DISSERTATION

# THE TOTAL SYNTHESIS OF (±)- AND (+)-BICYCLOMYCIN

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ROBERT W. ARMSTRONG ENTITLED "THE TOTAL SYNTHESIS OF (±)- AND (+)-BICYCLOMYCIN" BY ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT

THE TOTAL SYNTHESIS OF (±)- AND (+)-BICYCLOMYCIN

The completely regio- and stereocontrolled total synthesis of bicyclomycin (1) is described in 12 chemical steps. A new carbon-carbon bond-forming reaction of 1,4-dibenzyl- and 1,4-di-p-methoxybenzyl-3,6-bis-(2'-thiopyridyl)-2,5-piperazinediones (234 and 275) has been discovered involving complexation of 234 or 275 with silver(I)triflate followed by addition of the trimethylsilyl ketene acetal of γ-butyrolactone to afford 1,4-dibenzyl- and 1,4-di-p-methoxybenzyl-3-(2'-thiopyridyl)-6-(2"-γ-butyrolactonyl)-2,5-piperazinediones (236, 237, and 276-279) in good yield. The reaction proceeds in THF at 25°C with predominant syn-stereospecificity. $LiAlH_4$ reduction of lactones 276-279 provides the corresponding diols 280-282 which are cyclized to the bicyclo[4.2.2]nucleus 284 in the presence of silver(I)triflate in THF at 25°C. Dehydration of 284 in three steps affords the key olefinic intermediate 8,10-di-p-methoxybenzyl-8,10-diaza-5-(methylene)-2-oxabicyclo[4.2.2]decane-7,9-dione (294) which is regio- and stereoselectively elaborated at the bridgehead positions via: 1) C-6-bridgehead carbanion formation followed by quenching with $O_2$; and 2) C-1-bridgehead carbanion formation followed by aldol condensation with 2,2,4-trimethyl-1,3-dioxolane-4-carboxyaldehyde to afford a single diastereomer (279a) possessing the correct relative

configuration at C-1', C-2'. Protection of the secondary hydroxyl at C-1' as the trifluoroacetate followed by oxidative removal of all the protecting groups with ceric ammonium nitrate in $MeCN/H_2O$ affords directly, totally synthetic bicyclomycin. Condensation of the racemic bicyclic nucleus 296 with optically active S-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (83% ee) provides after protection and deprotection, (+)-bicyclomycin in 78% ee.

Preliminary results establishing a structure-activity correlation requiring an obligate partnership of the C-6 hydroxyl and the C-4, C-5 exomethylene are described.

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## DEDICATION

This dissertation is dedicated to my wonderful parents. Their constant support, encouragement, inspiration, and love have made this work possible and worthwhile.

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## ABBREVIATIONS

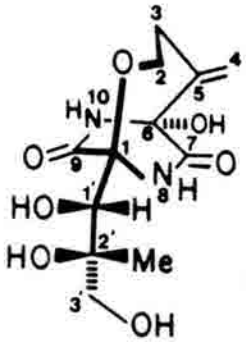
| | |
|---|---|
| $Ac_2O$ | acetic anhydride |
| CAN | cerric ammonium nitrate |
| m-CPBA | meta-chloroperbenzoic acid |
| CSA | camphorsulfonic acid |
| DBU | 1,5-diazabicyclo[5.4.0]undecene-5 |
| DCC | dicyclohexyl carbodiimide |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| HMPA | hexamethyl phosphorous triamide |
| HMPT | hexamethyl phosphoric triamide |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LICA | lithium isopropyldicyclohexylamide |
| MeOH | methanol |
| NBS | N-bromosuccinamide |
| Ms | methanesulfonyl |
| PTSA | para-toluenesulfonic acid |
| Py | pyridine |
| TBDMS | tert-butyldimethylsilyl |
| TBDPS | tert-butyldiphenylsilyl |

| | |
|---|---|
| Tf | trifluoromethylsulfonyl |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | para-toluenesulfonyl |

# CHAPTER I

# INTRODUCTION

Bicyclomycin is a cyclic dipeptide antibiotic that was isolated simultaneously[1] by two Japanese groups in 1972, Fujisawa Pharmaceutical Company and the Antibiotic Research Division of Niigata University.

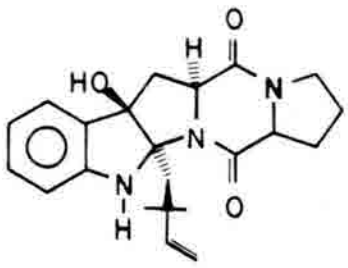



I

Bicyclomycin is a water soluble fungal metabolite obtained from the cultures of Streptomyces sapporonensis and S. aizunensis and possesses a very unique spectrum of antibiotic activity,[2] showing no relation to that of other known antibiotics. It exhibits no cross-resistance to any of the currently available antibacterial drugs. Because of its extremely low toxicity[1] (acute toxicity [LDo] by intravenous injection into mice is greater than 2g/kg and by subcutaneous, oral and intraperitoneal administration is greater than 4g/kg), bicyclomycin (Bicozamycin) is now being marketed worldwide by Fujisawa Pharmaceuticals as an antidiarrheatic antibacterial agent for both veterinary and human use.

Bicyclomycin is a member of a class of cyclic dipeptide antibiotics which have the intact diketopiperazine nucleus but which differ in the substituents at the amide nitrogens as well as the α-carbon of the dipeptide.

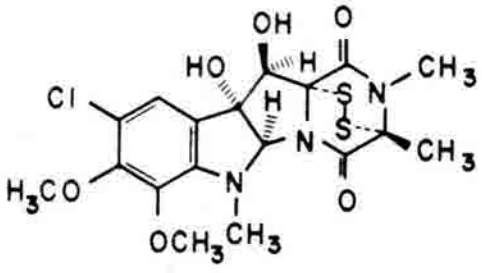
These compounds exist either monocyclic or bicyclic about the diketopiperazine ring, an example of the former being the recently synthesized antibiotic[3] Brevianamide.



Brevianamide

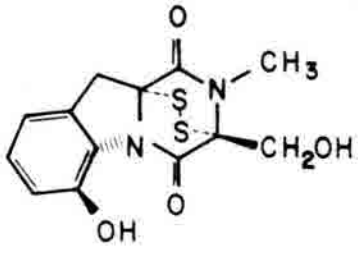
2

The bicyclic class is best represented by the epidithiodiketopiperazines which have received much synthetic interest in recent years, resulting in the total syntheses of gliotoxin[4] and sporidesmin A[5], amongst others.



Sporidesmins A

4



Gliotoxin

3

Bicyclomycin differs from the other diketopiperazine antibiotics by having a unique bicyclic structure that directly connects the two α-carbons of the amino acids via an oxypropyl bridge. No other antibiotic has ever been isolated which contains this basic bicyclic skeletal arrangement.

BIOSYNTHESIS. The diketopiperazine nature of the bicyclomycin nucleus suggests that it is biosynthesized by coupling of two different amino acids both containing six carbons. In a study by Iseki and coworkers[6] designed to elucidate the nature of these amino acids, a suspension of mycelium of Streptomyces sapporonensis was incubated over 24 hrs in the presence of eighteen different amino acids as shown in Table I. Only L-Leucine, L-isoleucine, L-phenylalanine, and L-glutamic acid were found to stimulate production, though an equimolar mixture of L-leucine and L-isoleucine showed the highest stimulatory effect.

TABLE I

| Amino Acid (1 mg/ml) | Bicyclomycin (μg/ml) | Amino Acid (1 mg/ml) | Bicyclomycin (μg/ml) |
|---|---|---|---|
| none (control) | -- | L-Hydroxyproline | -- |
| L-Alanine | -- | L-Serine | -- |
| L-Arginine | 40 | L-Methionine | -- |
| L-Glycine | -- | L-Threonine | -- |
| L-Histidine | 45 | L-Valine | -- |
| L-Lysine | -- | L-Isoleucine | 150 |
| L-Proline | 45 | L-Leucine | 135 |
| L-Phenyalanine | 92 | L-Tryptophan | -- |
| L-Glutamic Acid | 75 | L-Tyrosine | -- |
| L-Aspartic Acid | -- | | |

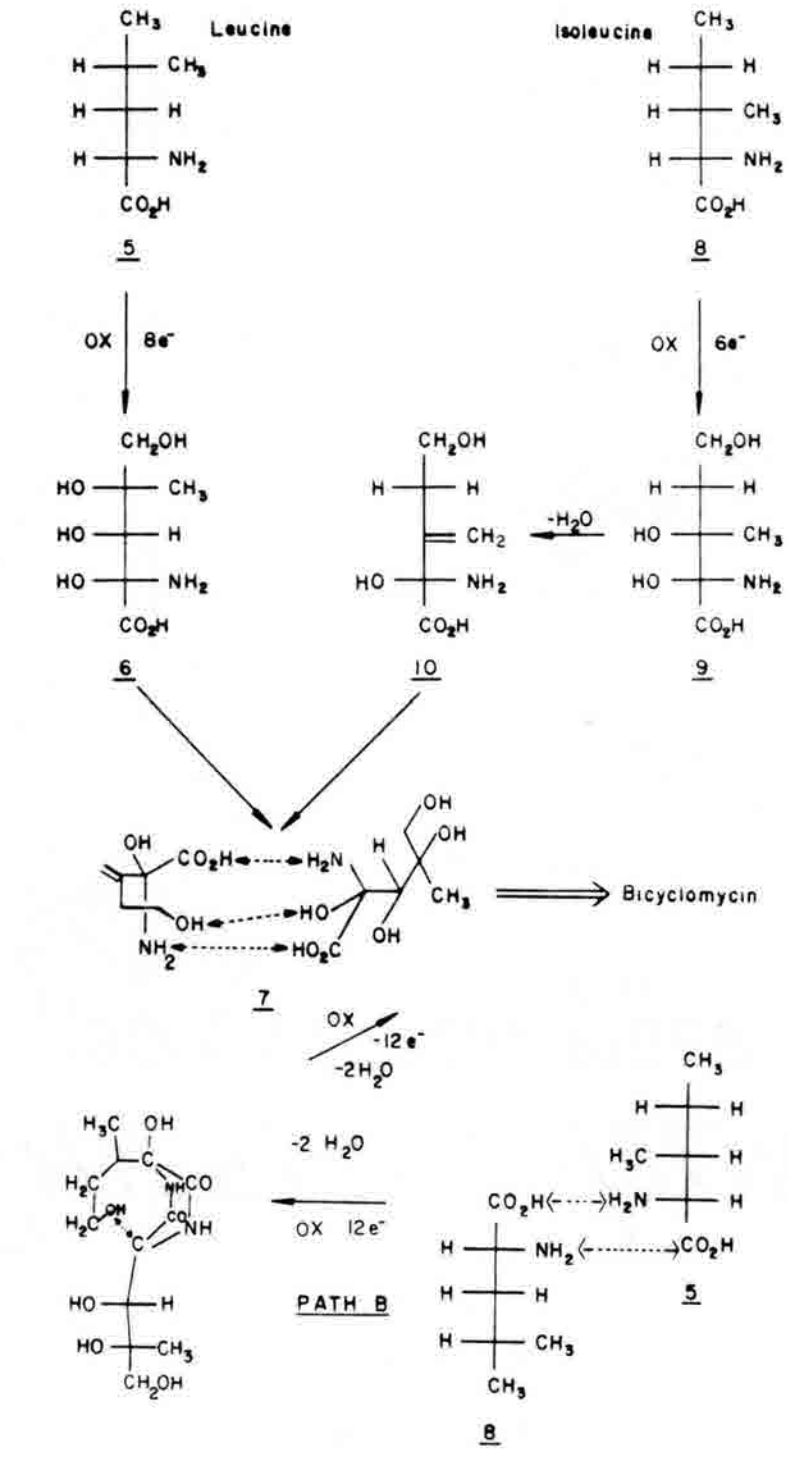
Labeling studies with $^{14}$C-L-Leucine and $^{14}$C-L-Isoleucine showed radioactive incorporation into bicyclomycin of 11.15% of the total radioactivity supplied to the medium. This data indicates that bicyclomycin is biosynthesized from the two six-carbon amino acids L-Leucine and L-Isoleucine. Two different pathways for the biosynthesis have been proposed[6] (Scheme 1). The first (path A) in which the bicyclic system is constructed simultaneously all in one step, and the other (path B) in which the diketopiperazine is synthesized prior to cyclization. A six electron oxidation of isoleucine 8 (Path A) affords 9 which selectively dehydrates to the exomethylene 10, then combines with the oxidation product of leucine (6) and in one step (7) affords bicyclomycin. The alternate path B involves the loss of two molecules of water and the subsequent twelve electron oxidation to afford the monocyclic piperazinedione 11 which undergoes further oxidation and dehydration to afford bicyclomycin. The overall process via either pathway involves the removal of fourteen electrons and the loss of four molecules of water.

Further elaboration of the biosynthetic course of bicyclomycin was proposed by Porter and coworkers[7] in 1981, although experimental evidence was not included.

It has recently been shown[7] that 2,5-dihydroxypyrazines can undergo [4+2] cycloaddition reactions with singlet oxygen to give bicyclic peroxides, allowing the authors to postulate that intermediate 42 occurs during the biosynthesis of bicyclomycin. Oxidation and elimination of the isoleucine-leucine dimer could lead to the pirazine 41, which upon exposure to oxygen generates the peroxide 42 which can simply decompose to a bicyclic system 43 (Scheme 2).

SCHEME I

PATH A



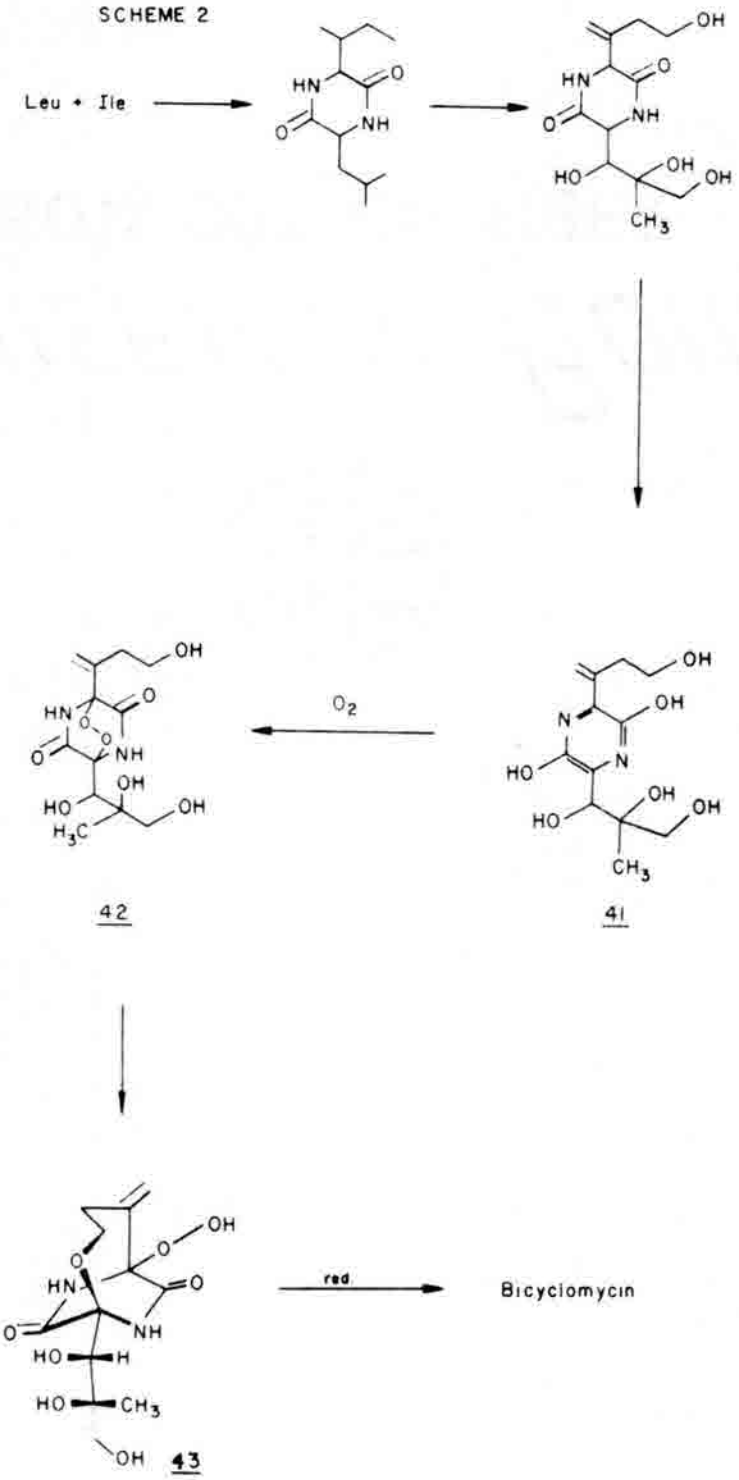
BIOLOGICAL STUDIES. Bicyclomycin is active against gram-negative bacteria such as Escherichia coli, Klebsiella, Shigella, Salmonella, Citrobacter, Enterobacter cloacae, and Nisseria, but inactive against Proteus, Psedomonas aeruginosa, and Gram-positive bacteria.[8] It is isolated from the fermentation broth, where most of the antibiotic activity is found in the broth filtrate and after a series of extractions the off-white crystals (mp. 188-191°C) can be isolated. Specific details of the antimicrobial activity of bicyclomycin and some synthetic analogs will be discussed in Chapter 4.

PHYSICAL PROPERTIES. Bicyclomycin is weakly basic, freely soluble in water and methanol, sparingly soluble in ethanol and acetone, and insoluble in chloroform, ethyl acetate, benzene and n-hexane. The optical rotation is $[\alpha]_D^{23}$ = +63.5 (c=1, methanol). It has a molecular weight of 302.29 and a melting point (rhombic crystals) of 188-191°C (decomp). The antibiotic is labile in alkaline solution as shown in the pH-activity correlation[1] in Table II.

TABLE II

| Condition | Percent of Residual Activity | | | | | | |
|---|---|---|---|---|---|---|---|
| | pH 2.2 | pH 4.0 | pH 5.0 | pH 6.0 | pH 7.0 | pH 8.0 | pH 9.0 |
| 100°C for 10 min | 70 | 50 | 50 | 0 | 0 | 0 | 0 |
| 60°C for 60 min | 100 | 90 | 90 | 75 | 50 | 20 | 0 |

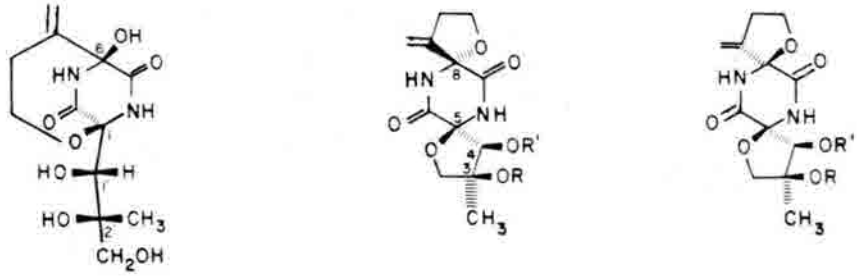
SCHEME 2



## STRUCTURE ELUCIDATION

The structure of bicyclomycin was determined by spectroscopic methods[9] in 1972 and two years later this structure was confirmed by x-ray analysis[10] which established the relative configuration. The absolute configuration was obtained by the total synthesis in racemic form of an acid-catalyzed ($HClO_4$, 100°C) dehydration product of bicyclomycin.[11] Maag and coworkers were able to obtain a single-crystal X-ray analysis of the para-bromobenzoate derivative of the trans-isomer 13 which had the 3S, 4S, 5S, 8R configuration, and since 13 and 14 were isomeric about carbon-8, compound 14 was assigned the 3S, 4S, 5S, 8S configuration.

SCHEME 2



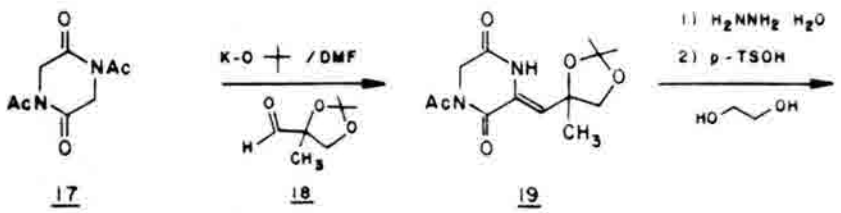
natural 12a R = R' = H 12b R = R' = H

natural 13 R = H, R' = $pBrC_6H_4CO$ 14 R = H, R' = $pBrC_6H_4CO$

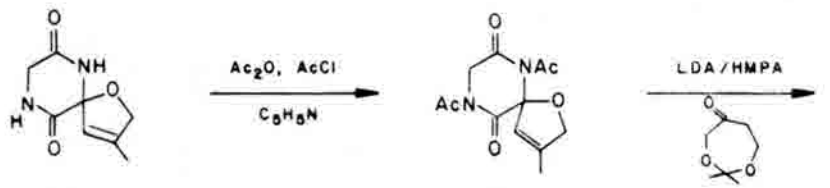
The rearrangement products 12a and 12b were obtained from an authentic sample of natural bicyclomycin as a 1:1 mixture of diastereomers. These diastereomers were synthesized in racemic form starting with N,N-diacetyglycine anhydride as shown in Scheme 3.

Anhydride 17 was condensed with aldehyde 18 in the presence of potassium t-butoxide/DMF to give the elimination product after intramolecular deacetylation of the neighboring amide. Hydrazinolysis afforded 19 and trans-ketalization gave the spiro diketopiperazine 20.

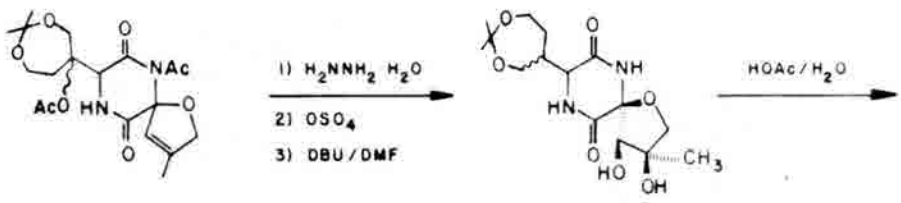
SCHEME 3




17 18 19

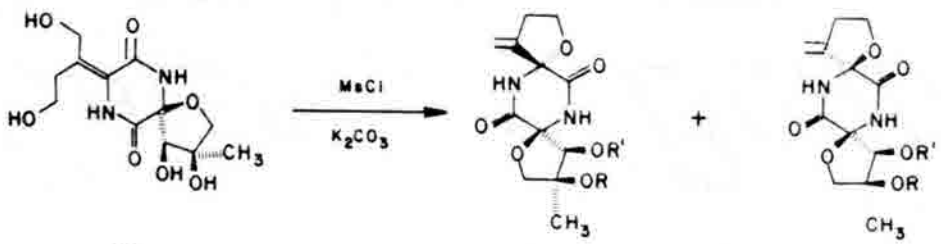



20 21 22




23 24

E/Z ISOMER




25 12b 12b

racemic 12b

racemic 15 R, R' = $C(CH_3)_2$

16 R, R' = $C(CH_3)_2$

Reprotection of the amides 21 allowed for enolate condensation with ketone 22 which afforded the deacetylated product 23. After deprotection of the remaining amide, osmium tetroxide oxidation of the olefin gave only one isomer. It appears that the only diol formed is due to approach of the reagent from the side of the proximal nitrogen which is the less hindered side. The remaining acetate was eliminated to give 24 as a mixture of E/Z isomers. Deprotection of the ketal gave the tetraol 25 which was not isolated, and was treated with mesyl chloride in the presence of potassium carbonate to first give the allylic mesylate which undergoes $SN_2'$ intramolecular displacement to afford the racemic mixture of the two diastereomers 12a and 12b which were obtained from natural bicyclomycin. The synthetic racemic isomers were separated after conversion to the acetonides 15 and 16. The trans-isomer 15 was confirmed by single-crystal X-ray analysis. These results established the absolute configuration of bicyclomycin as 1S, 6R, 1'S, 2'S.

A very important observation by Maag resulted from this work in which he states that synthetic "...schemes for bicyclomycin should probably be contrived in a way that circumvents the energy minimum represented by [the bis-spiro structures 12a and 12b]."[7,11] As will be seen in the next section, formation of spiro compounds have plagued many of the synthetic approaches to bicyclomycin.

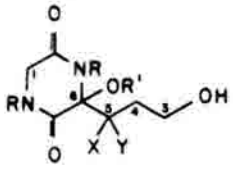
## SYNTHETIC STUDIES

Following the publication of the absolute stereochemistry of bicyclomycin by Maag in 1978, the total synthesis of bicyclomycin has received a considerable amount of attention. Within a period of six

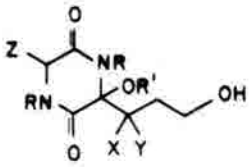
months in 1981, eight model studies by six different authors appeared in the literature. Several features characterize these and subsequent studies, including the use of "non-removable" protecting groups on the amides, a term referring to alkyl groups (methyl, isopropyl) which have no literature precedent for removal from amides (especially under conditions the fragile bicyclic structures would survive). The second feature which we, and others, have realized is key to a successful synthesis, is the cyclization of the diketopiperazine to a bicyclic product. As will be seen below, formation of the thermodynamically more stable spiro compound has plagued and even halted some synthetic approaches.

Every synthetic approach[12] and total synthesis of bicyclomycin which has appeared to date (June 1984) describes the synthesis of either a mono or a bis-substituted diketopiperazine which becomes the precursor to the bicyclic compound. This forces a decision on the synthetic strategist relating to the timing of the functionalization of the bridgehead carbons of the bicyclic molecule: should this be done at the monocyclic or bicyclic stage. All of the studies described in this section, except for those by Williams[13] and Maag,[11,14] describe the synthesis of a piperazinedione with either structure 111 or 112 as shown on the next page.

(Note: the numbering system indicated above for the monocyclic piperazinediones correlates to that used by convention for the bicyclic molecules and will be used to avoid confusion).

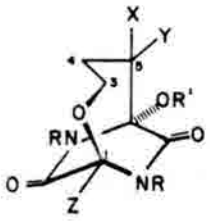


111



112

X = Y = H
X, Y = $CH_2$
R' = H, $CH_3$, Ac



113

X = Y = H
X, Y = $CH_2$
R' = H, $CH_3$, Ac

The problem faced in the cyclization reaction is the selective activation of the "bicyclic" diketopiperazine carbon (carbon-1) in the presence of the "spiro" carbon-6. Because the mechanism of cyclization (bicyclic or spiro) is thought to go via the intramolecular nucleophilic trapping of the intermediate iminium species, the problem can be restated as a selective activation of the distal (relative to the nucleophilic hydroxy moiety) iminium intermediate. Since both structures 111 and 112 contain a leaving group for iminium formation at the proximal carbon (carbon-6), the molecule must be "tricked" out of formation of the kinetically and thermodynamically favored spiro adduct and into formation of the less stable bicyclo[4.2.2] nucleus. ϒ or compound 111, activation of the unsubstituted methylene carbon-1 must occur during the cyclization step and has been successfully realized with only one compound, two other synthetic studies[15] using this approach ultimately result in only spiro compound or no bicyclic compound at all.

The slightly more productive approach is depicted by compound 112, in which the cyclization reaction is now only dependent on selective iminium formation. This route has led to the synthesis of several bicyclic products, though formation of spiro adducts has plagued some of these syntheses. In the case where Z is an olefin, selective activation of the olefin in the presence of the carbon-6 alkoxy group has given good results.[16]

The two studies which cannot be included in the previous analysis are those by Maag[11,14] and Williams.[13] Maag cyclized a diketopiperazine with an olefin at carbon-1 and no activating group at carbon-6, thus no spiro product could be formed. Williams gracefully circumvented this problem in the same manner as Maag, by having no leaving group at carbon-6, forming the bicyclic product, and then oxidizing the bridgehead position to obtain essentially the same product as the other studies without even the possibility of forming a spiro product. The following section will describe in more detail the synthetic studies analyzed above.

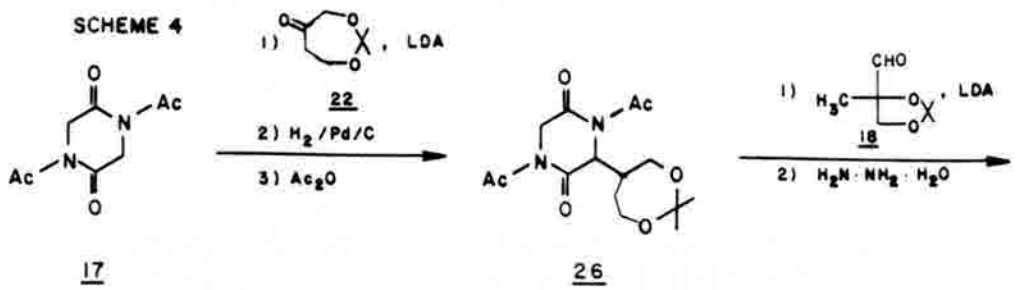
The first attempt at the total synthesis was done by Maag and coworkers[14] using much the same methodology which they had developed in the determination of the absolute stereochemistry. The strategy employed was to construct a fully functionalized monocyclic precursor diketopiperazine containing the leucine and isoleucine carbon skeleton, then cyclizing to form the bicyclic system. To circumvent formation of the bis-spiro adduct, the sidechain nucleophile was protected as the isopropylidene derivative and the tertiary alcohol on the diketopiperazine (the "leaving group" in the spiro rearrangement) was not introduced.

The lithium enolate of 17 was condensed with ketone 22 and the resulting elimination product was hydrogenated and reprotected with acetic anhydride to give 26 (Scheme 4). The enolate of 26 was condensed with the aldehyde 18 and after hydrazinolysis a mixture of both olefins 27 and 28 was obtained: only 27 was carried on. Selective removal of the seven-membered ring ketal and osmium tetroxide oxidation gave the tetraol 28.

Tetraol 28 was treated with p-toluenesulfonic acid in acetonitrile and a mixture of two bicyclic compounds was obtained as a result of either sidechain alcohol cyclizing to give the undesired seven- (29) or the desired eight- (30) membered rings. Mesylation, displacement by the o-nitroselenide and oxidation/elimination gave the desired olefins 31 and 32 which could be separated by chromatography. It was determined that the racemic olefin 31 had the 1S, 6S, 1'S, 2'S stereochemistry.

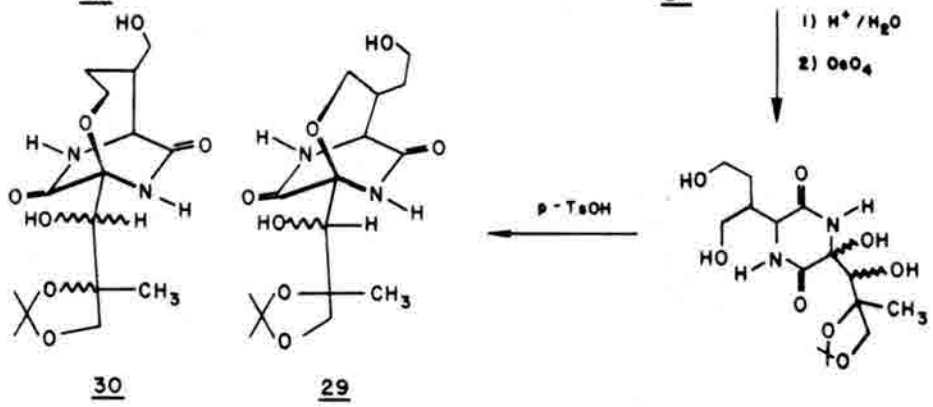
The Maag group also synthesized by very similar chemistry all four diastereomeric 33-36 desmethylene 6-desoxy bicyclomcyin acetonides (Scheme 5). Upon attempted deprotection of the acetonides, the compounds with the 1'R, 2'S (33) and 1'R, 2'R (36) sidechain stereochemistry yielded only bis-spiro adducts 37 and 39 respectively, whereas the two other acetonides 34 and 37 gave only the desired triols 38 and 40. This suggests that the R configuration at carbon-1' directs the conformation of the sidechain in such a way that it facilitates intramolecular cycloaddition by putting the carbon-3' hydroxy in close proximity and correct angular approach for displacement of the bridging ether. It appears the S configuration at carbon-11, the natural configuration, does not promote spiro formation.

SCHEME 4

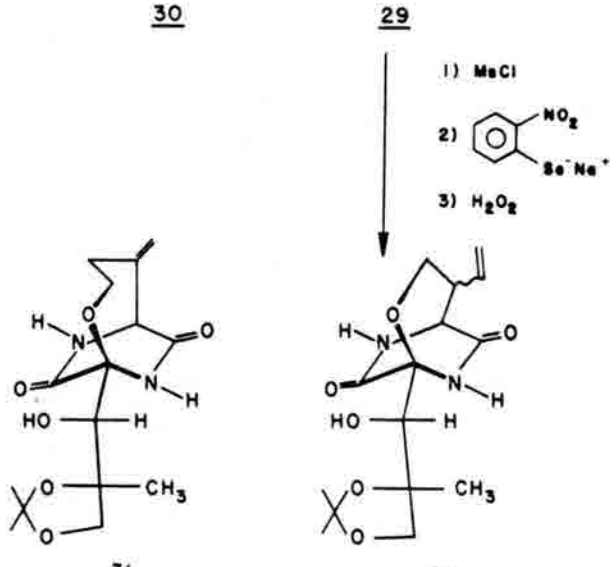



17 26

28 27



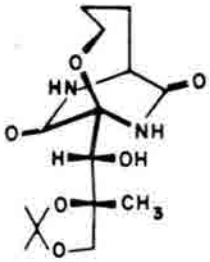

30 29 28




31 32

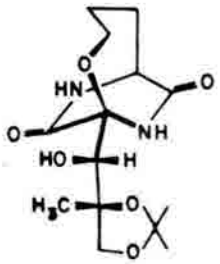
1S, 6S, 1'S, 2'S racemic

SCHEME 5



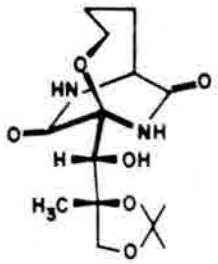
33

1'R, 2'S



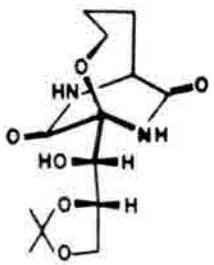
34

1'S, 2'R



35

1'R, 2'R



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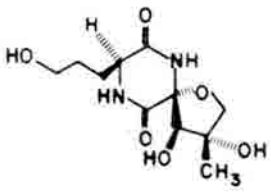
1'S, 2'S



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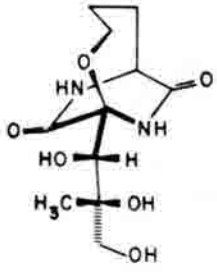

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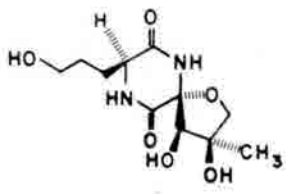

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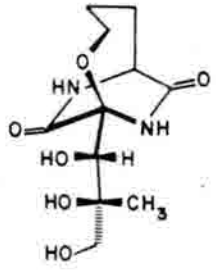


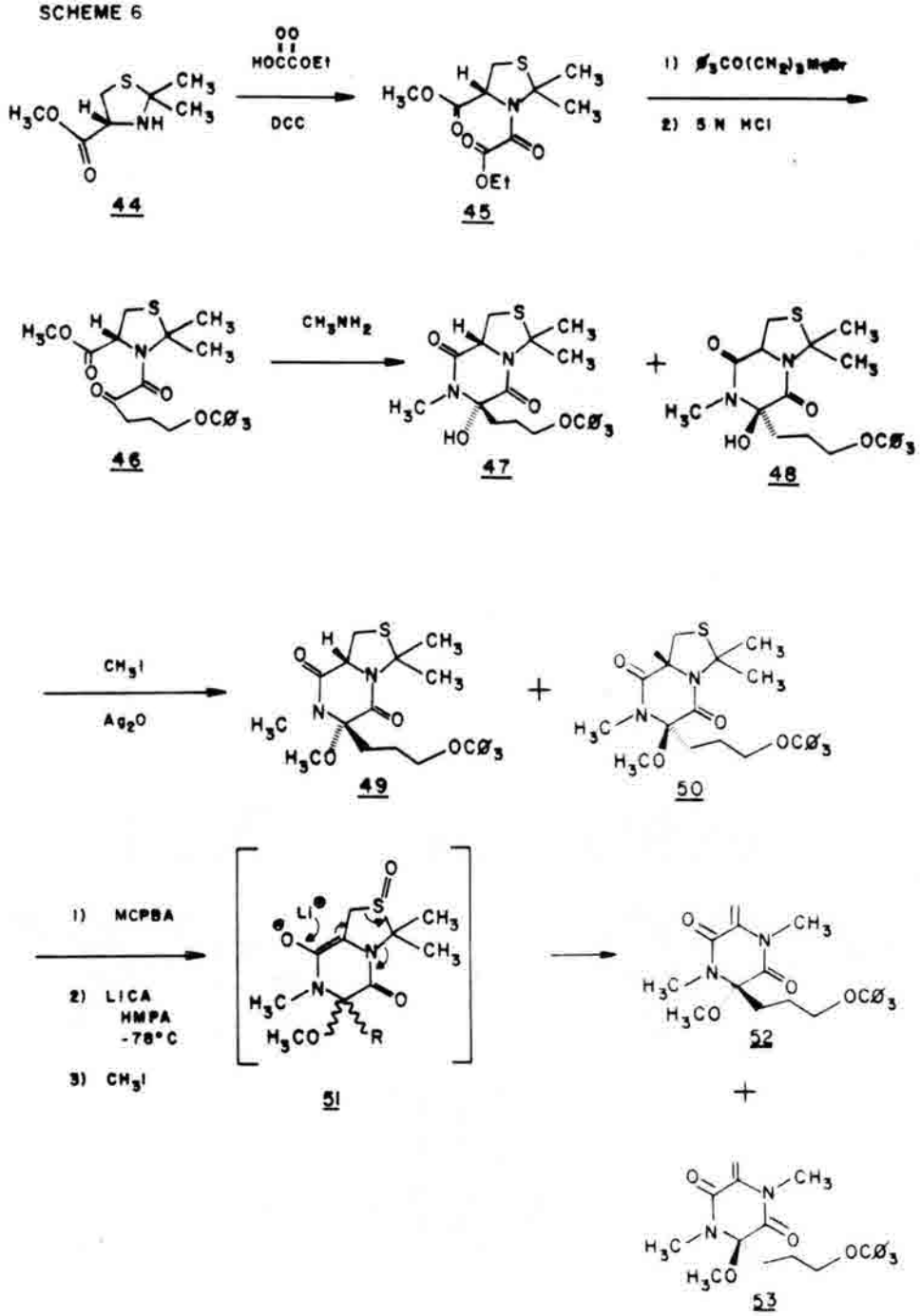
40

The remaining problem which the Maag group never addressed was introduction of the tertiary hydroxy group at carbon-6, the results of this study have not yet been fully published.[14]

A year after Maag described the absolute configuration of bicyclomycin, Dunkerton and coworkers[15] published the synthesis of a model alkoxyalkylidene piperazinedione which could serve as a precursor to construction of the second ring.

Starting with the thiazoline 44 (Scheme 6), condensation with ethyl oxalate in the presence of DCC gave the oxamate 45, which was homologated via a Grignard reagent to give the trityl protected

SCHEME 6


HOCCOEt
DCC
1) ØCO(CH2)3MgBr
2) 5 N HCl
CH3NH2
CH3I
Ag2O
1) MCPBA
2) LICA
HMPA
-78°C
3) CH3I
44
45
46
47
48
49
50
51
52
53

bridging side chain 46. Reaction of the oxamate 46 with methyl amine afforded the diketopiperazine as an isomeric mixture 47 and 48 at the tertiary alcohol. Protection of the alcohol as the methyl ether gave the mixture 49 and 50. The thiazolidines were oxidized to the β-sulfoxides with MCPBA followed by enolization of the proximal carbonyl 51 and decomposition via a retro-Michael intramolecular cleavage to give upon methylation of the amide a diastereomeric mixture of the alkylidine piperazinediones 52 and 53.

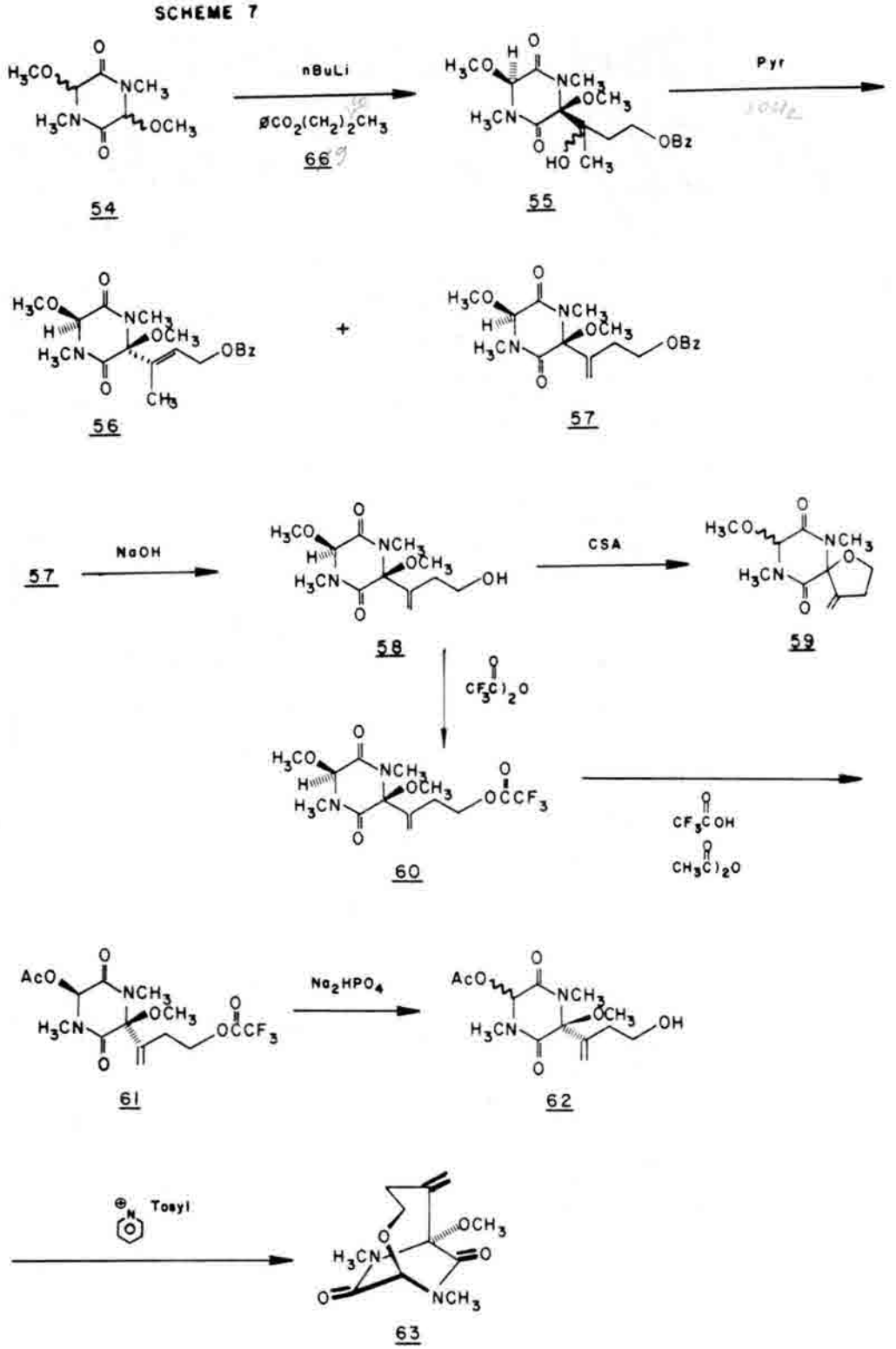
These highly functionalized diketopiperazines are very similar to those used by Maag to successfully construct the desoxy bicyclomycin diastereomer 31. Although formation of the spiro adduct could possibly be avoided by selective activation of the olefin prior to cyclization of 52 and 53, Dunkerton has not reported the synthesis of any bicyclic compounds.

Nakatsuka[16] has published a considerable amount of work on the model studies of bicyclomycin[17] and has recently completed the total synthesis[18] which will be described in the next section.

The strategy involved is much like that published by Dunkerton and involves construction of a functionalized diketopiperazine containing the tertiary alcohol at the bridgehead position (Scheme 7).

The lithium enolate of bis-methoxy sarcosine anhydride 54 (obtained from sarcosine anhydride in two steps)[16] was condensed with ketone 69 and the resulting aldol was eliminated with thionyl chloride and pyridine to afford a 1:1 mixture of the desired exomethylene 57 and the undesired endo-adduct 56. The alcohol 58 was obtained by treating the exo-olefin 57 with sodium hydroxide and all attempts at acid catalyzed cyclization resulted in formation of the spiro product 59.

SCHEME 7



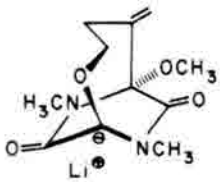
Because both methoxy leaving groups of compound 58 are identical, formation of the thermodynamically more stable spiro product was observed. A change of strategy was adopted in which the leaving groups were differentiated by converting the secondary methyl ether in 60 into the acetate 61 in poor to fair yields. After deprotection to the alcohol 62, pyridinium tosylate catalyzed cyclization afforded the bicyclic compound 63 in mediocre yields. Although not specifically stated, presumably some of the byproduct is the spiro compound. This low yield nonstereoselective synthesis of 63 was the first synthetic bicyclic compound bearing the alkoxy substituent (as a methylether) at carbon-6.

Generation of the bridgehead anion of 63 with n-BuLi and condensation with the aldehyde 18 gave in a nonstereoselective fashion all four possible diastereomers in a 9:3:3:1 ratio (Scheme 8) as determined by NMR.

The correct stereoisomer was converted to the triol by treatment with acid. This model study by Nakatsuka showed that although in low overall yield and in a nonstereoselective fashion, the bicyclomycin ring system was successfully constructed.

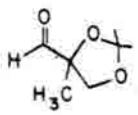
Simultaneously, Williams[13] in the same year published the synthesis of a bicyclic model compound which solved the problem of spiro versus bicyclic ring formation by introducing the carbon-6 hydroxy group after formation of the bicyclic system. This was via a novel bridgehead anion oxidation which successfully constructed the first synthetic bicyclic compound with a free hydroxy substituent at carbon-6.

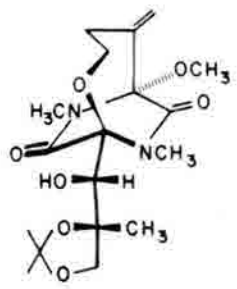
SCHEME 8



63

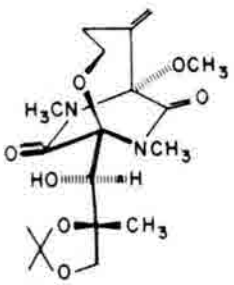
+





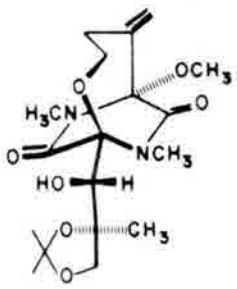
64

1'S, 2'S



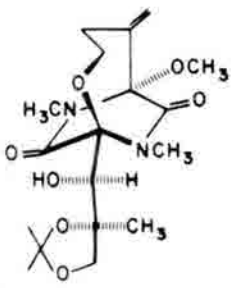
65

1'R, 2'S



66

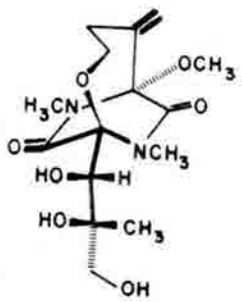
1'S, 2'R



67

1'R, 2'R

$H^{\oplus}$

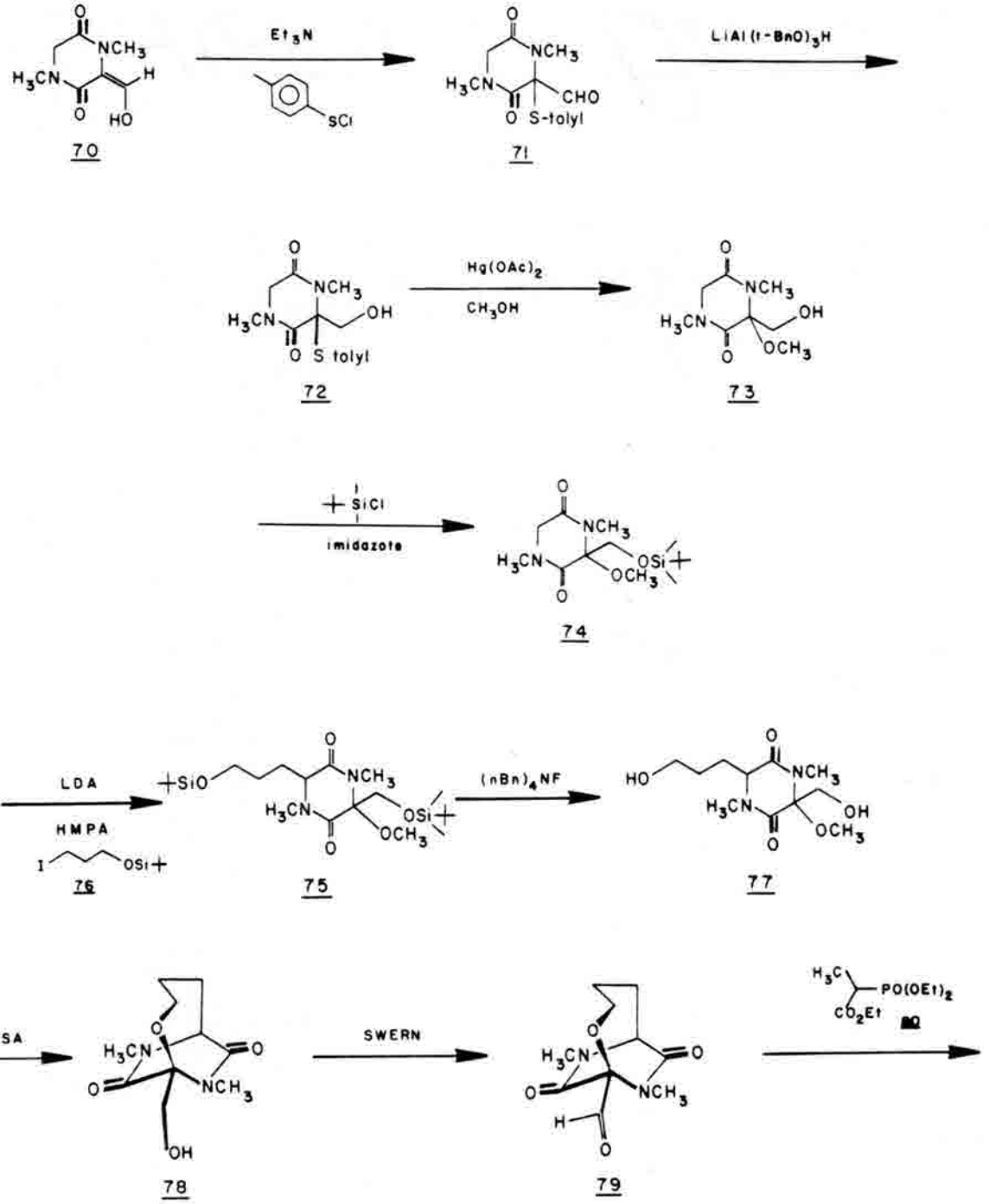


68

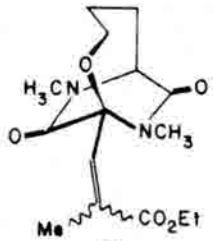
The formyl diketopiperazine 70 (Scheme 9) was condensed with tolyl sulfenyl chloride, reduced, and converted to the methyl ether 73 by methanolysis in the presence of mercury salts. After alcohol protection, the lithium enolate of 74 was condensed with the iodopropane 76 and the resulting condensation product 75 was deprotected with tetra n-butyl ammonium fluoride to give diol 77. It is of value to note that this functionalized monocyclic diketopiperazine cannot form a spiro bicyclic structure since there is no leaving group at the carbon bearing the hydroxypropyl sidechain. Camphor sulfonic acid closure of the diol 77 gave the bicyclic alcohol 78 which upon Swern oxidation and condensation with the Horner-Emmons reagent 80 gave the desired olefins 81 as a cis/trans mixture. Surprisingly, the deformylated product 83 was also obtained, and subsequent treatment with base gave a mixture of the two monoalkylated products 84 and 85 which was the first published report of bridgehead anion functionalization at both carbon-6 and carbon-1.[19] The primary alcohol 78 could be protected as the silyl ether and subsequent quenching of the bridgehead anion of C-6 with MoOPh, an electrophilic source of oxygen, afforded the desired bridgehead alcohol 82. The bridgehead anion functionalization of the unexpected product 83 (also synthesized via a more direct route) lead to a change in strategy by the Williams group and has resulted in the total synthesis of bicyclomycin; this comprises the major part of this thesis as will be described in the following chapters.

The same year Shin[20] synthesized a bicyclic model compound very similar to that published by Williams, but like Nakatsuka, the synthesis was plagued by formation of the thermodynamically more stable

SCHEME 9

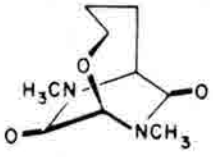

Et3N
SCl
LiAl(t-BuO)3H
Hg(OAc)2
CH3OH
imidazole
LDA
HMPA
(nBu)4NF
CSA
SWERN
PO(OEt)2
CO2Et
70
71
72
73
74
75
76
77
78
79

SCHEME 9 (continued)



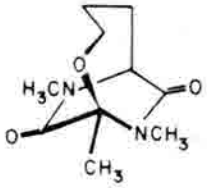

81

+

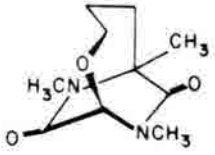



83

LDA, $CH_3I$

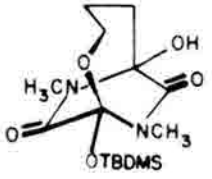



84




85

78 —(1) TBDMSCl, 2) LDA, 3) MoOPh)→




82

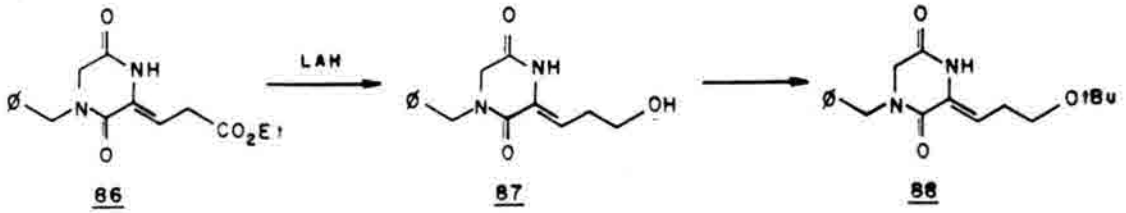
spiro compounds. Unlike the previous synthesis, the monocyclic diketopiperazine synthesized did not contain a leaving group at either α-carbon of the amides: this group was introduced in the cyclization step itself. Instead of differentiating the two bridgehead carbons by different leaving groups as in the Nakatsuka synthesis, the protecting groups adopt this role.

The monocyclic diketopiperazine[21] ester 86 (Scheme 10) was reduced with hydride and protected as the t-butyl ether 88. Initial attempts to probe the reactivity and selectivity of olefin activation by using NBS resulted in a dead end. If methanol was used as a solvent, the bromonium intermediate was trapped by the solvent to give the α-bromo methyl ether 84. On the other hand, in chloroform only a diastereomeric mixture of the spiro products (90) was observed. Successful construction of the bicyclic nucleus was accomplished by the fortuitous observation that in the absence of the olefin, the alcohol 91 will intramolecularly add only giving bicyclic rather than spiro product. Bromine (as $Br_2$ or NBS) is well known to add to the methylene position of diketopiperazines[22] and presumably activates the less hindered secondary (C-1) rather than the tertiary position (C-6).

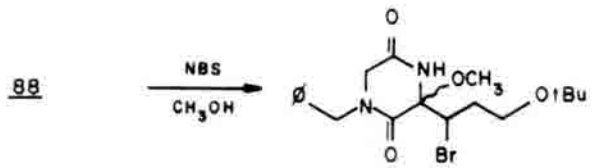
The selectivity observed is due to the hindered nature of the diketopiperazine, the less substituted carbon being more reactive. This is well substantiated by the fact that simple diketopiperazines undergo bromination very readily,[22] whereas substituted diketopiperazines are more difficult to brominate.[23]

As briefly discussed in the biosynthesis section, Porter[7] has proposed a bicyclic peroxide intermediate 42 which is generated by [4+2] singlet oxygen addition to the pyrazine 41, thus his model study

SCHEME 10




86 87 88

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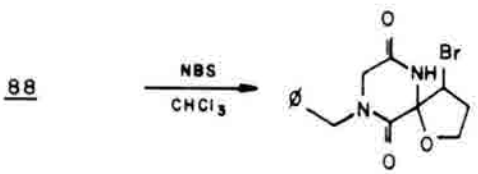
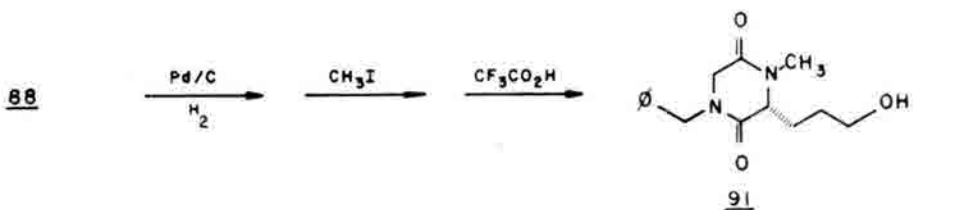
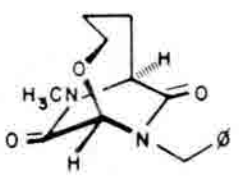



90




91

NBS, $CHCl_3$



92

centered on the synthesis of the pyrizine 98 (Scheme 11) which after undergoing cycloaddition to give the bicyclic peroxide, intramolecular phenolic cyclization would generate a model bicyclic compound.

Synthesis of pyrizine 98 was never accomplished, thus no bicyclic model compounds were ever synthesized. Diketopiperazine 93, obtained by cyclodimerization of 2-hydroxyphenyl alanine, was acetylated to 94 and then converted to the bis-imidate 95 with triethyl oxonium tetrafluoro-borate.

