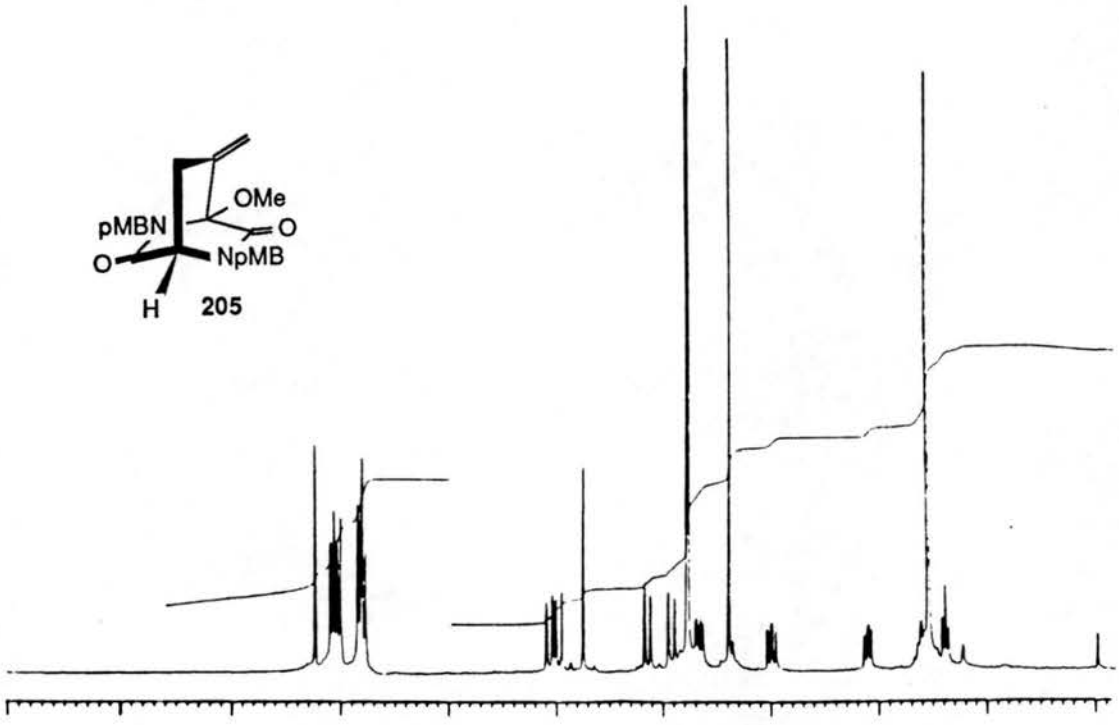


Figure 14. 270 MHz ^{1}H NMR of **205** in $CDCl_3$ δ $CHCl_3$

REFERENCES

1. Miyoshi, T.; Miyairi, N.; Aoki, H.; Kohsaka, M.; Imanaka, H. *J. Antibiot.*, **1972**, *25*, 569-575.

2. Miyamura, S.; Ogasawara, N.; Otsuka, H.; Niwayama, S.; Tanaka, H.; Take, T.; Uchiyama, T.; Ochiai, H.; Abe, K.; Koizumi, K.; Asao, K.; Matsuki, K.; Hoshino, T. *J. Antibiot.*, **1972**, *25*, 610-612.

3. Kamiya, T.; Maeno, S.; Hashimoto, M.; Mine, Y. *J. Antibiot.*, **1972**, *25*, 576-581.

4. Tokuma, Y.; Koda, S.; Miyoshi, T.; Morimoto, Y. *Bull. Chem. Soc. Jpn.*, **1974**, *47*, 18-23.

5. (a) Ritchie, R.; Saxton, J.E. *Tetrahedron*, **1981**, *37*, 4295-4303. (b) Birch, A.J.; Russell, R.A.*Tetrahedron*, **1972**, *28*, 2999-3008.

6. Fukuyama, T. Ph.D. Thesis, Department of Chemistry, Harvard University, 1977.

7. Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, H.; Imanaka, H. *J. Antibiot.*, **1976**, *29*, 155-167.

8. Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.*, **1978**, *31*, 712-718.

9. Hirota, Y.; Suzuki, H.; Nishimura, Y.; Yasuda, S. *Proc. Natl. Acad. Sci., U.S.A.*, **1977**, *74*, 1417-1420.

10. Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.*, **1979**, *32*, 402-407.

11. Mueller, B.W.; Zak, O.; Kump, W.; Tosch, W.; Wacker, O. *J. Antibiot.*, **1979**, *32*, 689-705.

12. Williams, R.M.; Armstrong, R.W.; Dung, J.-S. *J. Med. Chem.*, **1981**, *28*, 733-740.

13. Williams, R.M.; Tomizawa, K.; Armstrong, R.W.; Dung, J.-S. *J. Am. Chem. Soc.*, **1987**, *109*, 4028-4035.

14. (a) Burgi, H.B.; Dunitz, J.D.; Lehn, J.M.; Wipff, G. *Tetrahedron*, **1974**, *30*, 1563-1572. (b) Burgi, H.B.; Dunitz, J.D.; Shefler, E. *J. Am. Chem. Soc.*, **1973**, *95*, 5065-5067.