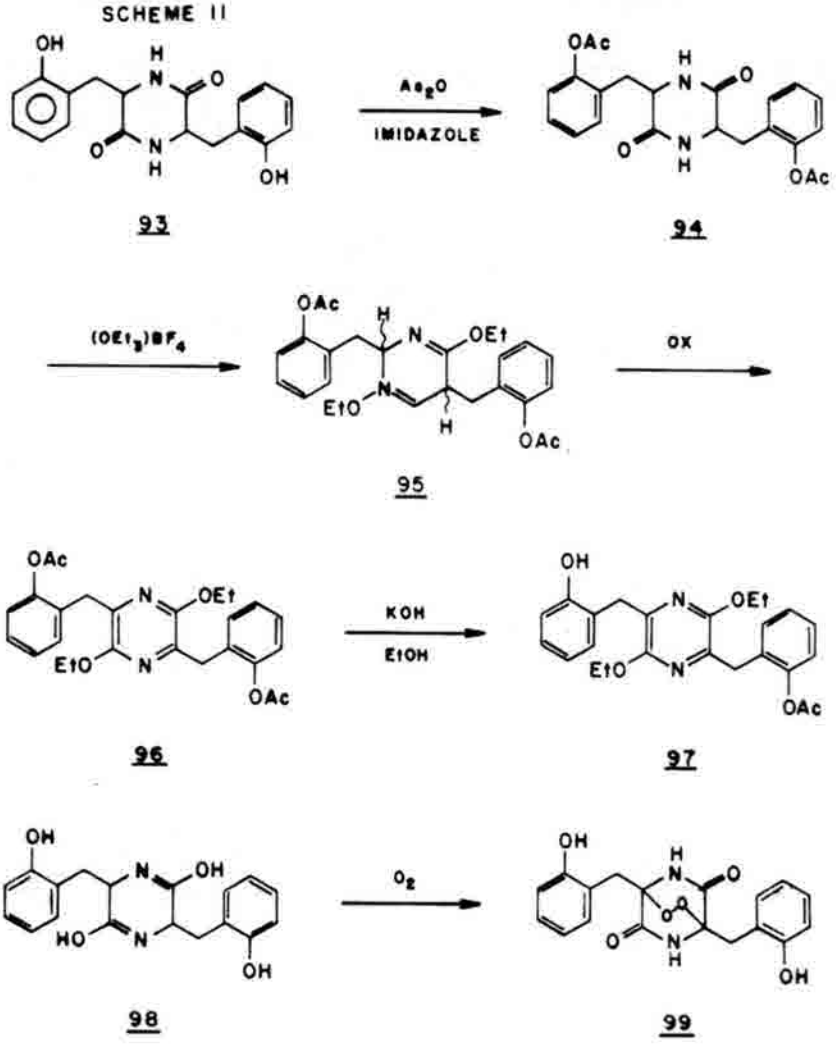
Deprotection of the acetates by ethanolic KOH treatment resulted in 97 which could not be deprotected. The authors state that this compound is virtually insoluble in any organic solvents and was never successfully deprotected.

In late 1981 Fukuyama[24] synthesized a bicyclic model system very similar to that published earlier by Williams[13] differing only in the amide protecting groups and the successful introduction of the exomethylene at carbon-5. The monocyclic diketopiperazine diol 103, when treated with acid gave only the undesired spiro product 104, but under neutral or basic conditions successfully gave moderate yields of the desired bicyclic derivative 105 or 106.

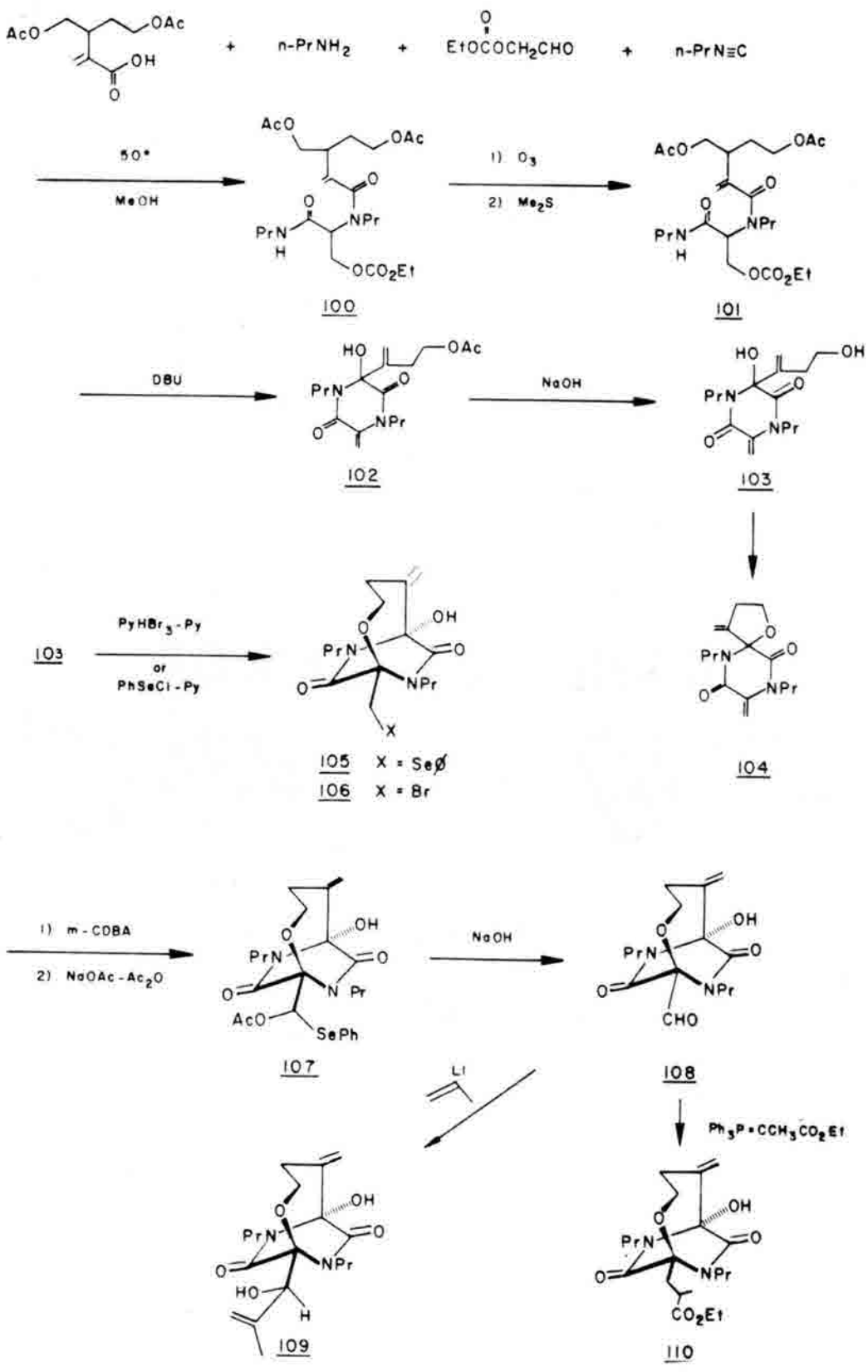
Fukuyama in effect was able to accomplish what Maag, Dunkerton, and Shin were unable to: differentiation of the "spiro" bridgehead hydroxy (alkoxy) carbon and the "bicyclic" vinyl carbon by selectively activating the olefin in the presence of the tertiary alcohol (Scheme 12).

Condensation of the appropriate carboxylic acid, amine, aldehyde, and isocyanide via the Ugi reaction[25] furnished the aminocarboxamide 100 which was ozonized to give the α-ketoamide 101. Treatment of 101

SCHEME II


OH
H
N
O
O
N
H
OH
93
Ac2O
IMIDAZOLE
OAc
H
N
O
O
N
H
OAc
94
(OEt3)BF4
OAc
H
N
OEt
EtO
N
H
OAc
95
ox
OAc
N
OEt
EtO
N
OAc
96
KOH
EtOH
OH
N
OEt
EtO
N
OAc
97
OH
N
OH
HO
N
OH
98
O2
OH
H
N
O
O
O
O
N
H
OH
99

SCHEME 12


AcO
OAc
OH
+ n-PrNH2 +
EtOCOCH2CHO
+ n-PrN≡C
50°
MeOH
1) O3
2) Me2S
PrN
H
NPr
OCO2Et
100
101
DBU
NaOH
HO
102
103
103
PyHBr3-Py
or
PhSeCl-Py
105 X = SeØ
106 X = Br
104
1) m-CPBA
2) NaOAc-Ac2O
AcO
SePh
107
NaOH
CHO
108
Li
Ph3P=CCH3CO2Et
109
110

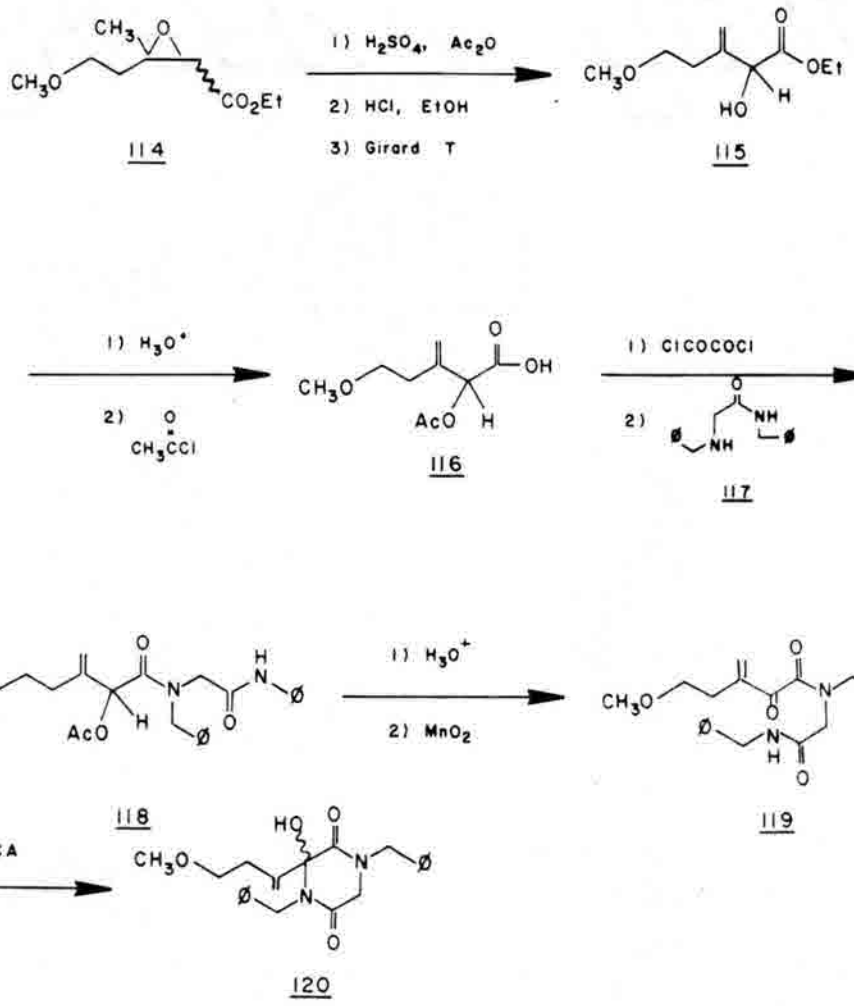
with base resulted in elimination of acetic acid to generate the sidechain exomethylene, cyclization to form the α-hydroxy diketopiperazine, and elimination of the carbonate to give the methylidene piperazinedione 102 in an overall moderate yield. Saponification of the acetate gave the diol which upon acid catalyzed cyclization gave only the spiro product 104. If cyclized under basic conditions (pyridinium hydrobromide perbromide) the bicyclic bromide 106 resulted, but was inert to further transformation. Under neutral conditions (phenyl selenium chloride) the bicyclic selenide was obtianed (105), which was oxidized to the selenoxide and converted to the α-acetoxy selenide 107 via the Pummerer rearrangement. Treatment with base and addition of the Horner-Emmons reagent 80, identical to that used in the Williams synthesis, led to the mixture of olefins 110. This concluded the synthesis of the functionalized bicyclic model system with "non-removable" protecting groups on the amides.

Yates[26] and coworkers published the synthesis of a monocyclic diketopiperazine with the alkoxy substitutent at carbon-6 but no leaving group at the carbon-1 methylene of the piperazinedione. This bicyclic precursor has led only to the spiro product.

The monocyclic diketopiperazine was synthesized by two different routes, using chemistry very similar to that published by Fukuyama in early 1981, the key reaction being the base-catalyzed intramolecular addition of the terminal amide to the α-ketone of the other amide, generating the desired alkoxy substituent of carbon-6 (Scheme 13).

Treatment of 4-methoxybutan-2-one with ethyl chloroacetate and sodium ethoxide gave the glycidate 114 which could be converted to the α-hydroxy ester by treatment with acetic anhydride and sulfuric acid to

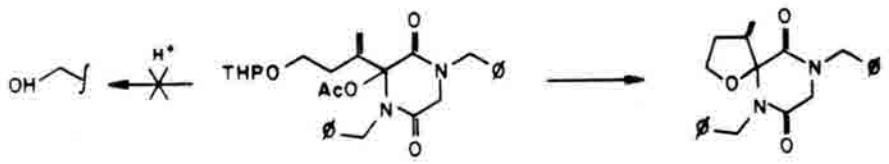
SCHEME 13




114 115 116 117 118 119 120 120 121 123 124 120

give the acetate and then removal of the latter with ethanolic HCl. The ester 114 was converted to the acid, the α-hydroxy group was protected as the acetate 116 followed by condensation of the resulting acid chloride with N,N'-dibenzylglycine cinnamide 117 to give the diamide 118. Base hydrolysis of the acetate followed by oxidation of the α-oxoamide generated the precursor 119 which upon treatment with isopropylcyclohexylamide gave the piperazinedione 120 in fairly low yields. An alternative approach to the synthesis of 120 was accomplished by epoxidation of the piperazinedione olefin 123 to give the epoxide 124 which could be eliminated with isopropyl-dicyclohexyl-amide to give 120. Yates was never successful at constructing the bicyclic diketopiperazine from 120. Utilizing the same methodology described above, Yates was able to synthesize the tetrahydropyran derivative (125) of 120 (Scheme 14) but upon attempts at acid catalyzed removal to give the alcohol, the only product observed was formation of the spiro adduct!

SCHEME 14

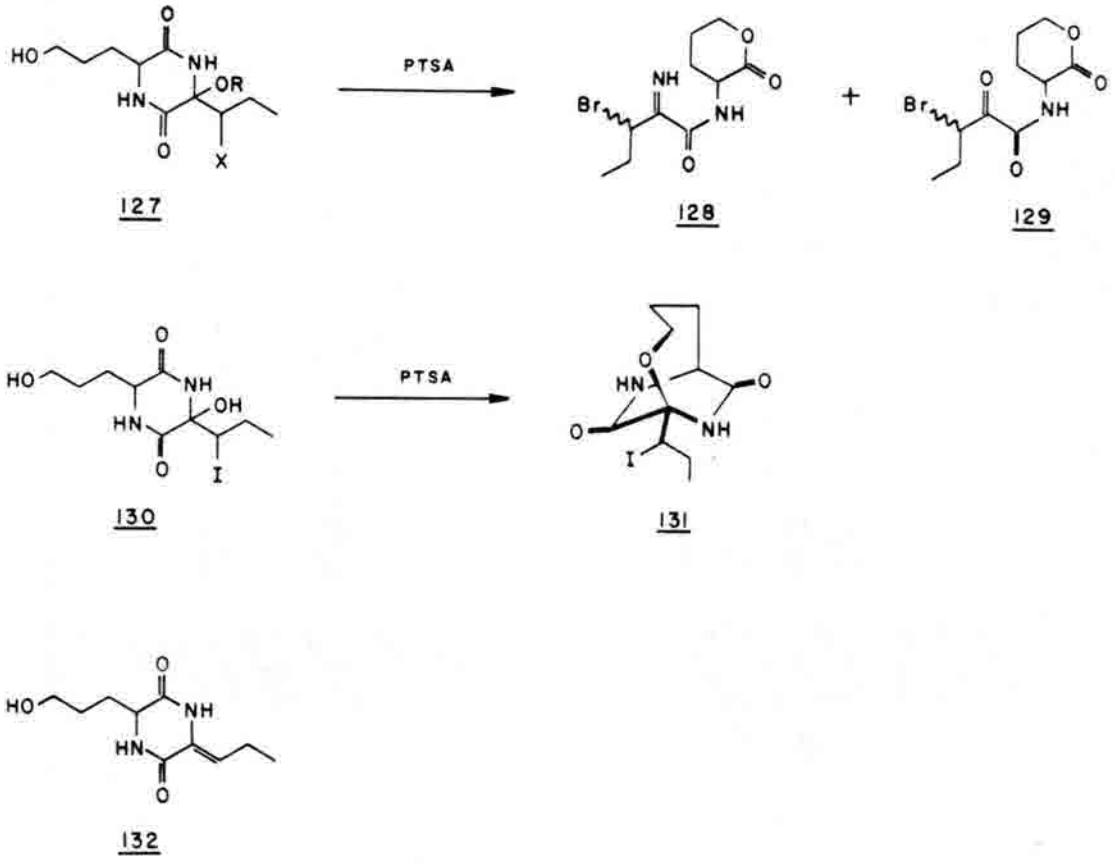



125 126

Dirlam recently described[27] the synthesis of a bicyclic diketopiperazine derivative 132 which was successfully cyclized to the bicyclic product 131 which, including the Maag synthetic work, are the

only two bicyclic model systems with free (N-H) amides. This bicyclic model has not led to any other products (Scheme 15).

SCHEME 15



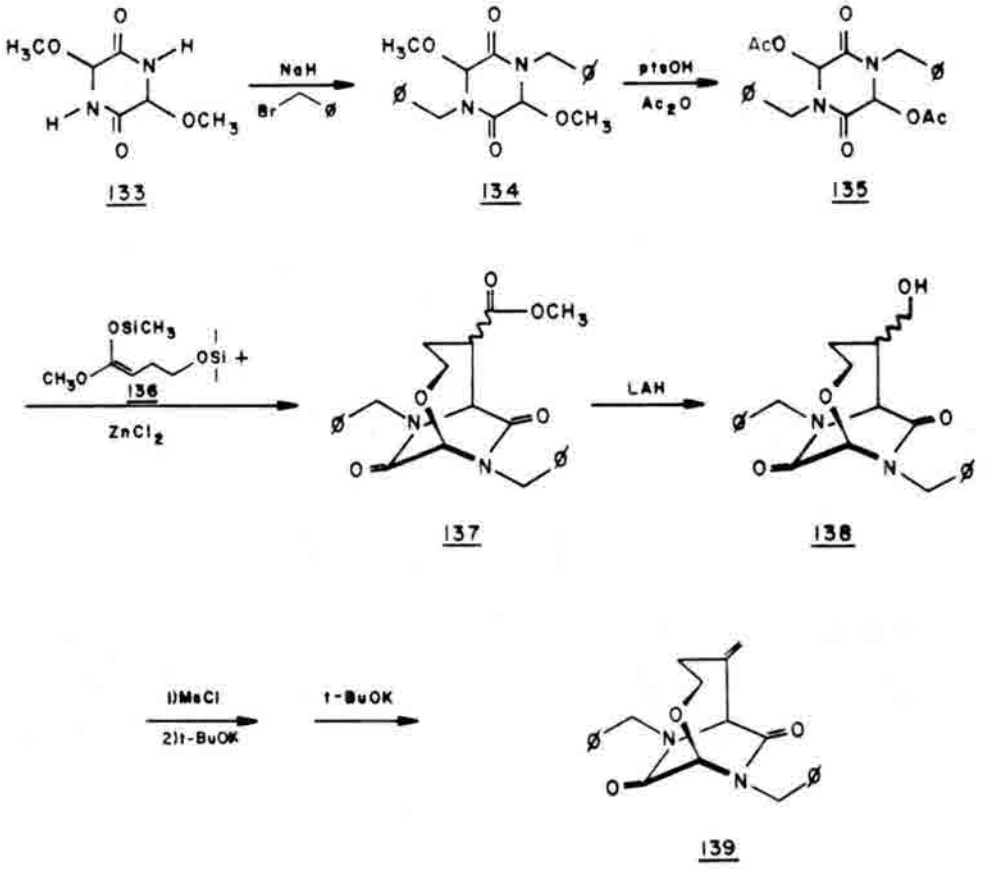

The attempted cyclization of the piperazinedione bicyclic precursor 132 in the presence of NBS led only to the two lactones 128 and 129. The mechanism presumably involves intramolecular amide cleavage either prior to or following formation of the iminium intermediate. The α-ketoamide 129 is formed by hydrolysis of 128 during workup.

Very recently Sera[28] and coworkers have reported an efficient synthesis of the bicyclic ring system based on chemistry which we reported early in 1983.[29] The strategy for carbon-carbon

bond-formation and subsequent cyclization differ markedly from all those previously described in this chapter and will be discussed in more detail in chapter 3. Suffice it to say that it circumvents the main problem previously described: formation of the thermodynamically more stable spiro adduct at the expense of the desired bicyclic system.

The bis-methoxy piperazinedione 133 (Scheme 16) was synthesized from glycine in 5% overall yield. Protection of the amides with benzyl bromide was followed by conversion to the bis-acetate 135. Zinc chloride catalyzed carbon-carbon bond-formation and concomitant cyclization resulted in the efficient construction of the bicyclic system. Reduction to the alcohol 138 and conversion by standard methods gave the bicyclic olefin 139. The required functionalization

SCHEME 16

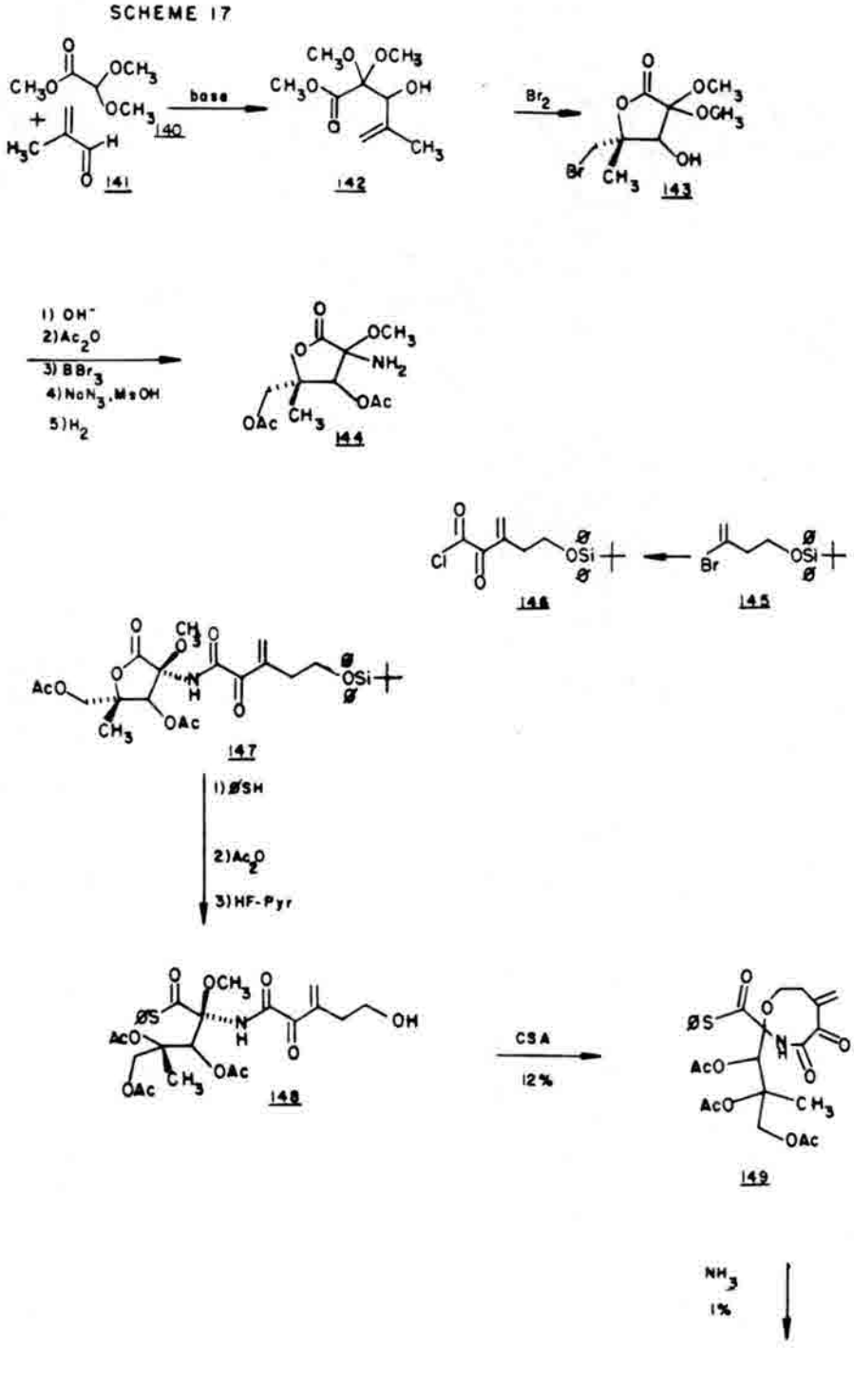



133 134 135 136 137 138 139

of this bicyclic intermediate would have to be carried out by chemistry which only we have developed. In fact we have carried out the synthesis of N,N'-dibenzyl bicyclomycin acetonide from olefin 139; this data will be presented in chapter 3.

Danishefsky[30] has recently completed the syntheses of the cyclic pyruvamide 149 which preliminary results indicate can be converted to bicyclomycin in 1% yield (Scheme 17). This creative approach to bicyclomycin shares some similarities to the Fukuyama model study, namely the construction of a highly functionalized pyruvamide which undergoes intramolecular addition, simultaneously generating the piperazinedione and the tertiary alcohol of C-6. Several new features of this syntheses include the elegant omission of amide protecting groups and the formation of the eight-membered ring cyclic pyruvamide prior to formation of the diketopiperazine, thus avoiding the thermodynamically more stable spiro byproducts. The anion of the ketal ester 140 was condensed with α-methyl acrolein 141 to afford the aldol product 142, which was converted to the γ-butyrolactone 143 via bromolactonization. The primary bromide 143 was converted to the alcohol and acetylated with acetic anhydride. The dimethyl ketal was treated with a Lewis acid ($BBr_3$) and the resulting oxonium intermediate was trapped with sodium azide, which in turn was hydrogenated in the presence of Lindlar catalyst to afford the aminal 144. The isoleucine portion of bicyclomycin was synthesized by condensation of the vinyl anion of 145 with oxalyl chloride to afford the pyruvyl chloride 146 which readily reacts with the γ-butyrolactone 144 resulting in the pyruvamide 147. Nucleophilic attack by phenyl mercaptan on the lactone results in the hydroxy thioester, which is first acetylated to afford

SCHEME 17


base
140
141
142
Br2
143
1) OH⁻
2) Ac2O
3) BBr3
4) NaN3, MsOH
5) H2
144
145
146
144 + 146
147
1) ØSH
2) Ac2O
3) HF-Pyr
148
CSA
12%
149
NH3
1%
Bicyclomycin

the triacetate and then treated with HF·pyridine complex to desilylate the primary alcohol 148. Treatment of the pyruvamide 148 with camphorsulfonic acid results in formation of the imminium species which is intramolecularly trapped by the primary alcohol to afford the cyclic pyruvamide 149 in 12% yield. Treatment of the reactive thioester 149 with ammonia affords the primary amide which intramolecularly adds to the pyruvate carbonyl affording racemic bicyclomycin. The unfortunate low yields in the last two key steps should not detract any interest from this novel and original synthesis of bicyclomycin.

TOTAL SYNTHESIS

Only two total syntheses of bicyclomycin have been completed to date, one in racemic form by Nakatsuka[18] and coworkers, and both a racemic and an optically active synthesis which we have completed[31] and which will be described in subsequent chapters.

The total synthesis completed by Nakatsuka follows directly from their model studies which are described at the beginning of this chapter: the only difference being the use of N-benzyl protecting groups and the doubling of yields for all key steps in the synthesis.

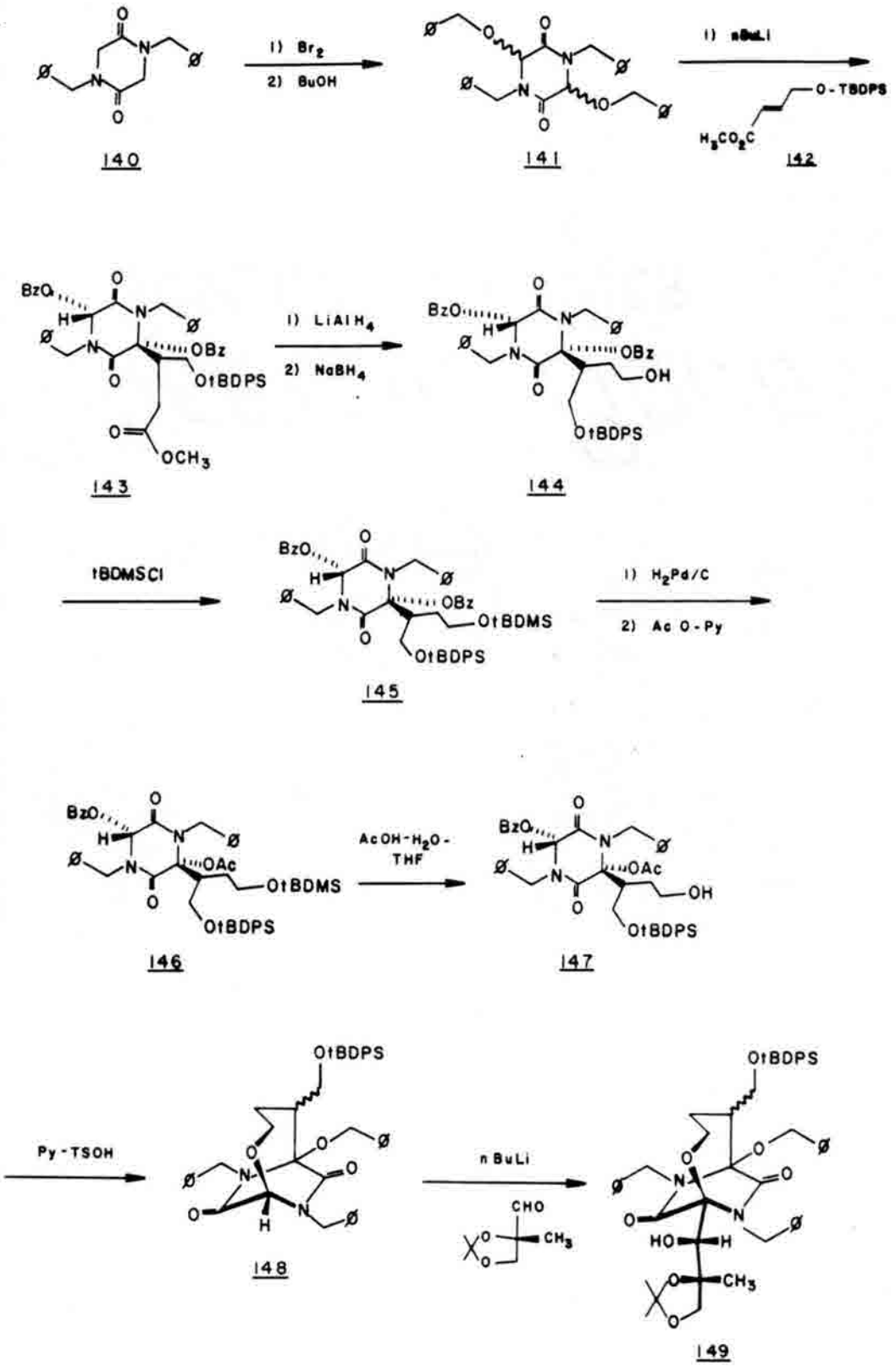
The bis-O-benzyl diketopiperazine 151 was prepared from N,N'-dibenzylglycine anhydride by bromination followed by displacement with benzyl alcohol in the presence of base (Scheme 18). The lithium anion of 151 was quenched with the $\alpha,\beta$-unsaturated ester 152 (made from methyl $\gamma$-hydroxycrotonate in three steps) to give the Michael addition product as one diastereomer. Successive reductions of the ester with lithiumn aluminum hydride followed by sodium borohydride gave the primary alcohol 154 which was protected as the t-butyldimethylsilyl

ether 155. Selective hydrogenation of the secondary benzyl ether and conversion of the resulting alcohol to the acetate 156, differentiated the two bridgehead oxygens at carbon-6 and carbon-1. Selective deprotection of the less bulky silyl ether followed by cyclization in the presence of pyridinium tosylate gave the bicyclic compound 158. Generation of the bridgehead anion followed by condensation with the "Maag" aldehyde 18 gave a mixture of three diastereomers, the major one being desired. Removal of the remaining silyl ether with fluoride ion gave the primary alcohol, which was the key precursor for reductive deprotection of the N-benzyl amides. It appears that indeed this is the only intermediate in the entire synthetic sequence that can be deprotected.[32]

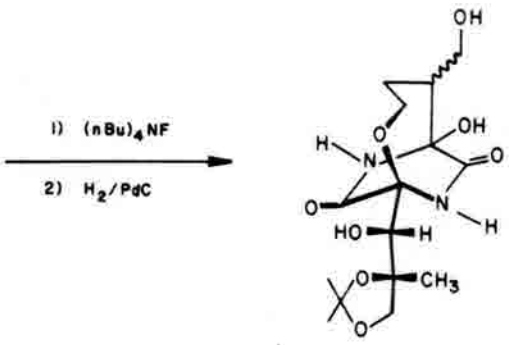
The deprotected compound 160 was converted to the olefin in poor yields by using standard methodology: mesylation, selenide displacement, and oxidation/elimination of the selenoxide to give the exomethylene 162. This compound was then converted to racemic bicyclomycin by mild acid hydrolysis of the side chain acetonide.

In conclusion, it is interesting to note that although many researchers have attempted the construction of the bicyclic nucleus, only a few have been successful in doing so. We have developed general methodology to accomplish this which is applicable and tolerable to a variety of substituents and which has allowed for the construction of a variety of bicyclic compounds without ever forming any undesired spiro adduct. This data will be presented in subsequent chapters.

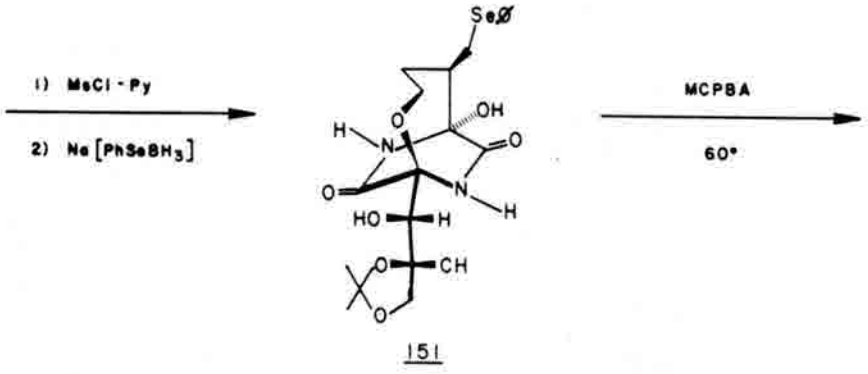
SCHEME 18


1) Br2
2) BuOH
1) nBuLi
O-TBDPS
H3CO2C
140
141
142
BzO
OBz
OtBDPS
OCH3
1) LiAlH4
2) NaBH4
OH
143
144
tBDMSCl
OtBDMS
145
1) H2Pd/C
2) Ac O-Py
OAc
AcOH-H2O-
THF
146
147
Py-TSOH
148
n BuLi
CHO
CH3
HO
H
149

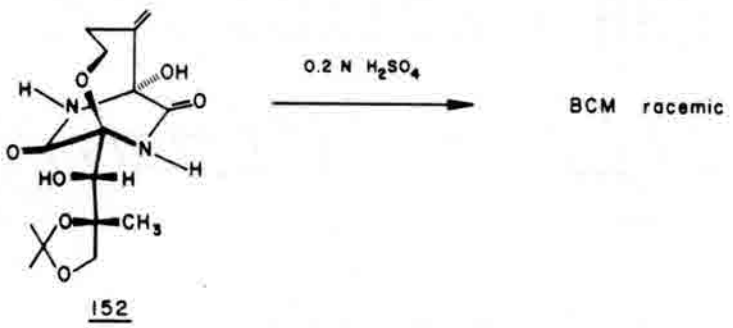
SCHEME 18 (continued)




150




151



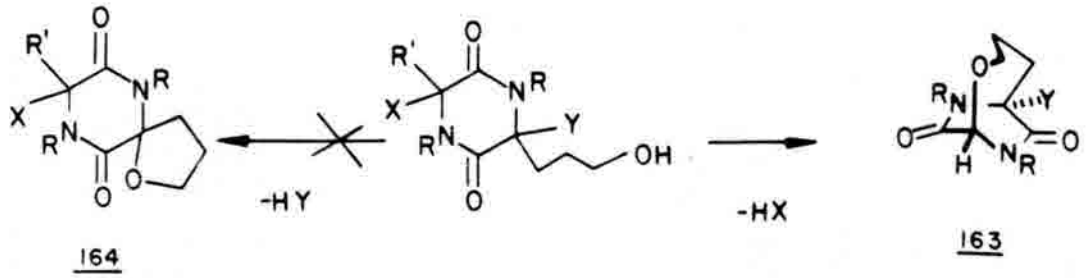

152

# CHAPTER II

# BICYCLIC MODEL STUDIES

The initial studies directed at the total synthesis of bicyclomycin involved developing methodology which would allow for the efficient construction of the bicyclic ring system 163 without competing formation of the undesired spiro product 164, and subsequent functionalization of the bicyclic compound 163. Two results from the work of Williams molded the synthetic strategy described herein.

EQUATION I



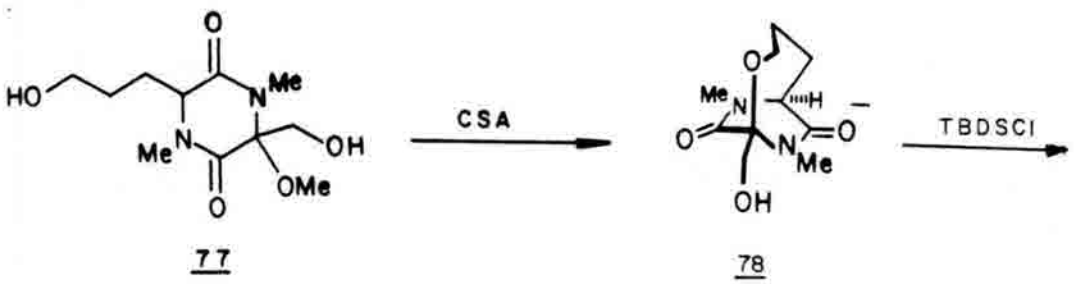

164 163

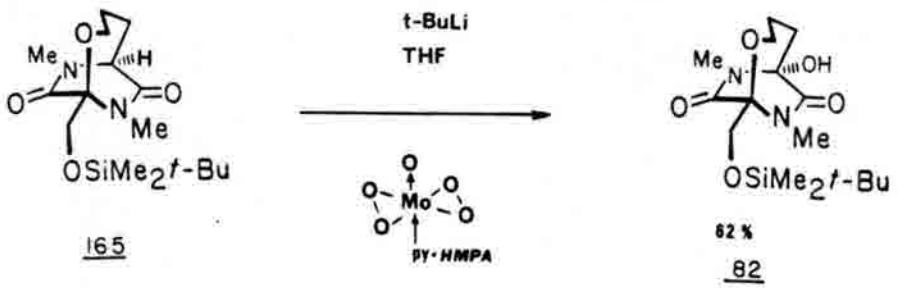
Williams had shown that a viable approach to 163 was through an acylic precursor which in effect contained only one leaving group (X = OMe, Y = H) and thus by default led to a non-spiro bicyclic product. The lack of an activating group at carbon-6 (Y = H) meant that the tertiary hydroxy group (Y = OH) found in the natural product would have to be introduced at the bicyclic-stage. This was done by quenching the bridgehead anion (Scheme 19) of the bicyclic derivative 166 with MoOPh affording the alcohol 82. This simple two step cyclization/oxidation provided an elegant solution to the cyclization problem (164 vs 163).

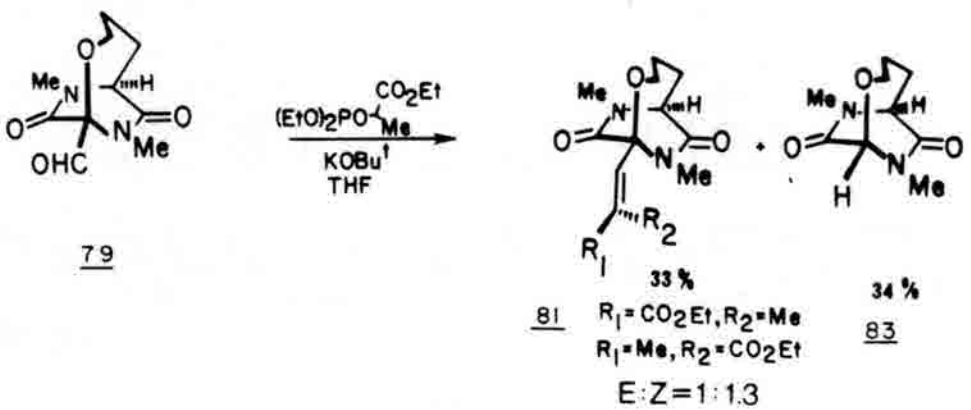
The second observation made by Williams was that upon reaction of aldehyde 79 (obtained by Swern oxidation of the primary alcohol 78) with the phosphonate 80, a cis/trans mixture of olefins 81 as well as the deformylated adduct 83 were obtained. The latter product resulted from decomposition of the initial addition intermediate 167 via retro-aldol cleavage of the C-1 bridgehead carbon-carbon bond affording the aldehyde and the bridgehead anion which upon workup afforded the simple bicyclic piperazinedione 83. The structure of 83 was assigned unambiguously by single crystal X-ray analysis (Figure 1). Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of 83 are available upon request. Treatment of 83 with t-butyllithium of $-78^{o}C$ followed by addition of methyl iodide afforded a mixture of monoalkylated products 168 and 169 (Scheme 19), a result of anion formation at either bridgehead carbon. This observation suggested that it might be possible to not only oxidize the C-6 bridgehead anion, but to also condense the C-1 bridgehead anion with a suitable sidechain equivalent, all from the simple unfunctionalized bicyclic piperazinedione 83. If it were possible to selectively introduce substituents at the bridgehead positions, not only would this approach lead to the total synthesis of bicyclomycin, but more importantly, it would result in a versatile method of synthesizing a large number of derivatives and analogs of bicyclomycin starting from a simple bicyclic compound such as 83. This concept we've referred to as regioselective bridgehead functionalization.

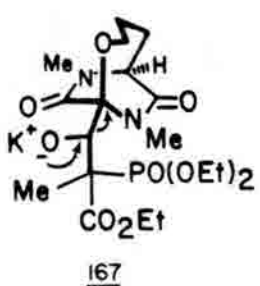
The first step in probing the selectivity of functionalization was the synthesis of a number of simple bicyclic compounds with different

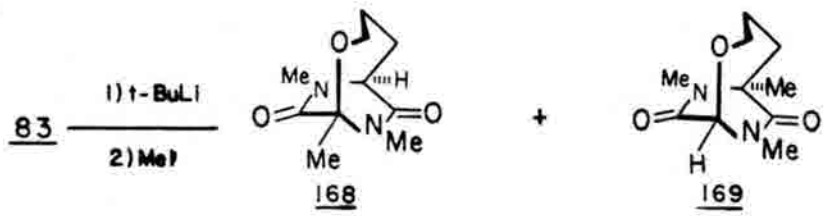
SCHEME 19


HO
Me
N
O
Me
N
OH
OMe
O
77
CSA
Me
N
H
O
N
Me
OH
78
TBDSCI


Me
N
H
O
N
Me
OSiMe2t-Bu
165
t-BuLi
THF
Mo
O
py·HMPA
OH
82 %
82


Me
N
H
O
N
Me
OHC
79
(EtO)2PO
CO2Et
Me
KOBut
THF
R1
R2
33 %
81
R1=CO2Et, R2=Me
R1=Me, R2=CO2Et
E:Z=1:1.3
34 %
83


Me
N
H
O
N
Me
K+O
Me
PO(OEt)2
CO2Et
167



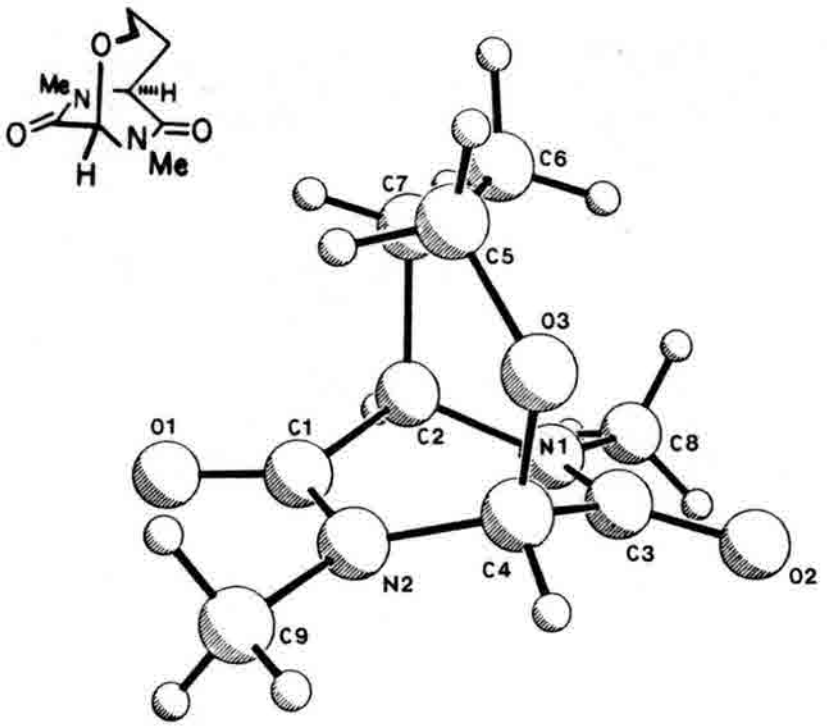



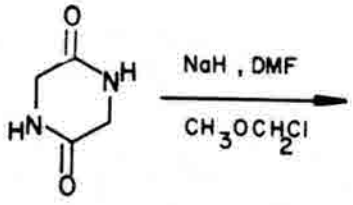

FIGURE 1. X-RAY structure of compound 83.

protecting groups on the amides. Instead of using the circuitous deformylation approach described above, a new efficient synthesis of bicyclic diketopiperazines was developed.[33]

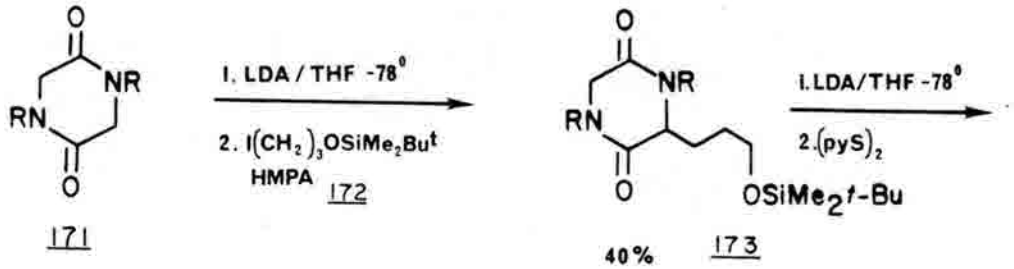
Treatment of glycine anhydride with base (NaH, DMF), followed by addition of chloromethyl methylether afforded the piperazinedione 171 in 50% yield (Scheme 20). Generation of the lithium enolate (LDA) of 171 in the presence of HMPA followed by quenching with 3-[(tert-butyldimethylsilyl)oxy]-1-iodobutane 172 afforded the alkylated diketopiperazine 173 in 41% yield. Formation of the kinetic enolate of 173 followed by condensation with 2,2'-dipyridyl disulfide resulted in the syn (with respect to the diketopiperazine ring) pyridyl thioether 174. The silyl ether was quantitatively converted to the alcohol 175 in the presence of tetra-n-butylammonium fluoride, and stirring of a THF solution of 175 in the presence of silver perchlorate cleanly afforded the desired unfunctionalized bicylcic diketopiperazine in excellent yields (>90%). This efficient cyclization reaction deserves further comment.

It is of interest to note thate in one attempt at the cyclization of the alcohol 174 in the presence of $\emptyset Hg(ClO_4)$, the bridgehead oxidized bicyclic compound 178 (equation 2) was the only product isolated. This is the first example we have analyzed which resulted in concomitant deprotection/cyclization and bridgehead oxidation in one step. The only source of $-OCH_3$ is the methoxymethyl protecting group on the amides since the reaction never comes in contact with methanol or any other source of $-OCH_3$ either before or after workup. This result has never been repeated.

SCHEME 20



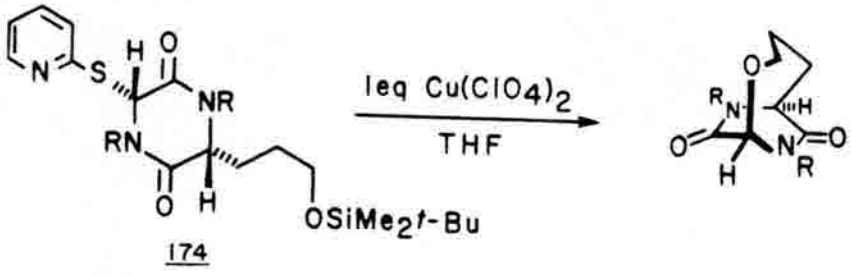

170




171

40%

173



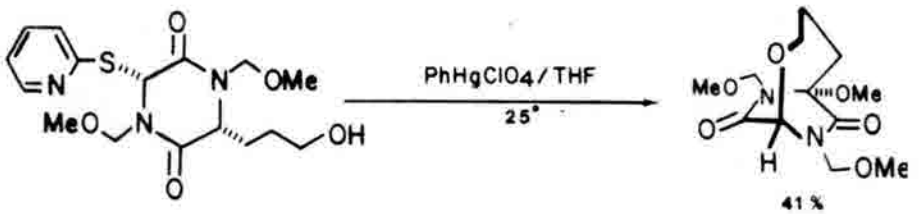

174

176

R= $CH_2OCH_3$

$CH_3$
$CH_2Ph$
$CH_2Ph$-p-OMe
Ph-p-OMe

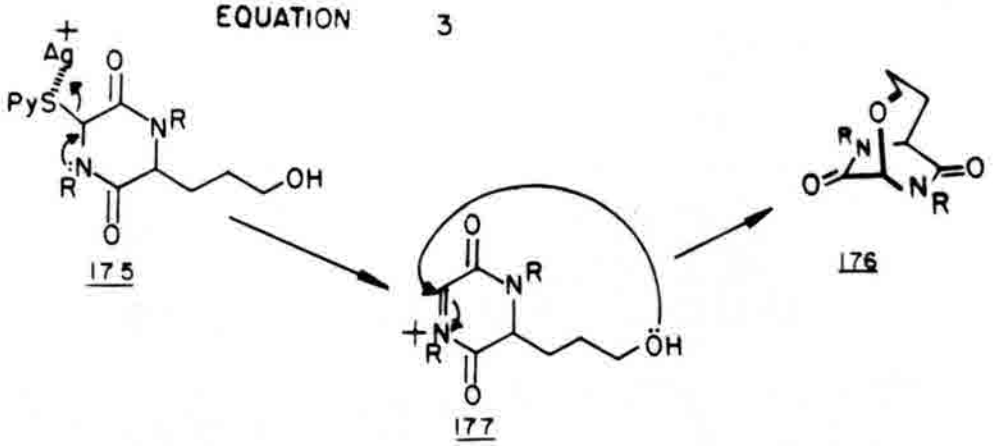
EQUATION 2




174 178

The mechanism of the cyclization reaction (174 176) appears to involve formation of an imminium intermediate 177 which undergoes intramolecular nucleophilic substitution affording the bicyclic product 176 (equation 3).

EQUATION 3




175 177 176

Compared to the mild conditions (THF, room temperature, 1 hr) used in this cyclization, the efficiency of cyclization reactions published by other workers (Maag, Nakatsuka) are consistently lower and require forcing conditions, indicating that the pyridylthioether activating group is very efficient in the formation of the imminium ion intermediate in the presence of the thiophilic Lewis acid silver perchlorate.

TABLE III

| Entry | Reagent | Equiv. | Temp. | Time | Substrate R | Substrate R' | Substrate R" | Isolated Yield of 178 |
|---|---|---|---|---|---|---|---|---|
| 1 | $Cu(ClO_4)_2$ | 2 | 25°C | 9h | $CH_2Ph$-p-OMe | H | TBDMS[a] | 91 |
| 2 | $AgClO_4$ | 2 | 25°C | 12h | | | | 89 |
| 3 | $Hg(ClO_4)_2$ | 3 | 25°C | 60h | | | | 88 |
| 4 | $Fe(ClO_4)_3$ | 3 | 25°C | 120h | | | | 60 |
| 5 | $Ni(ClO_4)_2$ | 2 | 25°C | 24h | | | | 84 |
| 6 | $Pb(ClO_4)_2$ | 2 | 25°C | 120h | | | | 87 |
| 7 | $Mg(ClO_4)_2$ | 2 | reflux | 96h | | | | 0 |
| 8 | $PhHg(ClO_4)$ | 3 | reflux | 2h | | | | 80 |
| 9 | $Tl(ClO_4)_3 \cdot 6H_2O$ | 0.9 | 25°C | 24h | | | | 57 |
| 10 | $PhHg(ClO_4)$ | 3 | 25°C | 0.5h | $CH_2Ph$ | $CH_2OMs$[b] | TBDMS | 78 |
| 11 | $PhHg(ClO_4)$ | 1 | 25°C | 0.3h | | $CH_2OTBDMS$ | TBDMS | 54[c] |
| 12 | $PhHg(ClO_4)$ | 2.15 | 25°C | 0.3h | | | | 81 |
| 13 | Ag(OTf) | 1.2 | 25°C | 0.25h | | $CH_2OTBDMS$ | H | 85 |
| 14 | Ag(OTf) | 4 | 25°C | 0.25h | | | | 91 |
| 15 | $Hg(ClO_4)$ | 1.5 | 25°C | 0.5h | | $CH_2OH$ | H | 73 |
| 16 | AgOTf | 1.5 | 25°C | 0.5h | | | | 95 |
| 17 | $Cu(ClO_4)_2$ | 1 | 25°C | 12h | $CH_2$-Ph-p-OMe | $CH_2OMS$ | TBDMS | 83 |
| 18 | AgOTf | 1 | 25°C | 1h | | $CH_2TBDMS$ | H | 85 |

a) tert-Butyldimethylsilyl

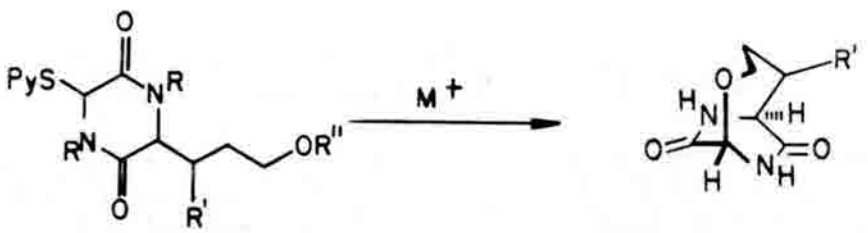
b) Methanesulfonyl

c) Mixture of bicyclic alcohols

The scope and limitations of this cyclization reaction have now been thoroughly investigated, and the results are presented in Table III. Unlike the N-methoxy methyl series where silyl ether removal is obligate for bicyclic compound formation, cyclization of the pyridyl thioether silyl ether compounds 178 (Scheme 21) lead directly to the bicyclic products 179 via a concomitant silyl ether cleavage/cyclization reaction.

Examination of the data in Table III (entries 1-9) reveals that the metal cations $Cu^{++}$, $Ag^{+}$, $Hg^{++}$, $Tl^{+++}$, $Pb^{++}$, $Fe^{+++}$, and $Ni^{++}$ as their perchlorate salts all yield cyclization products 179, except for $Mg^{++}$ which failed to produce any product. Although most of the perchlorate salts were azeotropically dried, the hydrated reagents $Tl(ClO_4)_5 \cdot 6H_2O$ and $Cu(ClO_4) \cdot 6H_2O$ yielded product without significant hydrolysis at C-1. (Entries 1-9 were prepared by Dr. J. S. Dung). In the special case where R' is a substituent other than hydrogen, careful

SCHEME 21




179

180

R = $CH_3$
$CH_2Ph$
$CH_2Ph$-p-OMe
Ph-p-OMe

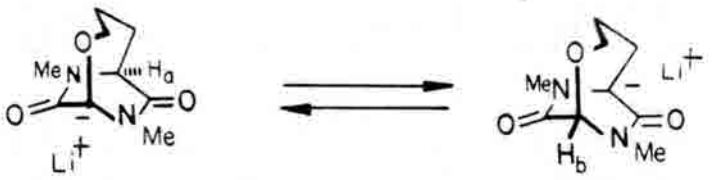
selection of the Lewis acid affords bicyclic compound. The mesylate (entry 17) can readily be cyclized in one step in the presence of $Cu(ClO_4)_2$ to afford the bicyclic product with the methane sulfonyl moiety intact, indicating that the deprotection/cyclization conditions are mild enough to tolerate other functionalities on the molecule. The N-benzyl mesylate (entry 10) also afforded the desired bicyclic product in the presence of $PhHg(ClO_4)$ in good yield (78%).

When Ag(OTf) is utilized to effect the deprotection/cyclization reaction (178 → 179), the reaction proceeds at a very slow rate, whereas treating the alcohol (R'=R''=H) with $Ag(ClO_4)$ results in immediate formation of bicyclic product, suggesting that the deprotection of the silylether by the triflate ion is the rate limiting step and is not as efficient as the perchlorate ion. Keeping this rate difference in mind, it is possible to cyclize the precursor 178 where one hydroxy substituent is the silyl ether (R') and the other is the alcohol (R) (entries 13, 14, 16) in the presence of AgOTf, and obtain the bicyclic product 179 without deprotection of the silyl ether. This selectivity is very important in the syntheses of bicyclomycin described in subsequent chapters. If several additional equivalents of AgOTf are added to the reaction mixture containing the bicyclic silyl ether (179, R'=TBDMS), the bicyclic alcohol (179, R'=OH) can be readily obtained in almost quantitative yield. When both intramolecular nucleophilic oxygens are silyl ethers (entries 11 and 12) a random assortment of every protected and/or deprotected bicyclic compound was obtained. Finally, when 178 is a simple diol (entries 15 and 16) cyclization affords mixtures of the seven- and/or eight-membered ring

bicyclic structures. This latter cyclization will be discussed in detail in Chapter III.

Having established a short and efficient synthesis of the unfunctionalized bicyclic compounds of the type described by structure 180 (R'=H), and as a result of the observations made by Williams on the deformylation product 83, it was now necessary to thoroughly investigate the selectivity of functionalization of the bridgehead anions, that is, to determine the competitive acidities of $H_A$ and $H_B$ (Scheme 22). The [3.2.2] bicyclic homolog containing one less carbon in the bridging fragment was also included in this study, and demonstrated the identical behavior displayed by the large [4.2.2] bicyclic compound.

SCHEME 22




181 182

An extensive study was undertaken by Dr. J. S. Dung in our laboratories, the results of which can be summarized as follows. When the bridgehead anion is formed under kinetic control (LDA, -78°C, THF) and is immediately quenched (30 seconds) with an electrophile, at best a 3:2 mixture of products favoring alkylation of the bridgehead carbon adjacent to the bridging ether (C-1) is obtained, indicating a slight preference for deprotonation of $H_B$. Alternatively, when the bridgehead anion is formed under thermodynamic control (LDA, HMPA, -78°C, THF) and

reacted with an electrophile after an elapsed period of time between 30 minutes and 1 hour, a 50:1 ratio of the alkylation product at the carbon adjacent to the bridging methylene is isolated, indicating that $H_A$ is thermodynamically more acidic. A similar trend was observed in the bicyclo[3.2.2] analog 183 which contains the hydroxyethyl bridging fragment.

Because of the symmetrical nature of the diketopiperazine, the differences in kinetic and thermodynamic acidities of the bridgehead protons must be due to the electronic effects of the bridging oxygen vs. the bridging methylene. It would appear that oxygen exerts a net destabilizing effect on the adjacent bridging carbanion due to electrostatic repulsion of the two vicinal electron pairs. When HMPA is present, separation of the lithium-carbanion ion pair should increase electron density on the bridgehead carbon increasing the repulsive interaction at carbon-1 ($H_B$) thus making the carbanion of $H_A$ thermodynamically more stable (Figure 2).

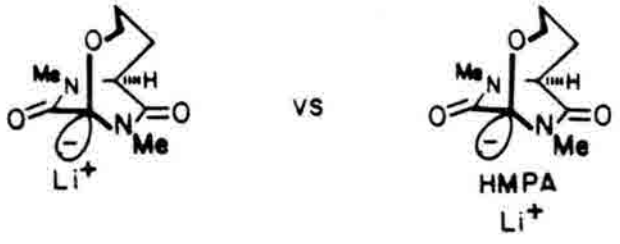



FIGURE 2

The nature of the bridgehead carbon-hydrogen bonds of the bicyclic diketopiperazine were investigated using $^{13}C$ NMR in an attempt to justify the observed acidities of $H_A$ and $H_B$, because unlike the monocyclic diketopiperazine anion being stabilized through resonance

delocalization, the bicyclic bridgehead anions (especially the seven-membered ring 183) are likely $sp^3$ in character since formation of the "bridgehead" enolate would be a violation of Bredt's rules. The true carbon-hydrogen coupling constants obtained by $^{13}C$-NMR can be used to determine the percent s-character of a given C-H bond by the following relationship:

$$J=_{C-H}=K_{C-H}Si$$

where Si is the fractional s character of the bond, and $K_{C-H}$ is an empirical relationship which is found to be approximately 500 Hz for compounds which do not contain polar substituents (ie., alcohols, acids). Table IV describes the $^{13}C$ NMR data for compounds 83 and 183, including the $^{13}C$-H coupling constants for each bridgehead carbon.

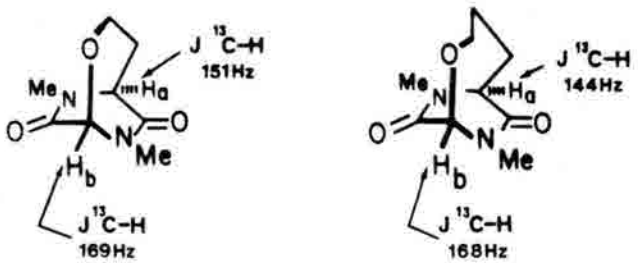
TABLE IV

| Compound 83 | | | | Compound 183 | | | |
|---|---|---|---|---|---|---|---|
| carbon | ppm[a] | multi-plicity[b] | J, Hz[c] | carbon | ppm[a] | multi-plicity[b] | J, Hz[c] |
| C-1 | 84.66 | d | 167.9 | C-1 | 87.06 | d | 169.12 |
| C-3 | 63.82 | t | | C-3 | 62.17 | t | |
| C-4 | 31.41 | t | | C-4 | 28.07 | t | |
| C-5 | 25.16 | t | | C-5 | 60.69 | d | 150.88 |
| C-6 | 61.12 | d | 143.9 | C-6 | 164.9 | s | |
| C-7 | 164.6 | s | | $N_7$-$CH_3$ | 32.23 | q | |
| $N_8$-$CH_3$ | 31.63 | q | | C-8 | 170.8 | s | |
| C-9 | 169.7 | s | | $N_9$-$CH_3$ | 31.99 | q | |
| $N_{10}$-$CH_3$ | 31.63 | q | | | | | |

a) The Chemical shifts of each carbon atom were determined from a noise-decoupled $^{13}C$ NMR spectrum. b) The multiplicities of each signal were determined by an off-resonance $^{13}C$ NMR spectrum. c) The J($^{13}C$-H) were obtained from a fully coupled $^{13}C$-H NMR spectrum.

Because s-orbitals are more compact than p-orbitals, the more s-character a bond has the more acidic the proton will be since the resulting anion will be held closer to the carbon nucleus.

Streitweiser[34] has successfully shown that in certain cases information on the s-character of a given C-$H_X$ bond may be used to determine the relative kinetic acidity of Hx. As shown in Figure 3, the eight-membered ring diketopiperazine 83 exhibits bridgehead $^{13}$C-H coupling constants of 143.9Hz and 167.9Hz for $H_A$ and $H_B$ respectively, which results in a 5% higher s-character for the bridgehead carbon-hydrogen bond adjacent to the bridging oxygen. This greater s-character would indicate that $H_B$ should be kinetically more acidic, a fact which correlates well with the experimental results for the kinetic quenching of the carbanion derived from 83. The same




183 83

29-34% S character

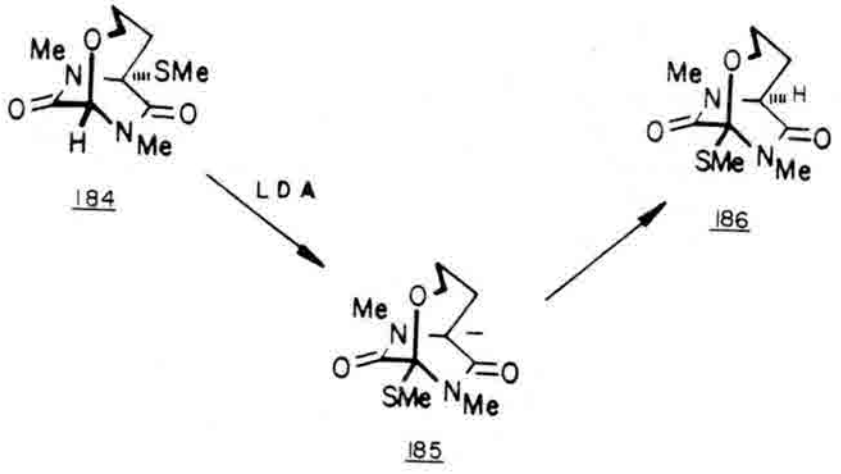
FIGURE 3

correlation of spectroscopic data and experimental results were observed for 183. Due to practical experimental limitations, true kinetic control was never achieved, though experimental reuslts show a trend to exclusive deprotonation of $H_B$. The high degree of s-character of the bridgehead C-H bonds might be responsible via hybridization for the acidity of these protons since the enolate resonance structure is

most likely geometrically inaccessible. The s-character of the C-$H_B$ bond of 83 (34% s) would appear to be more in line for that of an $sp_2$ hybridized carbon (33.3% s) than an $sp_3$ hybridized carbon (25% s).

Further proof of the thermodynamic stability of the carbanion 182 came from the unexpected rearrangement described below (Scheme 23). Treatment of the bicyclic thioether 184 with LDA at -78°C (kinetic conditions) resulted in rearrangement to the regioisomer 186. The intermediacy of the bridgehead anion 185 was confirmed by condensation with methyl iodide followed by Raney-nickel desulfurization to afford the methylated derivative 169 which had been previously synthesized from the unfunctionalized bicyclic compound (Scheme 19). Since it was

SCHEME 23

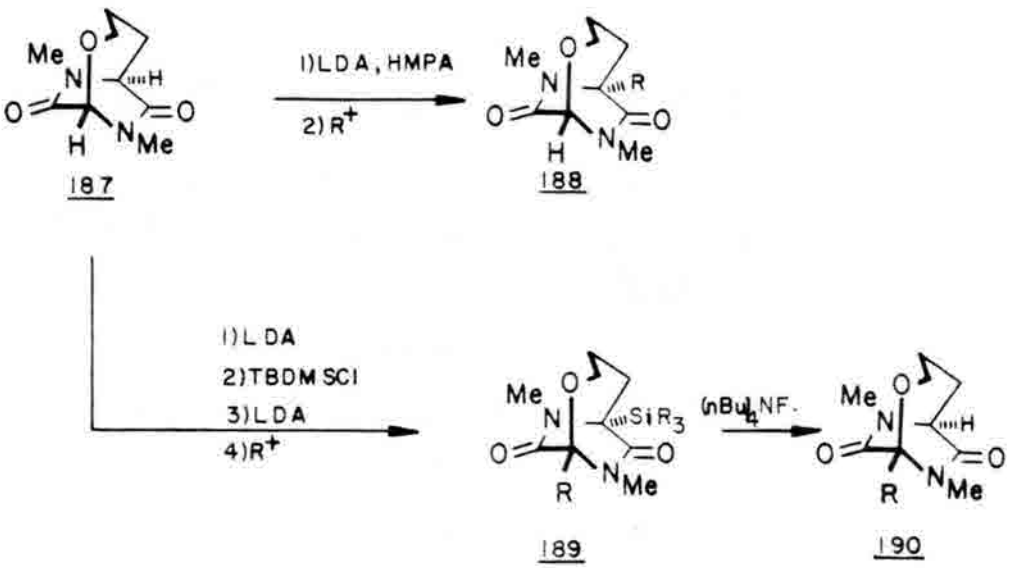



184 185 186

possible in one step to exclusively alkylate the C-6 bridgehead carbon under thermodynamic conditions to obtain the C-6 monosubstituted bicyclic product 188, a one-pot method was developed that would allow for the synthesis of C-1 monosubstituted regioisomers (Scheme 24). Generation of the C-6 bridgehead anion of 187 under thermodynamic conditions (LDA, HMPA, THF) followed by addition of trimethylsilyl

chloride afforded the bridgehead silyl derivative; addition of a second equivalent of LDA and quenching with an electrophile furnished the substituted derivative 189 which could be desilylated with tetra-n-butylammonium fluoride to afford the C-1 monosubstituted product 190.

SCHEME 24



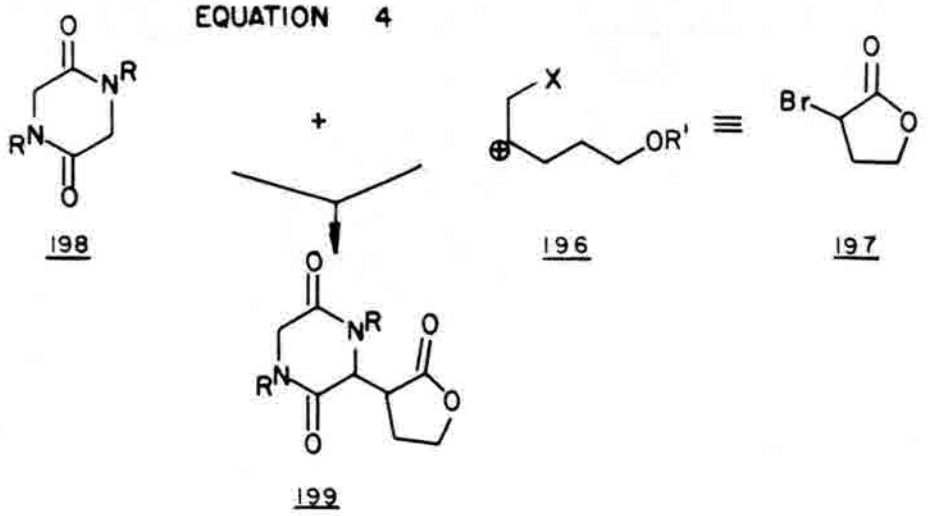

Having established conditions for regioselective functionalization of the bridgehead anions, members of our research group carried out the synthesis of the bicyclomycin analog 195 (Scheme 25) by selectively activating carbon-6 (thermodynamic control). Generation of the lithium anion of 83 and subsequent quenching with MoOPh afforded the tertiary alcohol 192, which when treated with two equivalents of base (the alcohol is protected as the lithio species 193) followed by the "Maag" aldehyde 18 afforded the desired aldol product 194 as a mixture of diastereomers, the predominant isomer being the correct one. This was rigorously established through a single crystal X-ray analysis of 194. Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal

structure of 194 are given in Appendix I. The isopropylidene derivative 194 could be converted to N,N-dimethyl 6-des-methylene bicyclomycin 195 when treated with mild acid (0.1 N $H_2SO_4$/MeOH).

At this point we had developed an efficient synthesis of 1,6-unfunctionalized bicyclic compounds and having successfully regioselectivity functionalized the bridgehead carbons, the remaining obstacles to the total synthesis (Scheme 25) were a) introduction of an exomethylene at carbon-5, and b) selection of a suitable protecting group for the amide nitrogens which could withstand the vigors of a multistep synthesis and yet be labile enough to be removed at a late stage in the synthesis.

The problem of introducing an exomethylene moiety centered about finding an isoleucine analog such as 196 which might contain a functionality X which could be used as a "handle" for olefin formation. Using the same methodology developed for the simple desmelthylene bicyclic compounds, condensation of the lithium enolate of a monocyclic piperazinedione 198 would result in a hydroxypropyl derivative 199 with a latent hydroxymethyl "handle" essential for the olefin synthesis.

EQUATION 4




198 196 197

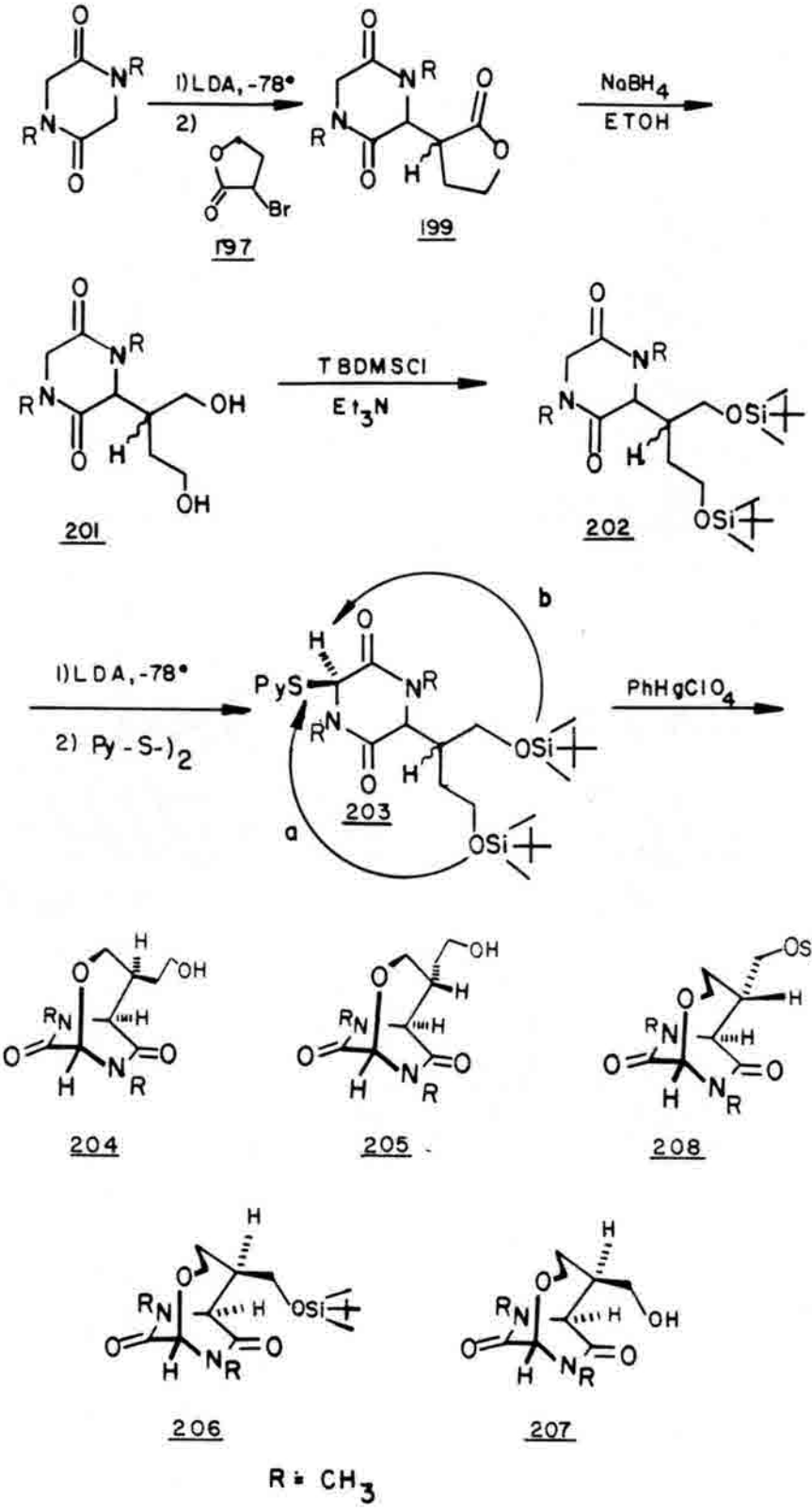
199

After discarding a large number of isoleucine analogs due to lack of reactivity, the lithium enolate of N,N'-dimethyl glycine anhydride was successfully condensed with α-bromo-γ-butyrolactone 197 to afford the lactone piperazinedione 199 (equation 4). Although the yield was quite low, it allowed us to investigate the synthesis of the exomethylene bicyclic adduct.

The butyrolactone condensation (Scheme 26) resulted in a mixture of two diastereomers which could be reduced with sodium borohydride to give the diol mixture 201. Protection of the alcohols with t-butyldimethylsilyl chloride resulted in the silyl ethers 202 which could be treated with base (LDA) and condensed with 2,2'-pyridyldisulfide to give the thioether 203. Unlike the previous cyclization reactions, the bicyclic precursor possessed two intramolecular nucleophiles which could lead to desired eight-membered ring bicyclic products (path a) or undesired seven-membered ring (path b) ones. Subjecting the thioether 203 to cyclization conditions (2 equiv, $PhHgClO_4$) gave a mixture of five bicyclic compounds. The seven-membered ring isomers 204 and 205 arise via path b, and the eight membered ring isomers went through path a. Compound 206 also contained the silyl ether moiety which was surprising in lieu of the fact that it was shown in Table III that $PhHgClO_4$ will deprotect silyl ethers under similar conditions. The pair of isomeric seven- and eight-membered rings were generated because the starting acyclic precursor was a mixture of compounds diastereomeric at what had been the α-carbon of the lactone. The combined yield for the cyclization was 92%.

The mixture of diastereomeric alcohols 204 and 205 were converted to the corresponding mesylates (MsCl, THF, $Et_3N$) 209 and 210 (Scheme

SCHEME 26

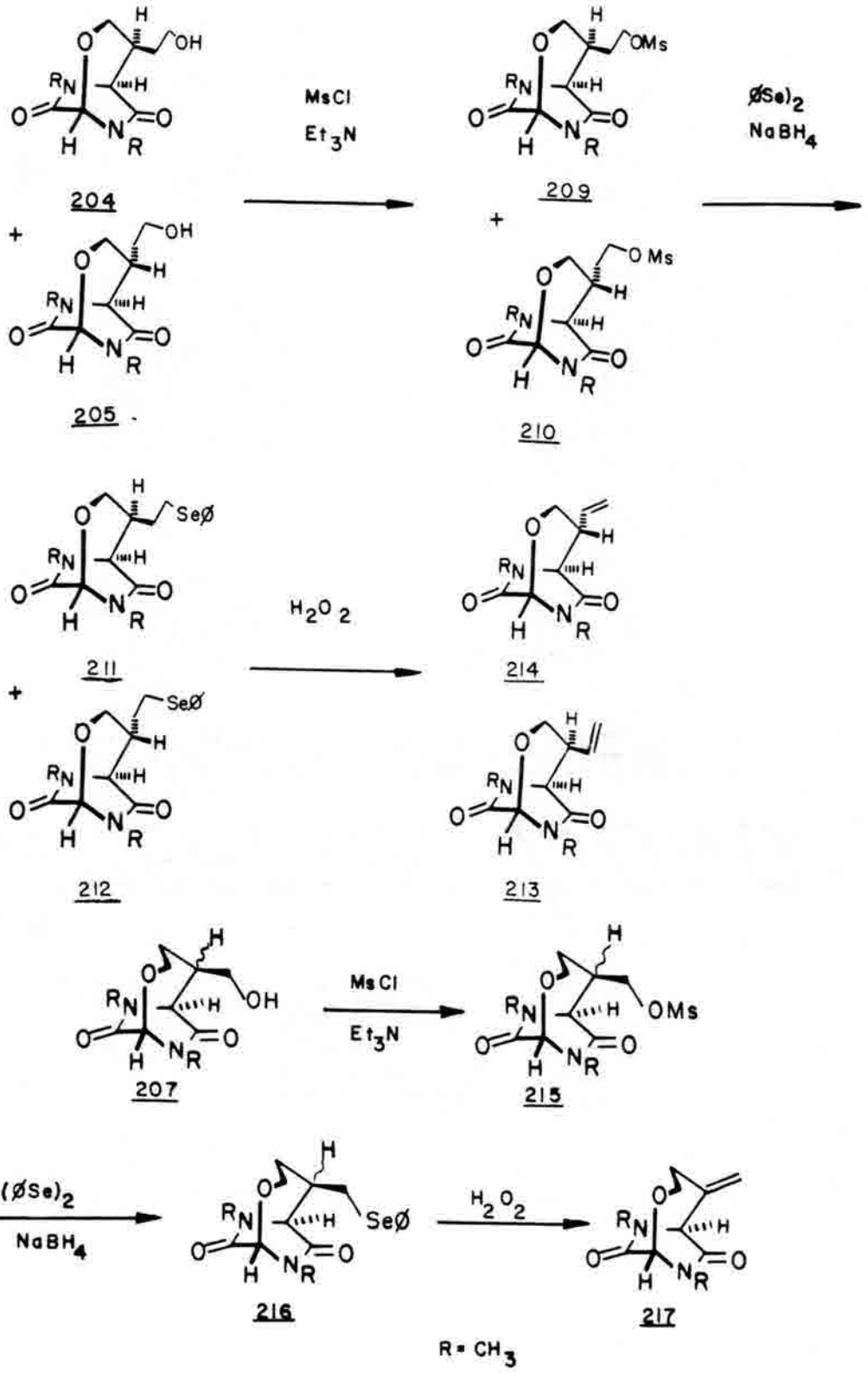

1) LDA, -78°
2)
NaBH4
ETOH
TBDMSCl
Et3N
1) LDA, -78°
2) Py-S-)2
PhHgClO4
a
b
197
199
201
202
203
204
205
208
206
207
R = CH3

27), then to the selenides 211 and 212 in overall 90% yield. The selenides were oxidized with $H_2O_2$ and without isolation the selenoxides were eliminated to obtain the mixture of olefins 213 and 214 which were easily separable by chromatography.

Using the same procedure described above, the mixture of eight-membered ring bicyclic alcohols 207 and 208 were mesylated, displaced with the selenide ion, oxidized and eliminated to give the same bicyclic exomethylene product 217 (Scheme 27) in minute quantities.

By synthesizing the bicyclic exomethylene piperazinedione 217, the isoleucine equivalent α-bromo-γ-butyrolactone was successfully used in the construction of the exomethylene moiety. The remaining problem to address was the selection of an amide protecting group, and at the time this synthesis was begun there were few if any examples of removable base-stable protecting groups for amides. It was decided to use the N-benzyl group since preliminary results from our laboratories and others indicated it might be reductively cleaved ($Li/NH_3/(\emptyset CH_2)_2O$; $H_2$, Pd/C). Chapter 3 describes the total synthesis of bicyclomycin.

SCHEME 27


MsCl
Et3N
(ØSe)2
NaBH4
H2O2
MsCl
Et3N
(ØSe)2
NaBH4
H2O2
204
205
209
210
211
212
213
214
207
215
216
217
R = CH3

# CHAPTER III

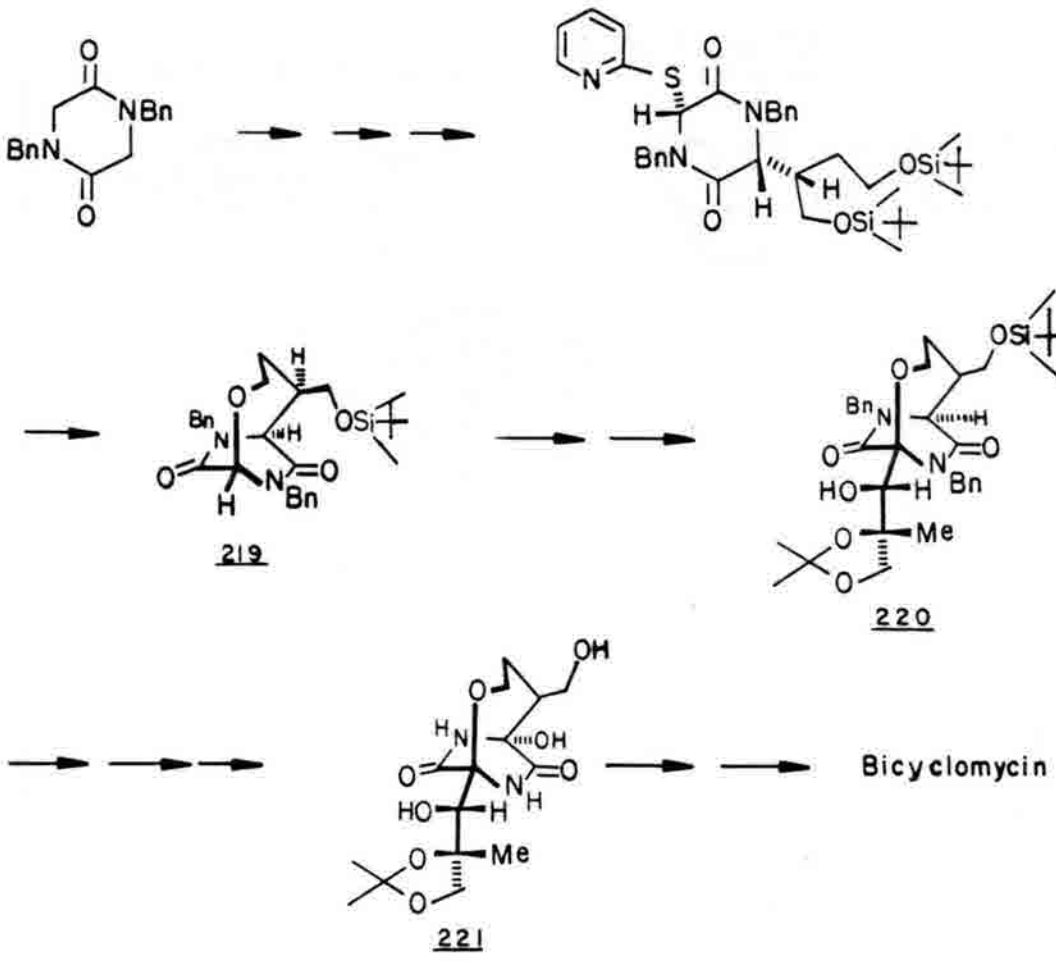
# THE SYNTHESIS OF BICYCLOMYCIN

Having developed the requisite chemistry to construct the simple exomethylene bicyclic compound 217, the synthesis of bicyclomycin appeared to be straightforward, and is described in Scheme 28. Selective bridgehead functionalization would furnish the fully substitute piperazinedione 220, which could be converted in the key deprotection step to give the free amide compound 221. Using standard elimination chemistry it would be possible to construct the exomethylene to give the racemic 2',3'-acetonide of bicyclomycin 216. Under dilute acid conditions (0.1 N $H_2SO_4$) naturally occurring bicyclomycin acetonide can be converted to bicyclomycin in good yields. Deprotection of the bridgehead functionalized compound had to be carried out on the hydroxymethyl derivative 220 due to the choice of N-benzyl protecting groups on the amides; the anticipated reductive deprotection conditions, ie., sodium or lithium in liquid ammonia or hydrogenation using palladium on carbon, were perceived to be incompatible with the exomethylene moiety.

Using the same methodology which was developed in the N-methyl series, we were disappointed to find that the condensation reaction of the N-benzyl diketopiperazine enolate with α-bromo-γ-butyrolactone gave none of the desired coupling product 218 (equation 5).

Although the yield in the N-methyl series was low (~12%), it was possible, due to cheap starting materials and being the first step in the synthesis, to obtain sufficient quantities of coupling product to have demonstrated a viable exomethylene synthesis.

SCHEME 28



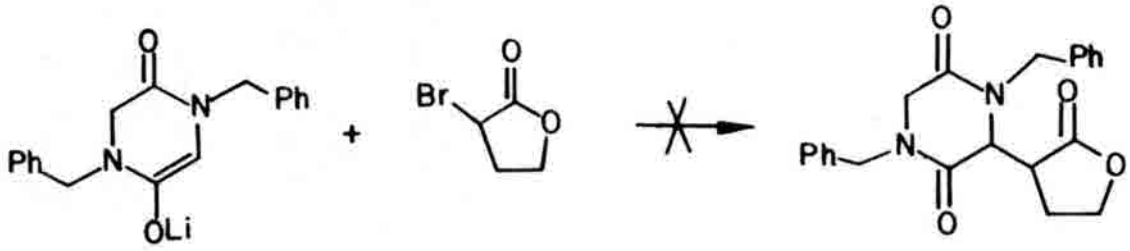

219

220

221

Bn = benzyl

EQUATION 5



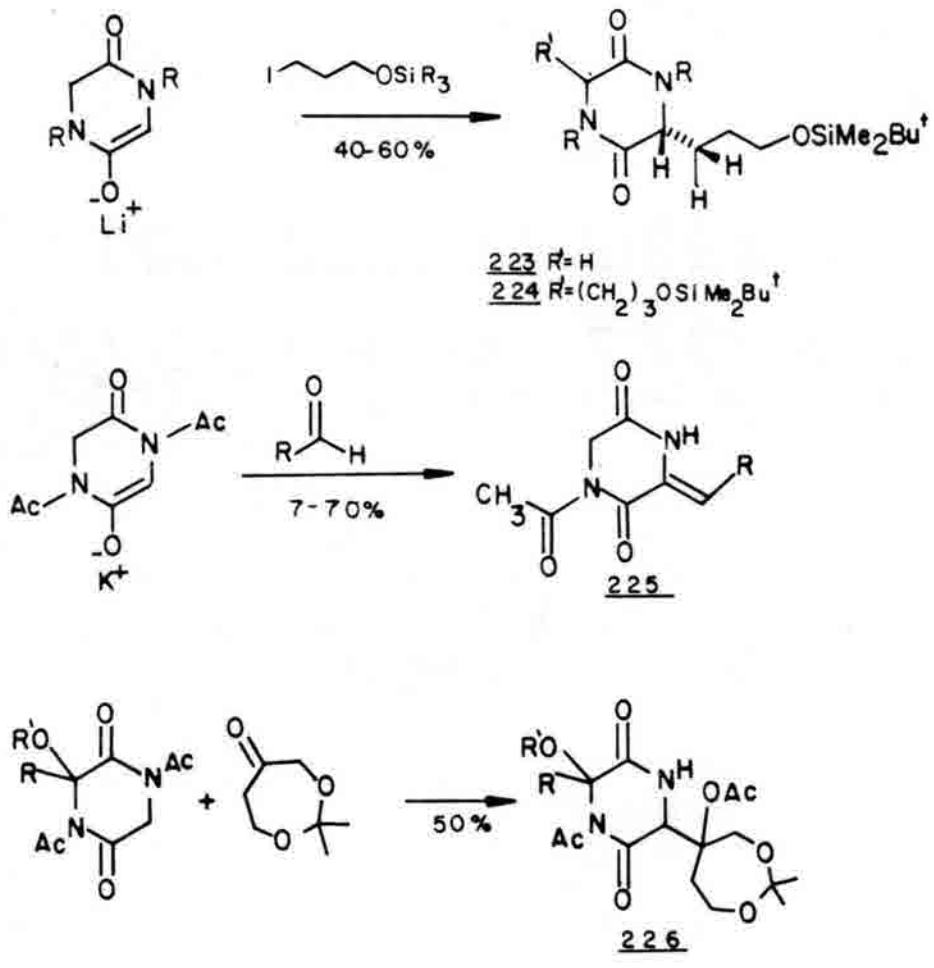

218

Searching the literature it was found that there are very few electrophiles which condense with high efficiency to form new carbon-carbon bonds with diketopiperazines. We had shown that condensation of the lithium enolate of a variety of N-protected diketopiperazines with primary iodides gave the desired products, but the yields were never much above 50%, and the major side reaction was the bis-alkylation of the cyclic amide (Scheme 29). Satisfactory yields of the monoalkylated product were obtained only when HMPA was used.

Gallina[35] and coworkers have had some success with coupling the potassium enolate of N,N-diacetyl glycine anhydride with a number of aliphatic and aromatic aldehydes in moderate yields. The driving force for the reaction appears to be the intramolecular trapping by the alkoxy intermediate of the neighboring N-acetate closest to the nucleophilic carbon. This subsequently eliminates acetic acid and after workup gives the mono-N-acetate diketopiperazine olefin 225, which is predominantly cis-with respect to the amide (N-H) and the precursor aldehyde substituent. The authors state that ketones do not react under these conditions. This synthesis exhibits severe limitations as to the choice of electrophiles and the product obtained. In the case of aliphatic aldehydes, the yields are consistently less than 30%.

Contrary to the results of Gallinas work, Maag has found that at least in one case a ketone successfully coupled with the diketopiperazine in moderate yield (41%) to give the O-acetate intermediate 226, with less than 5% elimination. As previously seen, the driving force for this reaction is intramolecular trapping of the proximal N-acetate.

SCHEME 29

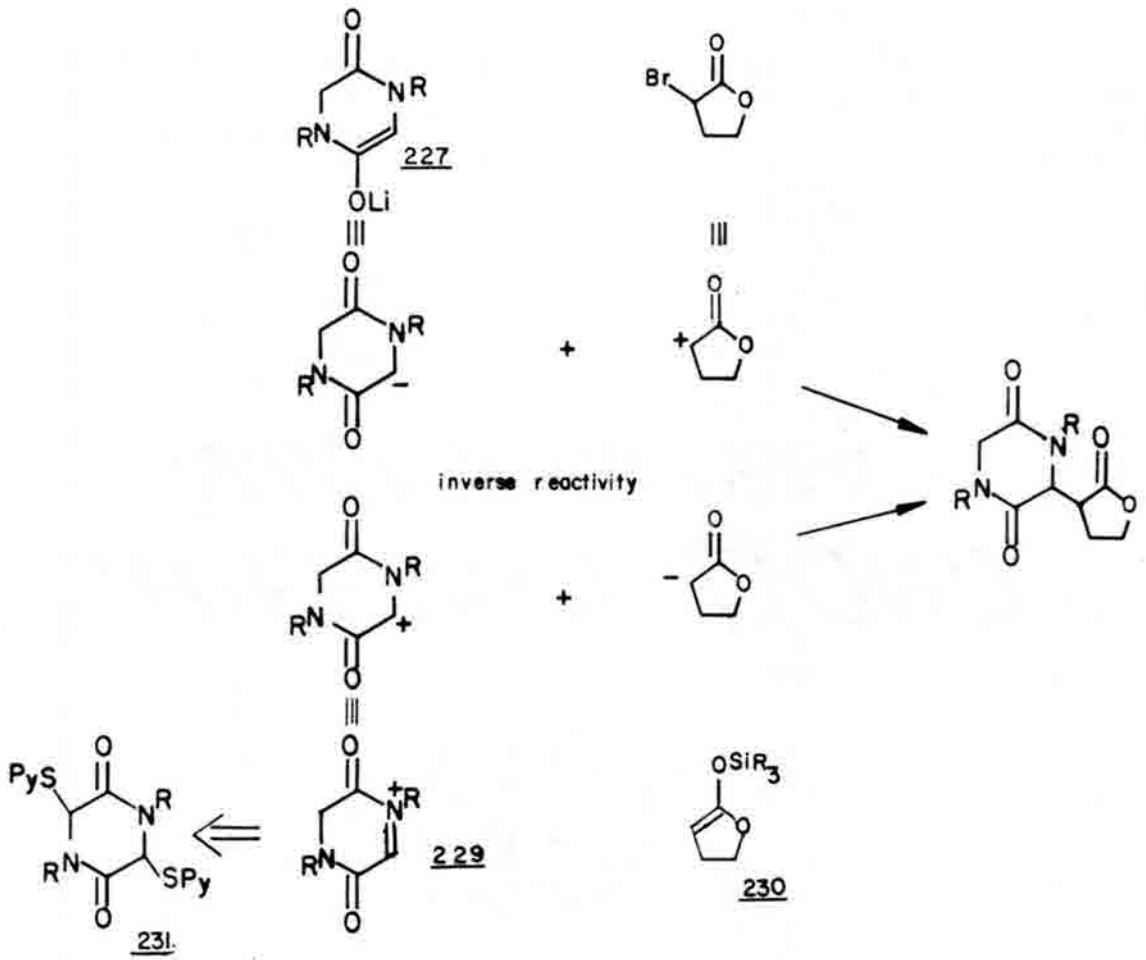

I
OSiR3
40-60%
OSiMe2Bu^t
223 R'= H
224 R'= (CH2)3OSiMe2Bu^t
Ac
K+
7-70%
225
50%
OAc
226

Coupled with our own work, the results of this study seem to indicate that the lack of success in forming the carbon-carbon bond is due to the low reactivity of the nucleophile rather than the nature of the electrophile. Two aspects define the problem of the nucleophile: 1) the enolate anion (lithium or potassium) of the diketopiperazine is very stable, and 2) the low solubility of both the diketopiperazine and the enolate anion are very low. It appears that the more substituted the diketopiperazine, the higher the yields observed upon condensation. This is probably due to an increase in solubility due to the aliphatic or aromatic substitution of the other α-methylene. For our purpose, since we wished to start our synthesis with an unsubstituted glycine anhydride, we were forced to conclude that the diketopiperazines were not good nucleophiles and were unsuitable for our synthesis.

At this point it occurred to us that the solution to the problem, the efficient synthesis of the carbon-carbon bond of the substituted diketopiperazine, rested in the reversal of reactivity of the substrates (Scheme 30). That is, the lactone becomes the nucleophile (230), and the piperazinedione α-carbon becomes the electrophile (229). This was a reasonable approach since we had already shown in the construction of the simple bicyclic model compounds, that the intramolecular addition of oxygen nucleophiles to the silver-mediated imminum intermediate gave us very high yields of the bicyclic product. The only difference would be that the reaction would have to be intermolecular, and the nucleophile would now be the α-carbon of the lactone.

Since the resulting lactone condensation product would have to be further sulfenylated, the bis-sulfide 231 was chosen as a substrate for

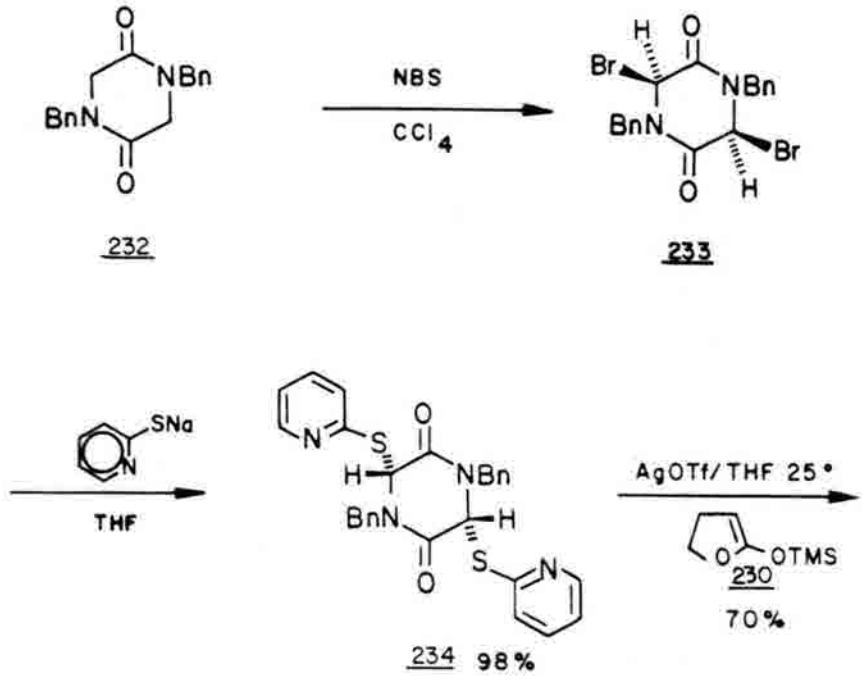
SCHEME 30



a monoalkylation reaction, thus automatically introducing the second leaving group for the subsequent ring cyclization.

Using a modified procedure of Trown[22] (Scheme 31), bromination (NBS, $CCl_4$) of the diketopiperazine 232 followed by displacement of the

SCHEME 31

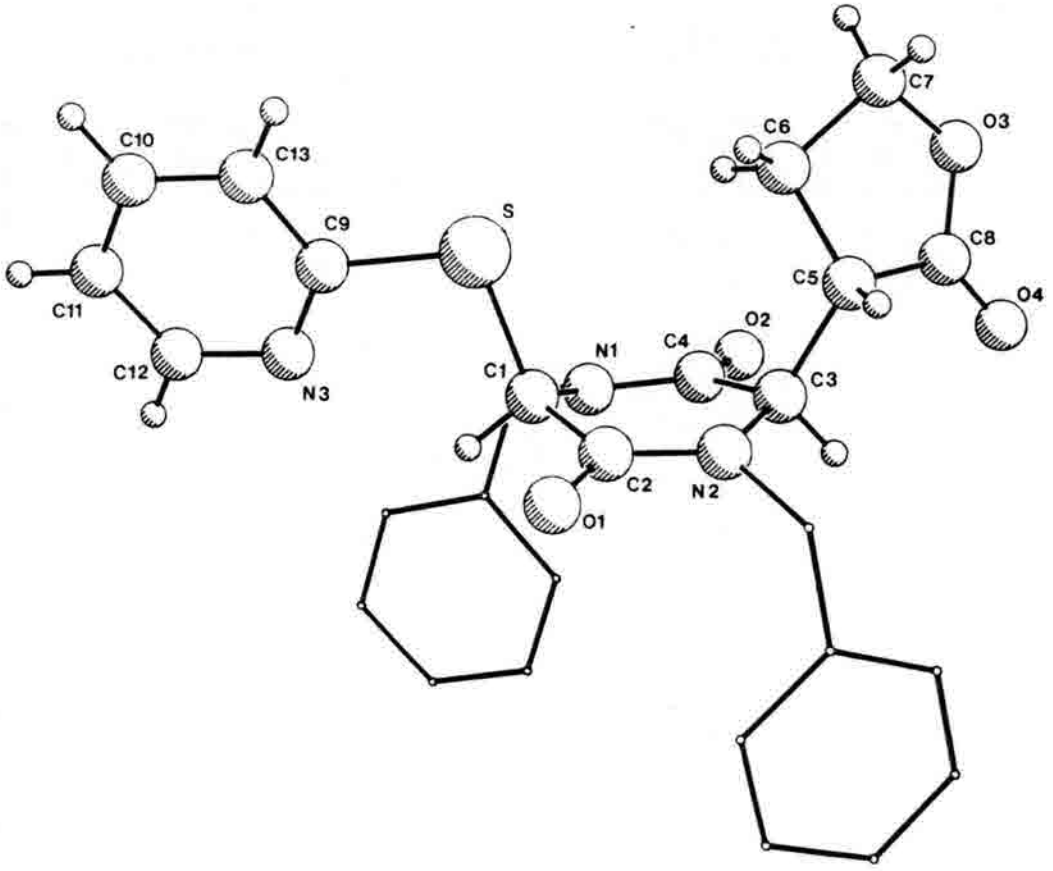


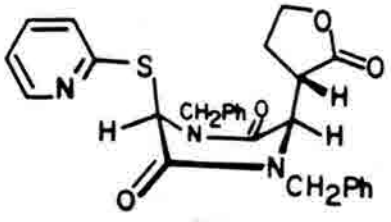

232 233 234 230 237 236

bromides with the sodium salt of 2-mercaptopyridine, gave a 95% overall yield of the syn-bis-pyridylthioether 234 as a white crystalline powder. By NMR the compound appears to be symmetrical, and the syn stereo relation of the sulfides (syn about the diketopiperazine) was assigned on the basis of the chemical shift of the methine singlet on the α-carbons, which is consistant with subsequent compounds we have synthesized and in one case have confirmed by x-ray analysis.

The syn bis-sulfide 234 was treated sequentially with silver triflate and the trimethylsilyl enol ether of γ-butyrolactone to afford the desired coupling products 236 and 237 in good yield (70%). The lactone product was found to be a mixture of two syn (about the diketopiperazine ring) diastereomers, and the relative stereochemistry of the predominant diastereomer (237) was determined by single crystal x-ray analysis (Figure 4). Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters and hydrogen atom positions for the crystal structure of 237 are given in Appendix II.

The coupling of the silylketene acetal with the electrophilic piperazinedione constitutes a new carbon-carbon bond forming reaction which promises to have great utility in the synthesis of α-C-functionalized-2,5-piperazinediones. Several features of this reaction deserve further comment. Though the bis-bromide precursor contains a suitable leaving group for formation of an imminium intermediate, no condensation has ever been observed using a number of Lewis-acid conditions. Coupling occurs only when the bis-sulfide is allowed to precomplex to the silver triflate prior to addition of the nucleophile. This silver complex is indefinitely stable in solution at room temperature to hydrolysis or decomposition. Upon addition of the



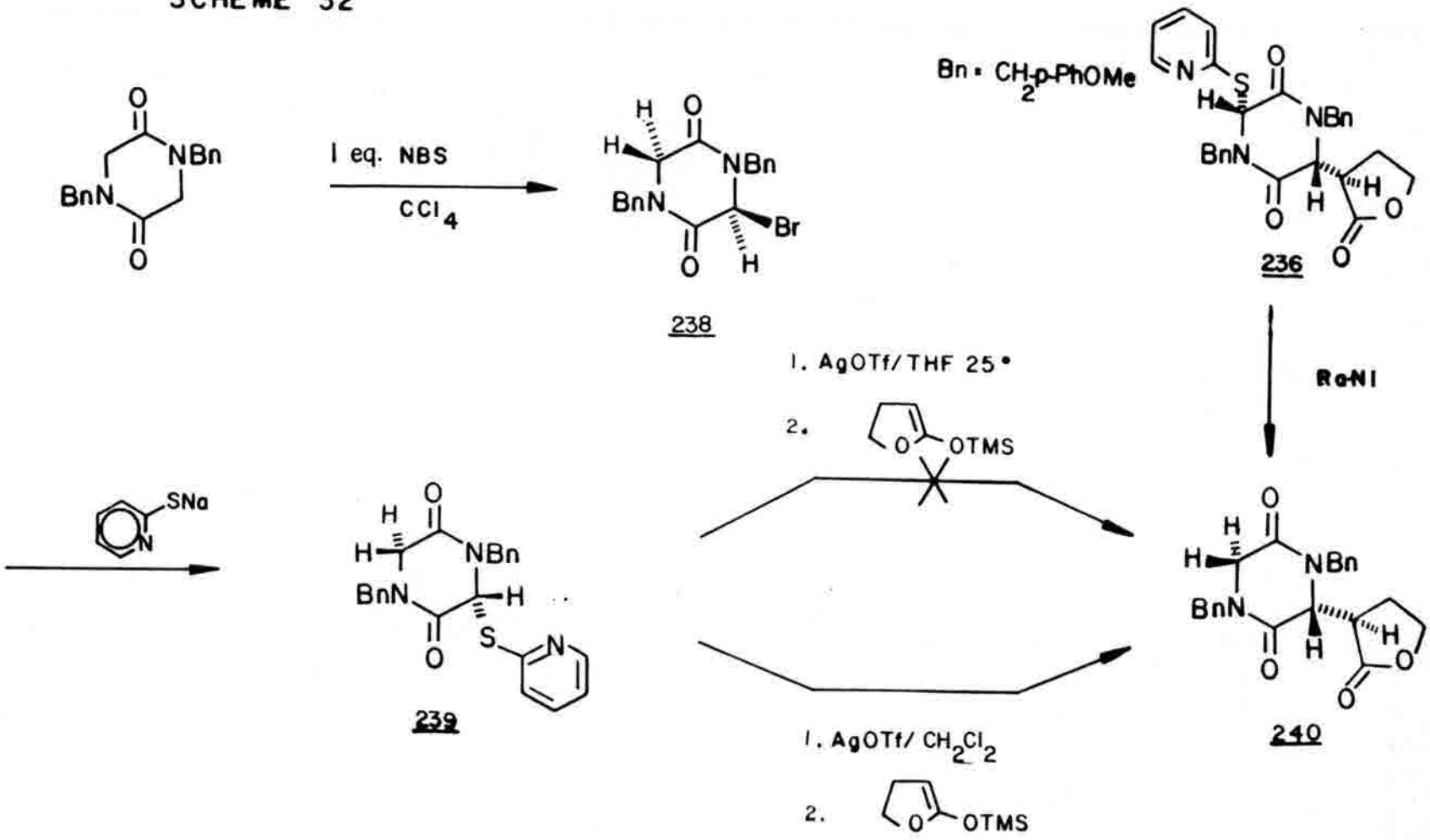

237

FIGURE 4. X-RAY of compound 237.

trimethylsilyl acetal, the silver complex reacts over a period of several hours to afford the desired lactone products. Even in the presence of excess silver triflate or silyl ketene acetal, no 3,6-bis-coupled products have ever been observed. This selective monofunctionalization of the diketopiperazine is extremely important since the major drawback to the enolate alkylation methods is 3-6-dialkylation. The reason the symmetrical bis-sulfide, containing two identical electrophilic carbons, is only monoalkylated could be a result of steric hinderance of the latter, resulting in a drastic decrease in the rate of formation of the second imminium intermediate. It is also possible that the silver complex requires two pyridyl thioether ligands in the formation of a single imminium intermediate. This postulate has been abandoned due to the successful coupling of the monothioether.

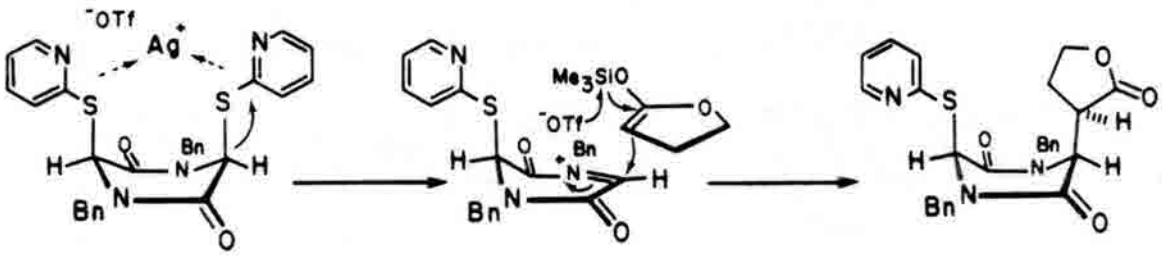
By using only one equivalent of NBS, the N,N'-di-para-methoxybenzyl monobromide 238 was synthesized in 60% yield (Scheme 32). Treatment with the sodium salt of 2-mercaptopyridine resulted in the monothioether 239. Attempts at alkylation of 239 under conditions utilized for the bis-sulfide, indicated that 239 is completely unreactive towards nucleophilic substitution. However, if the order of addition of the ketene acetal and the silver triflate are reversed, the mono-substituted piperazinedione 240 was obtained in good yields (60%). This structure was confirmed by Raney-nickel reduction of 236 obtained from monoalkylation of the bis-sulfide. If this same order of addition which successfully gives 240 is used on the bis-sulfide 234, no coupling is observed, indicating that it is necessary to precomplex the bis-sulfide with silver prior to nucleophilic substitution.

SCHEME 32


1 eq. NBS
CCl4
Bn = CH2-p-PhOMe
238
236
1. AgOTf/THF 25°
2.
OTMS
RaNi
239
240
1. AgOTf/ CH2Cl2
2.
OTMS

The mechanism of this reaction follows the course described in Scheme 33 where, decomposition of the stable silver complex 241 generates the imminium species 242 which undergoes nucleophilic attack to give the mixture of diastereomeric lactones. This mixture is readily separable by chromatography, and the minor diastereomer can be converted to the major in the presence of base (1N NaOH). The stereochemical results indicate that the nucleophile approaches the

SCHEME 33

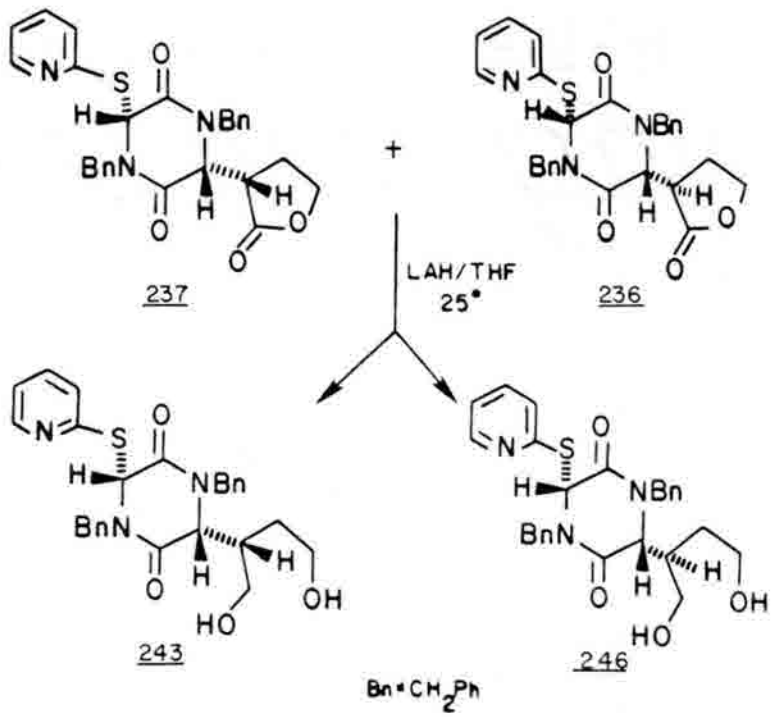



241 242 237

diketopiperazine from the same face as the departing pyridyl thioether, resulting in a mixture of syn-diastereomers. It has been shown in various 3,6-disubstituted piperazinediones previously described, that the syn-stereochemistry is thermodynamically more stable. The mixture of lactones is isomeric at the α-carbon of the butyrolactone, a result of the approach to the imminium intermediate 242 by either face of the ketene acetal. That one diastereomer predominates could be due to the imminium counterion (in close proximity to the nitrogen) assisting in the cleavage of the Si-O bond of the ketene acetal favoring formation of the major-syn diastereomer 237.

The diastereomeric lactones were separated and reduced with lithium aluminum hydride to afford the two diols 243 and 246 (Scheme 34). The reaction typically proceeds in 50% yield or less, and is

SCHEME 34

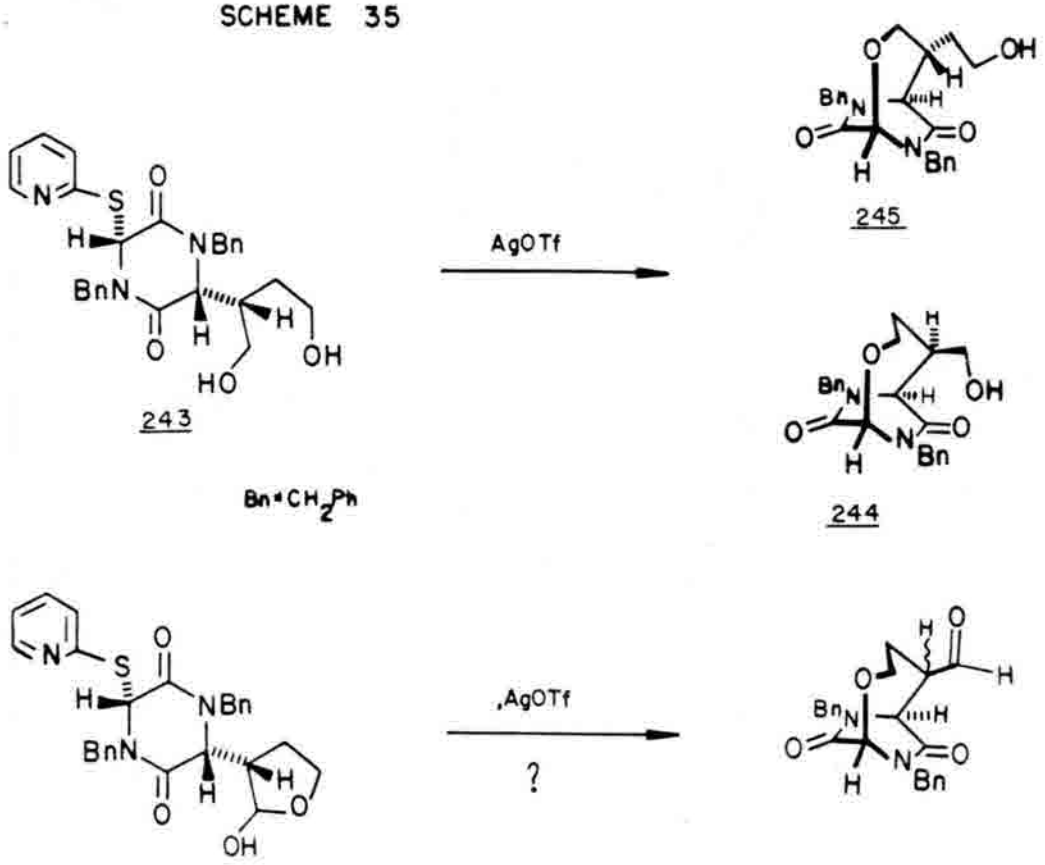



readily decomposed at room temperature or in the presence of excess hydride. Various reducing agents have been used ($NaBH_4$, $LiBH_4$) which afford diol, but the highest yield is obtained when only two hydride equivalents of $LiAlH_4$ are used at 0°C in THF. The main byproducts of this reduction have been isolated but have not been identified, though it is clear from $^1H$ NMR that the sulfide is still intact. This suggests that under the reaction conditions the diol intramoleculary rearranges via nucleophilic cleavage of one of the amides to give the lactone amine product. Dirlam discovered a similar rearrangement on his bicyclomycin model studies. A factor lending support to the rearrangement process is the observation that the yields of the reduction are very sensitive to the stereochemistry of the lactone. This has also been observed in the case of the four diastereomeric

lactones in the para-methoxybenzyl series described later, and would indicate that positioning of either alcohol for intramolecular amide cleavage would be affected by the stereochemistry of the sidechain, as would be expected. It is of interest to note that the protecting groups on the amides must be playing an important role in the reduction, by either participating intramolecularly in the reaction, or forcing a conformation on the molecule which might favor rearrangement. The yields of the reduction of the lactones in the N-methyl, N-benzyl, N-para-methoxybenzyl series show a steady decrease in that order, though the highest yield N-methyl lactone contains no pyridyl thioether at the C-6 position. The diol must be immediately chromatographed after the reduction since storing the crude (after workup) diol at $0^{o}C$ for 8 hours results in total decomposition; the pure diol has never been observed to rearrange or decompose.