15. Pisabarro, A.G.; Cañada, F.J.; Vazquez, D.; Arriaga, P.; Rodriguez-Tebar, A. *J. Antibiot.*, **1986**, *39*, 914-921.

16. Armstrong, R.W. Ph.D. Thesis, Chemistry Department, Colorado State University, 1984.

17. Williams, R.M.; Durham, C.A. *Chem. Rev.*, in press.

18. Maag, H.; Blount, J.F.; Coffen, D.L.; Steppe, T.V.; Wong, F. *J. Am. Chem. Soc.*, **1978**, *100*, 6786-6788.

19. Williams, R.M.; Armstrong, R.W.; Dung, J.-S. *J. Am. Chem. Soc.*, **1985**, *107*, 3253-3266.

20. (a) Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.*, **1983**, *24*, 5627-5630. (b) Nakatsuka, S.; Goto, T. *Heterocycles*, **1984**, *21*, 61-73.

21. Wacker, O.; Kump, W.; Müeller, B.W. *Tetrahedron Lett.*, **1983**, *24*, 5607-5610.

22. Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.*, **1983**, 1001.

23. (a) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.*, **1984**, 2157-2158. (b) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Shin, C. *Bull. Chem. Soc., Jpn.*, **1985**, *58*, 2812-2820.

24. Dawson, I.M.; Gregory, J.A.; Herbert, R.B.; Sammes, P.G. *J. Chem. Soc., Chem. Commun.*, **1986**, 620-621.

25. In the process of adhering to the limitations involved in representing a large number of compounds in one scheme and in an effort to maintain clarity, it was unavoidable that compounds **83** and **91** were named twice, having previously been designated as **46** and **47** (Scheme 13) respectively.

26. For a review, see Hart, D.J. *Science*, **1984**, *223*, 883-887.

27. Kozar, L.G.; Clark, R.D.; Heathcock, C.H. *J. Org. Chem.*, **1977**, *42*, 1386-1389.

28. Sera, A.; Itoh, K.; Yamada, H.; Aoki, R. *Heterocycles*, **1984**, *22*, 713-716.

29. (a) Chan, T.H.; Mychajlowskij, W.; Ong, B.S.; Harpp, D.N. *J. Organomet. Chem.*, **1976**, *107*, C1-C4. (b) Chan, T.H.; Mychajlowskij, W.; Ong, B.S.; Harpp, D.N. *J. Org. Chem.*, **1978**, *43*, 1526-1528. (b) Chan, T.H.; Ong, B.S. *J. Org. Chem.*, **1978**, *43*, 2994-3001.

30. (a) Sommer, L.H.; Bailey, D.L.; Goldberg, G.M.; Buck, C.E.; Bye, T.S.; Evans, F.J.; Whitmore, F.C. *J. Am. Chem. Soc.*, **1954**, *76*, 1613-1618. (b) Ottolenghi, A.; Fridkin, M.; Zilkha, A. *Can. J. Chem.*, **1963**, *41*, 2977-2979.

31. Overman, L.E.; Burk, R.M. *Tetrahedron Lett.*, **1984**, *25*, 5739-5742.

32. Chamberlin, A.R.; Nguyen, H.D.; Chung, J.Y.L. *J. Org. Chem.*, **1984**, *49*, 1682-1688.

33. Corey, E.J.; Beames, D.J. *J. Am. Chem. Soc.*, **1973**, *95*, 5829-5831, and references therein.

34. Neth. Appl. 6,400,946 (*Chem. Abstr.*, **1965**, *62*, 7761d.)

35. (a) Newman, H. *J. Heterocyclic Chem.*, **1974**, *11*, 449-451. (b) Strum, P.A.; Henry, D.W.; Thompson, P.E.; Zeigler, J.B.; McCall, J.W. *J. Med. Chem.*, **1974**, *17*, 481-487. (c) Eastwood, F.W.; Gunawardana, D.; Wernert, G.T. *Aust. J. Chem.*, **1982**, *35*, 2289-2298.

36. Kemp, D.S.; Sun, E.T. *Tetrahedron Lett.*, **1982**, *23*, 3759-3760.

37. Williams, R.M.; Dung, J.-S.; Armstrong, R.W.; Meyers, H. *J. Am. Chem. Soc.*, **1983**, *105*, 3214-3219.

38. Williams, R.M.; Glinka, T. *Tetrahedron Lett.*, **1986**, *27*, 3581-3584.

39. Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.*, **1965**, *87*, 1353-1364.

40. Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron*, **1984**, *40*, 1795-1802.

41. Baldwin, J.E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734-736.

42. Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.*, **1974**, *96*, 5270-5272.

43. (a) Streitweiser, A., Jr.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.*, **1969**, *91*, 529. (b) Bertrand, R.D.; Grant, D.M.; Allred, E.L.; Hinshaw, J.C.; Strong, A.B. *J. Am. Chem. Soc.*, **1972**, *94*, 997-999.

44. Anet, F.A.L.; Schenck, G.E. *J. Am. Chem Soc.*, **1971**, *93*, 556-557.

45. Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.*, **1972**, *46*, 59-71.