An alternative approach to conversion of the lactone to the diol is reduction to the hydroxyaldehyde stage, the lactol (Scheme 35). The attractive feature of this approach is the continued differentiation, inherent in the lactone, of the two sidechain carbons bearing the oxygen atoms, since this would circumvent the problem associated with selective cyclization of the diol which leads to a mixture of desired and undesired bicyclic products. Reduction to the lactol stage would necessitate an additional synthetic step overall to convert the bicyclic aldehyde to the alcohol. Attempts at reduction to the lactol (RedAl, $LiAlH_2$) were not successful, resulting in either unreacted starting materials or decomposition.

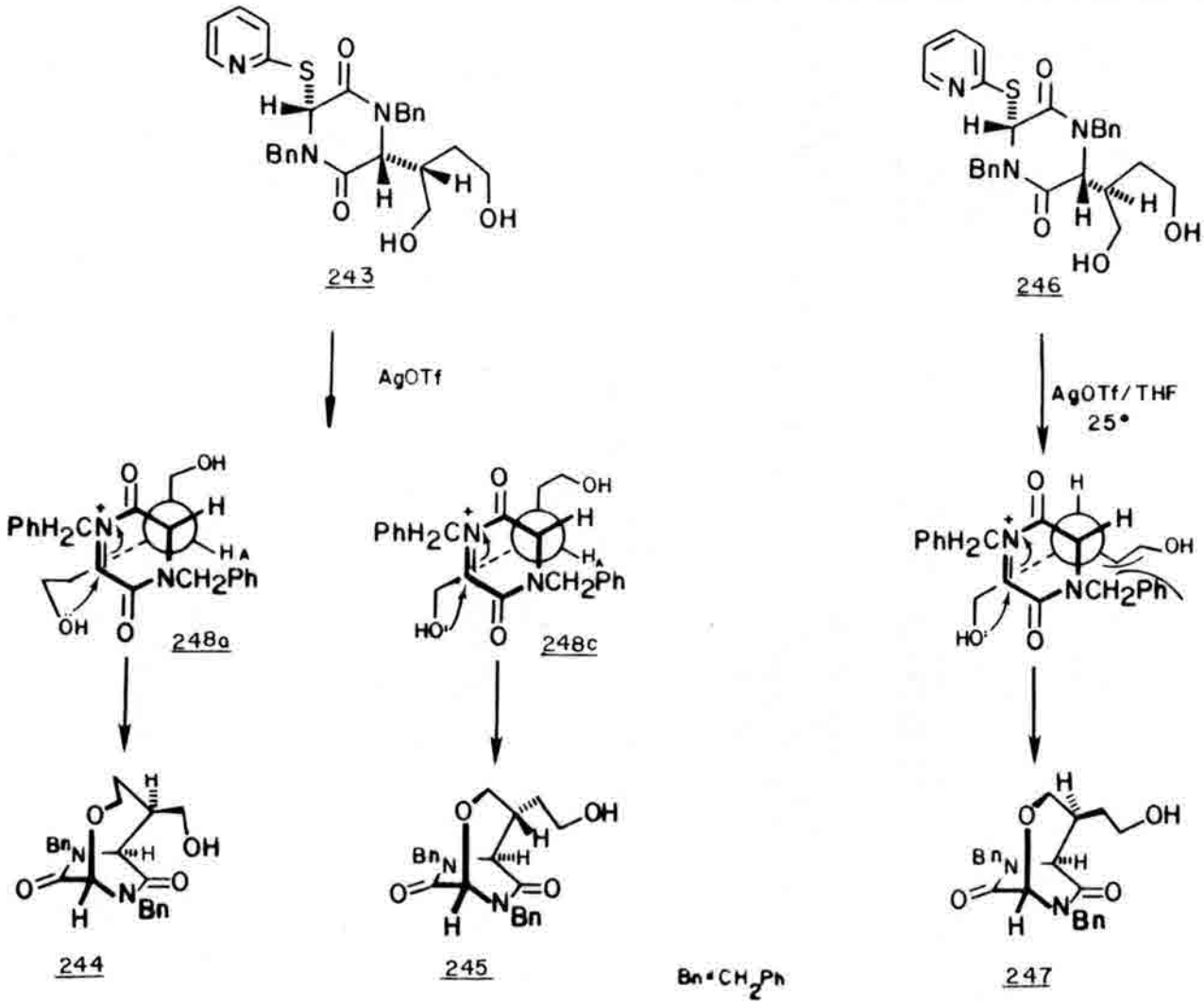
SCHEME 35




The separate diastereomeric lactones were reduced and the resulting diols were subjected to cyclization conditions. Treatment of the major-syn diastereomeric diol 243 with silver triflate in THF at room temperature afforded an inseparable mixture of the desired eight-membered ring 244 and the undesired seven-membered ring 245 bicyclic alcohols (Scheme 36) in very good yield (>90%), slightly favoring formation of the larger bicyclic alcohol 244. Subjecting the minor-syn diol to identical conditions exclusively afforded the seven-membered ring bicyclic alcohol 247.

Two factors appear to be influencing this ring-size selectivity. Kinetically, the molecule will preferentially cyclize to the seven-

SCHEME 36

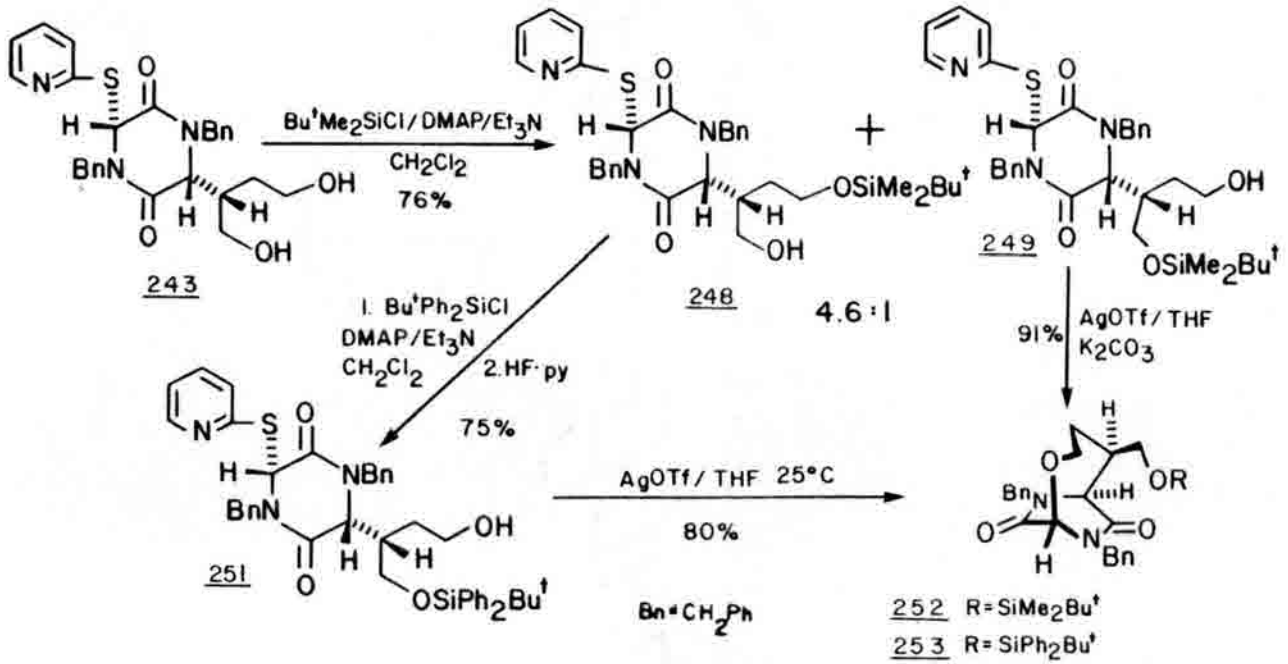


membered vs the eight-membered ring compound, and secondly, the bulk of the protecting groups on the amides influence the conformation of the newly introduced sidechain, forcing the respective hydroxyls into close proximity to the electrophilic carbon.

As a result of its axial position on the boat-like piperazinedione ring, the newly introduced four carbon diol sidechain experiences hindered rotation about the carbon-carbon bond (C6-C5) due to the steric interaction with the N-benzyl protecting group of the amide. Two of the three sidechain conformers (Scheme 36) of the imminium intermediate generated by addition of silver triflate to the thioether 243 place the hydroxymethyl 248c or hydroxyethyl 248b moeities in the crowded area occupied by the N-benzyl group. The remaining conformer 248a directs the smallest group ($H_A$) in a position which minimizes steric interaction and palces the hydroxyethyl portion directly above the electrophilic carbon, resulting in cyclization to the desired eight-membered ring bicyclic alcohol 244. Counteracting this effect is the favored kinetic closure to the seven-membered ring bicyclic alcohol 245 which must go through a highly strained intermediate 248c. Subjecting the minor syn-diol to cyclization results in exclusive formation of the seven-membered ring bicyclic alcohol 247 due to the complementary nature of the two effects previously described. The least sterically hindered imminium conformer 246 affords the same product 247 expected as a result of kinetic control.

Because cyclization of the simple diols 243 and 246 gave a preponderance of the undesired seven-membered ring bicyclic alcohols, a procedure was developed to circumvent this problem by differentiating the two intramolecular nucleophiles (Scheme 37).

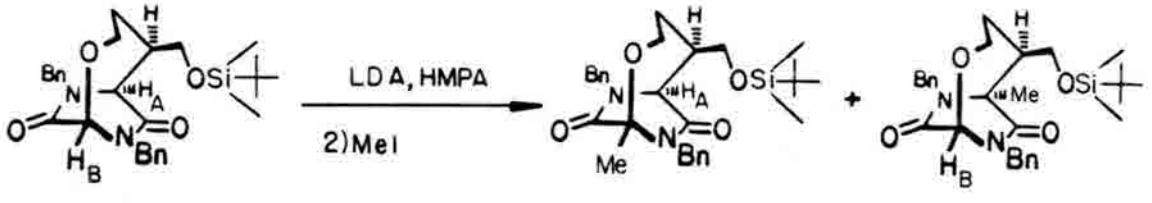
SCHEME 37


Bu'Me2SiCl/DMAP/Et3N
CH2Cl2
76%
243
248
249
4.6:1
1. Bu'Ph2SiCl
DMAP/Et3N
CH2Cl2
2. HF·py
75%
251
AgOTf/THF 25°C
80%
91%
AgOTf/THF
K2CO3
Bn = CH2Ph
252 R = SiMe2Bu'
253 R = SiPh2Bu'

Silylation of the major diastereomeric alcohol 243 with one equivalent of t-butyldimethylsilyl chloride gave a mixture of the two monosilylated alchols 248 and 249 in a 4.6:1 ratio respectively. The hydroxyethyl compound 249 could be directly cyclized with AgOTf to give only the desired eight-membered ring bicyclic ether 252. Subjecting the hydroxymethyl derivative 248 to the same conditions would afford undesired product. Further protection of the hydroxymethyl derivative was accomplished with t-butyldiphenylsilyl chloride to afford the bis-silylated adduct 250, which could be selectively monodeprotected with HF•pyridine complex to give the desired hydroxyethyl cyclization precursor 251. Treatment of 251 with silver triflate gave the bicyclic silyl ether 253.

To discern the selectivity of bridgehead functionalization (Scheme 38), the anion of bicyclic ether 252 was formed (1.1 eq. LDA/HMPA, -78°C, kinetic or thermodynamic conditions) and to our surprise the only product that was observed after methyl iodide quench was the methylated derivative 254 functionalized at the bridgehead carbon adjacent to the bridging oxygen.

SCHEME 38




252 254 none observed

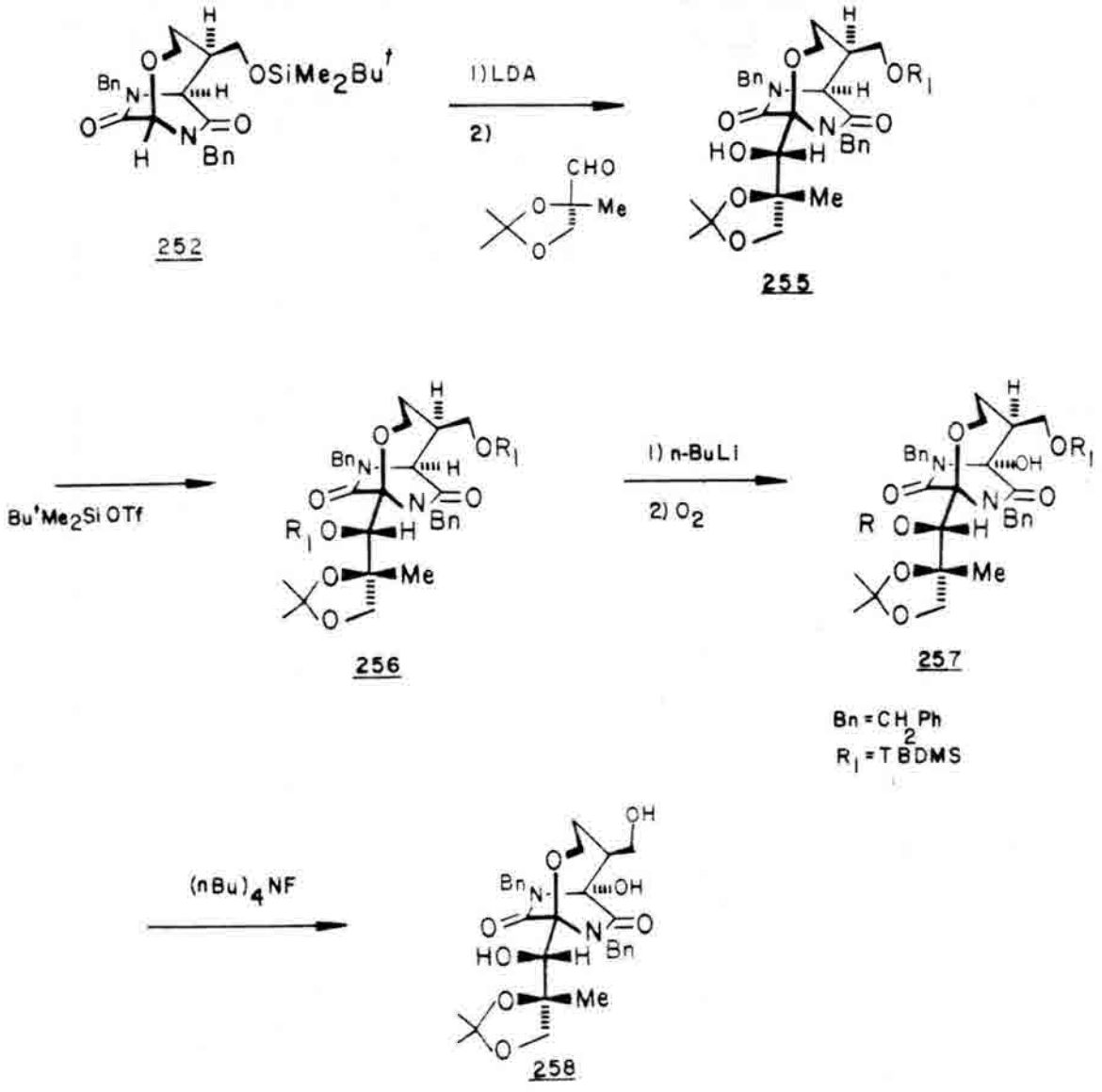
Bn•CH$_2$Ph

This result is opposite to that observed for the simple desmethylene bicyclic model system (192), where kinetic quenching favored carbon-1 functionalization and thermodynamic conditions favored carbon-6 functionalization. Space filling models of the bicyclic silyl ether 252 indicate that the t-butyl and methyl groups on silicon almost entirely shield bridgehead proton $H_A$ from approach by LDA, indicating that this reversal in bridgehead functionalization is steric in nature and that the hydroxymethyl moiety at carbon-5 is not electronically reversing the kinetic or thermodynamic acidities of the bridgehead protons $H_A$ or $H_B$. Electronic effects of the C-4 silyloxy moiety may also play a role in deprotonation at C-6.

This reversal in selectivity necessitated inversion of the order of bridgehead functionalization, resulting in introduction of the carbon-1 sidechain first, followed by oxidation at carbon-6. Quenching of the bridgehead anion of 252 (Scheme 39) with the "Maag" aldehyde 18 afforded the aldol product 255 as a single diastereomer. Protection of the resulting alcohol (256) with t-butyldimethylsilyl triflate gave the bis-silyl ether quantitatively (256).

Attempts at oxidation of the bridgehead carbon (C-6) failed using conditions (n-BuLi, MoOPh) which resulted in bridgehead alcohol in the model series. It appears that this electrophilic oxygen source (MoOPh) is too bulky to approach the hindered bridgehead anion in the correct geometry due to the silyl ether. If the anion, formed under similar conditions (n-BuLi, -100°C, THF) was quenched with oxygen gas, a 78% yield of the desired tertiary alcohol 257 was obtained. Bis-silyl ether 257 was quantitatively converted with tetra-n-butyl ammonium fluoride to the triol 258.

SCHEME 39




Attempts at reductive cleavage of the hydroxymethyl bicyclic derivatives in Chart I were unsuccessful under a variety of conditions, resulting in either recovery of starting material (>90% weight recovery) or decomposition (under more forceful conditions). Although

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Attempts at reductive cleavage of the hydroxymethyl bicyclic derivatives in Table IV were unsuccessful under a variety of conditions, resulting in either recovery of starting material (>90% weight recovery) or decomposition (under more forceful conditions). Although pressure and temperature vary for each specific compound in Table V, a typical procedure consisted in dissolving the bicyclic piperazinedione in EtOH under $H_2$ atmosphere in the presence of 20% Pd/C at 50°C and stirring the solution for 12-24 hrs under 1 atm pressure. Several compounds in the desmethylene series were also subjected to the same conditions and no debenzylated products were ever observed, instead, hydrogenation of the phenyl ring occurred affording the cyclohexane derivative which on initial inspection by $^1H$ NMR appears debenzylated due to the disappearnace of the aromatic hydrogen signals. It is interesting to note that the triol 258 did not undergo deprotection since its C-6 benzyl ether derivative 149 was successfully hydrogenated under similar conditions to afford the triol 150 in the recently completed synthesis of bicyclomycin by Goto. Due to the greater lability of benzyl ethers vs. benzyl amides under hydrogenation

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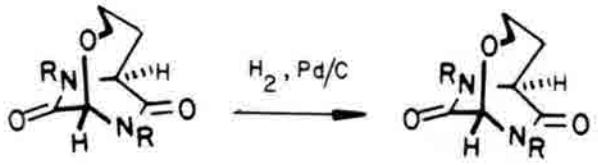
EQUATION 6

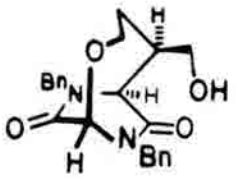



R = Benzyl

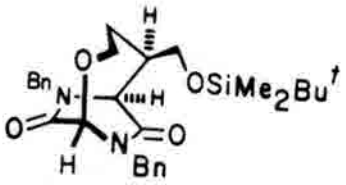
R = Cyclohexylmethyl

conditions, it would appear that the triol 258 is in fact an intermediate in the deprotection of 149; apparently the subtle difference between 149 and 226 (stereochemistry at C-5 may also differ) is obligate for deprotection. Based on the results obtained in the thwarted attempt at reductive cleavage of the N-benzyl amides (Table IV), and the observation made by Nakatsuka that only one of all the bicyclic intermediates in his synthesis yielded any debenzylated

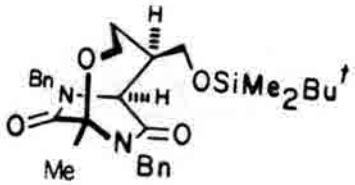
CHART I



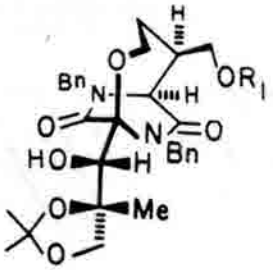
244



252



254



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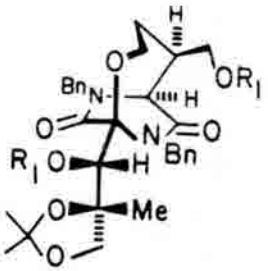

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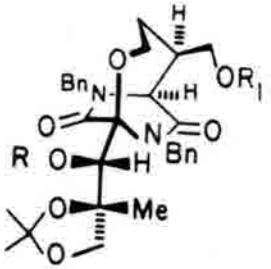

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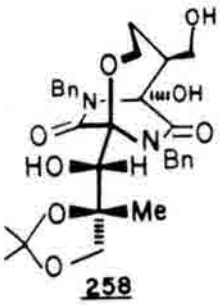
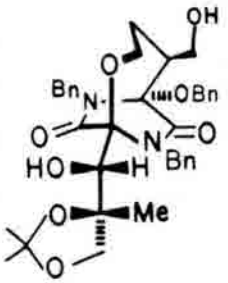
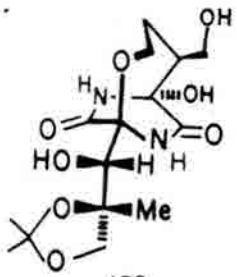


258



149

Bn = $CH_2Ph$

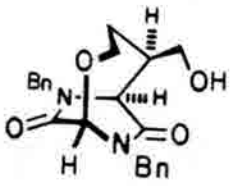


150

product, it was concluded that the N-benzyl amide protecting group is a poor choice in view of the synthetic strategy described herein which allows for the versatile synthesis of bicyclomycin and a plethora of analogs. By having access to the bicyclic deprotected amide analogs, inquires into the mechanism of action of bicyclomycin as well as structural requirements for its activity can be addressed. Though it appeared that we would not be able to remove the N-benzyl group, we decided to complete the total synthesis of N,N-dibenzyl bicyclomycin since we were very interested in its biological activity as well as its use as a substrate for mechanistic studies of bicyclomycin (Chapter IV).

For the synthesis of N,N-dibenzyl bicyclomycin acetonide 267 it was decided to first construct the exomethylene and then functionalize the bridgehead positions. Using the same procedure as previously described, the mixture of alcohols 245 and 244 (Scheme 40 ) resulting from cyclization of the major diastereomeric diol 243 were converted to the mixture of mesylates 259 and 260 ($Et_3N$, mesyl chloride, THF) in almost quantitative yield. The mesylates were converted to the selenides 261 and 262 via the usual method (diphenyl diselenide, $NaBH_4$, ethanol) and were easily separable by chromatography. The desired eight-membered ring selenide was refluxed in the presence of hydrogen peroxide to afford the exomethylene bicyclic compound 263 in 82% overall yield from the alcohol. Correspondingly, the seven-membered ring bicyclic selenide 262 was converted to the vinyl derivative 264 in 80% overall yield from the alcohol. The other seven-membered ring vinyl derivative can be prepared in a similar fashion (Appendix 4) from alcohol 247.

SCHEME 40



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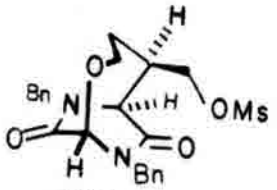
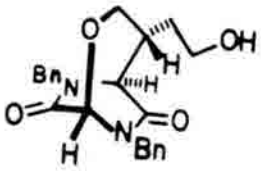


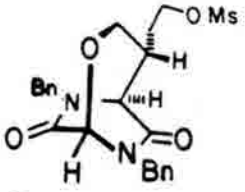
259

MsCl

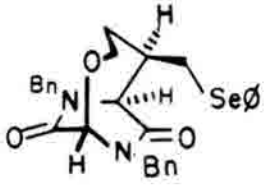
$Et_3N$



245



260



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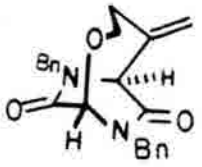
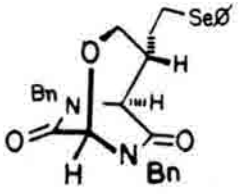


263

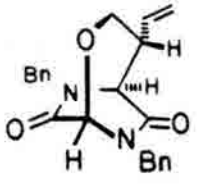
$\phi Se)_2$

$NaBH_4$

$H_2O_2$

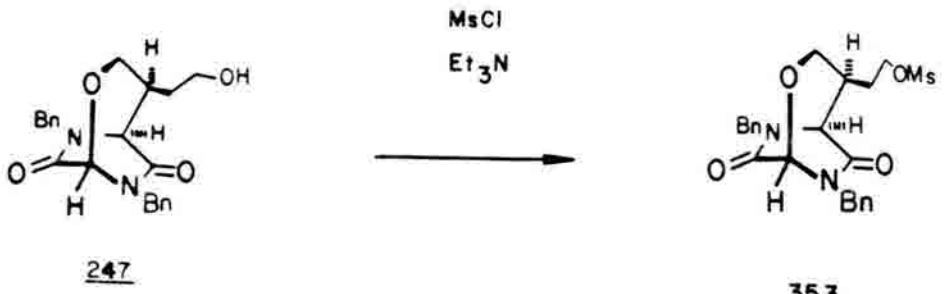


262

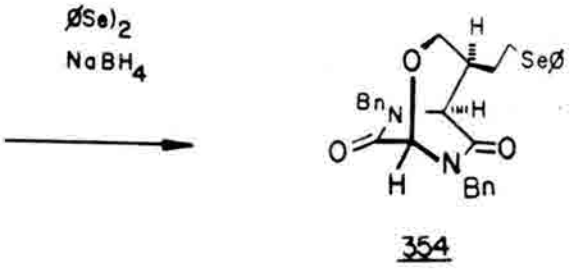


264

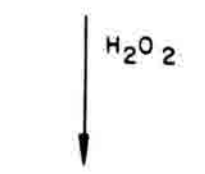
SCHEME 41

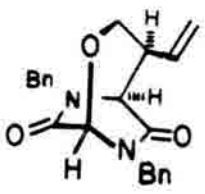



247 353




354




Bn = $CH_2Ph$

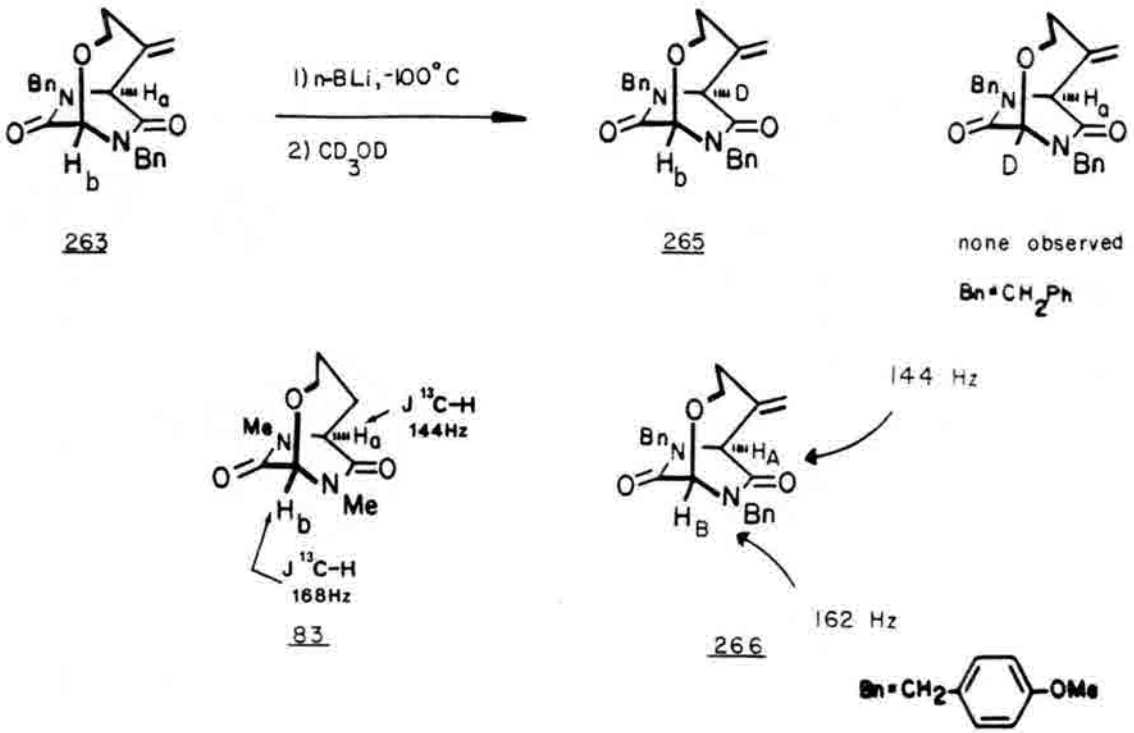
264a

Have obtained the simple bicyclic exomethylene compound 263, the only remaining synthetic steps were functionalization of the bridgehead carbons.

We expected the selectivity of bridgehead anion formation to be very similar to that of the desmethylene bicyclic model systems, because the relatively small olefin moiety would not block access to the carbon-6 bridgehead proton $H_a$ (unlike the siloxymethyl case). In addition, carbon-6 is "allylic"; however the p-orbitals of the exomethylene cannot interact in bridgehead carbanion delocalization due to the orthogonal geometrical constraints of the bicyclic system.

Generation of the anion of the bicyclic exomethylene (Scheme 41) with one equivalent of base (n-BuLi) gave, after methanol-$d_1$ quench, deuteration exclusively at the bridgehead carbon adjacent to the bridging exomethylene 265. It is of interest to note that we have never observed any deuteration, oxidation, or alkylation of the bridgehead carbon adjacent to the bridging oxygen (carbon-1) under either kinetic or thermodynamic conditions. That $H_A$ is more labile under thermodynamic conditions appears to be reasonable and consistent with our previous observations; the property(ies) of the olefin that make $H_A$ also kinetically favored remain unknown to us at this time. The coupling constants $J_{C-H}$ for both bridgehead carbon-hydrogen bonds have been calculated on the N,N-di-para-methoxybenzyl bicyclic exomethylene 266 which displays the same anion (thermodynamic and kinetic) behavior (Scheme 42).

SCHEME 42




263 265 none observed

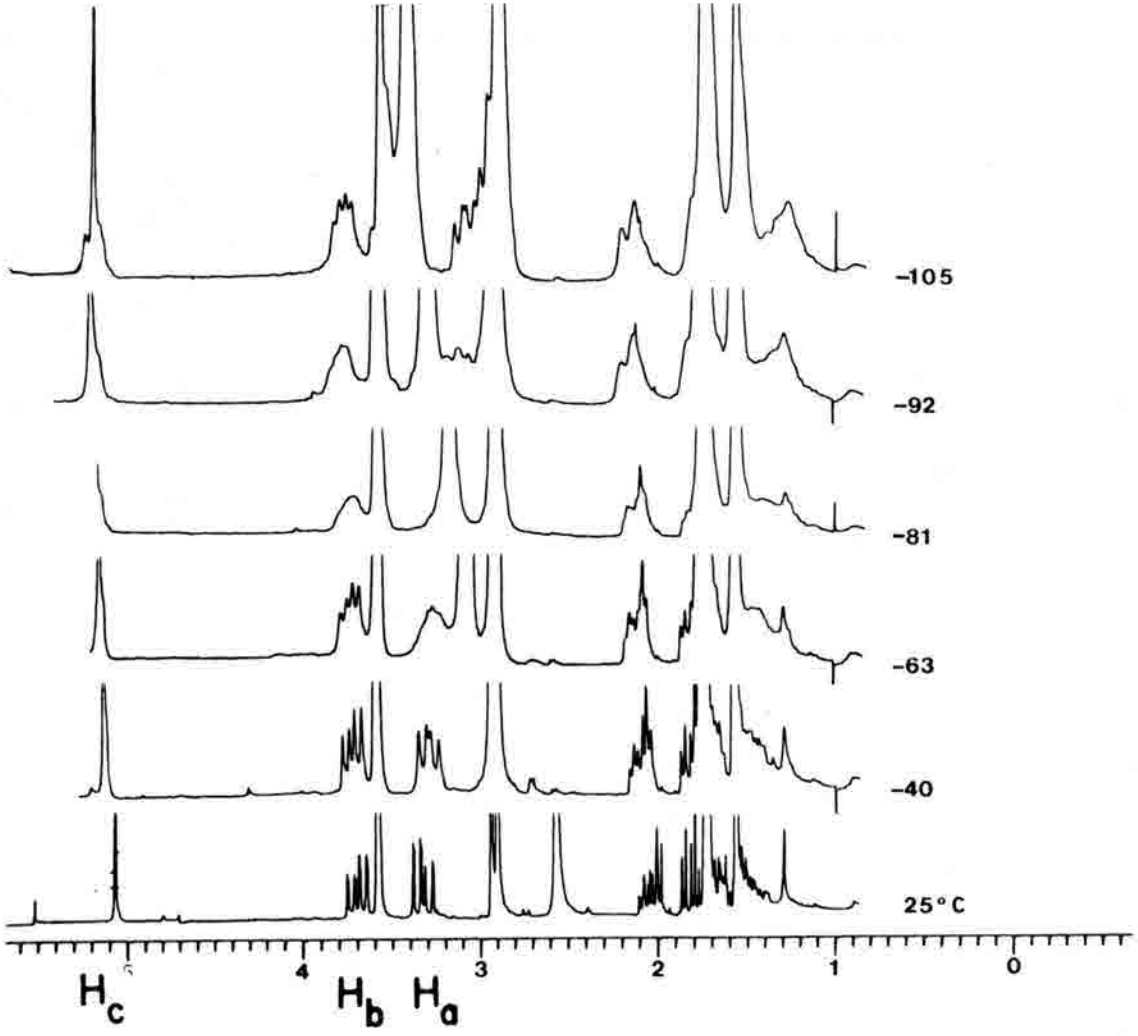
83 266

The $H_A$ carbon-6 coupling constant was found to be identical (144 Hz) as that for the des-methylene compound 83, but the $H_B$ carbon-1 coupling constant was 6 Hertz lower than the des-methylene adduct. This means that there is a 2% reduction in the s-character of the $H_B$ carbon-1 bond (32% s-character) making it much closer to that exhibited at the other bridgehead carbon (29% s-character). Though this data does not conclusively establish a reason for the observed selectivity, it does appear that the exomethylene, by "forcing" a planar arrangement of carbons 4, 5, and 6, induces a twist in the bridging isopropoxy chain which ultimately results in a greater eclipsing of one electron pair on the ether oxygen with the $H_B$ carbon-1 bond. This eclipsing manifests itself in a lower coupling constant.

In an attempt to freeze out a conformer, the desmethylene and exomethylene bicyclic analogs in Figures 5 and 6 were subjected to low temperature $^1$H NMR studies. On inspection of the $^1$H NMR spectrum in Figure 6, it is clear that at the lowest temperature the molecule is conformationally mobile, the broadened peaks being a result of the timescale of the NMR experiment. On the other hand, the desmethylene analog (Figure 5) freezes out a conformer as seen in the sharpening of the signals as the temperature decreases.

The exomethylene analog (294) was conformationally mobile at -98°C (in THF-$d_8$) whereas the desmethylene compound froze out at that temperature. This difference might mean that at the temperature at which the anion experiments are performed (-100°C, THF), the bridgehead anion at C-1 of compound 294 might "see" a lot of destabilizing conformer in which the lone pairs on the bridging oxygen atom eclipse the C-1 anion. The desmethylene compound 169 on the other hand may have a significant amount of gauche conformer (anomeric stabilization) that results in anion formation at C-1.

Using the "normal" sequence of bridgehead functionalization, the exomethylene was treated (Scheme 43) with n-BuLi (HMPA, THF, -100°C) and the resulting anion was subjected to a steady stream of dry oxygen for 10 min, giving the bridgehead alcohol 266. The alcohol was treated with 2 equivalents of n-BuLi (the tertiary alcohol is protected as its lithio salt) and quenched with the "Maag" aldehyde 18 to give the correct diastereomer 267 as the only product. The synthesis of N,N-dibenzyl bicyclomycin acetonide concluded our work on the N-benzyl series.



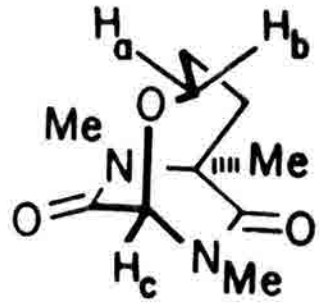




FIGURE 5. Low temperature $^{1}H$ NMR conformational study of compound 169.

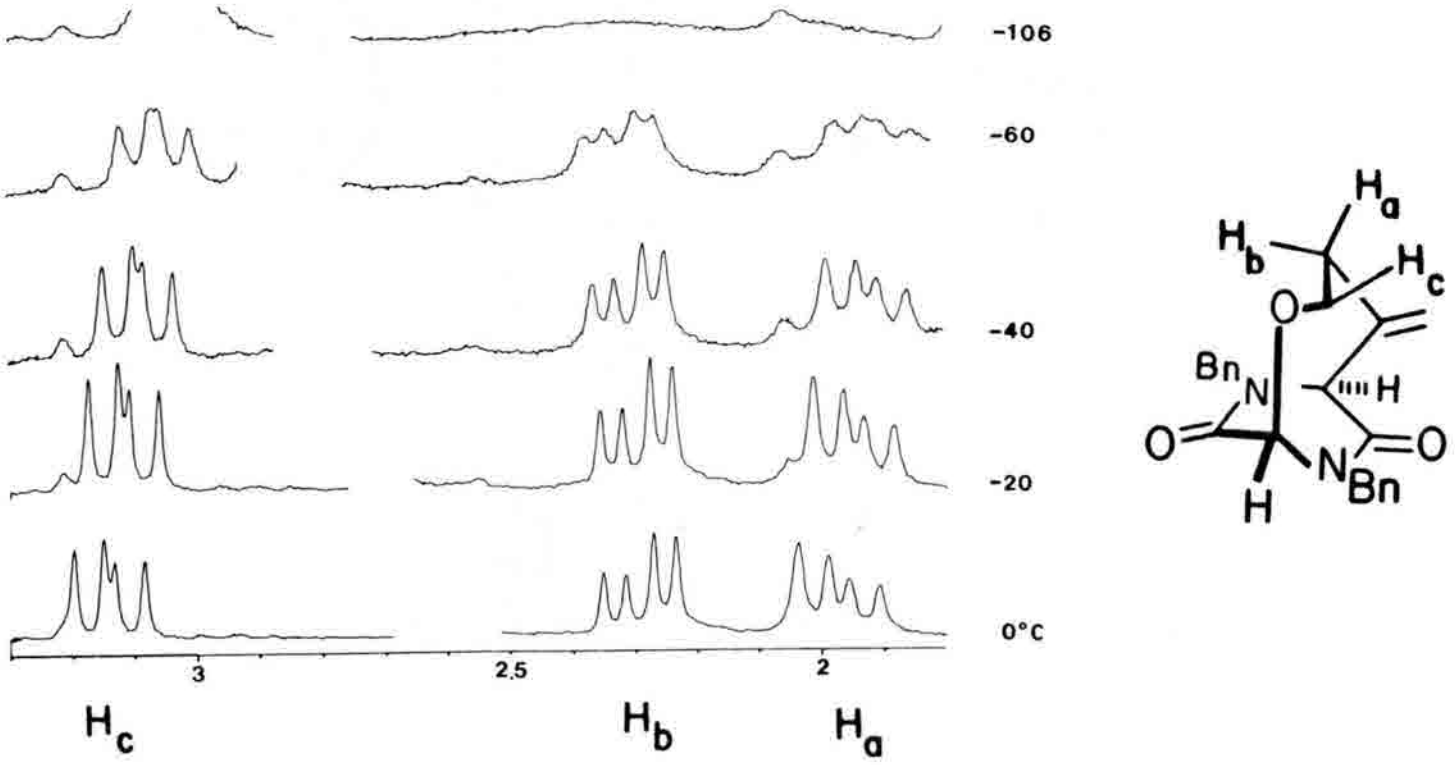
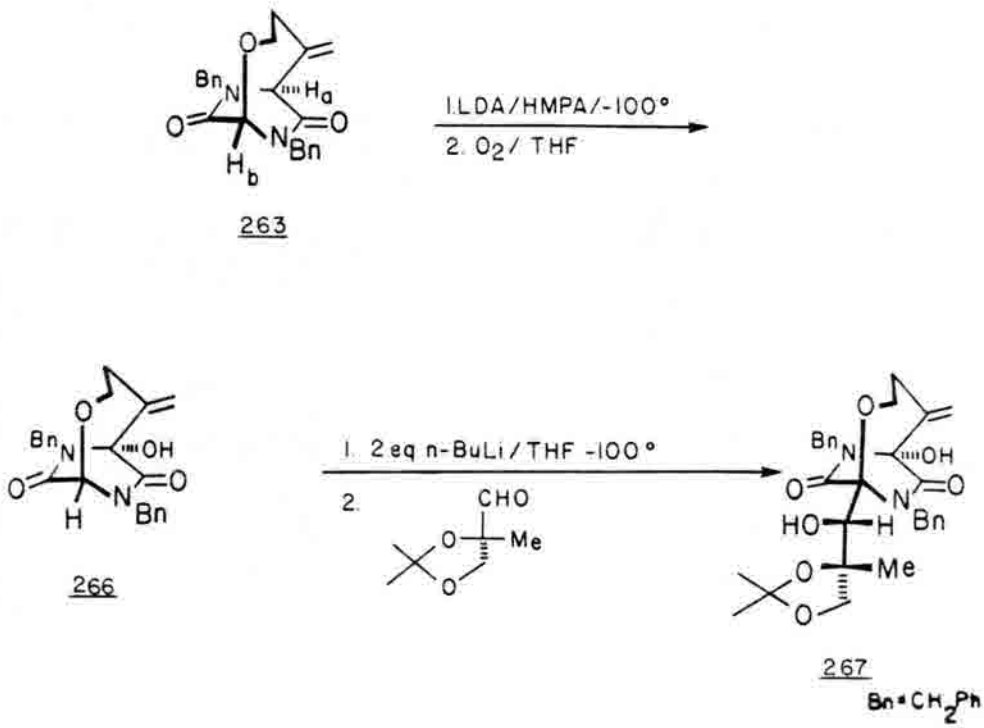



FIGURE 6. Low temperature $^{1}H$ NMR conformational study of compound 294.

SCHEME 43




It is worth noting that although dissolving metal reductions or hydrogenation reactions were not able to deprotect the N-benzyl compounds, we entertained the idea of oxidatively removing them as a result of the following experiments.

During our first series of experiments to determine the selectivity of bridgehead functionalization of the siloxymethyl bicyclic compound 252 (Scheme 37), we isolated several compounds which had resulted from alkylation or oxidation at the benzylic carbons. It is not unreasonable to assume that the acidities of the benzylic protons are competitive with those of the bridgehead carbons, and even competitive with the carbon-4 allylic protons, though we have never observed any reactions at the latter carbon.

By subjecting the silyl ether 252 to a five-step one-pot reaction sequence described in Scheme 44a,[36] we were able to isolate in 42% the benzyl carbon-silylated product 268, which resulted from formation of the benzylic anion. By NMR it is very easy to establish that one of the benzylic carbons has been alkylated, since one of the two characteristic AB quartets disappears and becomes a singlet. In an effort to further investigate this result, the more straightforward approach (Scheme 44b) was taken, where the lithium anion formed with LDA at -78°C was quenched with t-butyldimethylsilyl chloride. The first product isolated was the expected silylation at carbon-1 (270) which concurred with our previous observations with methyl iodide quench. The second product was the most unexpected: the deprotected bicyclic silyl ether 269. By NMR, one of the AB quartets disappears and the new $D_2O$ exhangable -NH signal appears. We are at a total loss to explain the mechanism of formation of this compound.

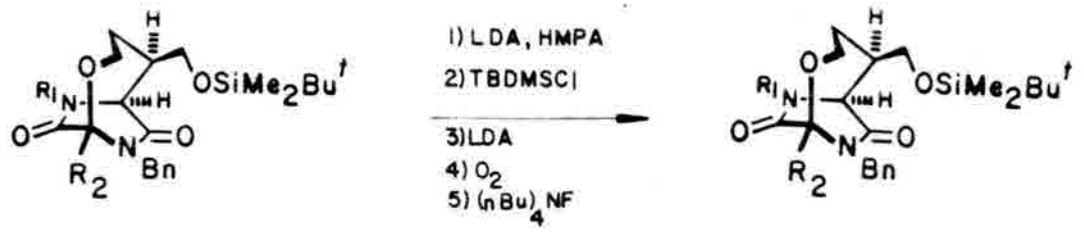
Once we had established conditions for formation of the bridgehead anion at carbon-1, condensation with the sidechain aldehyde gave the desired aldol product in good yields (>60%) as described previously. The second set of experiments which led to benzylic carbon activation occurred on our initial attempts at oxidizing carbon-6 to introduce the hydroxy group. Although bulky, we first chose t-butyllithium as the base because we felt that abstraction of $H_A$ might require a stronger base than LDA. We later discovered that n-BuLi was the base of choice due to the steric constraints imposed by the alkyl groups on silicon.

Treating a THF solution of bis-silylether 256 with t-butyllithium (Scheme 45a) followed by a steady flow of dry oxygen resulted in the

isolation of the N-benzoyl derivative 271. Since the bulky base cannot approach the bridgehead methine, it appears that the next most acidic

SCHEME 44

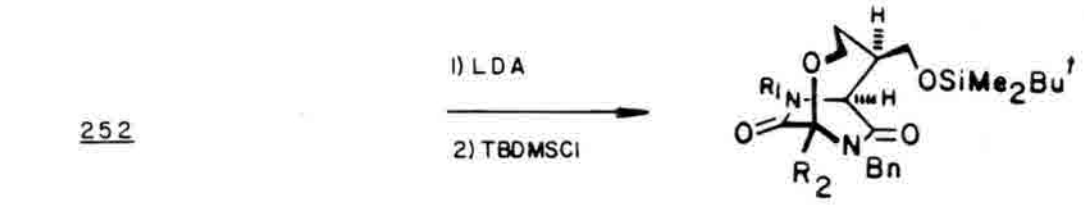
b)




252 $R_1$ = $CH_2Ph$, $R_2$ = H

268 $R_1$ = $CH(SiMe_3)Ph$, $R_2$ = H

a)




252

Bn = $CH_2Ph$

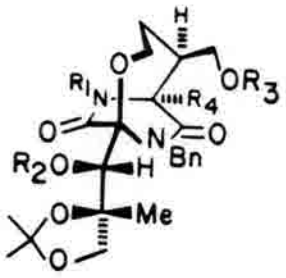
270 $R_1$ = $CH_2Ph$, $R_2$ = $SiMe_2Bu^t$

269 $R_1$ = $R_2$ = H

protons (benzylic) are abstracted and quenched with oxygen. A proposed mechanism (Scheme 45c) would involve quenching of the benzyl anion with $O_2$ to form the peroxide intermediate. Repeating this sequence would result in the formation of a peroxy ketal which could decompose during workup to the benzoyl derivative 271. Supporting this mechanism is the isolation of what appears to be the peroxide 272 when the temperature of the reaction is warmed to -78°C (Scheme 45b). The proton NMR of the N-benzoyl product 271 shows loss of one of the two AB quartets with no new signals appearing, all other protons being accounted for. The infrared spectrum shows the presence of a new carbonyl stretch. The NMR of the peroxide product 272 shows loss of an AB quartet and

SCHEME 45

a)

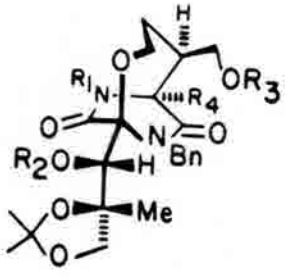


256

$R_1 = CH_2Ph$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$

1) nBuLi, -100°C

2) $O_2$



271

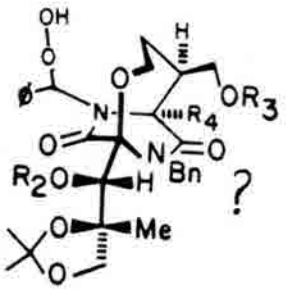
38, $R_1 = COPh$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$

b)

256

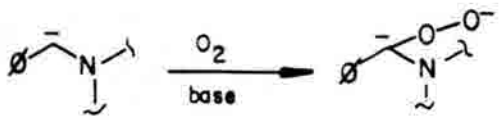
1) t-BuLi, -78°C

2) $O_2$

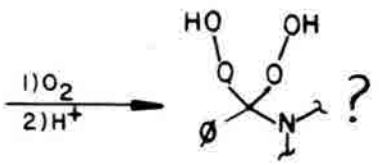


272 $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$

c)



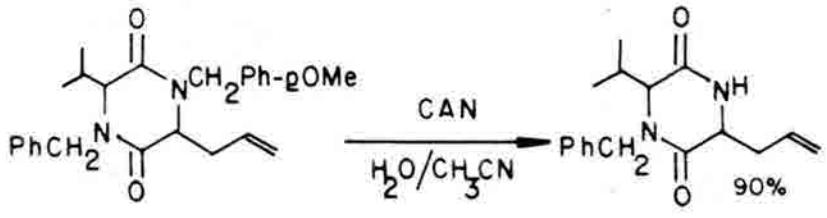
Bn = $CH_2Ph$



appearance of a new singlet in the same region. Peroxide 272 is very unstable and readily decomposes.

As we were completing the synthesis of the N,N'-dibenzyl bicyclomycin acetonide, several publications appeared which seemed to indicate that the para-methoxybenzyl protecting group on β-lactams could be removed under oxidative conditions. Of particular interest was the work of Yoshimura[37] who showed that in the presence of cerric ammonium nitrate (CAN), N-para-methoxybenzyl diketopiperazines could be deprotected in high yields (equation 7).

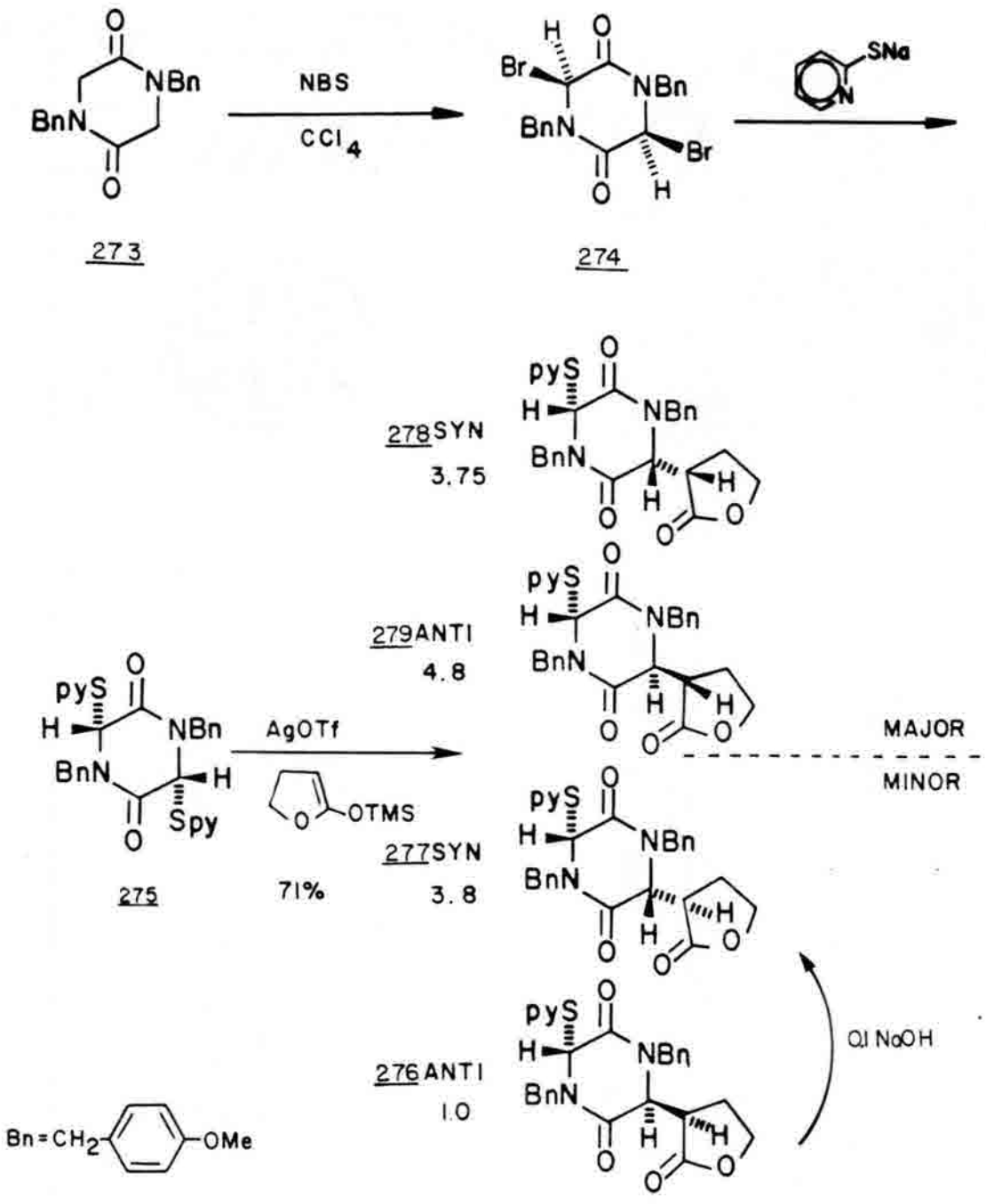
EQUATION 7




This was very interesting because we could not forsee any incompatibility of CAN with our fully functionalized bicyclomycin derivative which we would use as a precursor. We thus decided to undertake the synthesis of N,N'-di-para-methoxybenzyl bicyclomycin acetonide using the methodology we had already developed in the N-benzyl series.

Bromination of glycine anhydride derivative 273 (obtained from condensation of glycine with para-methoxybenzyl chloride) gave the syn-bis-bromide 274 which was condensed with the sodium salt of 2-mercaptopyridine to give the syn bis-sulfide 275 in good yield. Silver triflate mediated condensation of the silyl ketene acetal with the

SCHEME 46


NBS
CCl4
SNa
273
274
278SYN
3.75
279ANTI
4.8
AgOTf
OTMS
71%
275
277SYN
3.8
276ANTI
1.0
MAJOR
MINOR
0.1 NaOH
Bn=CH2
OMe

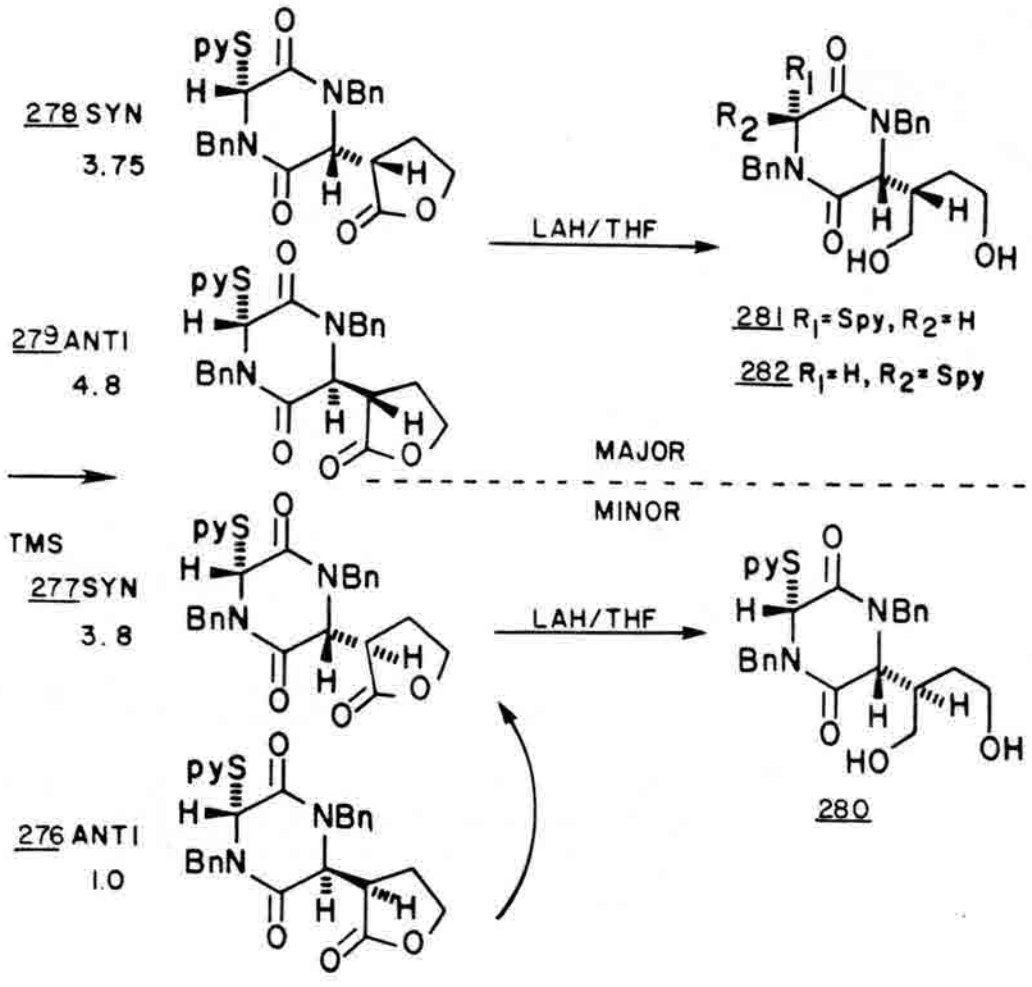
bis-sulfide gave the diastereomeric mixture indicated in Scheme 46. We were surprised to discover that, unlike the N-benzyl series, all four possible diastereomers were obtained. The diastereomeric lactones are labeled by the relationship of the lactone versus the sulfide with respect to the diketopiperazine ring (syn-anti), and by the relative stereochemistry at the α-carbon of the γ-butyrolactone (minor-major).

The relative stereochemistry of the lactones was assigned by comparison with the proton NMR spectra of the two diastereomeric lactones in the N-benzyl series, since a single-crystal x-ray was obtained on the major one (237). The assignment of the syn-anti relationship is very straightforward since the chemical shift of the methine singlet adjacent to the pyridylthioether is up to 1.1 ppm different. For the syn compounds, the methine is deshielded and the chemical shift ranges from 6.6-6.8 ppm. For the anti compounds, the methine is in the range 5.6-5.8 ppm. Since none of the thermodynamically less stable anti-lactone was formed in the N-benzyl series, the observed chemical shift for the two N-benzyl syn compounds was 6.6-6.8 PPM. Assignment of the major-minor stereochemistry is not as straightforward, but can still be done by comparing the coupling constants and chemical shifts of the protons on the α-carbon of the γ-butyrolactone and the α-carbon of the amide on the diketopiperazine.

It is worth noting that the stereochemical assignment of the diastereomers is consistent with all of the analogs that can be matched along both series of compounds.

All four diastereomeric lactones were easily separated by chromatography and were subjected to reduction with lithium aluminum hydride (Scheme 47). The yields in both the N-benzyl series and the

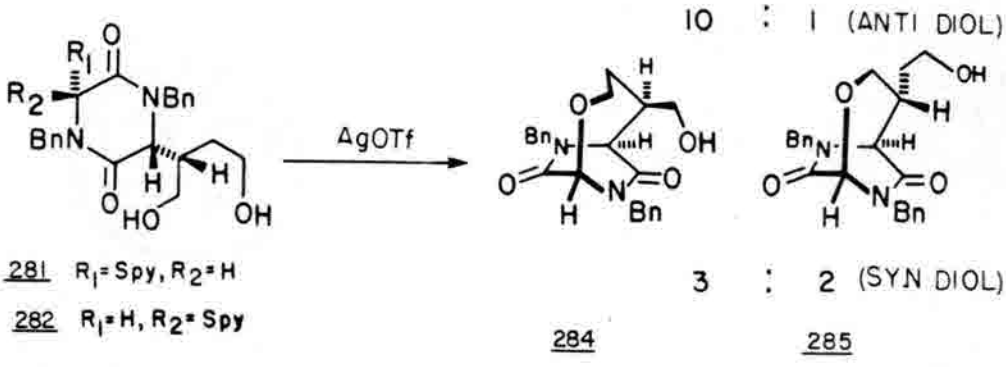
SCHEME 47


278 SYN
3.75
279 ANTI
4.8
TMS
277 SYN
3.8
276 ANTI
1.0
LAH/THF
LAH/THF
MAJOR
MINOR
281 R1=Spy, R2=H
282 R1=H, R2=Spy
280

N-para-methoxy benzyl series are about 50% or less, except in the case of the trans-minor diastereomer which had not been reduced successfully. This reaction is very sensitive and is carried out by adding two hydride equivalents over 10 minutes, then quenching excess hydride, filtering, and subjecting the crude to chromatography immediately, otherwise the material will decompose.

The cyclization of the diastereomeric diols using silver triflate was very similar to that observed in the N-benzyl series. The conformation of the syn-minor diastereomeric diol 280 which minimizes steric interaction of the amide protecting group and the sidechain, places the hydroxymethyl portion over the imminium carbon, resulting in formation of only the undesired seven-membered ring bicyclic alcohol 283 (Scheme 48). The most stable conformer of the syn-major diastereomer should give only eight-membered ring alcohol, but kinetic competition to make the seven-membered ring results in a slight excess of the desired compound 284. On the other hand, the cyclization of the anti-major diastereomer 282 (same stereochemistry at the lactone $\alpha$-carbon as 282) leads to a 10:1 ratio of the eight- to the seven-membered ring compounds respectively. This indicates that there is some sort of memory effect in the anti compound which favors the desired bicyclic alcohol, strongly suggesting that the syn-major and anti-major cyclizations cannot be going through the same intermediate (Scheme 49). This suggests that most if not all of the anti-major bicyclic eight-membered ring alcohol cyclizes via $SN_2$ displacement of the sulfide, a mechanism which is not accessible to the syn compound since the nucleophile approaches from the same face as the leaving group.

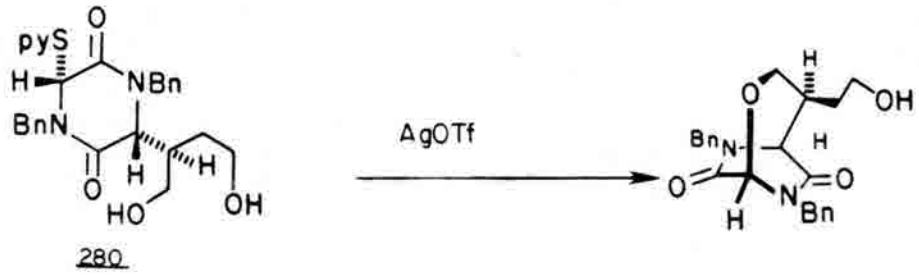
SCHEME 48




281 $R_1$ = Spy, $R_2$ = H

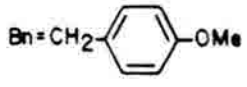
282 $R_1$ = H, $R_2$ = Spy

284 285

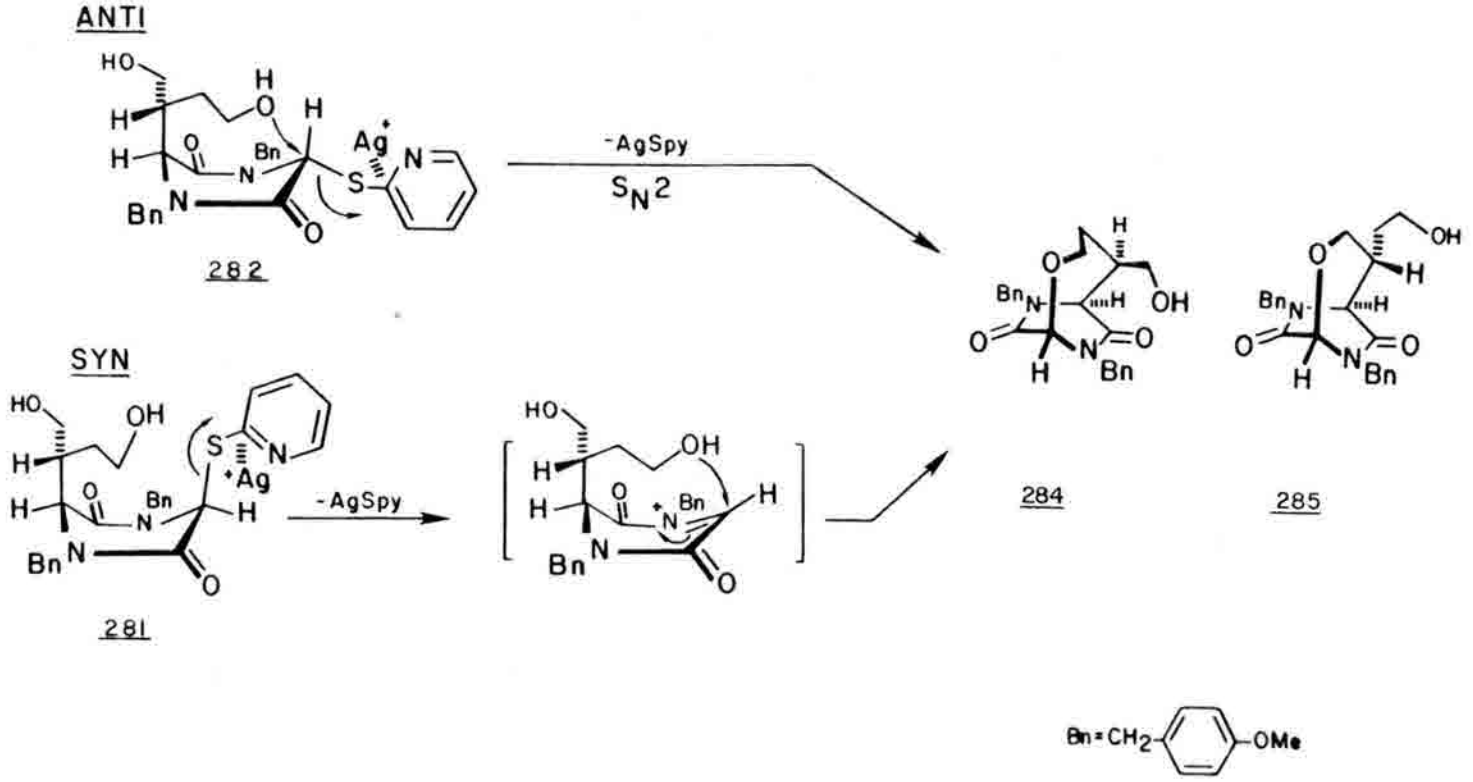



280

283



SCHEME 49



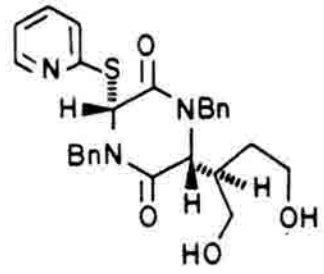
It is possible that the rotation barriers that dictate the sidechain conformation of the cis-major diol 281 are less once the more planar and reactive imminium intermediate is formed, thus increasing the amount of seven-membered ring at the expense of the eight-membered compound.

The syn-minor diastereomeric diol 280 gave only undesired seven-membered ring bicyclic alcohol, analogous to the syn-minor diol in the N,N'-dibenzyl series. For the latter series, a procedure was described in which a lengthy set of selective protections and deprotections led eventually to conversion only to the desired compound. We devised a much more efficient route for the N,N'-para-methoxybenzyl series which adds only one synthetic step and which has also been successfully applied to the N,N'-dibenzyl series. By varying the Lewis acid, it appears that the cyclization reaction is very tolerant to a variety of functionalities.

The syn-minor diol (Scheme 50) was reacted with one equivalent of t-butyldimethylsilyl chloride in the presence of base to give a 1:4 ratio of the hydroxysilyl ether compounds 285 and 286 respectively.

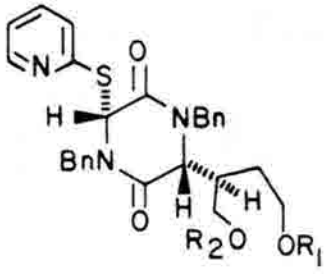
Upon inspection of the minor product 285 it is clear that cyclization (AgOTf) gives only the desired bicyclic alcohol 287, since silver triflate induces cyclization of the hydroxyethyl moiety, leaving the silyl ether intact. If after cyclization, two more equivalents are used, then the silyl ether is cleaved and the bicyclic alcohol 287 is obtained in good yield (>80%). If the same sequence is applied to the major hydroxy silyl ether 286, the only product which could be obtained would be the seven-membered ring compound, thus a second "protecting" group is required. The alcohol 286 was treated with mesyl chloride in

SCHEME 50

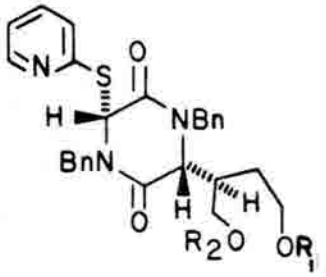


280

$Et_3N$ TBDMSCl

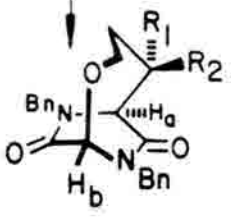


285 $R_1$=H $R_2$ $SiMe_2Bu^t$



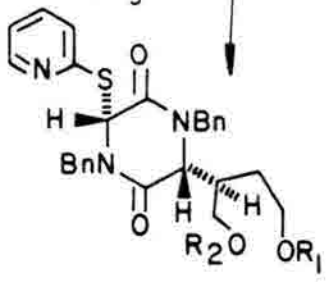
286 $R_1$= $SiMe_2Bu^t$, $R_2$=H

AgOTf



287 $R_1$=$CH_2OH$, $R_2$=H

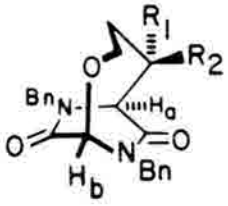
$Et_3N$ MsCl



289 $R_1$= $SiMe_2Bu^t$, $R_2$=Ms

MsCl, $Et_3N$

$Cu(ClO_4)$



288 $R_1$=$CH_2OMs$, $R_2$=H

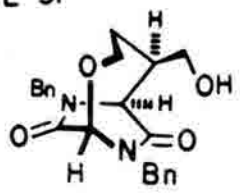
the presence of triethylamine to give the mesylate 289 almost quantitatively. The new "blocking group" is in fact the leaving group necessary for selenide displacement used in the formation of the exomethylene. Treating the mesylate with copper(II) perchlorate, results in the concomitant deprotection/cyclization reaction in which the silyl ether is deprotected and the resulting alkoxy intermediate cyclizes to give the bicyclic mesylate 288 in one step. Silver triflate does not give nearly as good yields as copper perchlorate. Thus an overall efficient convergent synthesis is utilized to give only desired bicyclic compounds which otherwise could not be made. (This procedure was also applied to the N-benzyl series, Appendix 5).

For the purpose of obtaining large quantities of bicyclic materials, the cis-minor diol was converted to bicyclic mesylate as described above; the trans-major diol was directly cyclized to a 10:1 ratio favoring eight-membered ring alcohol; and the cis-major diol was directly cyclized with silver triflate to give roughly an equal mixture of bicyclic alcohols.

The mixture of alcohols 284 and 285 could not be separated by chromatography and were thus converted to the mesylate mixture (Scheme 51). The mesylates 290 to 291 as well as the selenides (diphenyl diselenide, $NaBH_4$) 293 and 292 were separated and characterized, but for practical reasons the mixture was carried on to the olefin stage ($H_2O_2$, reflux) and then separated. The overall yield from the alcohols was 82%.

The selectivity of bridgehead functionalization of the simple bicyclic exomethylene 294 was the same as the N,N'-dibenzyl compound 263. The bridgehead anion at carbon-6 (n-BuLi, HMPA, -100°C) was

SCHEME 51



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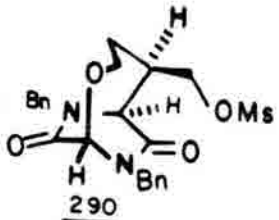
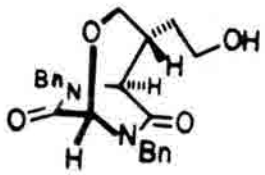


290

MsCl

$Et_3N$



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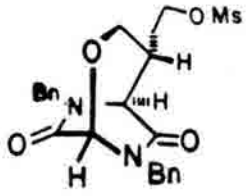

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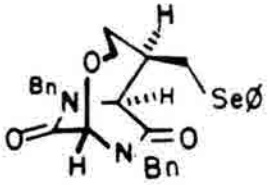

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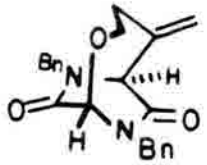
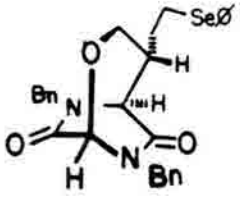


294

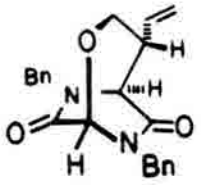
$\phi Se)_2$

$NaBH_4$

$H_2O_2$



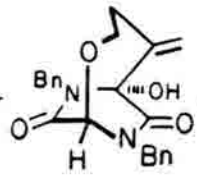
293



295

294 1. LDA/HMPA/-100°

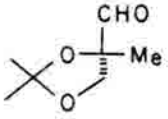
2. $O_2$/ THF

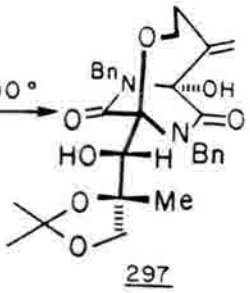


296

1. 2 eq n-BuLi/THF -100°

2.





297

exposed to a steady flow of $O_2$ for 10 minutes, then warmed to -50°C and quenched with MeOH to afford the bicyclic tertiary alcohol 296. A slight modification to this procedure was used which resulted in a 20% increase in the yield. The initial product from $O_2$ condensation with the bridgehead anion is the bridgehead peroxide, (which is stable enough that we have isolated it in the model series) which gets reduced by one of the components in the reaction mixture, possibly by the molecule itself since we have never observed over a 50% yield in the reaction. We decided to add hexamethyl phosphorus triamide, the reduced form of hexamethyl phosphoric triamide (HMPA), providing a reducing agent for the peroxide, and have observed a marked (>20%) increase in the yield.

The alcohol 296 was treated with 2 equivalents of n-BuLi (the first equivalent protects the alcohol as the lithio derivative) followed by condensation with the "Maag aldehyde in a doubly diastereoselective reaction to give only the desired diastereomer 297a, resulting in the synthesis of N,N'-di-para-methoxybenzyl bicyclomycin acetonide in ten steps from N,N'-di-para-methoxybenzyl glycine anhydride 273.

The doubly diastereoselective aldol condensation deserves further comment. Since there are two chiral centers involved in the reaction, the prochiral carbonyl and the chiral α-carbon of the aldehyde, four possible diastereomers may be generated in the aldol condensation (Scheme 52), compounds 297a-d. The fact that only one diastereomer is obtained (fortuitously the correct one) indicates that there is a large bias in the manner in which the aldehyde approaches the bicyclic

SCHEME 52

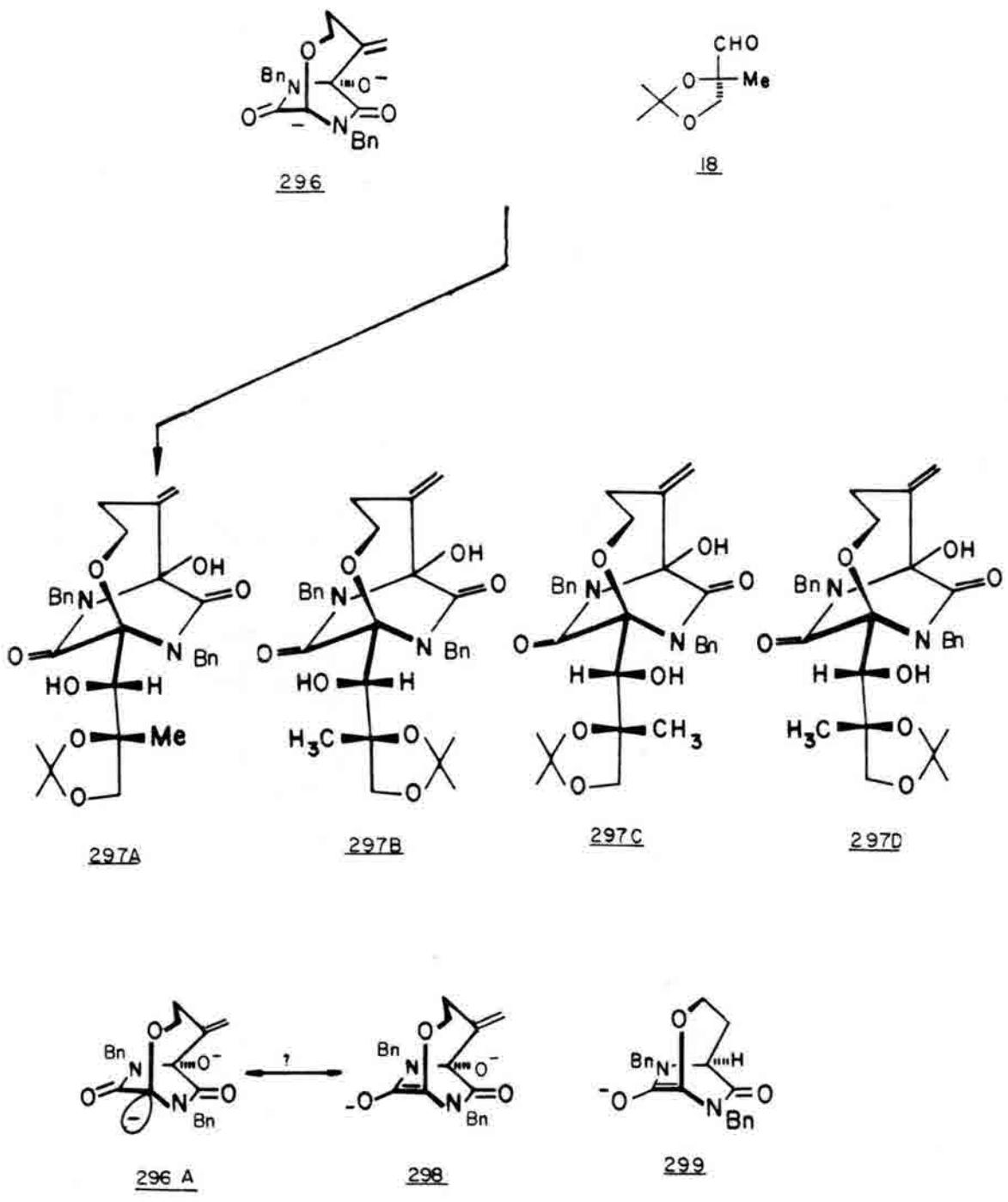


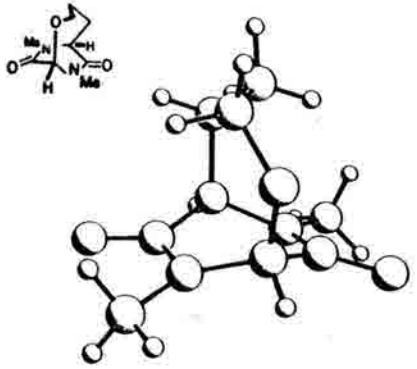

FIGURE 7. Diastereoselective aldol condensation

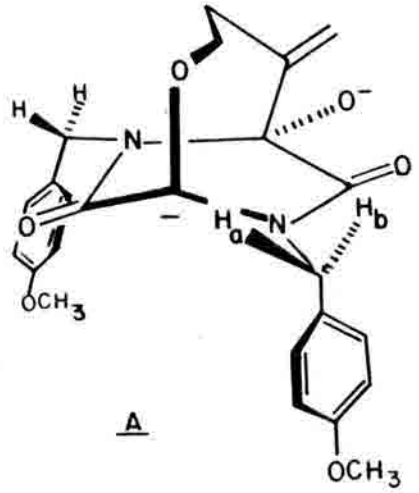
dianion 296a. Several important features of the dianion 296a contribute to the stereochemical outcome of the reaction.

The bridgehead anion at carbon-1 is not likely to be enolizable, (298, Figure 7), since the charge is localized on the bridgehead carbon 296a; to be an enolate anion it would have to form a carbon-carbon double bond at the bridgehead position resulting in a highly strained structure. This is supported by the fact that the seven-membered ring des-methylene analog undergoes the exact same bridgehead anion functionalization, and the enolate of that compound (299) would be prohibitely strained.

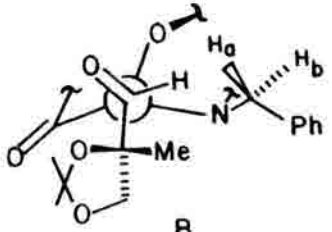
The X-ray structures of the bicyclic N-methyl derivative 83 and the monocyclic lactone 237 (Scheme 53) are very instructive in the analysis of the diastereoselective aldol condensation since they can be used to understand the steric constraints of the bridgehead anion 296a. Upon inspection of the monocyclic piperazinedione 237 it is clear that the lactone and the pyridylthioether moieties are both axial substituents of the boat-like six-membered ring diketopiperazine, and due to the bicyclic nature of the N-methyl derivative 83, the same observation is true. This boat-like conformation results in equatorial amide nitrogen substituents (methyl or benzyl) and places the $\pi$-amide orbitals in a pseudo-axial arrangement "below" the diketopiperazine, effectively crowding the bottom portion of the molecule; this can best be seen in the bicyclic compounds 83. A closer look at the monocyclic lactone shows that the N-benzyl groups are at approximately a $60^{\circ}$ angle below the plane of the diketopiperazine, pointing the benzylic hydrogens "up" towards the axial lactone and pyridyl thioether. Drawing on the structural information described above, the

SCHEME 53

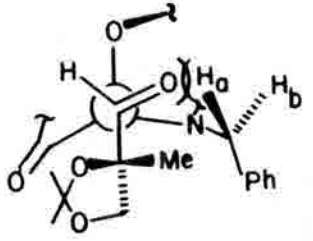




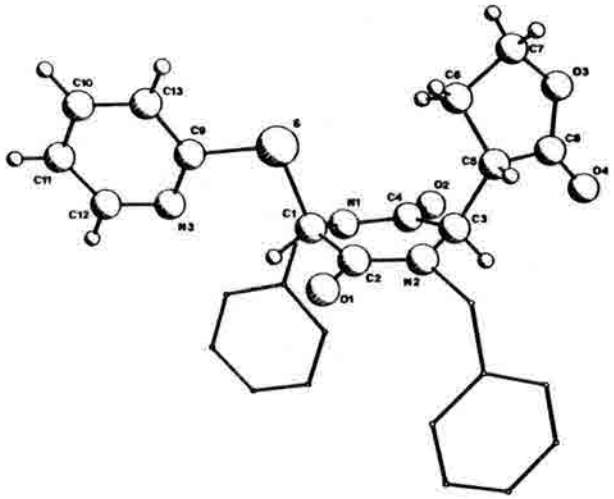
A



B



C

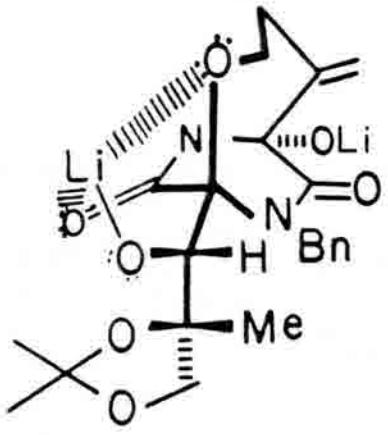


diastereoselectivity of the aldol is a result of specific electronic and steric constraints of the bridgehead anion which heavily bias the approach of the prochiral aldehyde. Structure A (Scheme 53) best describes the bridgehead anion by depicting the amide π-orbitals below the piperazinedione and by placing the benzylic hydrogen ($H_A$) equidistant from the bridgehead carbanion and the bridging oxygen atom, effectively crowding the right face of the molecule and preventing approach of the aldehyde in the manner described by 53c. This leaves a large cavity on the left face of the molecule between the amide carbonyl and the bridging oxygen, and thus the approach of the prochiral carbonyl is governed by this steric crowding and is forced to bisect the amide carbonyl-bridgehead carbon-bridging oxygen bond (53b) resulting in the desired S-configuration at C-1'. Goto has hypothesized a more standard chelated "enolate" aldol in their related condensation, but seems unreasonable due to geometrical constraints alluded to above. It is also worth mentioning that their aldol condensation is considerably less stereoselective (9:3:1:1) and in modest yield. The reason for the different efficiencies of their system vs ours is unknown.

The selectivity for the S-configuration at carbon-2' is more subtle, but appears to be influenced by the amide-nitrogen π-electrons which sit "below" the diketopiperazine. Since the approach of the aldehyde is extremely specific due to the steric requirements discussed above, the S-configuration at carbon-2' minimizes the interaction of the isopropylidene oxygen electron pairs with the nitrogen π-electrons pairs "under" the diketopiperazine ring. The R-configuration at

carbon-2' forces either the isopropylidene or the tertiary methyl at C-2' directly into contact with the nitrogen electron pairs.

One other factor in the diastereoselective aldol condensation is worth mentioning. Prior to workup, the initial aldol condensation product 300 is likely to tightly chelate the lithium atom between the two neighboring oxygens, making a very stable rigid intermediate.




300

This chelation effect might play a large role in the diastereoselectivity of the reaction, and might be responsible via a product development effect. A variation in the procedure of the aldol condensation, where the intermediate 300 is allowed to warm to room temperature before quenching with methanol (compared to a -80°C quench) results in the isolation of a second disatereomer in about a 1:1 ratío, which has been assigned the 1'R,2'S configuration (297c, Scheme 52). These results would indicate that the kinetic product from the aldol condensation where the anion is formed at -100°C, the aldehyde is added, and the reaction is quenched (MeOH at -60°C) is the desired stereoisomer 297a, and that the thermodynamic product (r.t. quench), compound 297c, is isomeric only at C-1'. It is not clear whether the anion is stable at warmer temperatures and that condensation under

these conditions is under thermodynamic control, or whether the diastereomer 297c is simply formed via a retro Aldol reaction of the kinetic product 297a, though the yields in the reaction do not reflect a "siphoning" effect of the desired product.

Supporting the intermediacy of the tightly held lithium chelate 300 is the observation by proton NMR that the resulting secondary alcohol (at C-1') is tightly hydrogen bonded to the amide carbonyl adjacent to it. The hydroxy proton exhibits a very distinctive doublet at 6.60 ppm (coupled to the C-1' methine) which we have used to both confirm a successful condensation and assign the stereochemistry of the sidechain as 1'S,2'S, the same as that for the natural product. Conversion of the aldol product to bicyclomycin has proved that the assignment is valid, showing that proton NMR can be a very useful tool for assigning the sidechain stereochemistry of synthetic bicyclomycin analogs.

The $^{1}H$ NMRs in Figure 8 shows the distinctive doublet of the C-2' hydroxy at 6.60 ppm for the correct S configuration. Figure 8 shows the other stereoisomeric aldol product. The doublet for the C-2' hydroxyl has now shifted 1 ppm upfield and corresponds to the R configuration. These assignments correlate very well with spectra of four diastereomers of 6-desoxy-4-desmethylene bicyclomycin models (33 36, Scheme 5) graciously provided to us by Dr. Hans Maag.

The second aldol product (297c) we have tentatively assigned as 1'R,2'S on the basis of its proton NMR spectrum which shows the OH doublet at 5.78 ppm. We have assigned 2'S stereochemistry because the isopropylidene singlets are very similar for both compounds. Although the C-2' methyl singlets are slightly different.

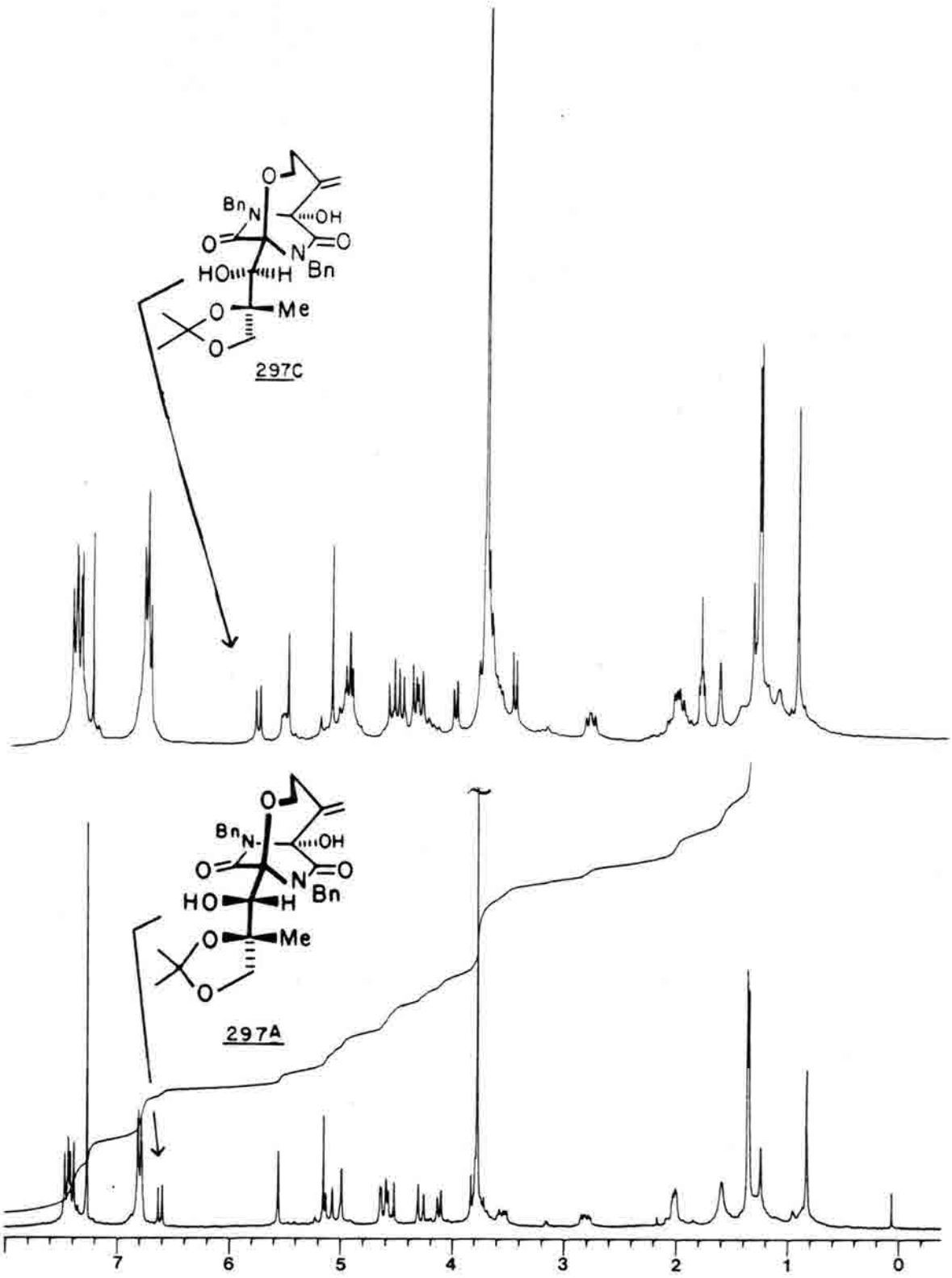
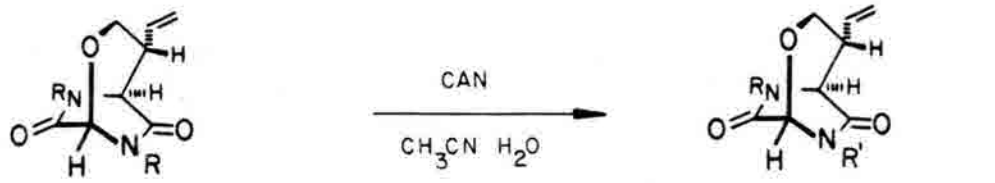



FIGURE 8.

During the synthesis of N,N'-di-para-methoxybenzyl bicyclomycin (297a) the controlled deprotection of some bicyclic precursors was investigated. The published procedure on the deprotection of simple bicyclic diketopiperazines indicated that it was crucial to use a 0.33M solution of CAN in a 3:1 mixture of acenitrile/$H_2O$ for 24 hours to obtain a maximal yield. We have found that our system is much more reactive and thus requires less time (typically 30 min - 2 hrs at room temperature) before there is some decomposition of the free amide product; it was also noted that the solvent ratio is not as critical in our case, though routinely a 0.8M - 0.3M solution is used. The commerically available anhydrous cerric ammonium nitrate, with no effort at drying or purification, contains a sufficient amount of water that the starting material need only be dissolved in $CH_3CN$.

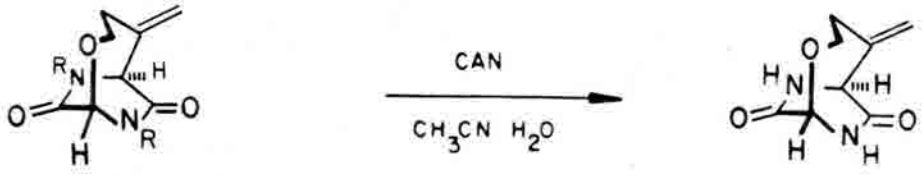
The first compound deprotected (Scheme 54) was the byproduct (295) of the exomethylene synthesis, and it resulted in a mixture of the two monodeprotected compounds 301 and 302 and the fully deprotected bicyclic vinyl adduct 303 in very good yields.

SCHEME 54




295 R= R'=$CH_2$pPh OMe

301 R=H R'=$CH_2$pPh OMe
302 R=$CH_2$pPh OMe
R'=H
303 R=H R'=H




294

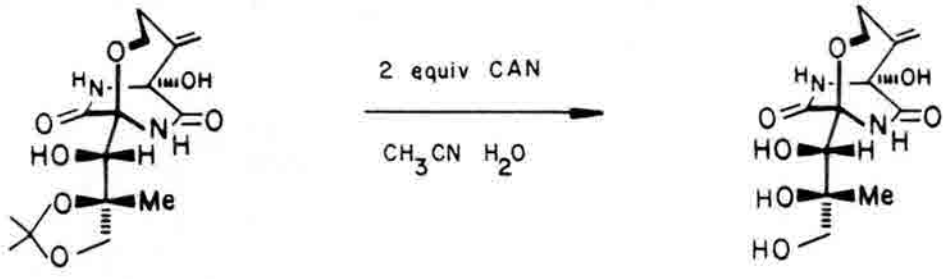
304

This indicated that CAN appeared to be a useful reagent for the removal of the para-methoxybenzyl groups on the bicyclic amide and that the conditions were compatable with the presence of a carbon-carbon double bond. The next ovbious compound to try was the exomethylene piperazinedione 294, an intermediate in the synthesis of bicyclomycin. Using similar conditions (6 equivelnts of CAN) we were very ecstatic to isolate a 90% yield of the deprotected exomethylene compound 304.

Subjecting natural bicyclomycin acetonide to the same conditions (CAN, $CH_3CN/H_2O$) revealed that 1) in the presence of 0.5 equivalents 0.04 M, of CAN, bicyclomycin was fairly stable, but with 3 or more

equivalents of CAN at higher concentrations bicyclomycin decomposed; and 2) that the first equivalent of CAN probably acts as a Lewis acid in the hydrolysis of the isopropylidene moiety since 10 minutes at room temperature with 0.5 equivalents CAN converts bicyclomycin acetonide 305 to bicyclomycin 1 (equation 8). This latter result meant that it would be possible to skip a step in the synthesis since deprotection of the synthetic acetonide 297a with CAN would remove both the N-amide protecting groups and the acetonide on the sidechain.

EQUATION 8



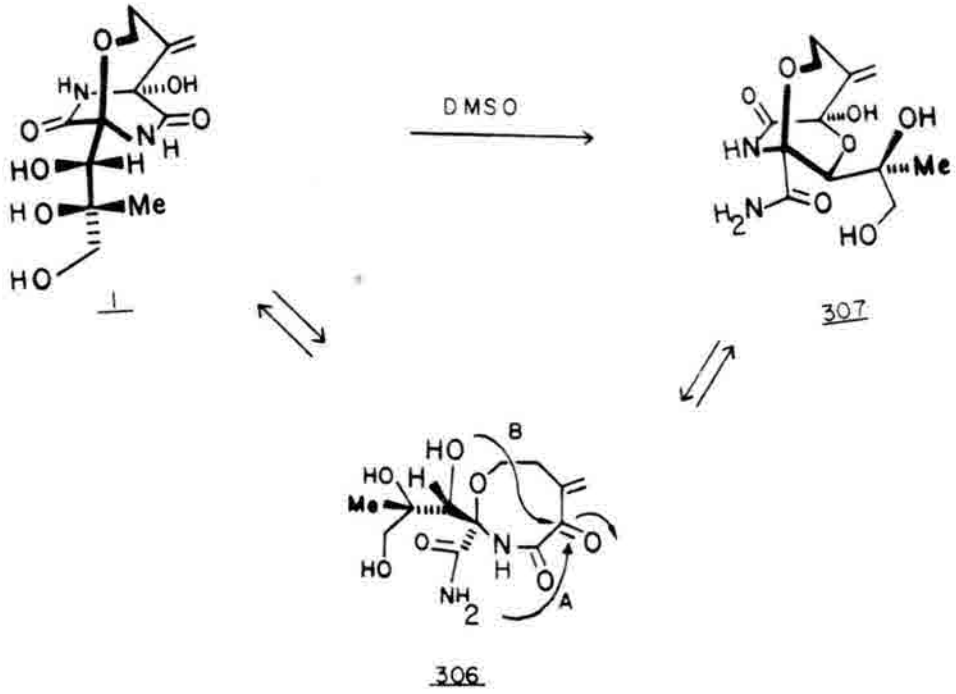

305 1

The first attempt at deprotection of the synthetic material was disappointing. Inspection of the TLC ten minutes after the addition of CAN showed a mixture of approximately 14 different compounds, with only one "major" (in a relative sense) product, and all of the starting material consumed. After isolation (22% yield), the proton NMR (Figure 9) revealed the presence of two methyl singlets at 3.80 ppm and the characteristic doublets in the 6.8-7.4 ppm region, establishing without a doubt the presence of both para-methoxybenzyl groups. Most of the other signals were in the same region and had the same multiplicity as the starting material (297a), except that one AB

quartet had now been replaced by a singlet and the characteristic secondary hydroxy doublet was gone. The infrared spectrum showed <u>two</u> carbonyl stretches, one at 1670 $cm^{-1}$ and the other at 1695 $cm^{-1}$.

At about the same time Wacker[38] published a rearrangement which N-alkylated bicyclomycin undergoes under slightly basic or even neutral conditions. If bicyclomycin is stirred for 24 hours in DMSO at room temperature, it is totally converted to a new compound which has been assigned structure <u>307</u> (Scheme 55). The compound is formed via rearrangement of bicyclomycin in which intermediate <u>306</u> is proposed, since it is clear that nucleophilic attack on the keto moiety of the pyruvamide would result in either formation of bicyclomycin (path a) or the rearrangement product (path b) <u>307</u>.

SCHEME 55



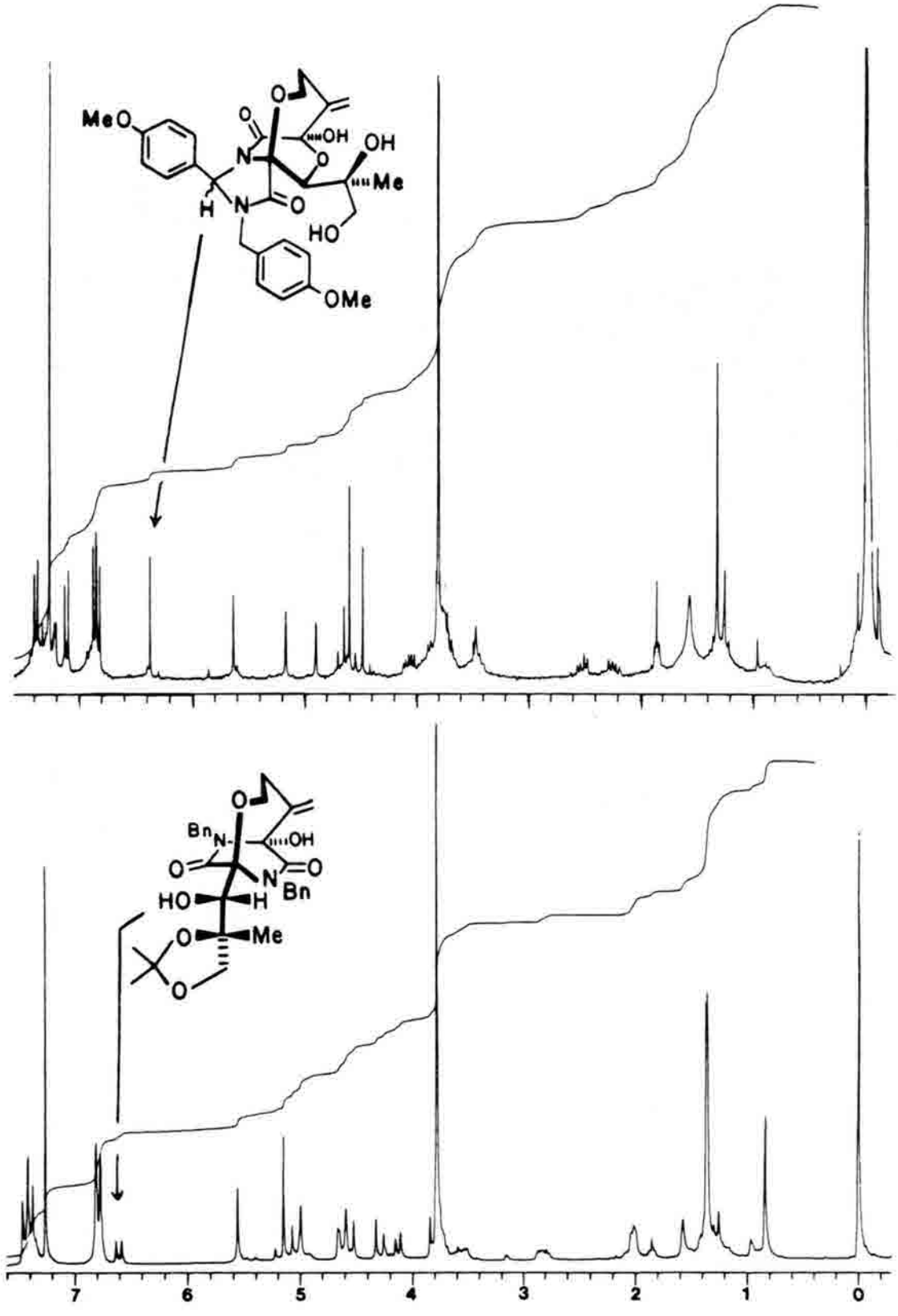


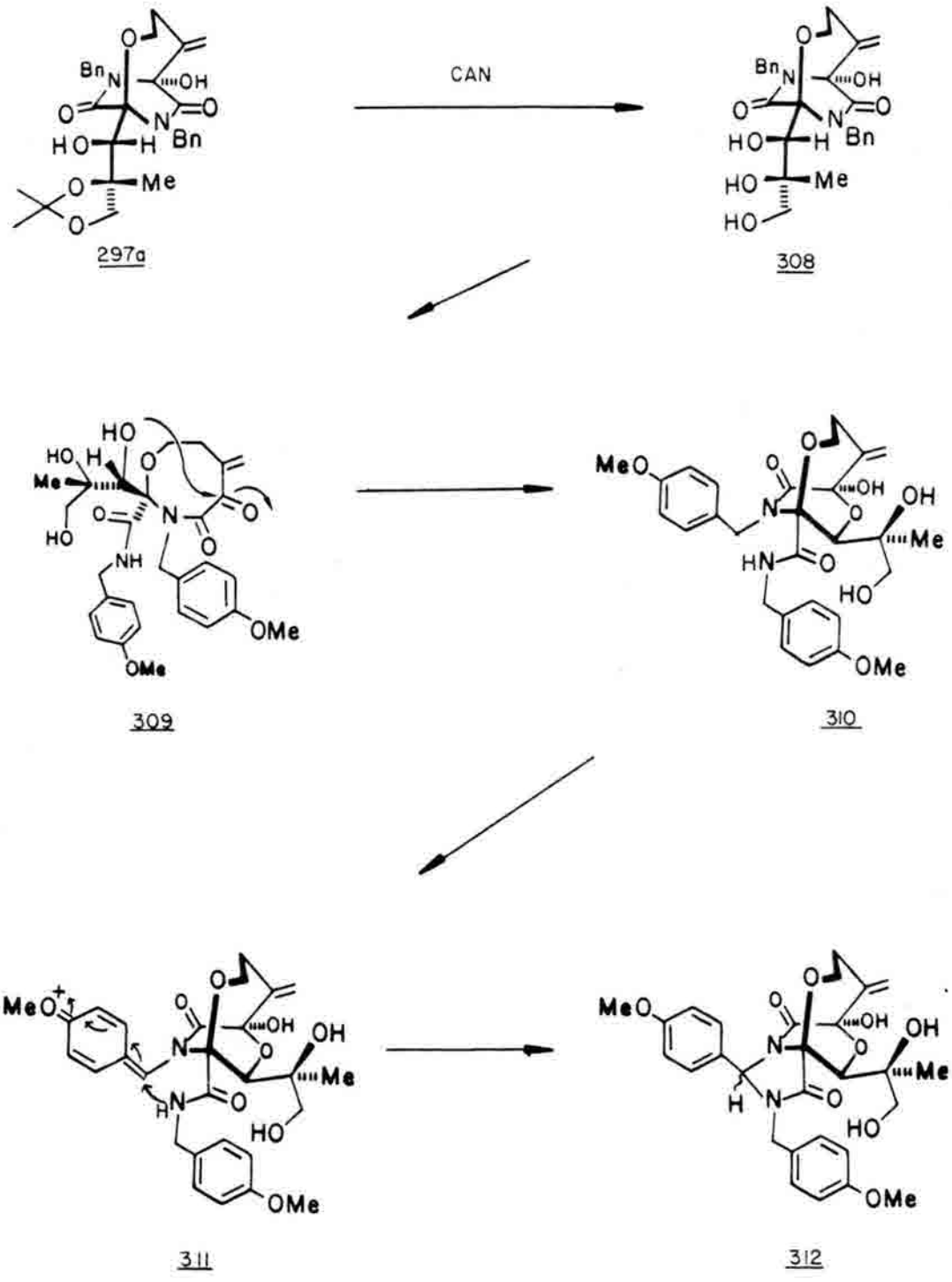

FIGURE 9. $^{1}H$ NMR comparison of rearrengement product.

It appears that the major deprotection product of the synthetic material is also a rearrangement product resulting from the formation of a monocyclic intermediate (Scheme 56).

As previously described, the first step is the loss of the isopropylidene to give the tetraol 308, which upon formation of the pyruvamide affords the monocyclic amide 309. The N-10 amide can readd to the electrophilic bridgehead carbonyl or the secondary alcohol can add nucleophilically to give the bicyclic structure 310. Since there is still CAN present, hydride abstraction of one of the benzyl protons results in the benzenium ion intermediate which instead of undergoing hydrolysis to give benzaldehyde and the free amide, intramolecularily adds the other amide to give the tricyclic compound 312. This compound fits the data very well by accounting for the substitution of one benzylic AB quartet for the benzyl singlet. The IR spectrum also shows the presence of two carbonyl stretches corresponding to the five- and six-membered ring amides. It appears that the substrate undergoes rearrangement prior to activation of the benzyl group. The fact that a large number of compounds were observed for this reaction supports the intermediacy of this monocyclic amide 309 since it is clear upon inspection of the structure that any of the three hydroxy groups on the sidechain could act as the nucleophile in the formation of the bicyclic compounds. Coupled with the resulting intramolecular trapping products from benzyl hydride abstraction, it is easy to draw over twenty reasonable products.

The mechanism for the rearrangement to the monocyclic amide in Scheme 56 indicates that the problem lies in the ability of the C-6 to form a pyruvamide and the C-1' hydroxyl to intramolecularily trap

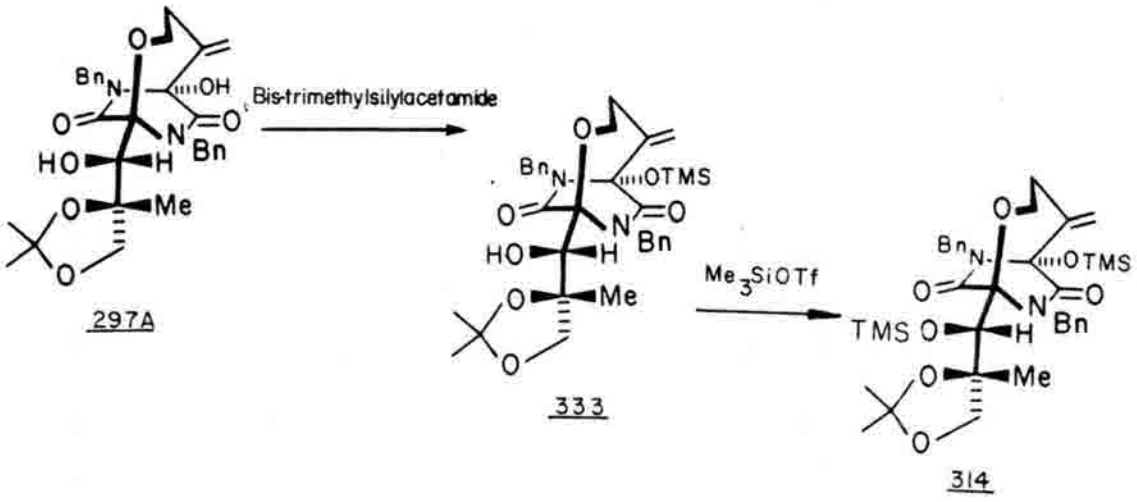
SCHEME 56



the latter, and suggests that the solution lies in the blocking of these groups by protecting the two alcohols.

The bicyclic diol 297a was treated with bis-trimethylsilyl-trifluoro acetamide (THF, room temperature) to give only the monosilylated product 313 which is reflective of the strong hydrogen bonding of the secondary alcohol at C-1' (Scheme 57). Subjecting alcohol 313 to the more reactive trimethylsilyl triflate (DMA, THF, room temperature) gave the bis-silyl ether 314 in quantitative yield.

SCHEME 57

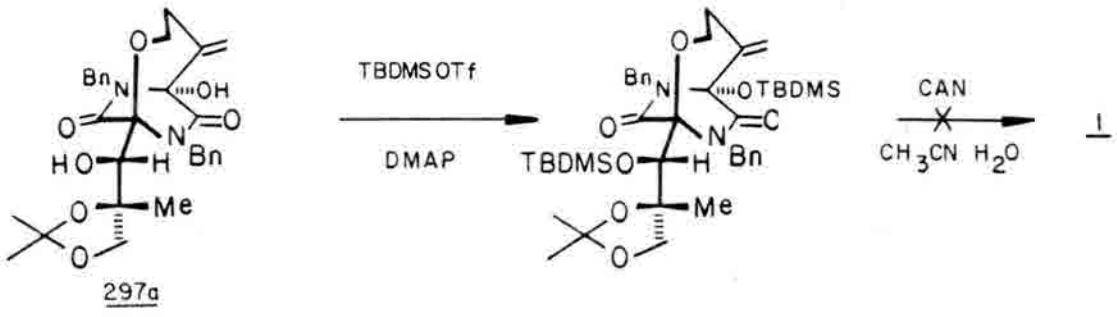



297A 333 314

Attempting the deprotection under the same conditions (CAN, $CH_3CN/H_2O$) previously discussed, the fully protected bicyclic diketopiperazine 314 gave the exact same results which we had observed for 297a, including a major product which co-eluted by TLC with the rearranged bicyclic amide 312. The labile trimethylsilyl protecting groups are incompatible with the reaction conditions, and in fact, the water present in the solvent mixture was sufficient to hydrolyze the silyl ethers.

A second attempt was made by blocking the two alcohols with the more stable t-butyldimethylsilyl protecting group. To a methylene chloride solution of 297a was added dimethylaminopyridine followed by addition of t-butyldimethylsilyl triflate to give the bis-silyl adduct 315 (Scheme 58). Upon submitting this compound to the CAN deprotection conditions, the same rearrangement product was obtained, confirming again the use of too labile of a protecting group.

SCHEME 58




297a

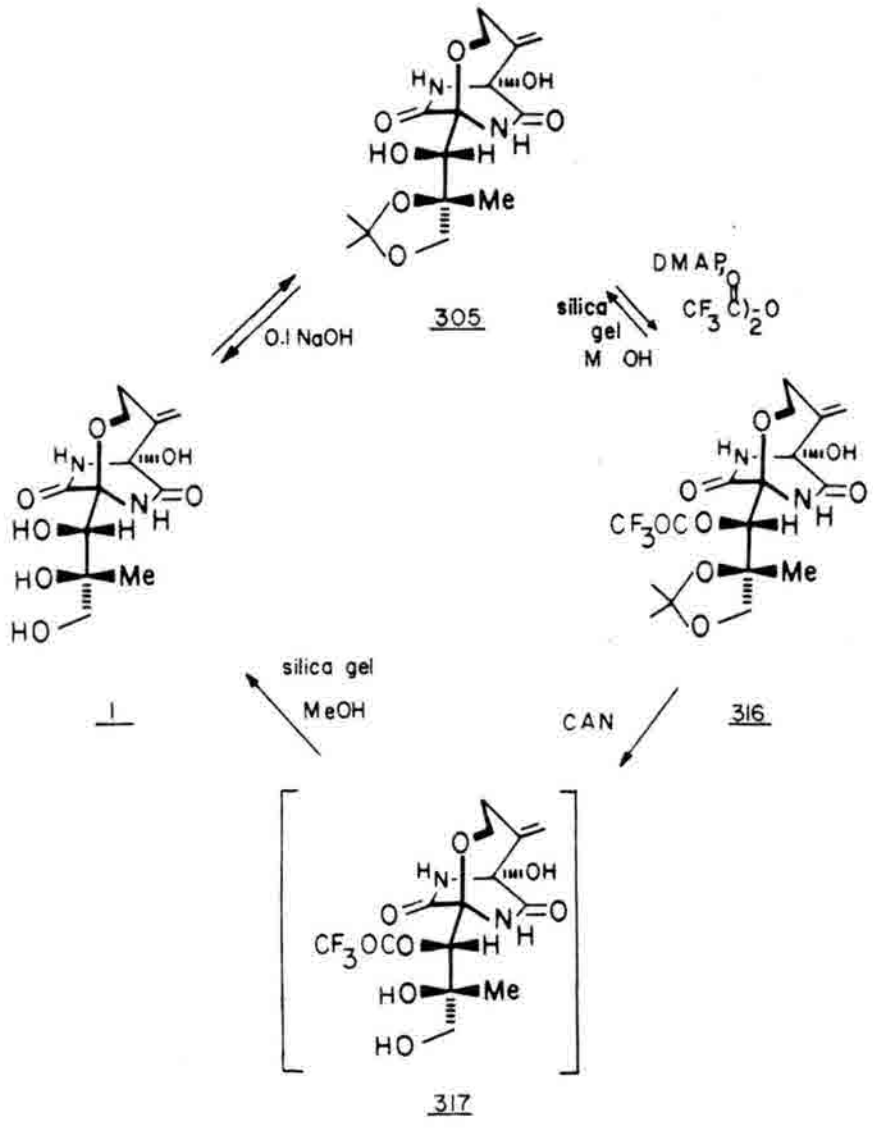
At this stage, it was decided to investigate the stability of protecting groups under the deprotection conditions (CAN, $CH_3CN/H_2O$) using authentic material instead of consumming the more difficult to obtain synthetic compound. We and others[32] have found naturally occurring bicyclomycin a difficult molecule to functionalize. Inspection of the structure reveals that there are four hydroxy and two N-H functionalities, a total of six functionalities which are difficult to selectively activate. It has been an especially difficult problem to functionalize the amide nitrogens with protecting groups in an

effort to synthesize an intermediate along the synthetic pathway of either the N-benzyl or N-para-methoxybenzyl series.

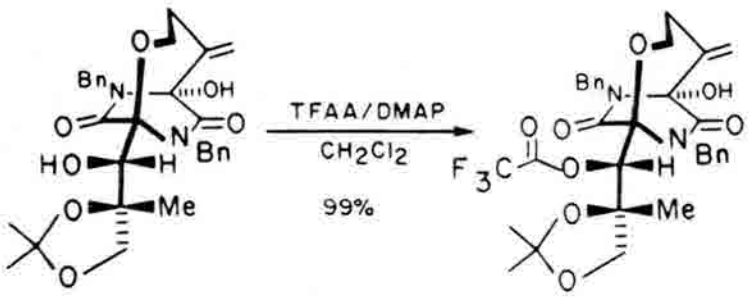
Most of the attempts have been on the bicyclomycin acetonide 305 using benzyl bromide, t-butyldimethylsilyl chloride, or methyl iodide under a variety of basic conditions, and the usual results are hard to separate complex mixtures of every combination of mono, di, tri, and tetrasubstituted products. An exception to the problem discussed above is the formation of the trifluoroacetate at C-1' (Scheme 59). By using methylene chloride as a solvent (instead of THF), the acetonide 305 can be monoacetylated exclusively at the secondary carbon C-1' in quantitative yields, and the resulting trifluoroacetate 316 appears stable when subjected to deprotection conditions (CAN, $CH_3CN/H_2O$), since following the reaction by TLC shows only one product which does not co-elute with bicyclomycin. Attempts at isolating the intermediate triol 317 gave only bicyclomycin, suggesting the trifluoroacetate triol 317 decomposes to the tetraol (bicyclomycin) in the presence of silica gel. This is consistent with the observation we have made during our initial studies on the trifluoroacetate: if the reaction mixture is chromatographed on silica gel and the silica is extracted with THF, a quantitative yield of the acetate 316 is obtained; when the silica gel is extracted with a mixture of MeOH/THF, only the starting diol 305 is recovered.

Having obtained an apparently suitable blocking group on the alcohol which was stable to CAN and easily removed under mild conditions (MeOH, silica gel) the trifluoroacetate (318) of the para-methoxybenzyl acetonide 297a was synthesized in quantitative yield using the same conditions (DMAP, $CH_2Cl_2$, TFAA) (Scheme 60). The

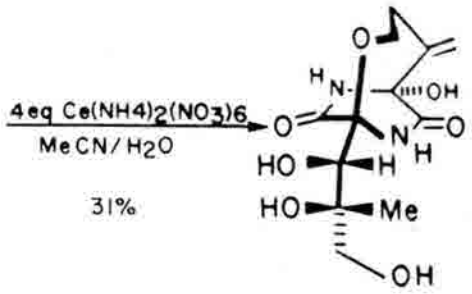
SCHEME 59



SCHEME 60




297a 318




319
racemic

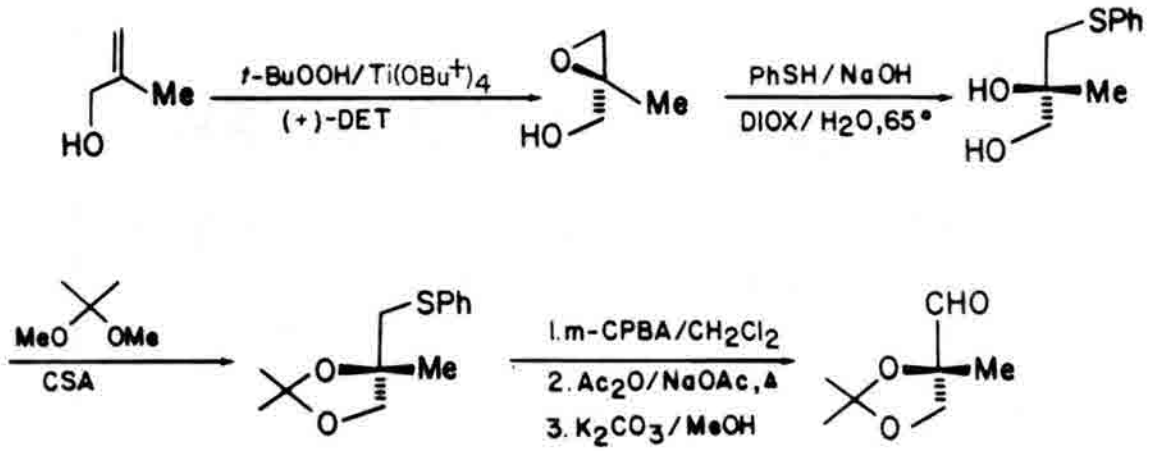
resulting alcohol was treated with CAN in acetonitrile/$H_2O$ and following chromatrography on silica gel, synthetic racemic bicyclomycin 319 was obtained in 35%! As previously mentioned, the trifluoroacetate is stable to CAN and is removed only after chromatography at which time the silica gel is extracted with methanol for 10 minutes. Monitoring the reaction by TLC shows that at no stage during the deprotection is bicyclomycin formed, only after extracting a non-UV band with a slightly higher $R_f$ than bicyclomycin off a silica gel plate, is the natural product obtained. This synthetic step amounts to the

deprotection of five atoms bearing three different protecting groups in one step.

The proton NMR of the racemic compound is shown next to that in Figures 10 and 11, and matches peak for peak confirming the correct stereochemistry of the synthetic compound. Scheme 61 depicts the twelve step synthesis of bicyclomycin proceeding in 4.6% overall yield. Figure 12 shows autobiographs of synthetic and natural bicyclomycin. The zone of inhibition of bacterial growth indicates that the (-)-bicyclomycin antipode is inactive since the synthetic sample appears to be half as active as the natural one at the same concentration.

We now directed our attention to the total synthesis of optically active (+)-bicyclomycin. We envisioned doing a resolution at the aldol condensation stage using the optically active aldehyde 18,[39] which has been synthesized using the Sharpless asymmetric epoxidation described in Scheme 62 (prepared by Dr. J. S. Dung).

SCHEME 62




The absolute stereochemistry of the optically active aldehyde 18 was unambiguously established as follows. The racemic alcohol 320 (Scheme 63) was coupled with (-)-camphanyl chloride 321 in pyridine to

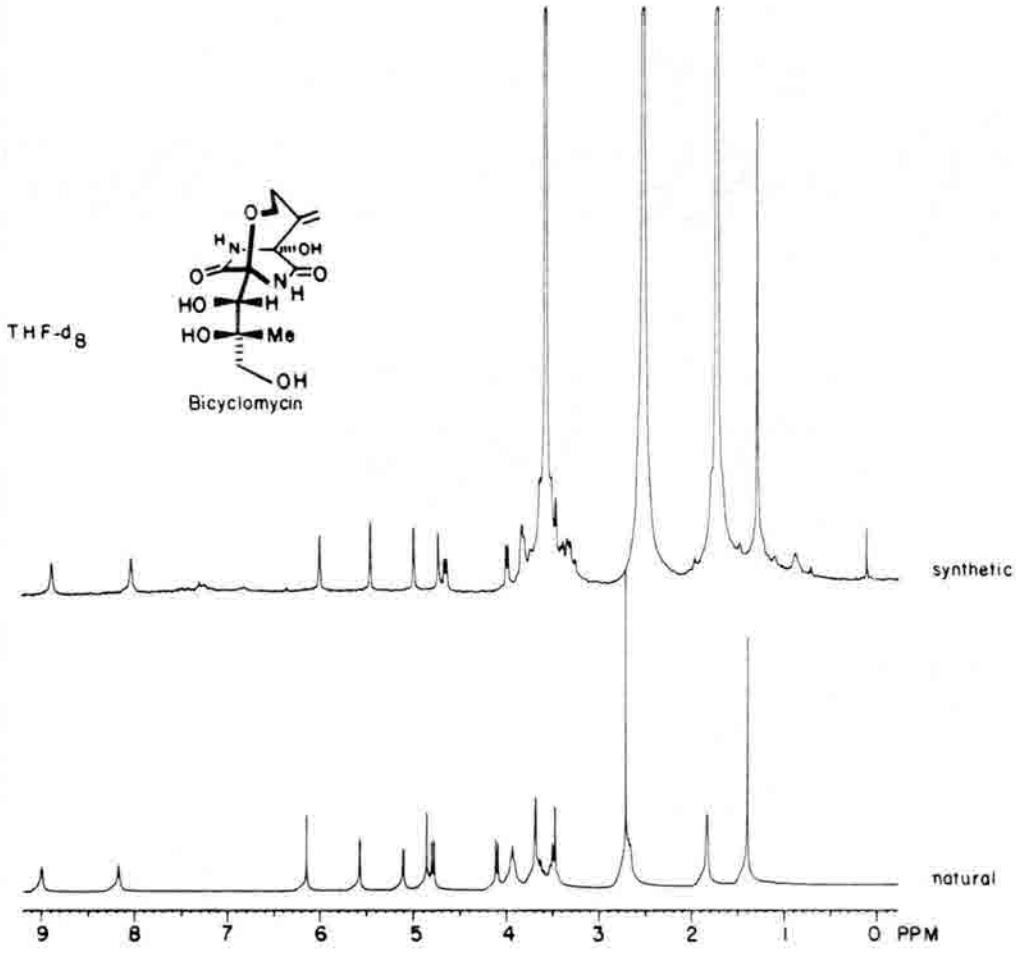



FIGURE 10. $^{1}H$ NMR of synthetic and natural bicyclomycin

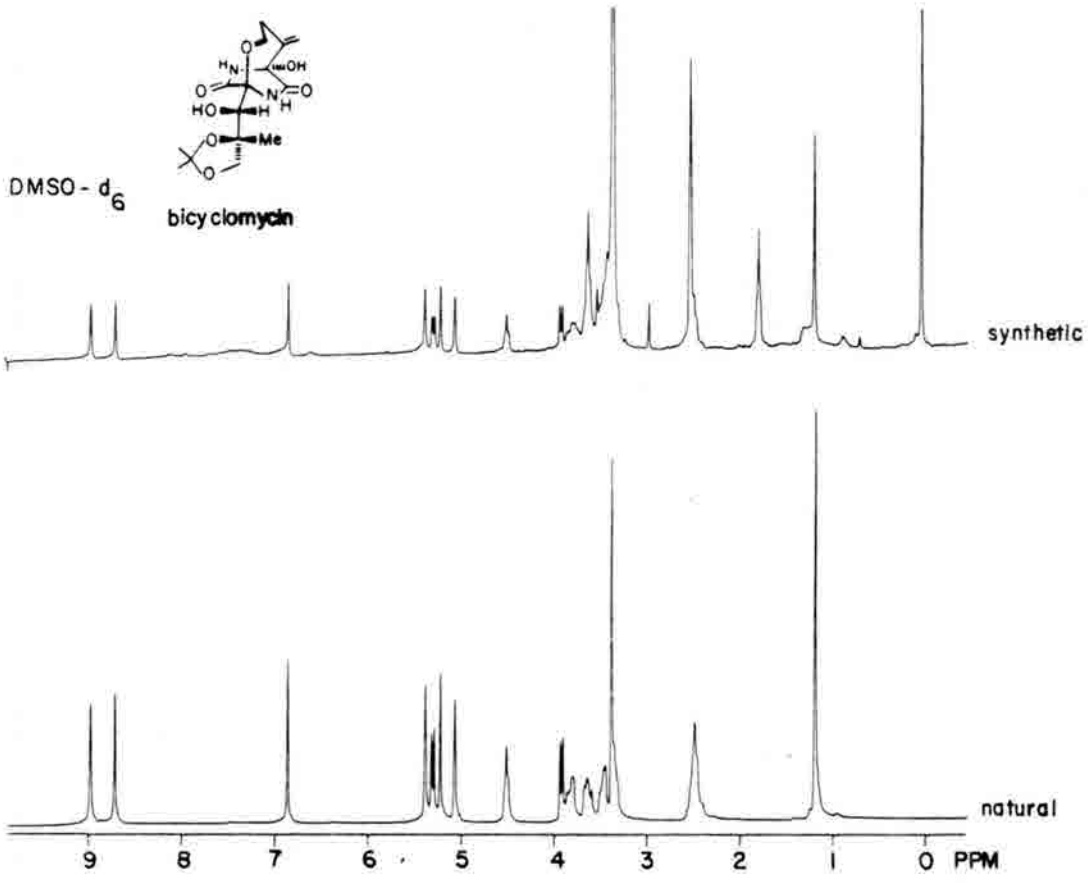
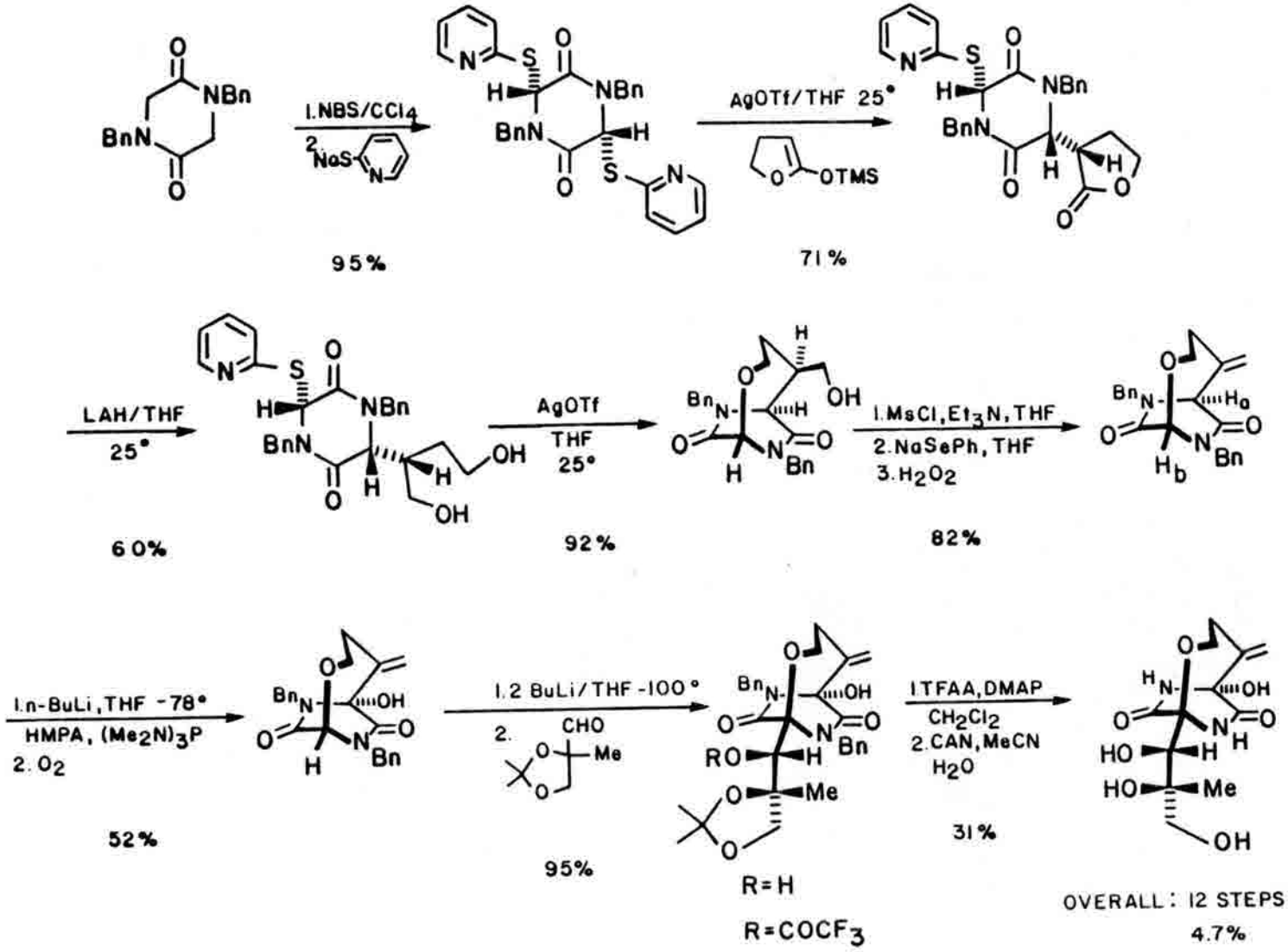
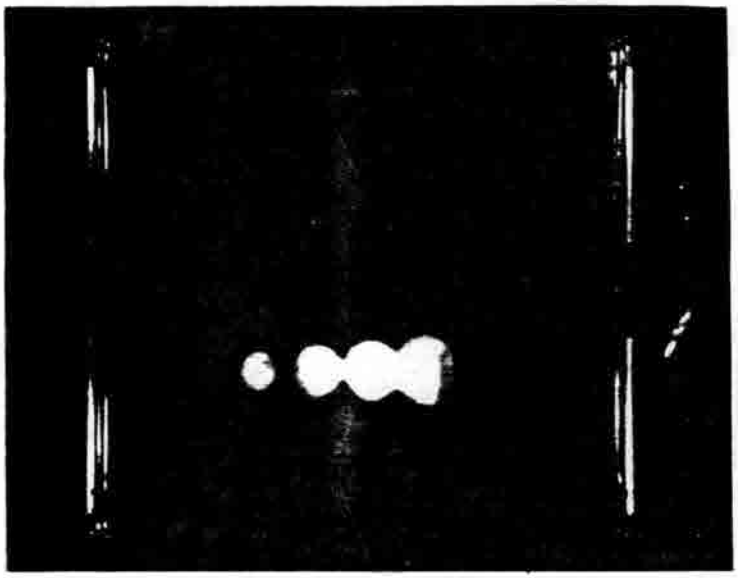



FIGURE 11. $^{1}H$ NMR of synthetic and natural bicyclomycin

SCHEME 61


1. NBS/CCl4
2. NaS
95%
AgOTf/THF 25°
OTMS
71%
LAH/THF
25°
60%
AgOTf
THF
25°
92%
1. MsCl, Et3N, THF
2. NaSePh, THF
3. H2O2
82%
1. n-BuLi, THF -78°
HMPA, (Me2N)3P
2. O2
52%
1. 2 BuLi/THF -100°
2.
95%
R=H
R=COCF3
1. TFAA, DMAP
CH2Cl2
2. CAN, MeCN
H2O
31%
OVERALL: 12 STEPS
4.7%

Bicyclomycin
Standards

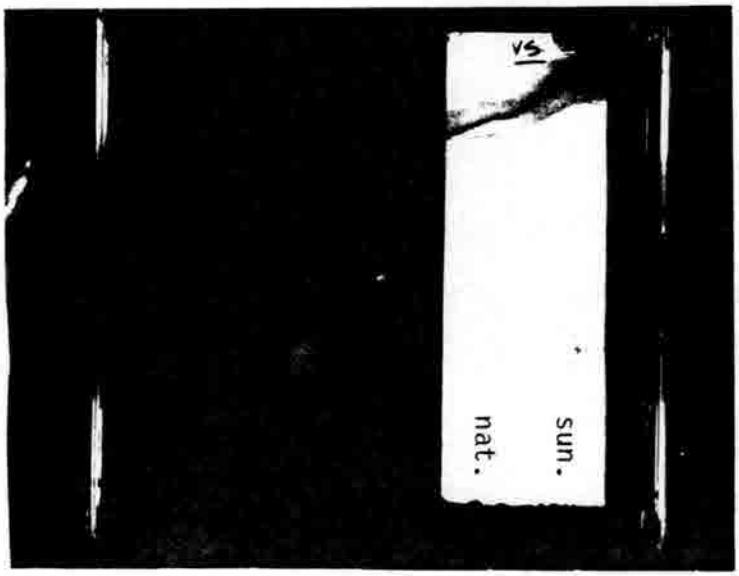


20% MeOH/$CHCl_3$

25 75 150 300

conc. µg/mL

Natural and
Synthetic
Bicyclomycin




25 50 200 100

TLC
Comparison

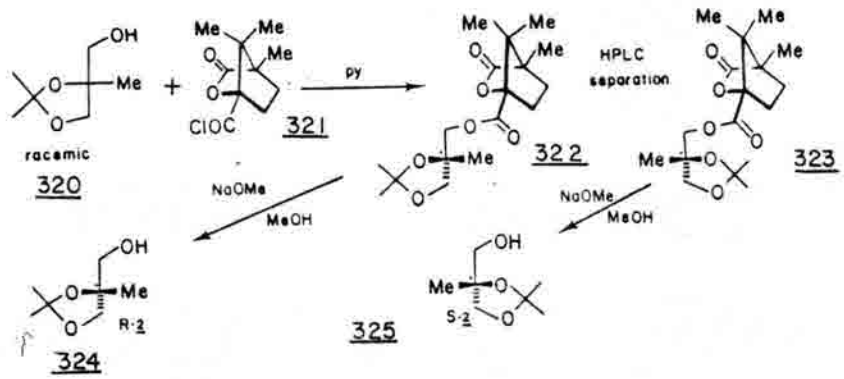
natural
synthetic
synthetic
natural

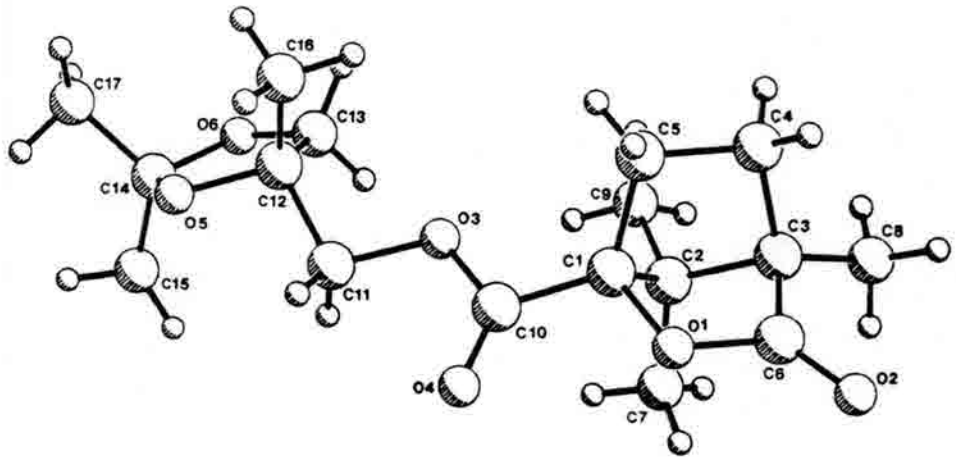
conc. µg/mL

FIGURE 12.

Photographs of Bioautograms of TLC's Dyed with Tetrazolium Red.

SCHEME 63




323

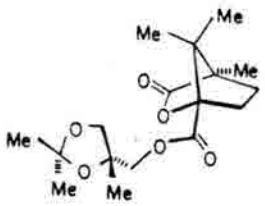
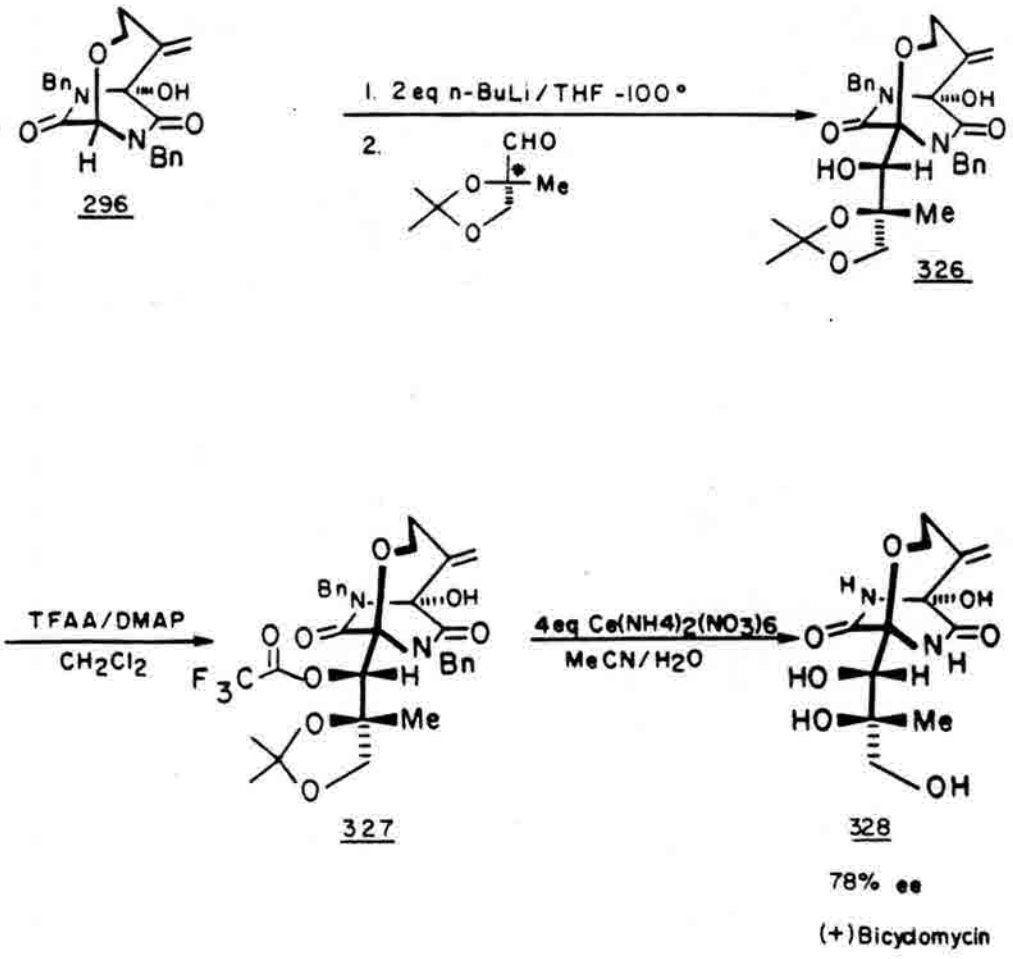


FIGURE 13. X-RAY of compound 323

afford the diastereomeric esters 322 and 323 which could be separated through HPLC chromatography and hydrolyzed with sodium methoxide to afford the optically active pure alcohols 324 (R) and 325 (S). A single crystal X-ray analysis was carried out on the ester (323), and the absolute stereochemistry of the optically pure alcohol 325 was shown to be S (Figure 13). The absolute configuration of the aldehyde 18 was determined by reduction ($LiAlH_4$) to the alcohol 324 and comparison of the optical rotations, which indicated that L-(+)-diethyl tartrate resulted in the S configuration at C-2 of the alcohol in 85% ee. This enantiomeric excess was also confirmed by conversion to the camphanyl esters and comparing the diastereomeric ratio after chromatography. Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of 323 are given in Appendix III.

Condensation of the racemic dianion of 296 with the optically active aldehyde resulted in the desired aldol product 326. One of the consequences of the high stereoselectivity of this reaction is the recovery of optically active starting material 321 since the condensation favored reaction of one of the enantiomers of the racemic 296 (Scheme 64). The optically active diol was converted to the trifluoroacetate, 327 using the usual procedure ($(CF_3C{=}O)_2$-O, DMAP, $CH_2Cl_2$) which was then deprotected to give optically active (+)-bicyclomycin 328 in an 78% enantiomeric excess. This product is identical by NMR and TLC with authentic bicyclomycin.

SCHEME 64




The synthesis of 328 is the first total synthesis of optically active (+)-bicyclomycin.[40]

# CHAPTER IV

# STRUCTURE-ACTIVITY CORRELATIONS OF BICYCLOMYCIN

The synthesis of bicyclomycin via the regioselective functionalization of the bridgehead anions of simple bicyclo[4.2.2] compounds has placed us in the unique position of probing the structural requirements necessary for antibiotic activity by synthesizing analogs which are not accessible through degradation of the natural product.

The mechanism of action of bicyclomycin is unknown and differs from that of the other antibiotics, including penicillin. In an effort to elucidate the biomechanistic role of bicyclomycin, Iseki looked at the effect on the synthesis of various cell substituents in the presence of the antibiotic, and found that in vivo DNA and lipid synthesis were not affected, whereas RNA and protein synthesis were significantly affected. A closer look at the latter two revealed that in vitro neither cell-free protein synthesis nor RNA synthesis were significantly affected by bicyclomycin. Since the protein synthesis in vitro remained invariant, the effects on the envelope and cytoplasmic protein synthesis were examined and the results indicated that the envelope protein synthesis was very sensitive to bicyclomycin. The envelope fraction of Escherichria coli 15 THU was pulse-labeled with $^{14}$C-L-arginine in the presence of the antibiotic and the envelope protiens were then separated by SDS-polyacrylamide gel electrophorens to afford two bands that were sensitive to bicyclomycin. The first was found to be the free form of lipoprotein (Figure III), a small protein (MW 7200) consisting of a lipid portion which is embedded in the outer

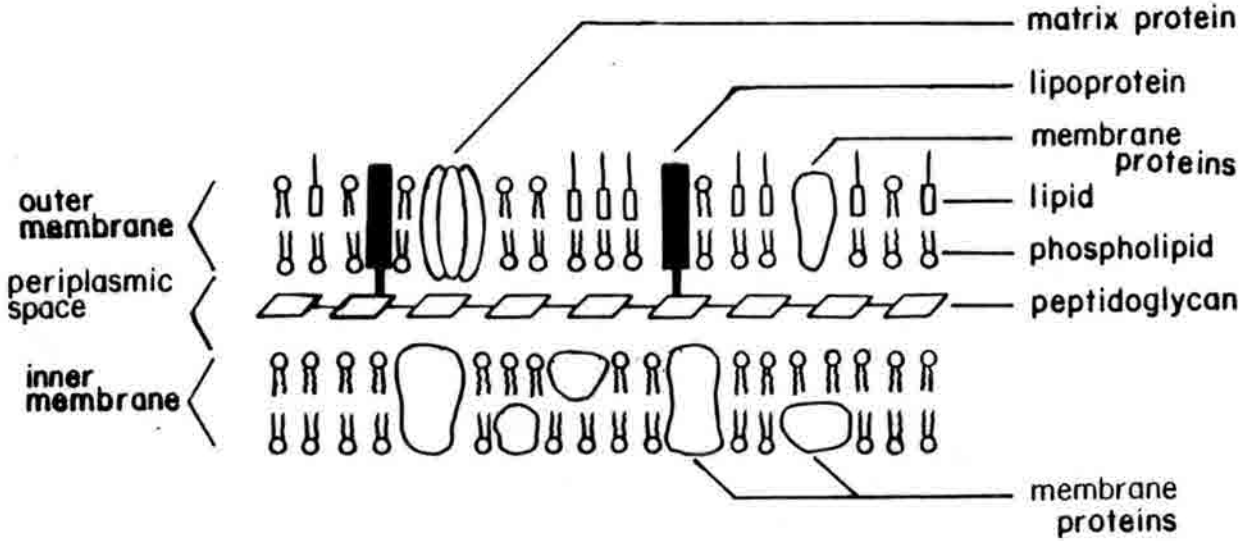



FIGURE 14. Bacterial cell envelope.

membrane of the cell envelope, and a C-terminal lysine which forms a covalent bond to the peptidoglycan, stabilizing the total structure of the cell wall. (Peptidoglycan is a covalently linked macromolecule consisting of repeating units of tetrapeptides and disaccharides which is found in the Periplasmic space between the outer and inner membranes of a gram-negative cell envelope) (see Figure 14).

The second band that was found sensitive to bicyclomycin appears to be the bound form of the lipoprotein linked to the peptidoglycan. Since the free form of lipoprotein is first synthesized on the ribosomes directed by m-RNA specific for lipoprotein and then converted to the bound form attached to the peptidoglycan, bicyclomycin may be affecting their synthesis in two ways. The free form of lipoprotein might be incomplete when synthesized in the presence of bicyclomycin, in which case the inhibition on the bound form is simply a secondary effect, or alternatively the antibiotic may be inhibiting the conversion of the free form to the bound form. When an E. coli mutant lacking lipoprotein was grown under a wide range of conditions, the presence of bicyclomycin was not fatal to the bacteria, indicating that although the antibiotic does inhibit lipoprotein biosynthesis, it is most likely a secondary effect rather than the primary mode of action. It is unlikely that bicyclomycin inhibits peptidoglycan biosynthesis by a path similar to other antibiotics since it does not prevent incorporation of alanine into peptidoglycan in vivo.

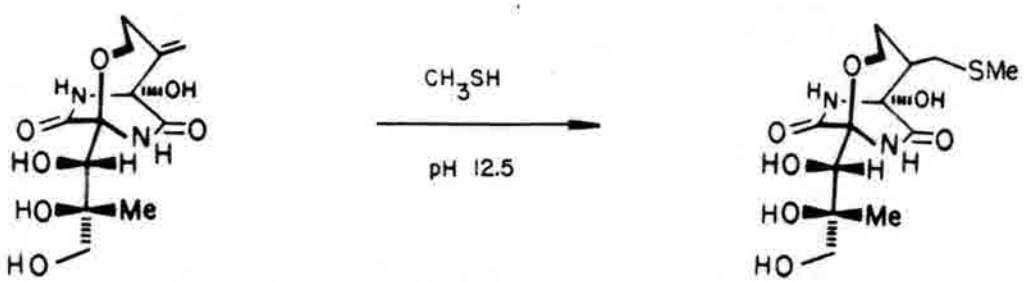
When E. coli were grown in the presence of labeled [$^{14}$C]bicyclomycin (prepared biosynthetically by introducing L-[$^{14}$C]leucine and L-[$^{14}$C]isoleucine into the culture broth of Streptomyces sapporonensis) bicyclomycin binding proteins (BBPs) were

found in the Sarkosyl-soluble fraction, which consists of inner membrane proteins, and gel electrophoresis afforded four major bands of BBPs and three minor ones. In a competitive experiment for penicillin binding proteins (PBPs), the cell envelope was treated with bicyclomycin prior to binding with [$^{14}$C]benzylpenicillin, and the results indicated that bicyclomycin did not interfere with the binding of penicillin to BBPs, suggesting PBPs differ from BBPs. When different concentrations of [$^{14}$C]bicyclomycin were incubated with aliquots of the envelope fraction and the extent of binding to each protein was treated as a bimolecular irreversible reaction, a linear relationship was observed between the concentration of the antibiotic and the protein binding for the four major BBPs; also, no bound [$^{14}$C]bicyclomycin was released from the membrane protein after a three hour incubation period. The above results indicate that bicyclomycin forms an irreversible 1:1 adduct with the BBPs in the inner membrane. Since it is known that bicyclomycin blocks cell division, it is plausible that the BBPs which the antibiotic binds to might be participating in cell division, much like PBP-3 which is known to be involved in cell division of *E. coli*.

The binding of [$^{14}$C]bicyclomycin to the BBPs was inhibited *in vivo* by dithothreitol or 2-mercaptoethanol. Iseki has shown that the reaction of sodium methanethiolate with bicyclomycin in a pH 12.5 solution affords the addition product 329 (Scheme 65) as the major component. Since catalytic hydrogenation of the 4,5-double bond of bicyclomycin results in loss of antimicrobial activity, it appears that the olefin might irreversibly form a covalent bond with sulfhydryl

groups of the inner membrane proteins (BBPs) resulting in the fatal disruption of cell division.

SCHEME 65




1 329

A Ciba-Geigy[42] group has prepared a large number of semisynthetic derivatives of bicyclomycin and has screened them for antimicrobial activity. Manipulation of the exomethylene moiety generally resulted in total loss of activity with the exception of three C-5-carboxyl compounds which were active against Proteus sp (bicyclomycin is not) indicating these derivatives might have alternate modes of action. Manipulations of the C-6 bridgehead hydroxy, the C-1 trihydroxy butyl sidechain or the amide nitrogens all resulted in loss of activity. Since all of the manipulations led to loss of activity, no clear structure-activity correlation was established.

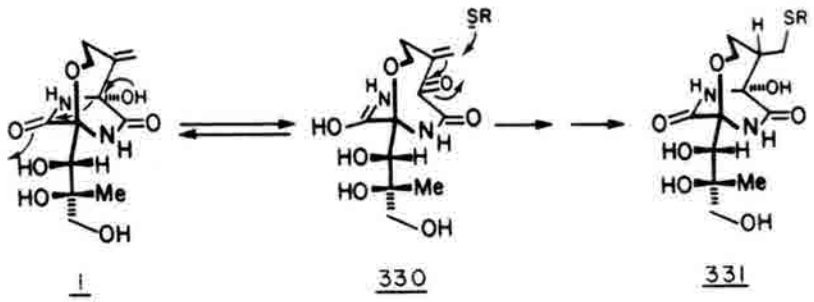
Using methodology described in Chapter III, we felt it would be possible to analyze the structure-activity relationship of bicyclomycin by synthesizing bicyclic analogs containing the minimum requirements for antimicrobial activity. Two lines of investigation were chosen to probe the biomechanistic requirements.

The first consisted of broad spectrum antimicrobial screening to establish the in vitro MIC's (minimum inhibitory concentration) of the

active synthetic analogs. Along with these tests, the above compounds would be subjected to thiolate addition studies under conditions in which the thiolate anion added to the exomethylene moiety of natural bicyclomycin. These latter studies would constitute the thiolate addition tests, and it was hoped that a clear correlation between in vitro activity and electrophilic capacity for thiolate additions could be established.

Upon inspection of the structure of bicyclomycin and the observation that mercaptides regioselectively add to the exomethylene moiety, we have proposed three mechanisms for the mode of action of bicyclomycin. The first involves base-catalyzed formation of a "latent" $\alpha,\beta$-unsturated pyruvamide 330 (Scheme 66) which acts as a Michael-type acceptor and undergoes 1,4-addition of the mercaptide anion. Intramolecular addition to the pyruvamide regenerates the bicyclic structure and results in the bridgehead alcohol 331.

SCHEME 66

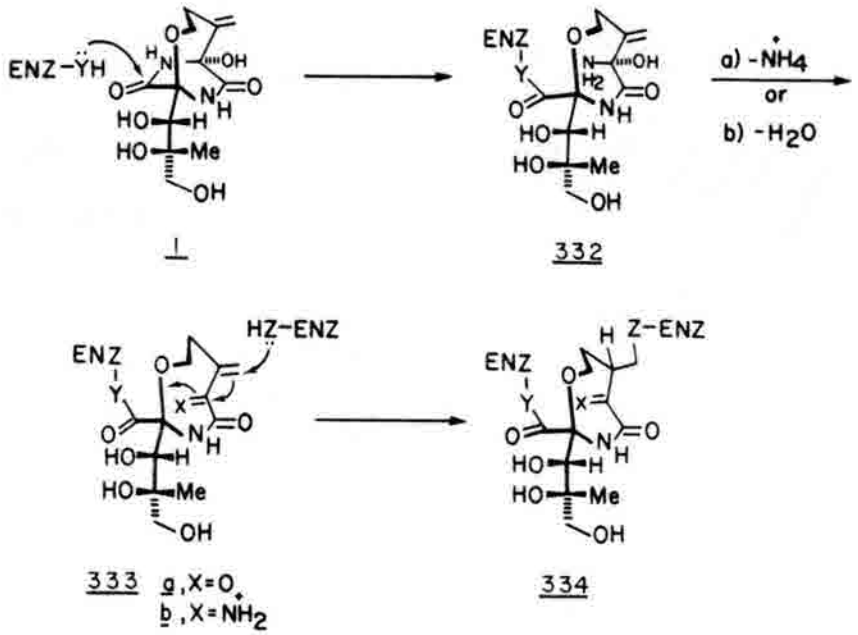



1 330 331

Alternatively, since bicyclomycin is a cyclic peptide it might first bind to a protease or transpeptidase-type protein whose function is to catalytically cleave a peptide bond during the biosynthesis of the cell envelope, resulting in the acyl-enzyme derivative 332 (Scheme 67). The $\alpha,\beta$-unsaturated pyruvamide can then be generated by loss of

ammonia (or $H_2O$) and the resulting Michael-type acceptor can be nucleophilically attacked by a nearby sulfhydryl (or other nucleophilic) group (333-334) resulting in the "suicide" inactivation of the BBPs.

SCHEME 67



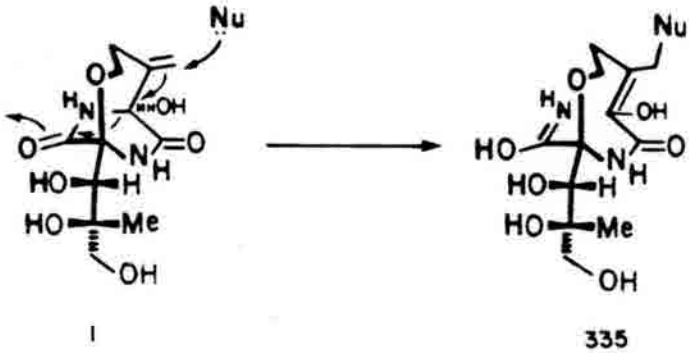

1 332

333 a, X=O
b, X=NH2

334

Finally, it is possible that the nucleophile adds to the exomethylene in an $SN_2'$ fashion without requiring the intermediacy of a monocyclic α,β-unsaturated pyruvamide intermediate 335 (Scheme 68).

SCHEME 68

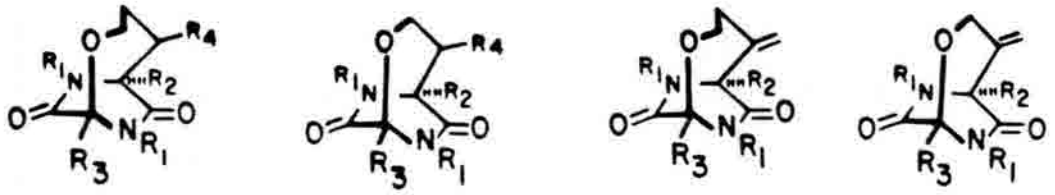



1 335

A large array of bicyclic compounds have been synthesized starting from the four basic bicyclic compounds (Chart I) as either their

N-methyl, N-benzyl, or N-para-methoxybenzyl derivatives via regioselective functionalization of the bridghead anions. The analogs

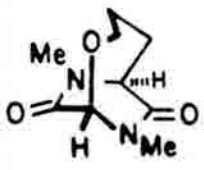
CHART II



targeted for synthesis were chosen in order of increasing complexity so as to systematically establish the requirements necessary for antimicrobial activity, particularly to establish the obligate partnership of the C-5 exomethylene and the C-6 bridgehead hydroxyl functionalities. The smaller seven-membered ring bicyclic analogs were also investigated since it is possible that the greter ring-strain present in the seven-membered ring series might favor formation of the monocyclic pyruvamide intermediate thus making the analog more active than its eight-membered ring counterpart. (Compounds 83a, b, c, 183, 192b, 335-343, 345, and 346 were prepared by Dr. J. S. Dung).

The first set of compounds tested are those described in Chart III and consisted of either seven- or eight-membered ring analogs which lacked the exomethylene moiety and which contained a variety of substituents at the bridgehead carbons other than a hydroxy moiety. Since all of these compounds did not contain the necessary functionalities which we have proposed are requisite for activity, it was not surprising that the compounds were inactive. The above results

CHART III



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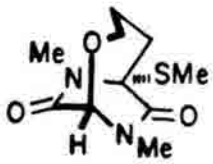

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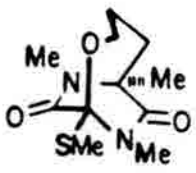

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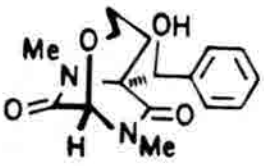

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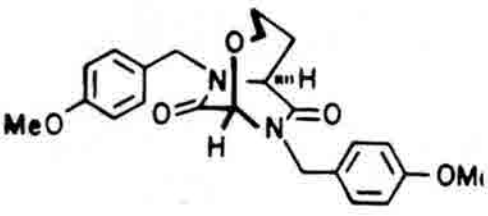

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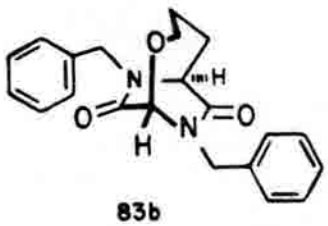
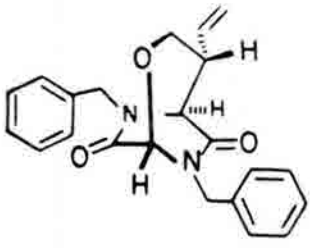


83b



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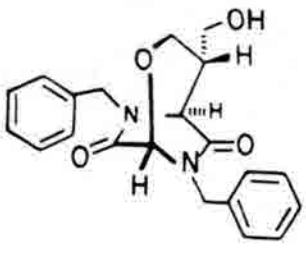

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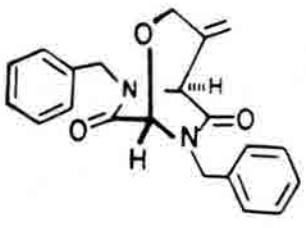

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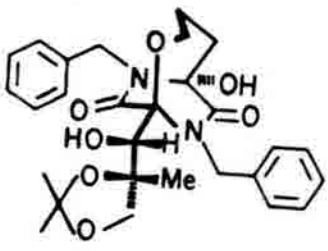

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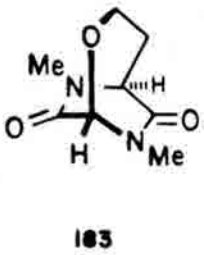

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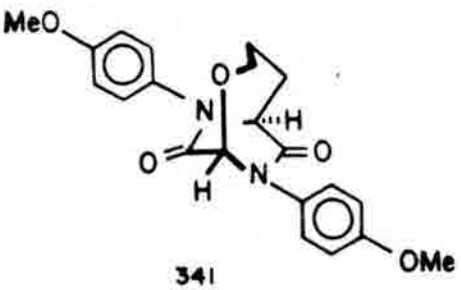


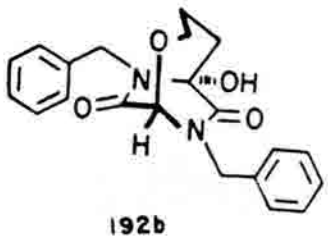
341

for the first time establish that the simple bicyclic nature of the molecule is not the source of antimicrobial activity.

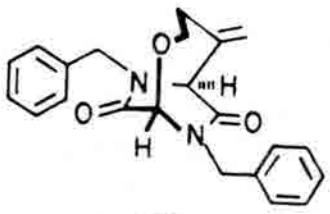
The second set of compounds were designed to increase the complexity of the bicyclic analogs by introducing two functionalities either independently or in conjunction. This would establish whether only the C-6 bridgehead hydroxyl or the C-5 exomethylene are necessary for activity, or whether their partnership is crucial as we have proposed in the two mechanisms described above. To this end, the molecules described in Chart IV were synthesized using methodology described in Chapter III.

Compound 192b contained the bridgehead hydroxyl necessary for formation of the monocyclic pyruvamide but lacked the electrophilic exomethylene necessary for Michael-type addition, and was found to be inactive. Compound 263 contained the exomethylene moiety but lacked the ability to form a pyruvamide, thus not enabling "activation" of the electrophile through conjugation. This molecule was also found to be inactive. The third compound (266) tested possessed both the bridgehead hydroxyl and the exomethylene and was found to show gram positive inhibition against Micrococcus leteus, Bacillus megaterium, Bacillus sp TA, and Streptomyces cellulosae. As indicated in Table V, the spectrum of antimicrobial activity differs from that of bicyclomycin, indicating that the mechanism of action might be different from that of bicyclomycin. It is of interest to note that even though 266 displayed weak activity, the tests were performed on a racemic mixture and presumably only one antipode is active. Pictures of the agar plates showing zones of inhibition of bacterial growth for

CHART IV



192b



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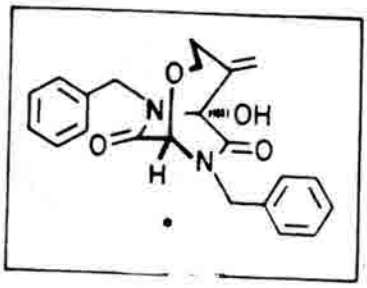


•displayed antibacterial activity

266

TABLE V

| | | 266 $R_1$=$CH_2Ph$ $R_2$=OH $R_3$=H | 319 $R_1$,$R_3$,$R_4$=H $R_2$=OH | Bicyclomycin Ro 21-7023 |
|---|---|---|---|---|
| G-rods | Pseudomonas aeruginose 56 | >1000 | 1000 | >1000 |
| | Proteus vulgaris 101N | >1000 | 1000 | >1000 |
| | Escherichia coli 94 | >1000 | 500 | 250 |
| | Klebsiella pneumoniae 369 | >1000 | 500 | 250 |
| | Serratia marcescens SM | >1000 | 1000 | >1000 |
| | Serratia sp. 101 | >1000 | | >1000 |
| | Acinetobacter calcoaceticus PCI$_3$ | >1000 | | 1000 |
| G+ cocci | Streptococcus faecium ATCC 8043 | >1000 | | >1000 |
| | Staphylococcus aureus 82 | >1000 | 1000 | >1000 |
| | Micrococcus luteus PCI | 500 | | >1000 |
| G+ rods | Bacillus megaterium 164 | 500 | | >1000 |
| | Bacillus sp. E | >1000 | | >1000 |
| | Bacillus subtilis 558 | 250 | 1000 | >1000 |
| | Bacillus sp. TA | 250 | | 1000 |
| | Mycobacterium phlei 78 | 1000 | | 1000 |
| G+ filament | Streptomyces cellulosae 097 | 500 | 1000 | 500 |
| Molds | Paecilomyces varioti M16 | 1000 | | 1000 |
| | Penicillium digitatum 0184 | 1000 | | 1000 |
| Yeasts | Candida albicans 155 | 1000 | | 1000 |
| | Saccharomyces cerevisiae 90 | 1000 | | 1000 |

*Lowest concentration still showing zone of inhibition by the agar-diffusion well method.

266 are shown in Figures 15 and 16. In view of the fact that the N,N'-dibenzyl exomethylene desoxy analogs were inactive, the activity of 266 suggests that the two mechanisms (Scheme 66 and 67) proposed above are plausible since we have established for the first time that the C-4, C-5 exomethylene and the C-6 hydroxyl in conjunction are minimal structural requirements for antibiotic activity.

The observation by Yoshimura that the N-para-methoxybenzyl amide protecting group can be removed from monocyclic piperazinediones in high yields has allowed for the first time the syntheses of free amide (-NH-) bicyclic analogs lacking substitution at either the C-6 and/or the C-1 bridgehead positions, analogs which are inaccessible from the natural product.

Treatment of the corresponding N,N-di-para-methoxybenzyl bicyclic derivatives with ceric ammonium nitrate in $CH_3CN/H_2O$ resulted in the deprotected amide derivatives described in Chart V. The removal of the amide blocking groups changes the solubility characteristics of the structure from being generally lipophilic/hydrophobic (N-alkylated) to hydrophilic/lipophobic (-N-H). The same logic was employed in the choice of analogs, that is, the systematic inclusion of functional groups including the exomethylene alcohol 344 and culminating with synthetic bicyclomycin. All the compounds in Chart V were found to be totally inactive, including desoxydesmethylene bicyclomycin 345 and desmethylene bicyclomycin 346.

As described in the mechanisms proposed above (Schemes 66, 67, and 68), we have felt that a "Michael" type addition to the $\alpha,\beta$-unsaturated pyruvamide is obligate for antimicrobial activity, regardless of the "activating" force (base, peptidase enzyme, etc.) necessary to

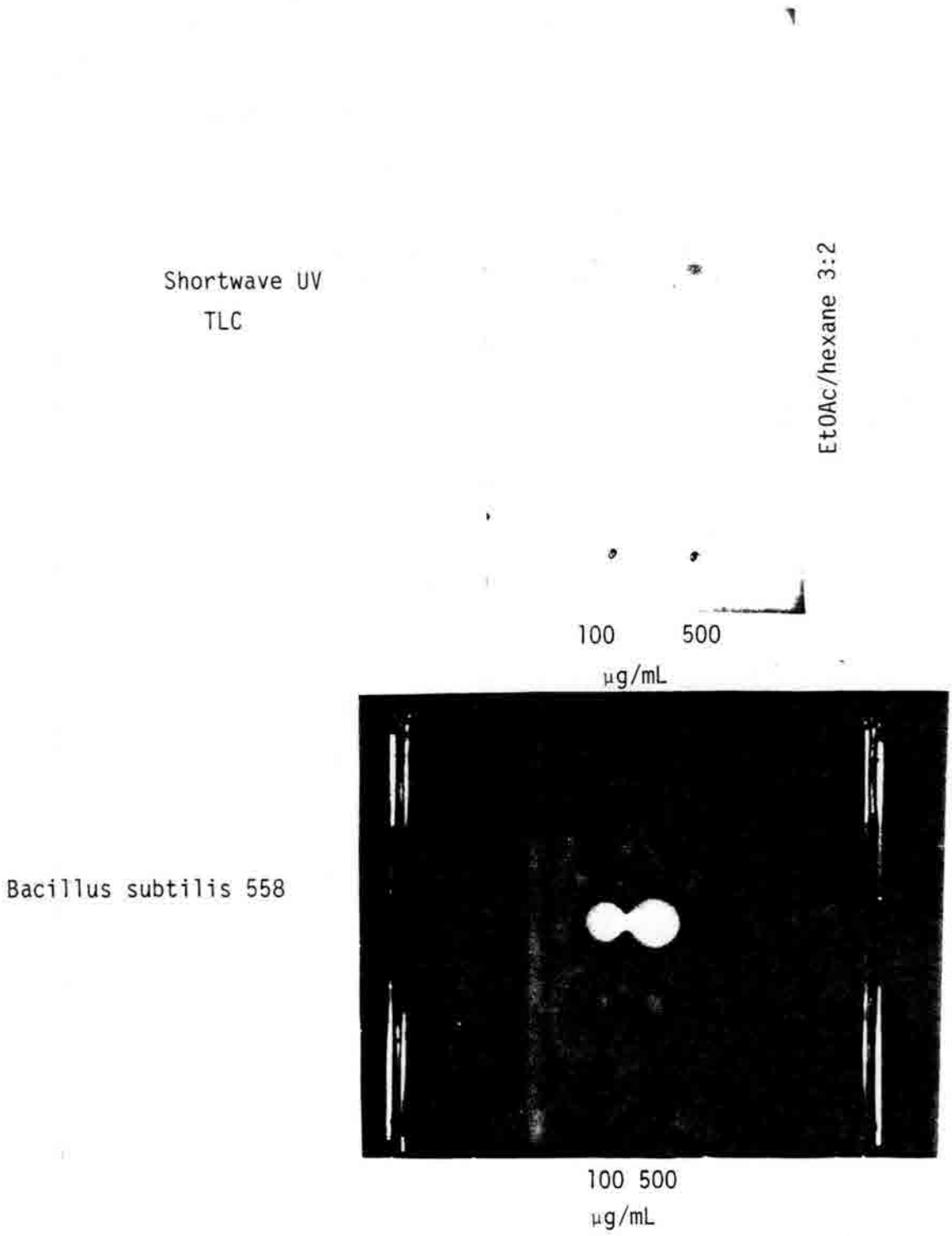



FIGURE 15.

Photographs of Bioautograms of TLC's Dyed with Tetrazolium Red of Compounds 266

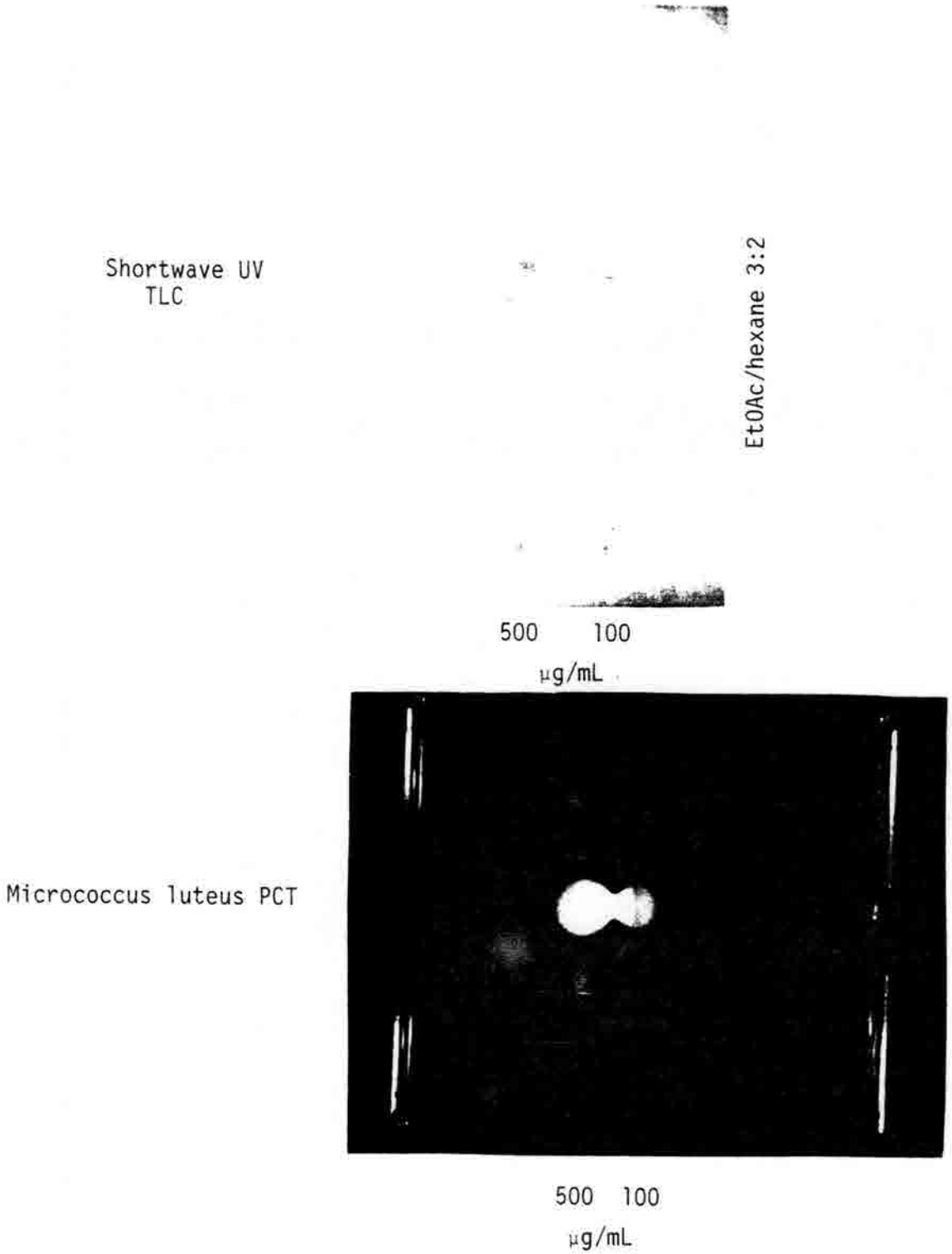
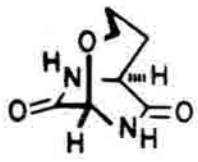



FIGURE 16.

Photographs of Bioautograms of TLC's Dyed with Tetrazolium Red of Compound 266

CHART V



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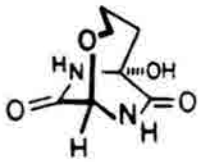

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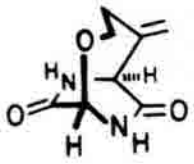

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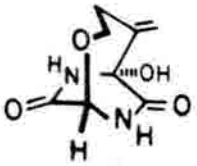

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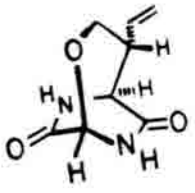

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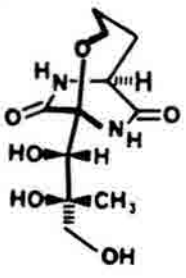

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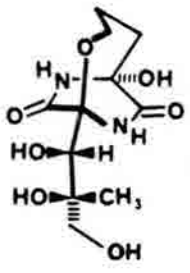

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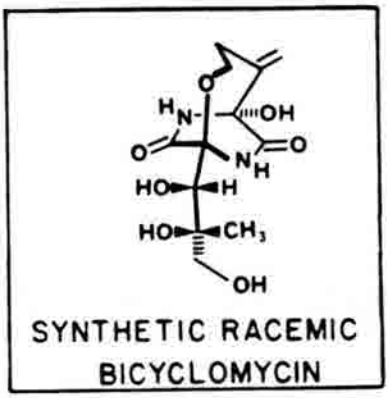



319

establish its intermediacy. The total lack of activity of the analogs in Chart V, especially the exomethylene alcohol 344, does not rule out the Michael acceptor theory, but rather indicates that the C-1' - C-3' sidechain triol induces subtle effects necessary for *in vitro* antimicrobial activity, possibly preventing the analogs from ever reaching the active site or properly aligning once there. If that is the case, the *in vitro* assays do not test the obligate partnership of the alcohol and exomethylene moieties. The effects of the sidechain triol are supported by the folloiwng observations.

As described in Chapter III, the C-1' hydroxyl is strongly hydrogen bonded to the amide carbonyl, reflected both in the downfield shift of the hydrogen doublet in the $^1$H NMR as well as the stubborn resistance to chemical manipulation under conditions in which secondary alcohols normally react. By decreasing electron density on the amide carbonyl, the strong hydrogen bonding might facilitate heterolytic bond cleavage in the formation of the monocyclic $\alpha,\beta$-unsaturated pyruvamide.

Alternatively, the highly polar sidechain might be responsible for target site specific hydrogen bonding resulting in the correct alignment of the bicyclic moiety, and specifically, the Michael acceptor. The Ciba-Geigy group has synthesized and tested the bicyclic isopropylidene derivative 305 derived from naturally occuring bicyclomycin, and have found it to be inactive. This is a particularily interesting compound since the isopropylidene is only blocking the C-2' and C-3' hydroxyls and is not affecting the intramolecular hydrogen bonding of the C-1' hydroxyl, as indicated by the characteristic downfield doublet in the $^1$H NMR, suggesting that the sidechain triol (or possibly only C-2' and C-3' hydroxyls) must

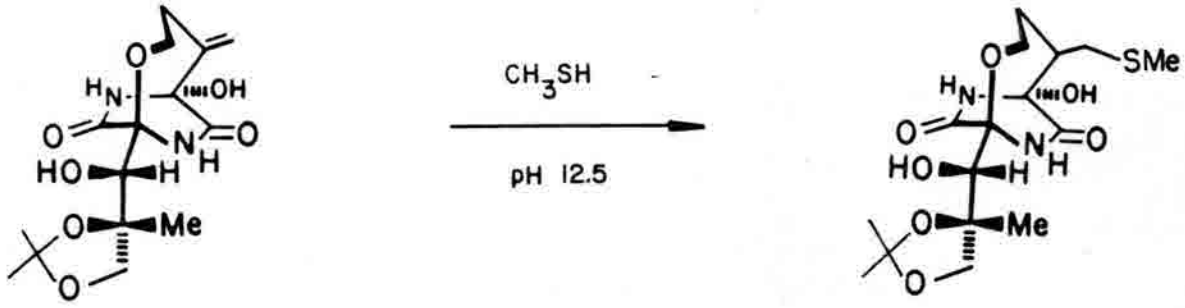
covalently or ionically interact with the active site. This again is supported by a large number of compounds synthesized by the Ciba-Geigy group that showed no antimicrobial activity when the C-1'- C-3' fragment was derivatized. As a consequence of both of the factors mentioned above, the sidechain might be responsible for conformational changes which might favor formation of a monocyclic pyruvamide; this latter effect will be described in more detail below.

Finally, and possibly most important, the lack of the C-1' - C-3' fragment might result in a membrane mass transport problem preventing the compound from ever reaching the target site.

A series of bicyclomycin analogs was subjected to thiolate addition conditions in an attempt to correlate the Michael acceptor capabilities of the analogs with their antibacterial activities.

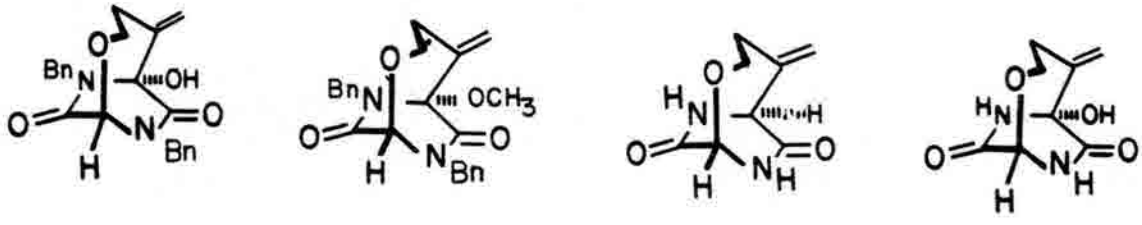
When 2',3'-iso-propylydine bicyclomycin 305 was exposed to methyl mercaptan at pH 12.5, an addition product was obtained which corresponded to the thioether 347 (Scheme 69). The regiochemistry of addition is bond formation at the terminal carbon, suggesting that it adds in a 1,4 fashion to an intermediate pyruvamide. Chart VI shows the bicyclic exomethylene compounds chosen for thiolate addition studies. The N-alkyl series of compounds (348, 266, and 304) lacking substitution at the C-1 bridgehead carbon were targeted since they would systematically establish whether it was possible for the mercaptide anion to add to the inactivated exomethylene (compound 304), or whether it could add to the exomethylene alcohol (compound 266) which can form the $\alpha,\beta$-unsaturated pyruvamide. If the latter were successful, alkylation of the bridgehead alcohol resulting in the

SCHEME 69




305 347

CHART VI




266 348 304 344

Bn = $CH_2Ph$


267 297a

Bn = $CH_2Ph$ Bn = $CH_2Ph$-p-OMe

methyl ether 348 would prevent addition, conclusively establishing the existance of a pyruvamide intermediate.

None of the compounds 348, 266, and 304 were found to undergo addition under conditions identical to those used for the successful addition to 2',3'-isopropylidine bicyclomycin 305. These results also preclude a free radical addition which would also be expected to give the same regiochemistry. It is of interest to note that even the N-benzyl exomethylene analog (266) that was found to be active in the microbial screen failed to result in addition of mercaptide anion.

Both synthetic N,N'-dibenzyl (267) and N,N'-di-para-methoxybenzyl (297a) isopropylidene bicyclomycin adducts were subjected to mercaptide addition reaction and were recovered intact from the reaction mixture in greater than 90% mass recovery. These are particularly interesting compounds since the free (N-H) amide naturally derived isopropylidene derivative 305 readily forms the thioether (347) and differs only in the abscence of the N-alkyl moieties.

Careful inspection of the bicyclic structures (Scheme 70) indicates that the iminium alcohol tautomer 349 which is not accessible in the N-alkyl derivatives might facilitate rupture of the C-6, N-10 bond resulting in formation of the electrophilic species 350.

The deprotected cyclic exomethylene 304 was subjected to thiolate addition and was recovered unreacted. Since this compound did not contain the N-alkyl moieties which were shown above to prevent mercaptide addition, it appears that the failure to add is a result of the lack of reactivity of the isolated exomethylene.

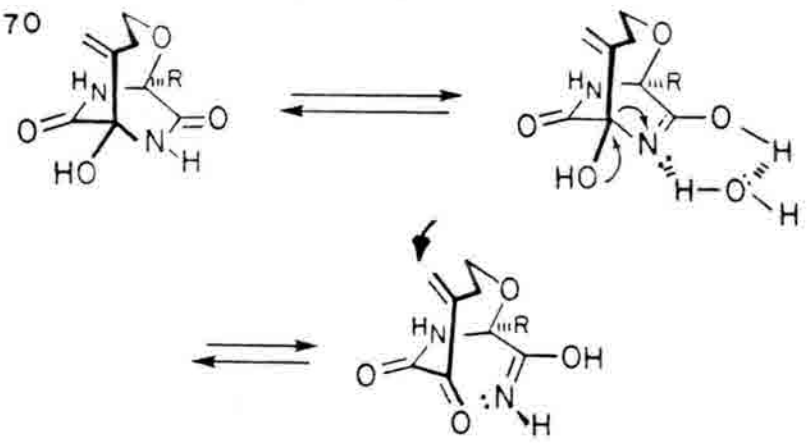
The free (N-H) amide bicyclic exomethylene alcohol 344 was subjected to mercaptide addition, and though monitoring of the reaction

by TLC suggests that the molecule is unreactive, recovery of any product or starting material from the reaction mixture has never been accomplished.

The above studies have succeeded in establishing a structure-activity correlation of a synthetic bicyclomycin analog 266, for the first time showing the requisite partnership of the vicinal exomethylene and C-6 bridgehead hydroxyl moieties. This result lends support to the Michael-type addition postulate that an intermediate α, β-unsaturated pyruvamide may be the reactive biomechanistic intermediate responsible for antibiotic activity of this structural class. Further studies are needed to distinguish between the suicide mechanism (Scheme 67) and the tautomeric ring opening mechanism (Scheme 66).

These studies have failed to establish a link between mercaptide addition and antimicrobial activity of the compounds listed in Scheme 69, however, they do not rule out the possibility of establishing a link given the correct substrates and/or conditions. The isopropylidene derivative 305 which undergoes successful mercaptide addition has been shown by the Ciba-Geigy group to be inactive.

SCHEME 70



# CHAPTER V

# EXPERIMENTAL

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. The field strength (MHz) is indicated for each spectrum in the experimental section. Varian T-60 or Varian EM360 60 MHz spectrometers without lock. Jeol JNM-FX100 100 MHz spectrometer with lock. Nicolet EM-150 150 MHz spectrometer with lock. Brucker WP-200SY 200 MHz spectrometer with lock. Brucker WP-270SY 270 MHz spectrometer with lock. Nicolet EM-360 360 MHz spectrometer with lock. The EM-150 and EM360 Nicolet instruments were used courtesy of the Colorado State University Regional NMR Center.

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 $\delta$-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, the chemical shift of protons of an ABq (1/2ABq) were calculated using a standard weighting formula, the terms $J_{vic}$ and $J_{gem}$ refer to the vicinal or geminal proton coupling

constants. The abbreviation exch = exchangeable for protons that exchange with $D_2O$ "shake".

$^{13}C$ NMR spectra were recorded on the following instruments, and the field strength (MHz) is listed individual for each compound, Jeol JNM-FX100, 25 MHz; Brucker 270, 67.5 MHz; Nicolet EM360, 90 MHz.

Chemical shifts are reported in parts per million downfield from $CHCl_3$ ($\delta$) as an internal standard. The same abbreviations are used as $^1H$ NMR for spin multiplicity.

Measurement for the "true" $^{13}C$, $^1H$ coupling constants was accomplished by pulsing the sample while the broad band decoupler was off.

Low resolution mass spectra were obtained on a V. G. Micromass Ltd., Model 16F spectrometer. High resolution mass spectra were obtained courtesy of the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation facility (Grant No. CHE 8211164).

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, and by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

Optical rotations were obtained on a Perkin-Elmer 24 polarimeter at wavelength 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of one mL. Specific rotations, $[\alpha]_D$, were reported in degrees per decimeter at the specified temperature and the concentration (c) given in grams per 100 mL in the specified solvent.

The single crystal X-ray analyses were obtained on a Nicolet R3m/E diffractometer. Antimicrobial tests were carried out at Hoffman-

LaRoche, Nutley, New Jersey, courtesy of Drs. Hans Maag and David L. Pruess.

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 preadsorbed 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. Other column chromatography adsorbents included florasil (Fisher, 60-100 mesh) and aluminum oxide-basic (Baker).

Reagents and Solvents

Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophene ketyl. Diisopropyl amine was distilled from $CaH_2$ and kept under $N_2$ over activated 4A molecular sieves. 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 at 0°C and

was used after stirring 10 min. LDA solutions were transferred via cannula to the reaction vessel using $N_2$ pressure. Diethylether was freshly distilled from sodium benzophene ketyl under $N_2$ atmosphere. Dry methylene chloride, chloroform, and carbon tetrachloride were obtained by distillation over $P_2O_5$. Trimethylsilyl chloride was distilled from $CaH_2$ and immediately used.

When required, dry DMF, DMSO, pyridine, 2,6-lutidine, HMPA, oxalyl chloride, acetonitrile, trifluoroacetic anhydride 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. The authentic sample of (+)-bicyclomycin was obtained courtesy of Fujisawa Pharmaceutical Company, Japan. All organolithium reagents and inorganic reagents were purchased from either Aldrich or Alfa Ventron, Danvers, Ma.

General Experimental Considerations

All moisture or oxygen sensitive reactions were conducted in glassware that was flame dried under high vacuum ( 0.5-2.0 mm Hg) and then purged with $N_2$.

All reactions were magnetically stirred with Teflon coated stir bars. For reactions extremely sensitive to moisture, nitrogen was dried by passing through a concentrated sulfuric acid bubbler followed by a column of potassium hydroxide.

The following low temperature baths were used: $0^{\circ}C$ (Ice water), $-78^{\circ}C$ (acetone, dry ice), $-105^{\circ}C$ to $-110^{\circ}C$ (4% water in methanol, liquid nitrogen).

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 (0.3-0.5 mm Hg) using a vacuum pump.

# CHAPTER VI

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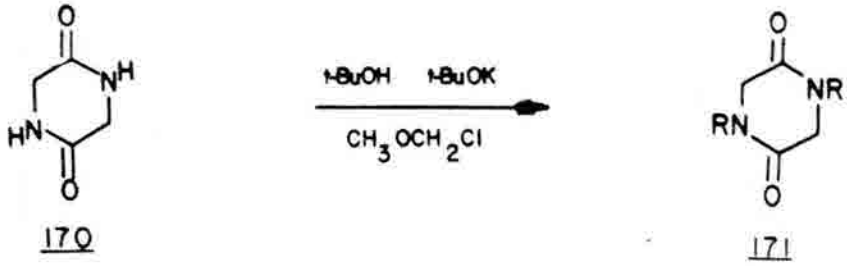
# APPENDIX I

## DATA




170 171

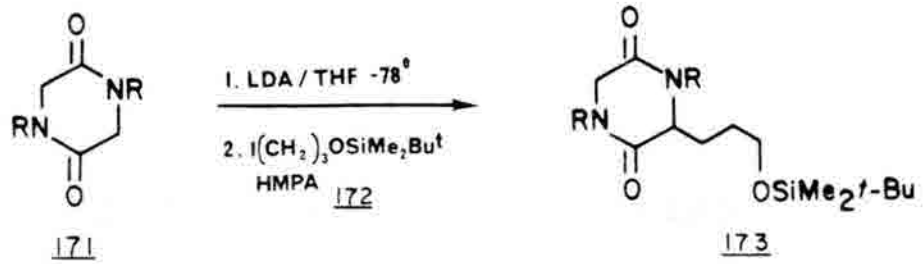
R= $CH_2OCH_3$

1,4-Bis(methoxymethyl)-2,5-piperazinedione (171)

To a stirred solution of potassium tert-butoxide (26.28 g, 234.2 mmol, 2.5 equiv) in t-BuOH (500 mL) at room temperature was added solid 170 (18.0 g, 93.7 mmol, 1.0 equiv) and the solution was stirred for 20 min. To this solution was added chloromethyl methyl ether (17.78 mL, 234.2 mmol, 2.5 equiv). The reaction was stirred 24 h, the solvent was removed under reduced pressure, and the remaining solid was triturated with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and recrystallized from ethyl acetate/hexanes (1:1) to afford 15.86 g (48%) of 171.

$^1H$ NMR (60 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 3.32(6H, s); 4.10(4H, s), 4.88(4H, s).

IR(NaCl, neat): 1670, 1450, 1025 $cm^{-1}$.



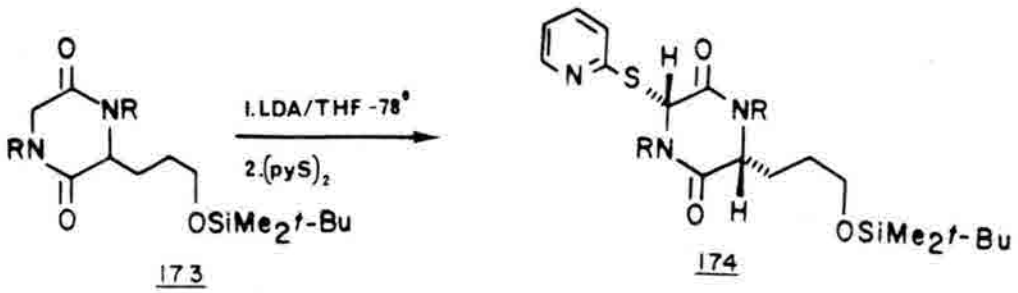

1,4-Bis(methoxymethyl)-3-[3'-[(tert-butyldimethylsilyl)oxy]propyl]-2,5-pipiperazinedione (173)

To a stirred solution of piperazinedione 171 (1.428 g, 7.07 mmol, 1.0 equiv) in THF (10 mL) at -78°C was added a solution of LDA (8.48 mmol, 1.2 equiv) in THF (5 mL). HMPA (2.21 mL, 12.7 mmol, 1.8 equiv) was added and the dark enolate solution stirred for 20 min at -78°C. This solution was transferred via cannula into a solution of 3-[(tert-butyldimethylsilyl)oxy]-1-iodopropane (3.8 g, 12.7 mmol, 1.8 equiv) in THF (10 mL) at -78°C. The mixture was allowed to stir for 20 min at -78°C and 2 h at room temperature. The mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and extracted thoroughly with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted sequentially with hexane, 75% hexane/EtOAc, 50% hexane/EtOAc, 25% hexane/EtOAc) to afford 0.740 g (28% or 41% based on recovered 171) of 173 (oil).

$^1$H NMR (100 MHz) ($CDCl_3$) $\delta$ $Me_4Si$: 0.00(6H, s), 0.85(9H, s), 1.4-2.1(4H, m), 3.25(6H, s), 3.56(2H, br t), 3.98(3H, m), 4.55(1H, 1/2ABq, J=10Hz), 4.56(1H, 1/2ABq, J=10Hz), 4.85(1H, 1/2ABq, J=10Hz), 4.92(1H, 1/2ABq, J=10Hz).

IR(NaCl, neat): 2960, 2855, 1675, 1618, 1460, 1260, 1100, 835 $cm^{-1}$.

Mass Spectrum, m/e: 359($M^+ - CH_3$, 3.37), 317($M^+ - C_4H_9$, 100), 213(29.3), 45($C_2H_5O$, 85).




173 174

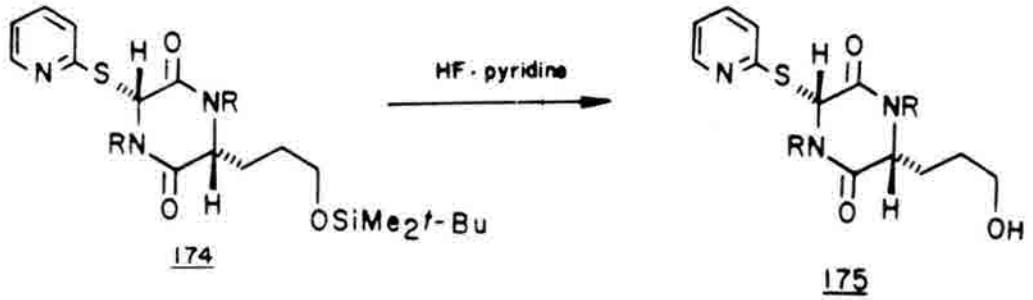
R = $CH_2OCH_3$

1,4-Bis(methoxymethyl)-3-[3'-[(tert-butyldimethylsilyl)oxy]propyl]-6-(2"-thiopyridyl)-2,5-piperazinedione (174)

To a stirred solution of 173 (250 mg, 0.67 mmol, 1.0 equiv) in THF (5 mL) at -78°C was added LDA (0.87 mmol, 1.3 equiv) in THF (2 mL). After being stirred for 20 min at -78°C, the dark enolate solution was transferred via cannula into a solution of 2,2'-dipyridyl disulfide (220 mg, 1.0 mmol, 1.4 equiv) in THF (2.5 mL) -78°C. The mixture was allowed to stir for 20 min at -78°C and for 1 h at room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and extracted thoroughly with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted sequentially with hexane, 25% acetone/hexane, 50% acetone-hexane) to afford 255 mg (79%) of 174 (oil).

$^1$H NMR (100 MHz) ($CDCl_3$) δ $Me_4Si$: 0.17(6H, s), 0.91(9H, s), 1.5-2.4(4H, m), 3.36(6H, s), 3.71(2H, m), 4.1(1H, t, J=7Hz), 4.59(1H, 1/2ABq, J=10Hz), 4.59(1H, 1/2ABq, J=11Hz), 5.09(1H, 1/2ABq, J=10Hz), 5.05(1H, 1/2ABq, J=11Hz), 6.87(1H, s); 7.20(2H, m); 7.35(1H, m); 8.40(1H, m).

IR(NaCl, neat): 1670, 1420 $cm^{-1}$.




174 175

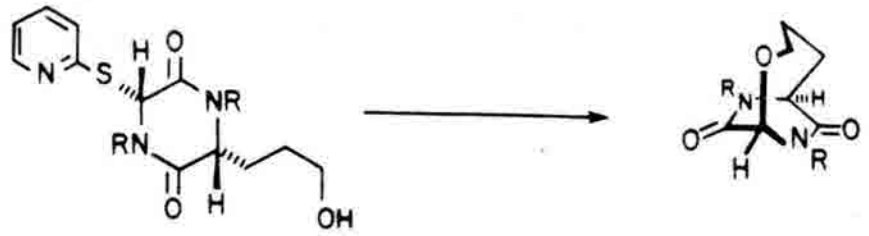
R= $CH_2OCH_3$

1,4-Bis(methoxymethyl)-3-[3'-[hydroxy]propyl]-6-(2"-thiopyridyl)-2,5-piperazinedione (175)

To a stirred solution of 174 (105 mg, 2.39 mmol, 1.0 equiv) in THF (1 mL) was added excess HF·pyridine, and the reaction was allowed to stir for 1 h at room temperature. The mixture was diluted with $CH_2Cl_2$, poured into 0.1N NaOH, and thoroughly extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 80 mg (99%) of the diastereomerically pure 175, which was used for the cyclization without further purification.

$^1H$ NMR (100 MHz) ($CDCl_3$) δ $Me_4Si$: 2.2-2.4(5H, m), 3.37(6H, s), 3.68-3.80(2H, m), 4.26(1H, t, J=6Hz), 4.63(1H, 1/2ABq, J=10Hz), 5.11(1H, 1/2ABq, J=10Hz), 4.78(1H, 1/2ABq, J=10Hz), 5.27(1H, 1/2ABq, J=10Hz), 6.87(1H, s), 7.04-7.36(2H, m), 7.40-7.72(1H, m), 8.36-8.60(1H, m).

IR(NaCl, neat): 3400-3200, 1675, 1410 $cm^{-1}$.



175 176

R= $CH_2OCH_3$

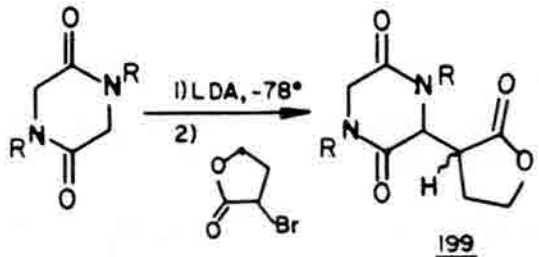
8,10-Bis(methoxymethyl)-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (176)

The alcohol 175 (80 mg, 0.29 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (15 mL) at room temperature, and $AgClO_4$ (143 mg, 0.382 mmol, 1.3 equiv) was added in one portion. The mixture was allowed to stir for 2 h at room temperature, diluted with $CH_2Cl_2$, poured into 0.1N NaOH, and thoroughly extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of $CH_2Cl_2$/9 parts of MeOH/1 part of $NH_4OH$) to afford 64 mg (84.3%) of bicyclic piperazinedione 176 (oil).

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $Me_4Si$: 1.77-1.86(2H, m), 2.07-2.21(2H, m), 3.32(3H, s), 3.34(3H, s), 3.59-3.69(1H, m), 3.78-3.91(1H, m), 4.27(1H, t, J=4Hz), 4.62(1H, 1/2ABq, J=10Hz), 4.75(1H, 1/2ABq, J=11Hz), 4.85(1H, 1/2ABq, J=11Hz), 5.03(1H, 1/2ABq, J=10Hz), 5.34(1H, s).

IR(NaCl, neat): 2940, 1682, 1450, 1110 $cm^{-1}$.

Mass Spectrum, m/e: 258($M^+$, 8.03(, 243($M^+$, $-CH_3$, 5.16), 227($M^+$, - $CH_3O$), 198(7.37), 45($C_2H_5O$), 100).




199

R= $CH_3$

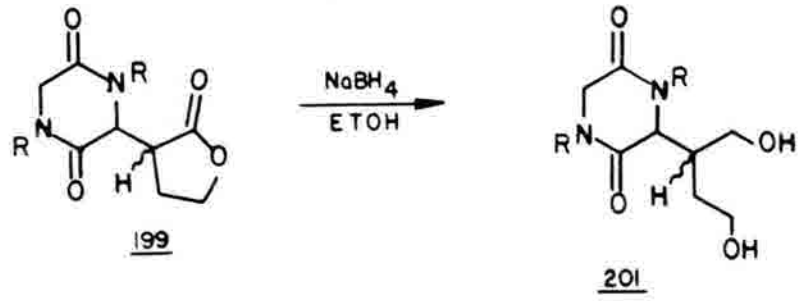
1,4-Dimethyl-3-(2'-γ-butyrolactonyl)-2,5-piperazinedione (199)

To a stirred solution of sarcosine anhydride (10 gm, 70.4 mmol, 1.0 equiv) in THF (100 mL) was added a solution of LDA (77.5 mmol, 1.1 equiv) in THF (32 mL) at -78°C. After stirring the enolate for 30 min at -78°C, this solution was transferred via cannula into a solution of α-bromo-γ-butyrolactone (17.5 mL, 211.3 mmol, 3.0 equiv) in THF (20 mL) at -78°C. The mixture stirred 2 h at -78°C, 3 h at room temperature, cooled to 0°C, quenched with 1N HCl in MeOH (275 mL), diluted with $CH_2Cl_2$, poured into $H_2O$, and thoroughly extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and chromatographed twice on a silica gel flash column (eluted with 10% MeOH in $CH_2Cl_2$) to afford 1.9 gm (12%) of lactone 199 as an oil (18% based on recovered starting material).

$^1H$ NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 2.88(6H, s), 2.08-2.25(1H, m), 2.2-2.5(2H, m), 3.78(1H, 1/2ABq, J=10.84Hz), 4.05(1H, 1/2ABq, J=16.84Hz), 4.09-4.50(2H, m), 4.33(1H, bs).

IR(NaCl, neat): 1765, 1665 $cm^{-1}$.

Mass Spectrum, m/e: 226($M^+$, 23.5), 141(100).




199 201

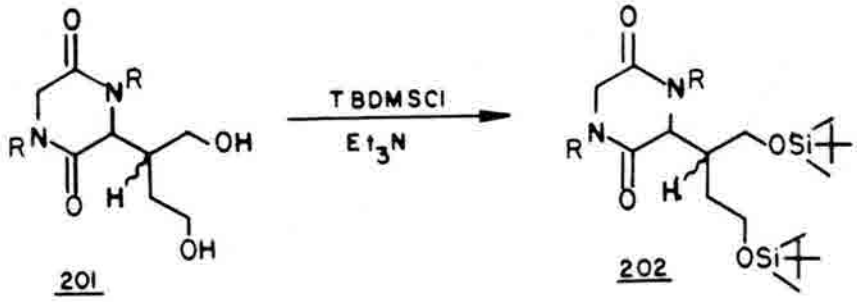
R= $CH_3$

1,4-Dimethyl-3-[(1'-hydroxymethyl)-3'-hydroxy-propyl]-2,5-piperazine-dione (201)

To a stirred solution of 199 (300 mg, 0.8 mmol, 1.0 equiv) in 10% EtOH/THF (15 mL) at 0°C was added $NaBH_4$ (90 mg, 2.38 mmol, 3.0 equiv), portionwise. The mixture stirred for 10 min at 0°C, 12 h at room temperature and quenched with excess HCl in MeOH. After the evolution of $H_2$ had ceased, solid $NaHCO_3$ was added with stirring over a 20 min period, and the mixture was filtered. Evaporation of the solvent and separation on a silica gel flash column (eluted with 10% MeOH in $CH_2Cl_2$) afforded 134 mg (44% or 53% based on recovered 199) of the diol mixture 201 which was directly used for the next step.

IR(NaCl, neat): 3600-3100, 1660 $cm^{-1}$.

Mass Spectrum, m/e: 230($M^+$, 24.1), 141(91.4), 113(100).




201 202

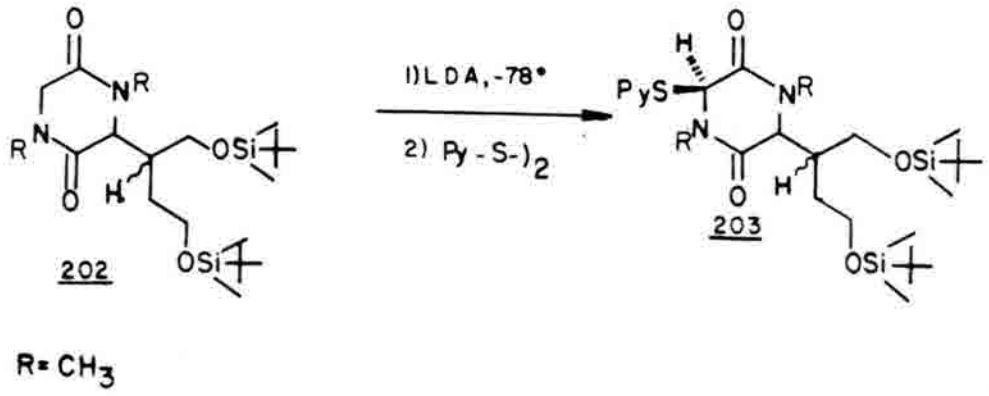
R= $CH_3$

1,4-Dimethyl-3-[2'-[1',4'-bis[(tert-butyldimethylsilyl)oxy]]propyl]-2,5-piperazinedione (202)

To a solution of 201 (120 mg, 0.58 mmol, 1.0 equiv) in DMF (7 mL) at 0°C was added tert-butyldimethylchlorosilane (219 mg, 1.45 mmol, 2.5 equiv) and triethylamine (0.2 mL, 1.45 mmol, 2.5 equiv) and a white precipitate immediately formed. The solution was warmed to room temperature, stirred 25 min, filtered, washed with EtOAc, concentrated to afford 192 mg (84%) of the silyl ethers 202 as an oil in a 4:5 mixture of diastereomers which were inseparable by chromatography and were carried on as a mixture.

IR(NaCl, neat): 1660, 1250 $cm^{-1}$.

Mass Spectrum, m/e: 458($M^+$, 2.3), 443(3.8), 401(90.6), 327(1.6), 141(6.4), 28(100).




1,4-Dimethyl-3-(2'-thiopyridyl)-6-[2"-[1",4"-bis[(tert-butyldimethylsilyl)oxy]]propyl]-2,5-piperazinedione (203)

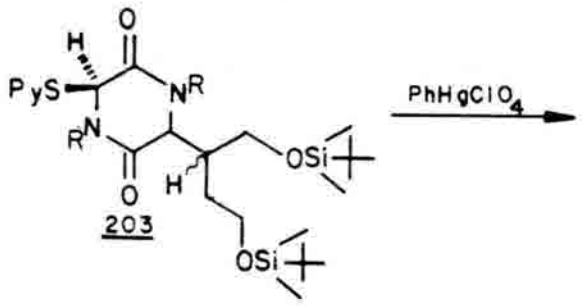
To a stirred solution of 202 (64 mg, 0.15 mmol, 1.0 equiv) in THF (5 mL) was added LDA (0.3 mmol, 2.0 equiv) in THF (1 mL) at -78°C. After stirring 1 min at -78°C, a solution of 2,2'-dipyridiyl disulfide (32 mg, 0.15 mmol, 1.0 equiv) in THF (1 mL) was added and the mixture stirred 10 min at -78°C. The reaction was diluted with $CH_2Cl_2$, poured into $H_2O$ and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a short silica gel column (eluted with hexane, then EtOAc) to afford 79 mg (98%) of 203 as an oil.

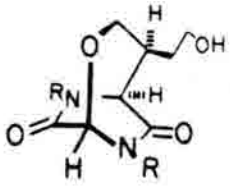
Major Diastereomer

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.034(3H, s), 0.054(3H, s), 0.071(3H, s), 0.10(3H, s), 0.855(3H, s), 0.870(3H, s), 0.892(12H, s), 1.44-1.92(2H, m), 2.32-2.40(1H, m), 2.98(3H, s), 3.03(3H, s), 3.44-3.88(5H, m), 6.67(1H, s), 7.00-7.18(2H, m), 7.52-7.62(1H, m), 8.36-8.50(1H, bd).

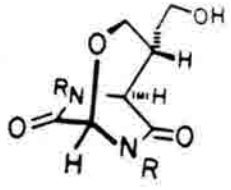
IR(NaCl, neat): 1665, 1410 $cm^{-1}$.

Mass Spectrum, m/e: 567($M^+$, 0.2), 510(0.2), 457(1.4), 400(1.5), 73(100).

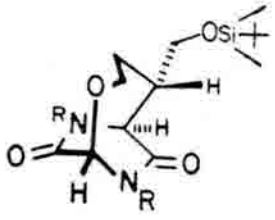


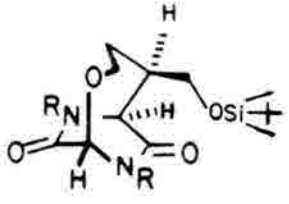
204



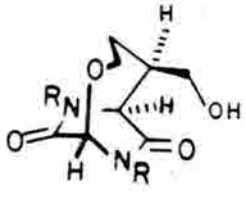
205



208



206



207

R = $CH_3$

7,9-Dimethyl-7,9-diaza-4-[2'-(hydroxyethyl)]-2-oxabicyclo[3.2.2]nonane-6,8-dione (204) and (205); 8,10-Dimethyl-8,10-diaza-5-(hydroxy)-methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (207) and (208) and 8,10-Dimethyl-8,10-diaza-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (206)

To a stirred solution of 203 (39 mg, 0.07 mmol, 1.0 equiv) in THF (1 mL) at room temperature was added a solution of $\emptyset HgClO_4$ (0.239 mmol, 3.5 equiv) in THF (2 mL) and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with $CH_2Cl_2$, poured into 0.1N NaOH, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 10% MeOH, in $CH_2Cl_2$) to afford a 91% yield of the mixture of isomers as oils, two of which could be separated and chracterized.

Compound 204:

$^1H$ NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.53(1H, m), 1.67(1H, m), 2.29(1H, m), 2.60(1H, m), 3.00(3H, s), 3.06(3H, s), 3.49(1H, dd, J=8.2Hz, J=12.92Hz), 3.72(1H, m), 3.78(1H, m), 3.91(1H, d, J=3.07Hz), 3.97(1H, dd, $J_{gem}$=12.92Hz, $J_{vic}$=5.25Hz), 4.96(1H, s).

IR(NaCl, neat): 3600-3200, 1680, 1465 $cm^{-1}$.

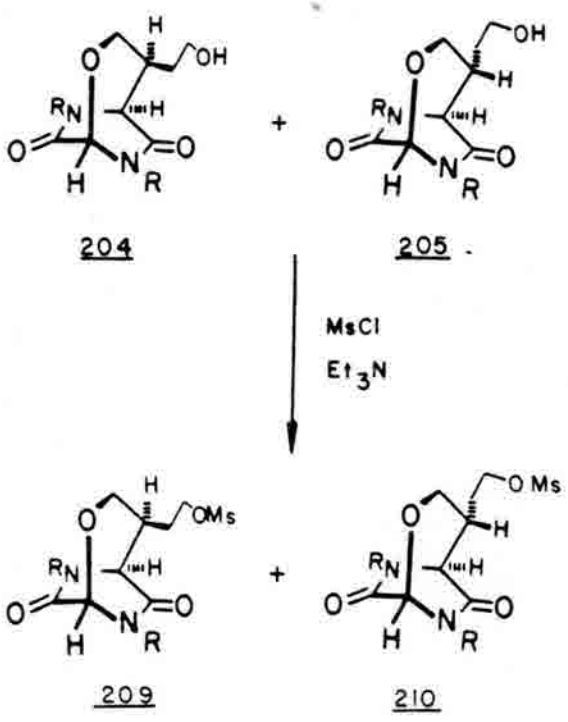
Mass Spectrum, m/e: 228($M^+$, 11.4), 198(18.2), 140(47.5), 42(100).

Compound 206:

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.12(3H, s), 0.14(3H, s), 0.98(9H, s), 1.9-2.3(3H, m), 3.04(3H, s), 3.06(3H, s), 3.4-3.60(5H, m), 4.39(1H, d, J=2.0Hz), 5.12(1H, s).

IR(NaCl, neat): 1670, 1450 $cm^{-1}$.

Mass Spectrum, m/e: 327($M^+$, $-CH_3$, 2.5), 285(100), 140(8.6).




204 205

209 210

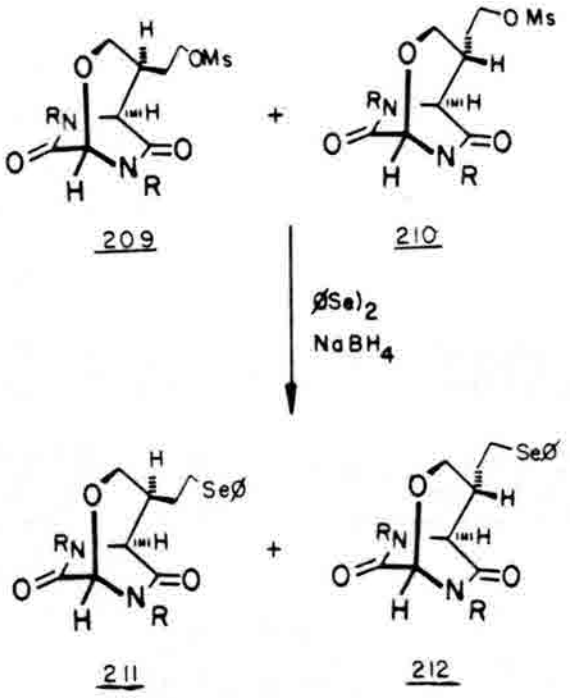
R = $CH_3$

7,9-Dimethyl-7,9-diaza-4-[2'-(methanesulfonyl)ethyl]-2-oxabicyclo-[3.2.2]nonane-6,8-dione (209) and (210)

To a stirred solution of a mixture of 204 and 205 (45 mg, 0.197 mmol, 1.0 equiv) in THF (3 mL) was added $Et_3N$ (0.03 mg, 0.217 mmol, 1.1 equiv) followed by mesyl chloride (0.017 mL, 0.217 mmol, 1.1 equiv) and the mixture was stirred at 0°C. After 2 h, the mixture was filtered, concentrated, and separated by PTLC silica gel (eluted with 10% MeOH in $CH_2Cl_2$) to afford 54 mg (89%) of a mixture of isomers 209 and 210 which were not separable by chromatography.

Major diastereomer (from 3:1 mixture)

$^1H$ NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 1.6(2H, m), 2.30(1H, m), 3.06(6H, s), 3.04(3H, s), 3.47(1H, dd, $J_{gem}$=12.90Hz, $J_{vic}$=8.02Hz), 3.82(1H, bs), 3.95(1H, dd, $J_{gem}$=12.90Hz, $J_{vic}$=2.07Hz), 4.2-4.45(2H, m), 4.96(1H, s).




209 210

211 212

R = $CH_3$

7,9-Dimethyl-7,9-diaza-4-[-2'-(phenylselenyl)ethyl]-2-oxabicyclo-[3.2.2]nonane-6,8-dione (211) and (212)

To a stirred mixture of 209 and 210 (26 mg, 0.085 mmol, 1.0 equiv) in THF (3 mL) at room temperature was added a solution of $BH_3$·PhSeNa (0.093 mmol, 1.1 equiv) and the mixture was stirred at room temperature. After 6 h, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 5% MeOH in $CH_2Cl_2$) to afford 16 mg (51.3%) of 212 and 12 mg (38%) of 211 as oils.

Compound 211

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 1.5-1.8(3H, m), 2.35-2.45(2H, m), 2.92(3H, s), 3.02(3H, s), 4.32(1H, dd, $J_{gem}$=12.50Hz, $J_{vic}$=8.10Hz), 4.60(1H, d, J=3.0Hz), 4.85(1H, dd, $J_{gem}$=12.50Hz, $J_{vic}$=5.50Hz), 4.90(1H, s), 7.20-7.32(3H, m), 7.38-7.56(2H, m).

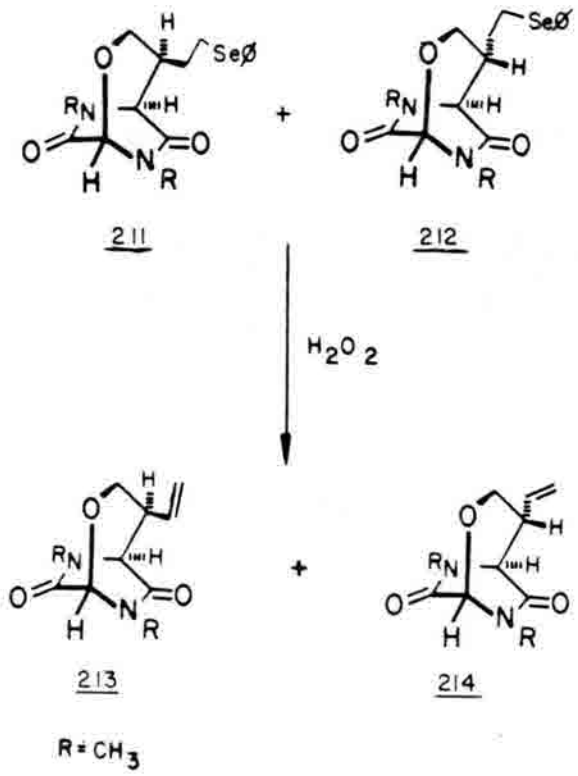
IR(NaCl, neat): 1680, 1275 $cm^{-1}$

Mass Spectrum, m/e: 352($M^+$-15, 1.2), 196(3.1), 181(0.2), 15(100).

Compound 212

$^1$H NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.5-1.8(3H, m), 2.35-2.45(2H, m), 2.92(3H, s), 2.98(3H, s), 3.30-3.50(1H, m), 3.62(1H, d, J=1Hz), 3.78-4.02(1H, m), 4.88(1H, s), 7.20-7.32(3H, m), 7.38-7.56(2H, m).

IR(NaCl, neat): 1680, 1465 $cm^{-1}$.




7,9-Dimethyl-7,9-diaza-4-(vinyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (213) and (214)

To a stirred solution of a mixture of 211 and 212 (16 mg, 0.044 mmol, 1.0 equiv) in THF (3 mL) at room temperature was added 30% $H_2O_2$ (0.014 mL, 0.436 mmol, 1.0 equiv) and the mixture was stirred at room temperature. After 3 hr, the mixture was diluted with $CH_2Cl_2$, poured inot $H_2O$ and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 4 mg (51%) of 214 and 2 mg (24%) of 213 as oils.

Compound 213

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 2.89(1H, m), 3.02(3H, s), 3.07(3H, s), 3.75(1H, dd, $J_{gem}$=12.80Hz, $J_{vic}$=9.58Hz), 3.80(1H, s), 3.87(1H, dd, $J_{gem}$=12.80Hz, $J_{vic}$=5.41Hz), 4.96(1H, s), 5.20-5.30(2H, m), 5.66(1H, ddd, J=7.62Hz, J=10.10Hz, J=10.27Hz).

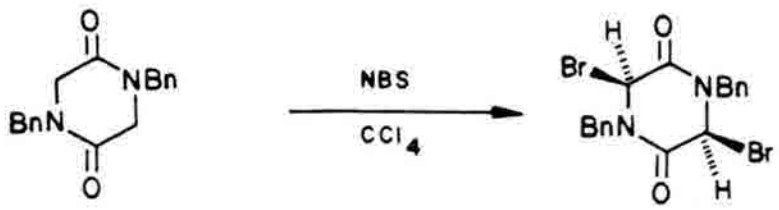
IR(NaCl, neat): 1680, 1050 $cm^{-1}$.

Compound 214

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 2.68(1H, m), 3.00(3H, s), 3.07(3H, s), 3.55(1H, dd, $J_{gem}$=12.91Hz, $J_{vic}$=9.05Hz), 3.75(1H, d, J=2.60Hz), 3.94(1H, dd, $J_{gem}$=12.91Hz, $J_{vic}$=5.47Hz), 4.99(1H, s), 5.21(1H, dd, $J_{gem}$=1.5Hz, $J_{cis}$=10.22Hz), 5.25(1H, dd, $J_{gem}$=1.5Hz, $J_{trans}$=16.75Hz), 5.66(1H, ddd, $J_{cis}$=10.22Hz, $J_{trans}$=16.75Hz, $J_{vic}$=8.15Hz).

IR(NaCl, neat): 1680, 1230 $cm^{-1}$.

Mass spectrum, m/e: 210($M^+$, 7.1), 195(1.1), 180(9.0), 140(39.1), 42(100).




232 233

Bn = $CH_2Ph$

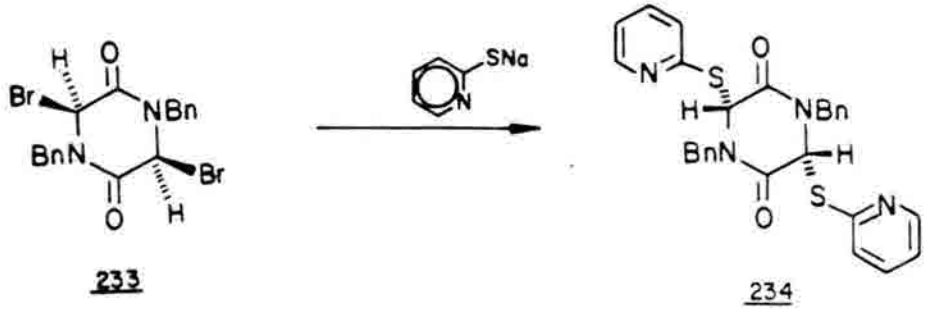
1,4-Dibenzyl-3,6-bis-bromo-2,5-piperazinedione (233)

To a stirred solution of 232 (4.60 g, 15.6 mmol, 1.0 equiv) in $CCl_4$ (250 mL) at room temperature was added NBS (6.13 g, 34.4 mmol, 2.2 equiv) followed by a catalytic amount (1 mol %) of benzoyl peroxide. The mixture was brought to reflux temperature for 1 h, cooled to ambient temperature, filtered, and concentrated to give 233 (6.98 g, 98%) as a solid, mp 185-186°C (recryst. EtOAc/hexanes).

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ TMS: 4.04(2H, 1/2ABq, J=14.52Hz), 5.36(2H, 1/2ABq, J=14.52Hz), 5.89(2H, s), 7.16-7.50(10H, m).

IR(NaCl, neat): 2990, 1670, 1395, 710 $cm^{-1}$.

Mass spectrum, m/e: 371(0.8), 292(4.4), 99(91), 56.2(100).



233 234

Bn = $CH_2Ph$

1,4-Dibenzyl-3,6-bis-(2'-thiopyridyl)-2,5-piperazinedione (234)

To a 35 ml THF solution of 233 (7.2 g, 15.93 mmol) at 0°C was added via cannula a 40 mL THF solution of the sodium salt of 2-mercapto-pyridine which was prepared as follows: a 50 mL flask was equipped with an addition funnel and NaH (1.34 g, 33.46 mmol) was added and dissolved in 10 mL THF at 0°C. A 30 mL THF solution of mercapto-pyridine (3.72 g, 33.46 mmol) was slowly added via the addition funnel and stirred for 20 min at 0°C.

The mixture was stirred for 30 min at 0°C, warmed to room temperature, diluted with $CH_2Cl_2$, and extracted with $H_2O$. The aqueous layer was extracted 3 times with $CH_2Cl_2$, the combined orgnaic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 8.9 g of yellow oil. Crude was separated on 200 g silica gel flash column (eluted with 50% Hexane/EtOAc) to give 7.67 g (94%) of 234. Mp 149-151°C ($CH_2Cl_2$/hex).

$^{1}H$ NMR (100 MHz) ($CDCl_3$) δ $(CH_3)_4Si$: 4.22(2H, 1/2ABq, J=14.65Hz), 5.23(2H, 1/2ABq, J=14.65Hz), 6.76(2H, s), 6.95-7.53(16H, m), 8.41(2H, bd, J=4.1Hz).

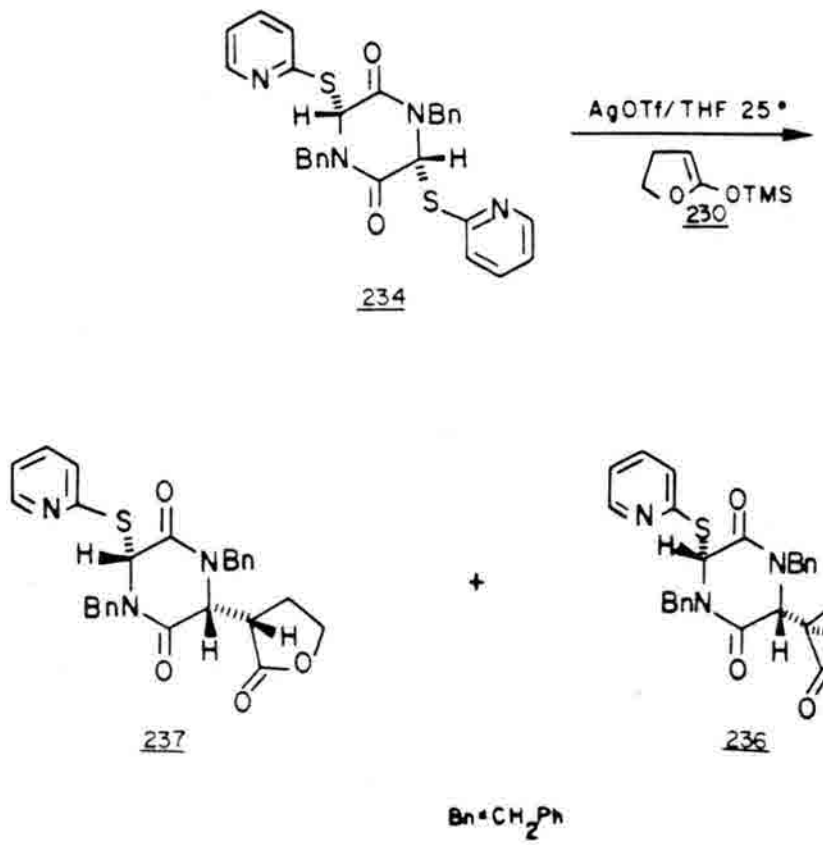
$^{13}C$ NMR (25.0 MHz) ($CDCl_3$) δ: 164.17(s), 153.95(s), 148.87(d), 136.32(d), 135.03(s), 127.91(d), 127.27(d), 122.13(d), 120.61(d), 60.3(d), 46.87(t).

IR(NaCl, neat): 2910, 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 402($M^+-C_5H_4NS$, 0.6), 292(0.2), 111(60.7), 91(12.0), 49(100).

Analysis (recrystallized from hexanes/$CH_2Cl_2$):

| | | | |
|---|---|---|---|
| Calcd. for $C_{28}H_{24}N_4O_2S_2$ | C=65.60%; | H=4.72%; | N=10.93% |
| Found | 65.63 | 4.77 | 10.84 |




1,4-Dibenzyl-3-(2'-thiopyridyl)-6-(2"-γ-butyrolactonyl)-2,5-piperazinedione (236) and (237)

To a 35 mL THF solution of 234 (4.00 g, 7.81 mmol, 1.0 equiv) at room temperature was added $AgSO_3CF_3$ (2.00 g, 7.81 mmol, 1.0 equiv) all at once and the mixture was stirred for 10 min until the solution turned cloudy, then neat trimethylsilyl enol ether of γ-butyrolactone (1.358 mL, 8.60 mmol, 1.1 equiv) was added and stirred for 20 min, diluted with $CH_2Cl_2$, poured into $H_2O$, and thoroughly extracted with $CH_2Cl_2$. The combined extracts were filtered, evaporated, and separated on a silica gel flash column (eluted with 50% EtOAc/hexanes) to afford two diastereomers in 68% overall yield 237, 1.751 g (46%), 236, 0.837 g (22%).

Major syn-diastereomer 236: mp 184-185°C (recyrst. $CH_2Cl_2$/hexanes)

$^1H$ NMR (360 MHz) ($CDCl_3$) δ TMS: 2.25-2.35(1H, m), 2.35-2.50(1H, m), 3.02(1H, ddd, J=10.33Hz, J=9.34Hz, J=4.30), 4.08(1H, 1/2ABq, J=14.57Hz), 4.20(1H, m), 4.36(1H, m), 4.58(1H, 1/2ABq, J=15.05Hz), 4.60(1H, d, J=4.30Hz), 5.00(1H, 1/2ABq, J=15.05Hz), 5.24(1H, 1/2ABq, J=14.57Hz), 6.58(1H, s), 7.16-7.20(1H, m), 7.2-7.4(11H, m), 7.58-7.62(1H, m), 8.46-8.48(1H, m).

$^{13}C$ NMR (25.0 MHz) ($CDCl_3$) δ: 176.37(s), 165.57(s), 164.34(s), 154.59(s), 149.28(d), 136.84(d), 135.03(s), 128.50(d), 127.85(d), 122.48(d), 121.19(d), 66.31(t), 60.42(d), 58.72(d), 48.39(t), 46.99(t), 43.02(d), 23.75(t).

IR(NaCl, neat): 2905, 1770, 1670, 1450, 1150, 1020 $cm^{-1}$.

Mass spectrum, m/e: 487($M^+$, 2.1), 396(1.2), 477(1.0), 91(100), 85(27).

Analysis (recrystallized from $CH_2Cl_2$/hexanes):

| | | | | |
|---|---|---|---|---|
| Calcd. for $C_{27}H_{30}N_2O_7S_2$ | C=66.51%; | H=5.17%; | N=8.62%; | S=6.57 |
| Found | 66.30 | 5.33 | 8.60 | 6.50 |

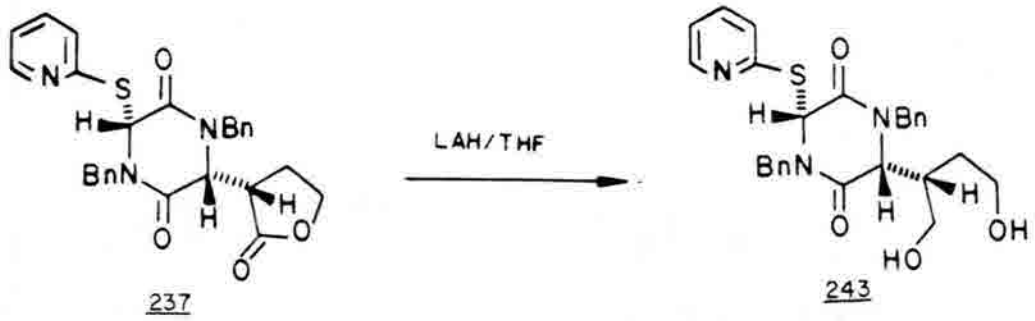
Minor syn-Diastereomer 237:

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.76-2.16(1H, m), 2.40-2.88(2H, m), 3.99-4.42(2H, m), 4.03(1H, 1/2ABq, J=15.0Hz), 4.05(1H, 1/2ABq, J=15.0Hz), 4.77(1H, s), 4.97(1H, 1/2ABq, J=15.0Hz), 5.19(1H, 1/2ABq, J=15.0Hz), 6.62(1H, s), 6.96-7.62(13H, m), 8.30-8.42(1H, m).

IR(NaCl, neat): 1770, 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 487($M^+$, 2.2), 402(0.2), 396(2.0), 377(5.4), 111(18.7), 91(100).

Treatment of this diastereoisomer with 0.1 N NaOH in THF at 25°C produced a 1:1 mixture of the two syn-diastereomers.




237 243

Bn = $CH_2Ph$

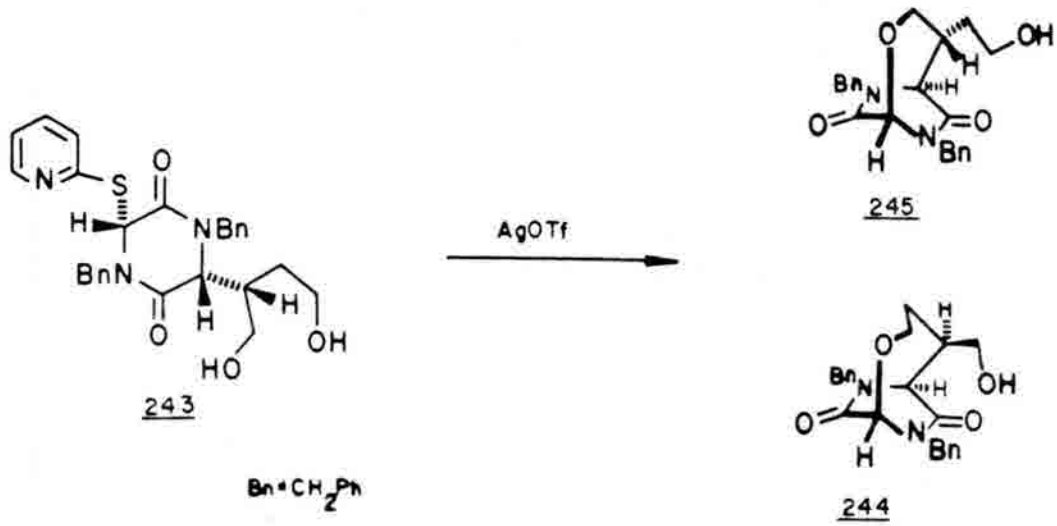
1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1"-hydroxymethyl)-3"-hydroxypropyl]-2,5-piperazinedione (243)

To a stirred solution of 237 (899 mg, 1.88 mmol, 1.0 equiv) in THF (25 mL) at 0°C over $N_2$ was added solid lithium aluminum hydride (35.02 mg, 0.943 mmol, 0.5 equiv) and the mixture was stirred for 30 min at 0°C. The mixture was then quenched with excess $Na_2SO_4 \cdot 10H_2O$, filtered, concentrated, and separated by flash column silica gel (sequentially eluted with 1:1 EtOAc/hexanes to 100% EtOAc) to afford 380 mg (54%) of 243 as an oil.

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 1.80-1.90(1H, m), 1.90-2.00(1H, m), 2.2-2.25(1H, m), 3.69(1H, t, J=5.2Hz, $D_2O$ exch), 3.83(5H, m), 4.07(1H, 1/2ABq, J=15.38Hz), 4.16(1H, 1/2ABq, J=15.14Hz), 4.28(1H, s), 5.20(1H, 1/2ABq, J=15.14Hz), 5.21(1H, 1/2ABq, J=15.38Hz), 6.71(1H, s), 7.04-7.44(11H, m), 7.44-7.68(2H, m), 8.42(1H, bd, J=5.5Hz).

IR(NaCl, neat): 3400, 2910, 1670, 1450, 1415, 1115, 720 $cm^{-1}$.

Mass spectrum, m/e: 380(2.4), 292(1.8), 91(100).




243

245

244

8,10-Dibenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]-decane-7,9-dione (244) and 7,9-Dibenzyl-7,9-diaza-4-[2'-(hydroxy)ethyl]-2-oxabicyclo[3.2.2]nonane-6,80dione (245)

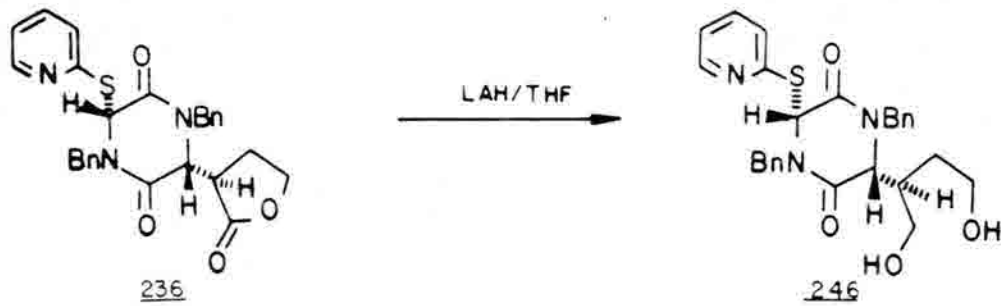
To a stirred solution of 243 (40 mg, 0.08 mmol, 1.0 equiv) in THF (1.5 mL) at room temperature was added solid silver triflate (24 mg, 0.12 mmol, 1.5 equiv). The mixture was stirred 10 min, diluted with $CH_2Cl_2$, poured into 0.1 N NaOH, and exhaustively extracted wtih $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:9:89 $NH_4OH/MeOH/CH_2Cl_2$) to afford 25 mg (80%) of an inseparable mixture of 244 and 245.

Compound 245

$^1H$ NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.25(2H, m), 1.82(1H, $D_2O$ exch), 2.38(1H, m), 3.60(3H, m), 3.82(1H, dd, $J_{vic}$=5.33Hz), $J_{gem}$=12.47), 4.01(1H, s), 4.30(1H, 1/2ABq, J=15.05Hz), 4.39(1H, 1/2ABq, J=14.74Hz), 4.84(1H, 1/2ABq, J=15.05Hz), 4.94(1H, 1/2ABq, J=14.74Hz), 5.05(1H, s), 7.20-7.30(10H, m).

IR(NaCl, neat): 3600-3200, 1670 $cm^{-1}$.

Mass spectrum, m/e: 380(4.5), 292(11.6), 202(4.4), 91(100).




236 246

Bn = $CH_2Ph$

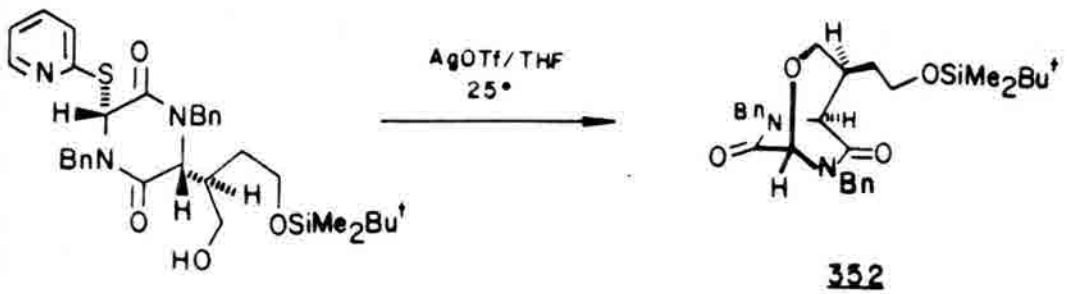
1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[(1"-hydroxymethyl)-3"-hydroxypropyl]-2,5-piperazinedione (246)

To a stirred solution of 236 (652 mg, 1.34 mmol, 1.0 equiv) in THF (30 mL) at 0°C was added a solution of lithium aluminum hydride (25.4 mg, 0.669 mmol, 0.5 equiv) in THF (2 mL). After stirring 20 min at 0°C, excess $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was stirred 10 min, then warmed to room temeprature, filtered, concentrated, and separated by PTLC silica gel (eluted with 4:1 MeOH/$CH_2Cl_2$) to afford 310 mg (47.3%) of 246 as an oil.

$^1H$ NMR (100 MHz) ($CDCl_3$) $CHCl_3$: 1.60-2.08(2H, m), 2.20-2.36(1H, m), 3.60-3.96(6H, m, $D_2O$ exch), 4.06(1H, 1/2ABq, J=15.14Hz), 4.13(1H, 1/2ABq, J=14.65Hz), 4.16(1H, bs), 5.25(1H, 1/2ABq, J=14.65Hz), 5.39(1H, 1/2ABq, J=15.14Hz), 6.73(1H, s), 7.02-7.68(13H, m), 8.46(1H, d, J=4.15Hz).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) δ $CHCl_3$: 31.52(t), 42.96(d), 46.81(t), 49.73(t), 60.18(d), 60.71(2C, t), 61.53(d), 121.02(d), 122.54(d), 128.26(d), 128.38(d), 128.73(d), 135.33(s), 135.62(s), 136.73(d), 149.11(d), 154.83(s), 164.69(s), 167.32(s).

Mass spectrum, m/e: 380($M^+$-111, 7.5), 362(3.5), 297(2.1), 292(9.4), 274(9.7), 111(92.8), 91(100).




351 352

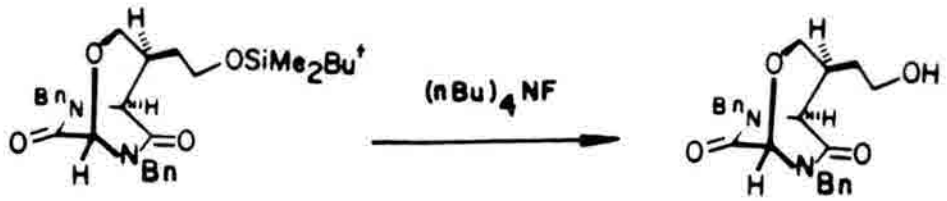
Bn = $CH_2Ph$

7,9-Dibenzyl-7,9-diaza-4-[2'-[(tert-butyldimethylsilyl)oxy]ethyl]-2-oxabicyclo[3.2.2]nonane-6,8-dione (352)

To a stirred solution of 351 (90 mg, 0.149 mmol, 1.0 equiv) in THF (3 mL) at room temperature was added solid AgOTf (57 mg, 0.223 mmol, 1.5 equiv) and the mixture was stirred at room temperature. After 10 min, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted in 1:1 EtOAc/hexanes) to afford 69 mg (95.8%) of 352 as an oil.

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.009(6H, s), 0.843(9H, s), 2.40-2.68(2H, m), 2.72-3.02(1H, m), 3.33(1H, dd, J=8.05Hz, J=8.30Hz), 3.48(2H, t, J=5.86Hz), 3.60-3.92(1H, m), 3.82(1H, d, J=3.42Hz), 4.43(1H, 1/2ABq, J=14.64Hz), 4.45(1H, 1/2ABq, J=14.65Hz), 4.66(1H, 1/2ABq, J=14.64Hz), 4.78(1H, 1/2ABq, J=14.65Hz), 5.07(1H, s), 7.02-7.52(10H, m).

IR(NaCl, neat): 1680, 1445, 1250 $cm^{-1}$.

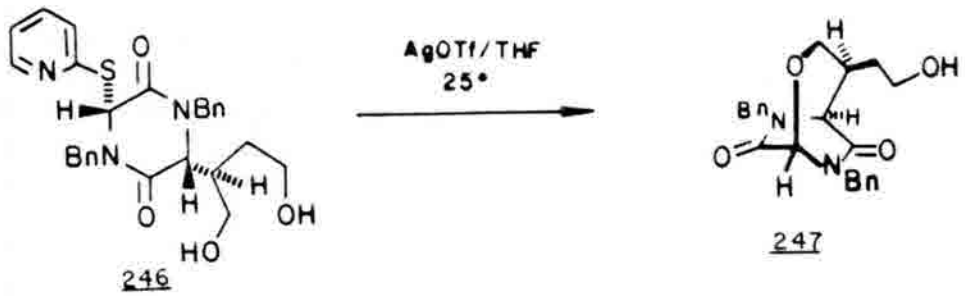



247

Bn = $CH_2Ph$

7,9-Dibenzyl-7,9-diaza-4-[2'-(hydroxyethyl)]-2-oxabicyclo[3.2.2]-nonane-6,8-dione (247)

To a stirred solution of silyl ether 352 (66 mg, 0.134 mmol, 1.0 equiv) in THF (1.75 mL) at room temperature was added solid $(n\text{-}Bu)_4NF$ (102 mg, 0.340 mmol, 2.5 equiv), the mixture was stirred for 20 min at room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 50 mg (99%) of 247 as an oil. (See preparation for 246 for spectroscopic data).




Bn = $CH_2Ph$

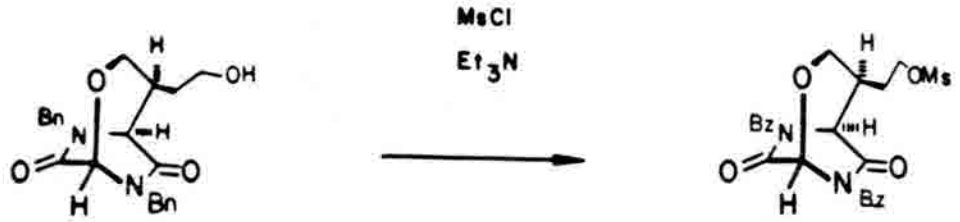
7,9-Dibenzyl-7,9-diaza-4-(2'-hydroxyethyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (247)

To a stirred solution of 246 (43.6 mg, 0.089 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added solid silver triflate (36.8 mg, 0.177 mmol, 2.0 equiv) and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with $CH_2Cl_2$, poured into 0.1 N NaOH, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:9:89 $NH_4OH/MeOH/CH_2Cl_2$) to give 26 mg (78%) of 247 as an oil.

$^1H$ NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 1.20-1.35(1H, m), 1.35-1.60(2H, m), 1.82-1.95(1H, m), 3.26(1H, dd, $J_{vic}$=8.72Hz, $J_{gem}$=11.50Hz), 3.48(2H, bt, J=6.16Hz), 3.78(1H, dd, $J_{vic}$=6.20Hz, $J_{gem}$=11.50Hz), 3.93(1H, d, J=2.34Hz), 4.45(1H, 1/2ABq, J=14.87Hz), 4.53(1H, 1/2ABq, J=14.67Hz), 4.65(1H, 1/2ABq, J=14.67Hz), 4.79(1H, 1/2ABq, J=14.87Hz), 5.12(1H, s), 7.12-7.46(10H, m).

IR(NaCl, neat): 3600-3200, 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 380($M^+$, 9.3), 292(12.4), 274(5.7), 183(2.2), 91(100).




247 353

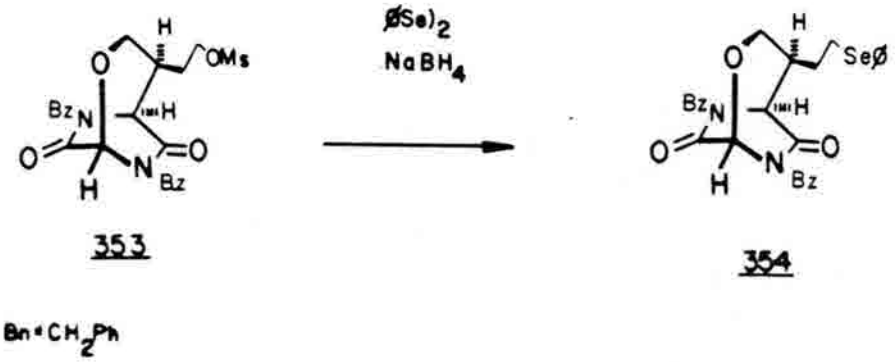
Bn = $CH_2Ph$

7,9-Dibenzyl-7,9-diaza-4-[2'-(methanesulfonyl)ethyl]-2-oxabicyclo-[3.2.2]nonane-6,8-dione (353)

To a stirred solution of alcohol 247 (28 mg, 0.073 mmol, 1.0 equiv) in DMF (1 mL) at 0°C was added triethylamine (0.01 ml, 0.081 mmol, 1.1 equiv) followed by mesyl chloride (0.006 mL, 0.081 mmol, 1.1 equiv) and the mixture was stirred at 0°C. After 5 min, the mixture was warmed to room temperature, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 23 mg (79.5%) of mesylate 353 as an oil.

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 1.79-1.88(2H, m), 2.34-2.44(1H, m), 2.99(3H, s), 3.77(1H, dd, J=10.31Hz, J=12.90Hz), 3.94(1H, dd, J=9.70Hz, J=12.90Hz), 4.09-4.15(2H, m), 4.15(1H, d, J=2.39Hz), 4.19(1H, 1/2ABq, J=14.50Hz), 4.20(1H, 1/2ABq, J=14.79Hz), 5.05(1H, 1/2ABq, J=14.50Hz), 5.09(1H, 1/2ABq, J=14.79Hz), 5.21(1H, s), 7.20-7.40(10H, m).

IR(NaCl, neat): 1670, 1450, 1150 $cm^{-1}$.

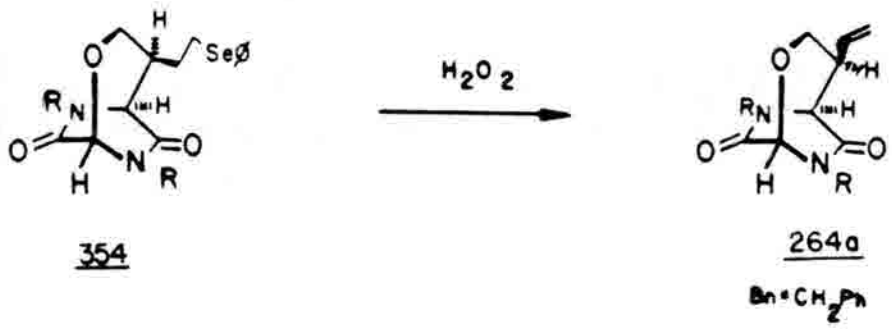



353 354

Bn = $CH_2Ph$

7,9-Dibenzyl-7,9-diaza-4-[2'-(phenylselenyl)ethyl]-2-oxabicyclo[3.2.2]-nonane-6,8-dione (354)

To a stirred solution of diphenyldiselenide (21.5 mg, 0.068 mmol, 1.05 equiv) in EtOH (2 mL) at 0°C was added solid sodium borohydride (5.2 mg, 0.137 mmol, 2.1 equiv) and the mixture was stirred at 0°C. After 10 min, a solution of mesylate 353 (30 mg, 0.065 mmol, 1.0 equiv) in THF (1 ml) was added and the mixture was stirred for 10 min, warmed to room temperature, filtered, evaporated, and separated on PTLC silica gel (eluted with 1:9:89 $NH_4OH/CH_3OH/CH_2Cl_2$) to afford 12 mg (73%) of 354 selenide as an oil which was carried on to the next step directly.




354 264a

Bn = $CH_2Ph$

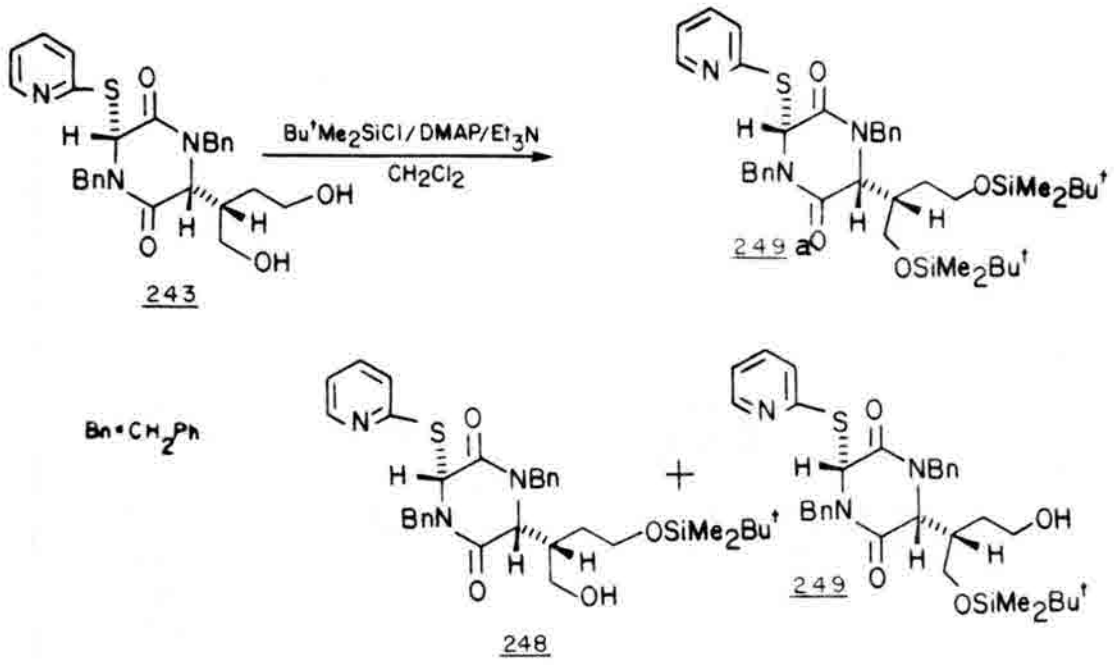
7,9-Dibenzyl-7,9-diaza-4-(vinyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (264a)

To a solution of selenide 354 (10 mg, 0.02 mmol, 1.0 equiv) in THF (1 mL) was added 30% $H_2O_2$ (0.006 ml, 0.2 mmol, 10.0 equiv). The mixture was stirred 10 min, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, separated on PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 3 mg (35%) of 264a as an oil.

$^1H$ NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 3.67(1H, m), 4.05(1H, m), 4.12(1H, d, J=2.1Hz), 4.74(1H, 1/2ABq, J=14.70Hz), 4.76(1H, 1/2ABq, J=14.70Hz), 4.99(1H, 1/2ABq, J=14.70Hz), 5.07(1H, 1/2ABq, J=14.70Hz), 5.17(1H, d, J=15.2Hz), 5.34(1H, m), 5.39(1H, s), 5.76(1H, m), 7.5(10H, m).

IR(NaCl, neat): 1670, 1610, 1450 $cm^{-1}$.

Mass spectrum, m/e: 362($M^+$, 10.0), 271(6.3), 91(100).




1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[[1"-hydroxymethyl]-3"-[(tert-butyl-dimethylsilyl)oxy]propyl]-2,5-piperazinedione (248), 1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1"-[(tert-butyldimethylsilyl)oxy)methyl]-3"-(hydroxypropyl)]-2,5-piperazinedione (249), and 1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1'[(tert-butyldimethylsilyl)oxy)methyl]-3'-[(tert-butyl-dimethylsilyl)oxy)propyl]]-2,5-piperazinedione (249a)

To a stirred solution of 243 (34 mg, 0.069 mmol, 1.0 equiv) in $CH_2Cl_2$) (2 mL) at room temperature was added tert-butyldimethylsilyl chloride (10.4 mg, 0.069 mmol, 1.0 equiv) and solid N,N-dimethylamino pyridine (1 mol %) followed by triethylamine (0.01 mL, 0.069 mmol, 1.0 equiv). The mixture was stirred for 30 min, evaporated to dryness and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 16 mg (63%) of 249 and 3.4 mg (13.5%) of 248 and 1.6 mg (6.3%) of 249a.

Compound 248

$^{1}H$ NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.09(6H, s), 0.91(9H, s), 1.50-1.96(2H, m), 2.24-2.56(2H, m), 3.60-3.92(4H, m), 4.07(1H, 1/2ABq, J=14.65Hz), 4.12(1H, 1/2ABq, J=13.96Hz), 4.21(1H, d, J=7.50Hz), 5.18(1H, 1/2ABq, J=13.96Hz), 5.38(1H, 1/2ABq, J=14.65Hz), 6.68(1H, s), 7.02-7.62(13H, m), 8.39-8.45(1H, m).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) δ $CHCl_3$: 5.32, 18.32, 25.97, 30.87, 41.73, 46.93, 48.50, 60.30, 60.59, 60.79, 61.59, 121.08, 122.48, 127.91, 128.38, 128.73, 135.56, 135.74, 136.73, 149.22, 155.00, 164.46, 167.03.

IR(NaCl, neat): 3600-3200, 1675 $cm^{-1}$.

Mass spectrum, m/e: 503($M^{+}$-102, 1.7), 437(4.1), 355(5.2), 281(9.1), 149(34.4), 105(100), 91(79.1).

Compound 249

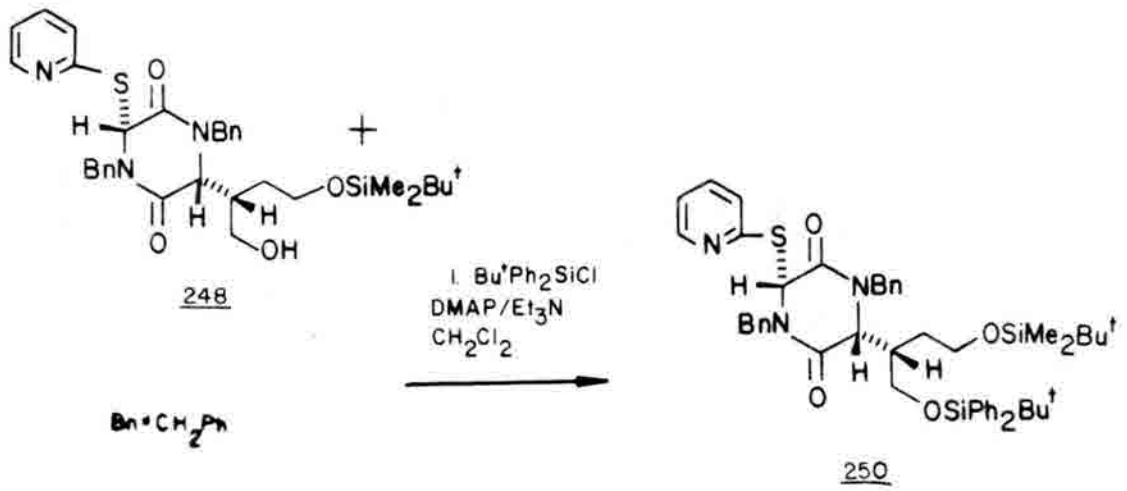
$^{1}H$ NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.12(6H, s), 0.92(9H, s), 1.6-2.0(2H, m), 2.10-2.42(1H, m), 3.60-3.96(5H, m), 4.10(1H, 1/2ABq, J=14.0Hz), 4.22(1H, 1/2ABq, J=14.0Hz), 4.23(1H, bs), 5.22(1H, 1/2ABq, J=14.0Hz), 5.29(1H, 1/2ABq, J=14.0Hz), 6.66(1H, s), 7.04-7.68(14H, m), 8.40-8.48(1H, m).

IR(NaCl, neat): 3600-3300, 1675, 1450 $cm^{-1}$.

Compound 249a

$^1$H NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.05(6H, s), 0.83(9H, s), 1.09(9H, s), 1.6-2.0(2H, m), 2.2-2.4(1H, m), 3.0-3.5(2H, m), 3.80-3.96(2H, m), 4.18(1H, 1/2ABq, J=14.0Hz), 4.20(1H, 1/2ABq, J=14.0Hz), 4.34(1H, bs), 5.10(1H, 1/2ABq, J=14.0Hz), 5.17(1H, 1/2ABq, J=14.0Hz), 6.66(1H, s), 6.88-7.68(13H, m), 8.24-8.36(1H, m).

IR(NaCl, neat): 1681, 1450 $cm^{-1}$.



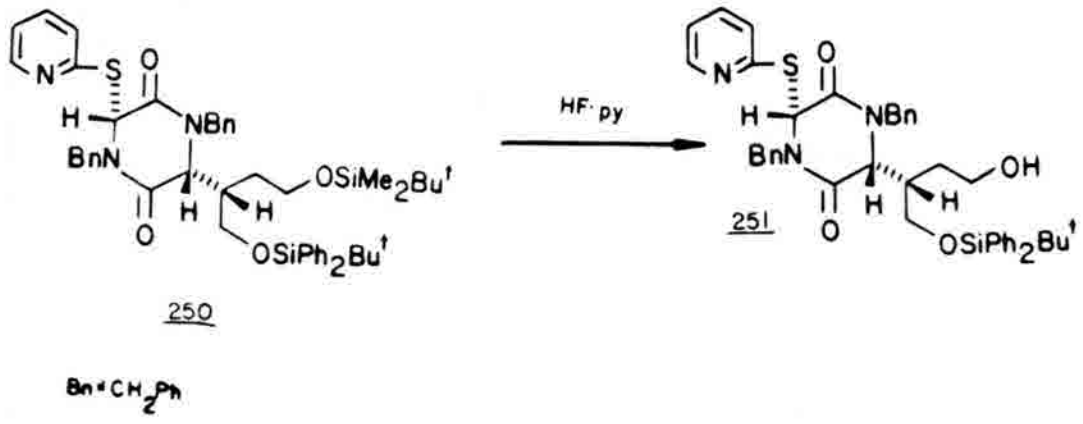

1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[[1"-[(tert-butyldiphenylsilyl)oxymethyl]]-3"-[(tert-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (250)

To a stirred solution of 248 (35 mg, 0.058 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) at room temperature was added N,N-dimethylamino pyridine (1 mol %), tert-butyldiphenylsilyl chloride (0.038 mL, 0.145 mmol, 2.5 equiv) and triethylamine (0.01 mL, 0.07 mmol, 1.2 equiv). After stirring for 12 h, the mixture was evaporated to dryness and separated on PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 46 mg (94%) of 250 as an oil.

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.048(6H, s), 0.835(9H, s), 1.093(9H, s), 1.40-1.80(2H, m), 2.08-2.22(1H, m), 3.00-3.55(2H, m), 3.80-3.96(2H, m), 4.15(1H, 1/2ABq, J=14.65Hz), 4.16(1H, 1/2ABq, J=14.65Hz), 4.37(1H, bs), 5.09(1H, 1/2ABq, J=14.65Hz), 5.18(1H, 1/2ABq, J=14.65Hz), 6.66(1H, s), 6.92-7.67(23H, m), 8.40-8.46(1H, m).

IR(NaCl, neat): 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 732($M^+-CH_3$, 0.3), 691(2.3), 675(9.6), 543(3.2), 439(4.4), 328(65.0), 294(7.7), 91(100).

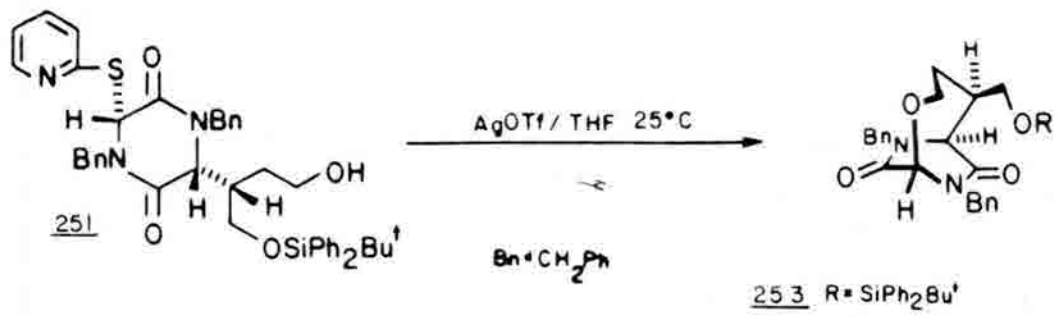



250

Bn = $CH_2Ph$

1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[[1"-(tert-butyldiphenylsilyl)oxymethyl]-3"-hydroxypropyl]-2,5-piperazinedione (251)

To a stirred solution of 250 (13 mg, 0.015 mmol, 1.0 equiv) in THF/$CH_2Cl_2$ (1:1, 2 mL) at room temperature was added all at once excess HF·pyridine complex. The mixture was stirred for 20 min, diluted with $CH_2Cl_2$, poured into 0.1 N NaOH and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, evaporated to dryness and separated on PTLC silica gel (eluted with 1:9:89 $NH_4OH$/MeOH/$CH_2Cl_2$) to afford 9 mg (80%) of 251 as an oil which was carried on directly to 252.



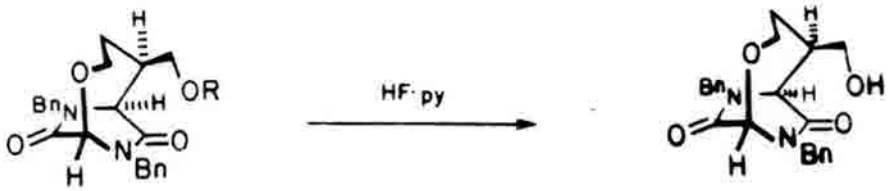

8,10-Dibenzyl-8,10-diaza-5-[(tert-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (253)

To a stirred solution of 251 (12 mg, 0.016 mmol, 1.0 equiv) in THF (0.5 mL) at room temperature was added solid silver triflate (21.1 mg, 0.08 mmol, 5.0 equiv). The mixture was stirred for 30 min at room temperature, diluted with $CH_2Cl_2$ and poured into 0.1 N NaOH and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 100% EtOAc) to afford 8 mg (79%) of 253 as an oil.

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$): 1.07(6H, s), 1.08(3H, s), 2.10(3H, m), 3.42(1H, dd, $J_{vic}$=5.5Hz, $J_{gem}$=12.0Hz), 3.54-3.88(3H, m), 4.10(1H, 1/2ABq, J=14.82Hz), 4.15(1H, 1/2ABq, J=14.82Hz), 4.40(1H, d, J=1.96Hz), 5.12(1H, 1/2ABq, J=14.82Hz), 5.12(1H, 1/2ABq, J=14.82Hz), 5.19(1H, s), 7.08-7.48(15H, m), 7.48-7.76(5H, m).

IR(NaCl, neat): 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 561($M^+$-t-butyl, 74.0), 527(39.1), 292(2.7), 199(17.5), 91(100).




253 R = $SiPh_2Bu^t$

244

Bn = $CH_2Ph$

8,10-Dibenzyl-8,10-diaza-5-(hydroxmethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (244)

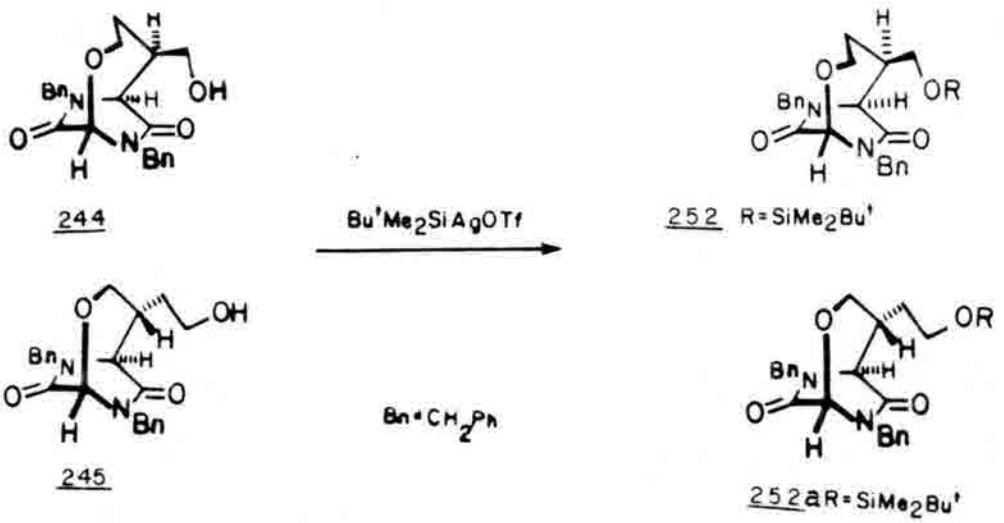
To a stirred solution of 253 (5 mg, 0.008 mmol, 1.0 equiv) in THF (0.5 mL) at room temperature was added excess HF·pyridine complex. The solution was stirred for 30 min, diluted with $CH_2Cl_2$, poured into 0.1 N NaOH and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 3 mg (98%) of 244 as an oil.

$^1H$ NMR (360 MHz) ($CDCl_3$) δ TMS: 1.58-1.65(1H, m), 1.70-1.85(1H, m), 2.19-2.28(1H, m), 2.46(1H, t, J=5.5Hz, $D_2O$ exch), 3.58-3.70(2H, m), 3.72-3.81(2H, m), 4.21(1H, 1/2ABq, J=14.63Hz), 4.25(1H, 1/2ABq, J=14.73Hz), 4.28(1H, d, J=3.42Hz), 4.97(1H, 1/2ABq, J=14.73Hz), 4.97(1H, 1/2ABq, J=14.63Hz), 5.21(1H, s), 7.18-7.40(10H, m).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 28.8(t), 45.0(d), 47.6(t), 47.9(t), 60.18(d), 63.3(t), 63.5(t), 78.2(d), 128.2(d), 128.2(d), 128.3(d), 128.9(d), 134.9(s), 135.1(s), 163.2(s), 168.3(s).

IR(NaCl, neat): 3600-3150, 1675, 1450, 1160 $cm^{-1}$.

Mass spectrum, m/e: 380(0.6), 312(1.1), 149(6.9), 91(11.4), 84(100).




8,10-Dibenzyl-8,10-diaza-5-[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (252) and 7,9-Dibenzyl-7,9-diaza-4-[[2'-(tert-butyldimethylsilyl)oxy]ethyl]-2-oxabicyclo[3.2.2]nonane-6,8-dione (252a)

To a stirred solution of 244 and 245 (274 mg, 0.741 mmol, 1.0 equiv) in THF (10 mL) at room temperature was added tert-butyldimethylsilyl triflate (0.599 ml, 2.16 mmol, 3.0 equiv) and the mixture was stirred at room temperature. After 12 h, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on a silica gel flash column (eluted with 1:3 EtOAc/hexanes) to afford 162 mg (47%) of 252a and 170 mg (49%) of 252 as oils.

Compound 252

$^1$H NMR (100 MHz) (CDCl) $\delta$ $CHCl_3$: 0.06(6H, s), 0.89(9H, s), 1.9-2.3(3H, m), 3.41(1H, dd, $J_{vic}$=5.50Hz, $J_{gem}$=9.81Hz), 3.54(1H, d, $J_{gem}$=9.81Hz), 3.76(1H, m), 3.88(1H, m), 4.09(1H, 1/2ABq, J=14.64Hz), 4.15(1H, 1/2ABq, J=14.90Hz), 4.22(1H, d, J=1.95Hz), 5.10(1H, 1/2ABq, J=14.90Hz), 5.12(1H, 1/2ABq, J=14.64Hz), 5.18(1H, s), 7.30(10H, m).

$^{13}$C NMR (25 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 5.32(q), 18.32(s), 25.97(q), 29.06(t), 46.93(t), 47.63(t), 59.30(t), 63.45(d), 65.09(t), 83.48(d), 127.79(d), 127.97(d), 128.26(d), 128.73(d), 135.27(s), 162.47(s), 166.97(s).

IR(NaCl, neat): 1670, 1445, 1052 $cm^{-1}$.

Mass spectrum, m/e: 479($M^+CH_3$, 1.1), 437(44.6), 292(1.1), 208(16.0), 91(100).

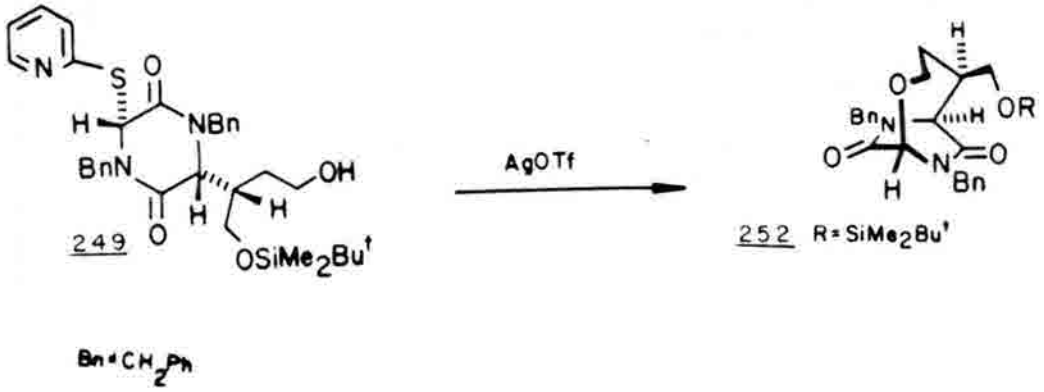
Compound 252a

$^1$H NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.01(6H, s), 0.84(9H, s), 1.6(2H, m), 2.38(1H, m), 3.60(2H, m), 3.86(2H, m), 3.96(1H, s), 4.30(1H, 1/2ABq, J=15.09Hz), 4.34(1H, 1/2ABq, J=14.77Hz), 4.84(1H, 1/2ABq, J=15.09Hz), 4.97(1H, 1/2ABq, J=14.77Hz), 5.03(1H, s), 7.25(10H, m).

$^{13}$C NMR (25 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 5.44(q), 18.20(s), 25.85(q), 33.09(t), 37.41(d), 48.21(t), 50.08(t), 60.47(t), 62.81(d), 67.89(t), 85.17(d), 127.68(d), 127.85(d), 128.55(d), 128.79(d), 135.67(s), 163.76(s), 170.53(s).

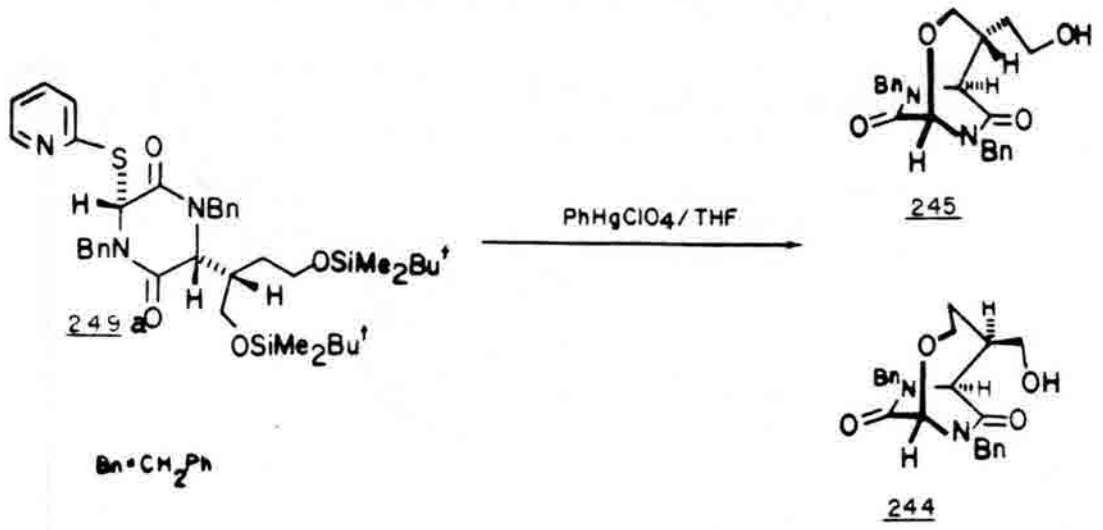
IR(NaCl, neat): 1670, 1450 $cm^{-1}$.

Mass spectrum, m/e: 479($M^+$-15, 0.8), 437(35.6), 409(12.6), 293(2.7), 274(21.1), 167(4.1), 91(100).



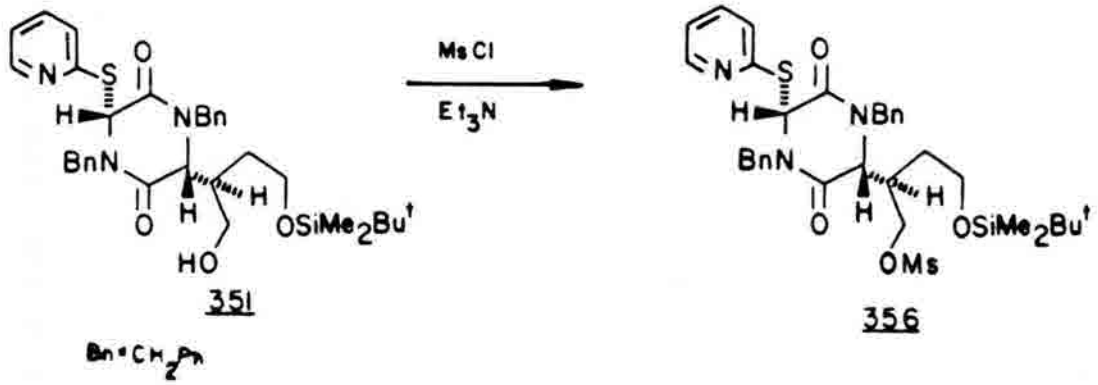

8,10-Dibenzyl-8,10-diaza-5-[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (252)

To a stirred solution of 249 (279 mg, 0.461 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added solid AgOTf (142.1 mg, 0.5532 mmol, 1.2 equiv) and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with $CH_2Cl_2$, poured into 0.1 N NaOH, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 172 mg (91%) of 252 that was identical to that obtained from 244.




8,10-Dibenzyl-8,10-diaza-5-[hydroxymethyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (244) and 7,9-Dibenzyl-7,9-diaza-4-[2'-(hydroxyethyl)]-2-oxabicyclo[3.2.2]nonane-6,8-dione (245)

To a stirred solution of 249a (30 mg, 0.0417 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added a solution of $PhHgClO_4$ (0.0847 mmol, 2.15 equiv) in THF (2 mL) and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with $CH_2Cl_2$, poured into 0.1 N NaOH, exhaustively extracted with $CH_2Cl_2$, the combined extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with 100% EtOAc) to afford 12 mg (80.56%) of 244 and 245 as an oil.




351 356

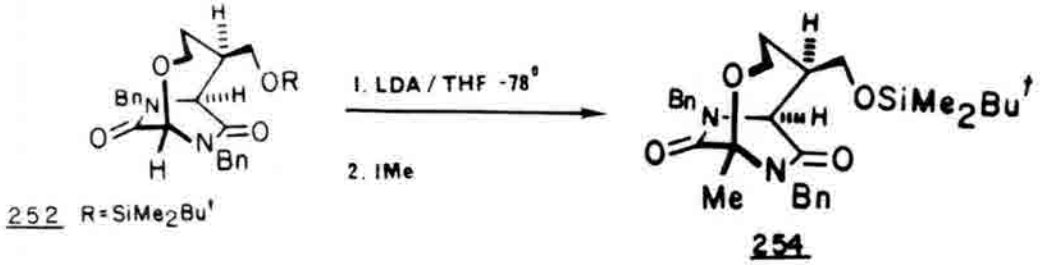
1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[[1"-(methanesulfonyl)oxy)methyl]-3"-[(tert-butyldimethylsilyl)oxy)propyl]-2,5-piperazinedione (356)

To a stirred solution of 351 (22 mg, 0.526 mmol, 1.0 equiv) in THF (0.5 mL) was added $Et_3N$ (0.11 ml, 0.789 mmol, 1.5 equiv) followed by methanesulfonyl chloride (0.06 ml, 0.789 mmol, 1.5 equiv) at room temperature. After 10 min, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 25 mg (98%) of 356 as an oil.

$^1H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.10(6H, s), 0.93(9H, s), 2.60(2H, m), 2.80(1H, m), 3.64(3H, s), 3.73(2H, m), 3.92(2H, m), 3.93(1H, 1/2ABq, J=14.90Hz), 4.02(1H, 1/2ABq, J=14.64Hz), 4.43(1H, d, J=3.18Hz), 5.16(1H, 1/2ABq, J=14.64Hz), 5.45(1H, 1/2ABq, J=14.64Hz), 6.66(1H, s), 7.20-7.40(11H, m), 7.56(2H, m), 8.43(1H, d, J=4.93Hz).

IR(NaCl, neat): 1670, 1450, 1045 $cm^{-1}$.

Mass spectrum, m/e: 367($M^+$-91, 2.1), 272(1.2), 181(3.1), 91(100).




252 R = $SiMe_2Bu^t$

254

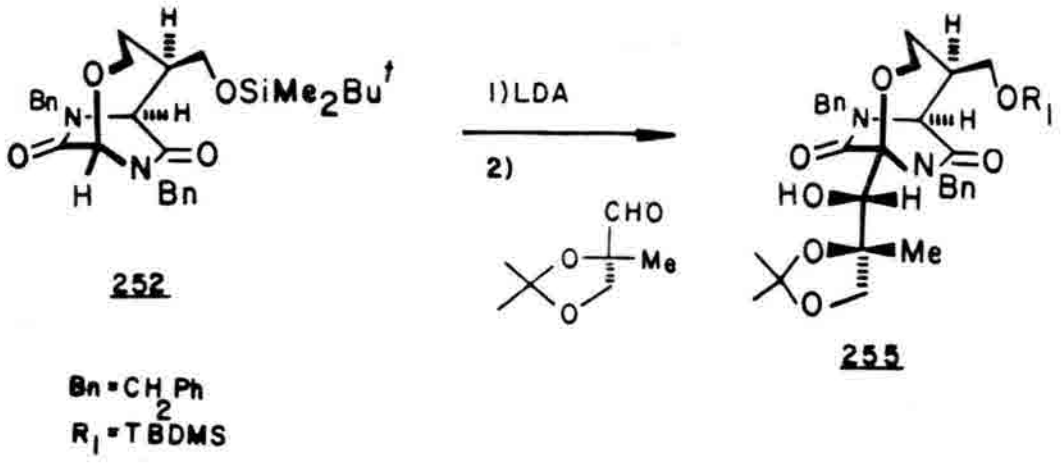
Bn = $CH_2Ph$

8,10-Dibenzyl-8,10-diaza-1-methyl-5-[[(tert-butyldimethylsilyl)oxy]-methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (254)

To a stirred solution of 252 (22 mg, 0.047 mmol, 1.0 equiv) in THF (2 mL) at -78°C equipped with a constant $N_2$ flow, was added HMPA (0.009 mL, 0.0517 mmol, 1.05 equiv) followed by a solution of LDA (0.0517 mmol, 1.05 equiv) in THF (1 mL). The yellow enolate was stirred for 65 min at -78°C, at which time methyliodide (0.014 mL, 0.235 mmol, 5 equiv) was added. After 5 min, the mixture was warmed to room temperature, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 12 mg (39%, 71% based on recovered starting material) of 254 as an oil.

$^1$H NMR (100 MHz) ($CDCl_3$) $\delta$ TMS: 0.05(6H, s), 0.89(9H, s), 1.66(3H, s), 1.60-1.80(2H, m), 1.93-2.33(1H, m), 3.19-3.93(4H, m), 4.13(1H, 1/2ABq, J=14.41Hz), 4.31(1H, bs), 4.40(1H, 1/2ABq, J=13.91Hz), 5.08(1H, 1/2ABq, J=13.91Hz), 5.26(1H, 1/2ABq, J=14.41Hz), 7.26(5H, bs), 7.32(5H, bs).

IR(NaCl, neat): 1670, 1450, 1150 $cm^{-1}$.




252

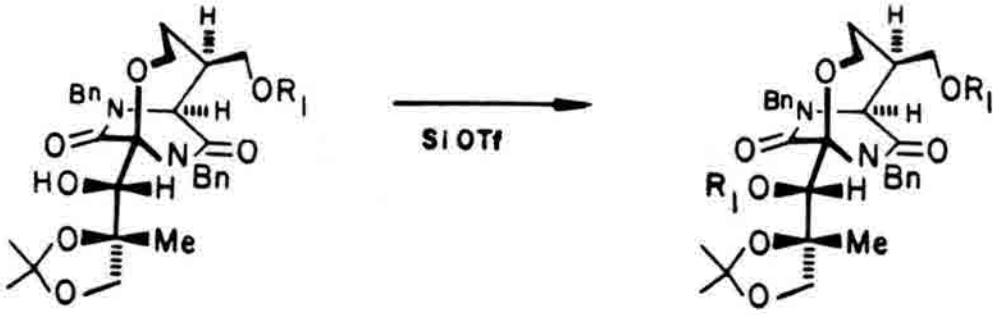
255

Bn = $CH_2Ph$

$R_1$ = TBDMS

8,10-Dibenzyl-8,10-diaza-1-[1'-hydroxy-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (255)

To a stirred solution of 252 (38 mg, 0.08 mmol, 1.0 equiv) in THF (1 mL) at -100°C was added a solution of LDA (0.089 mmol, 1.1 equiv) in THF (1 mL). After stirring the dark yellow enolate at -100°C for 5 min, (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.035 mL, 0.243 mmol, 3.0 equiv) was added and the mixture was stirred 2 min at -100°C, then warmed to room temperature. The mixture was then diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:5 EtOAc/hexanes) to give 6.3 mg (13%, 80% based on recovered starting material) of 255 as an oil. Compound 255 was very difficult to sepa rate from starting material and was carried on as a mixture to the next step.




255

Bn = $CH_2Ph$
$R_1$ = TBDMS

256

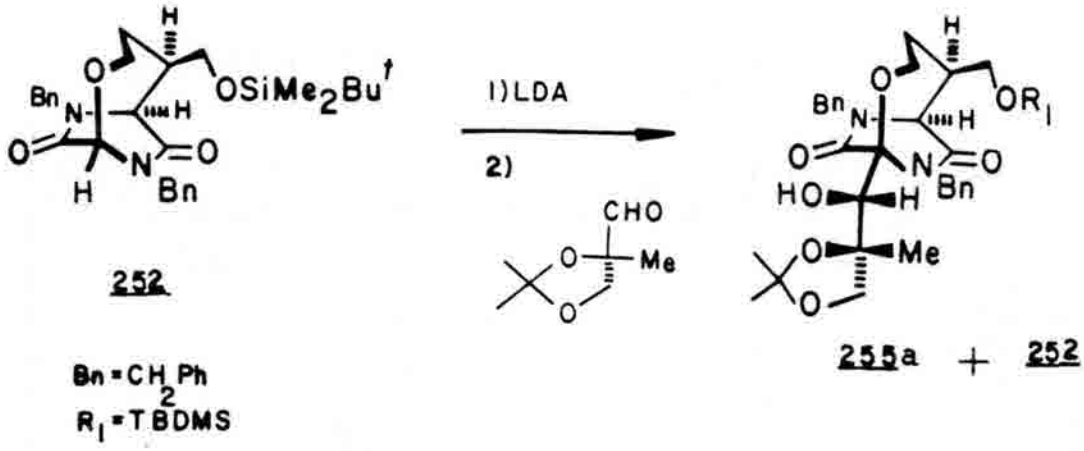
8,10-Dibenzyl-8,10-diaza-1-[(1'-O-tert-butyldimethylsilyl)-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (256)

To a stirred solution of 255 (7.8 mg, 0.012 mmol, 1.0 equiv) in $CH_2Cl_2$ (1 mL) at room temperature was added 2,6-lutidine (0.003 mL, 0.024 mmol, 2.0 equiv) followed by tert-butyldimethylsilyl triflate (0.005 mL, 0.018 mmol, 1.5 equiv). After stirring 2 h at room temperature, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 9 mg (99%) of 256 as an oil.

$^1$H NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.021(3H, s), 0.026(3H, s), 0.029(3H, s), 0.104(3H, s), 0.855(9H, s), 0.918(9H, s), 1.020(3H, s), 1.284(3H, s), 1.297(3H, s), 1.40-1.655(2H, m), 2.16(1H, m), 3.39(1H, dd, $J_{vic}$=5.93Hz, $J_{gem}$=10.13Hz), 3.528-3.783(3H, m), 3.65(1H, 1/2ABq, J=8.60Hz), 3.76(1H, 1/2ABq, J=14.48Hz), 4.14(1H, 1/2ABq, J=8.60Hz), 4.13(1H, s), 4.62(1H, 1/2ABq, J=15.23Hz), 4.745(1H, s), 4.91(1H, 1/2ABq, J=15.23Hz), 5.35(1H, 1/2ABq, J=14.48Hz), 7.18-7.56(10H, m).

IR(NaCl, neat): 1670, 1370, 1130, 1080 $cm^{-1}$.

Mass spectrum, m/e: 737(1.0), 696(2.6), 637(3.4), 581(23.9), 517(1.9), 436(2.5), 201(5.2), 145(2.0), 91(100).




252

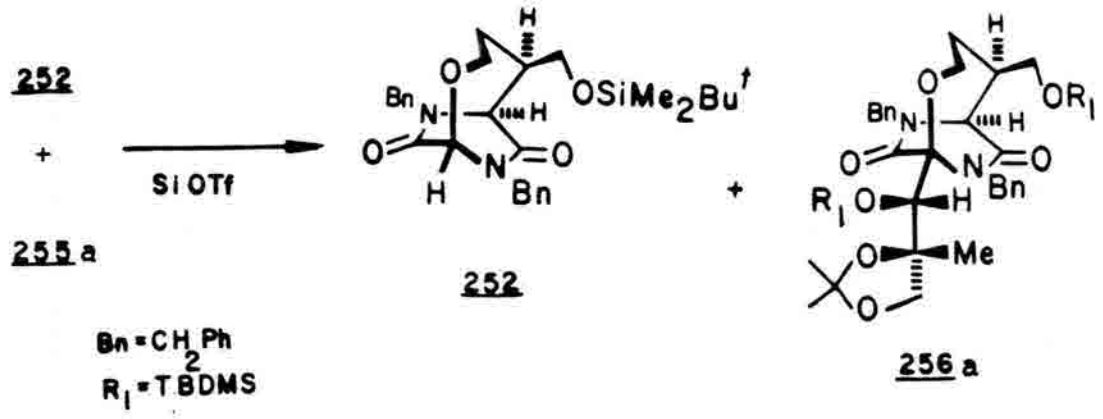
Bn = $CH_2Ph$

$R_1$ = TBDMS

255a + 252

8,10-Dibenzyl-8,10-diaza-1-[1'-hydroxy-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (255a) (Optically Active)

To a stirred mixture of 252 (55 mg, 0.1175 mmol, 1.0 equiv) in THF (1 mL) at -100°C was added a solution of LDA (0.008 ml, 0.058 mmol, 0.5 equiv) in THF (0.5 mL) and the dark enolate was stirred for 30 min at -100°C. A solution of (-)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (optically pure from HPLC resolution) in THF (1 mL) was added and the mixture was allowed to stir for 15 min at -100°C. The mixture was warmed to room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, exhaustively extracted with $CH_2Cl_2$, the extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel/eluted with 1:2 EtOAc/hexanes to afford 48 mg of a mixture of 255a and 252 which looked identical by $^1H$ NMR with that of the racemic series.



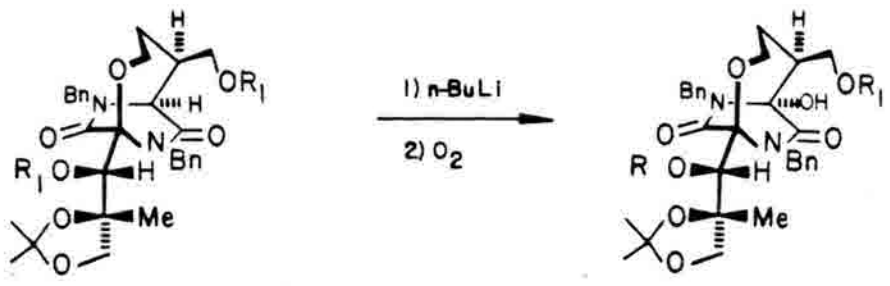

8,10-Dibenzyl-8,10-diaza-1-[(1'-O-tert-butyldimethylsilyl)-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (256a) (Optically Active)

To a stirred solution of 252 and 255a (30 mg) in $CH_2Cl_2$ (2 mL) at room temperature was added 2.6 lutidine (0.014 mL) followed by tert-butyldimethylsilyl triflate (0.058 mL). The mixture was stirred at room temperature for 12 hr, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:4 EtOAc/hexanes) to afford 18 mg (28%, 59% based on recovered starting material) of 256a as an oil.

256a $[\alpha]_D^{25}$ = +9.68 ($CH_2Cl_2$) c=2.2. NMR and IR are identical to those of the racemic compounds 256.

Mass spectrum, m/e: 738($M^+-CH_3$, 0.7), 686(1.9), 638(5.6), 582(12.3), 91(74), 75(100).

252 $[\alpha]_D^{25} = -6.21$ ($CH_2Cl_2$) c=2.9. NMR and IR identical with those of the racemic compound 252.




256 257

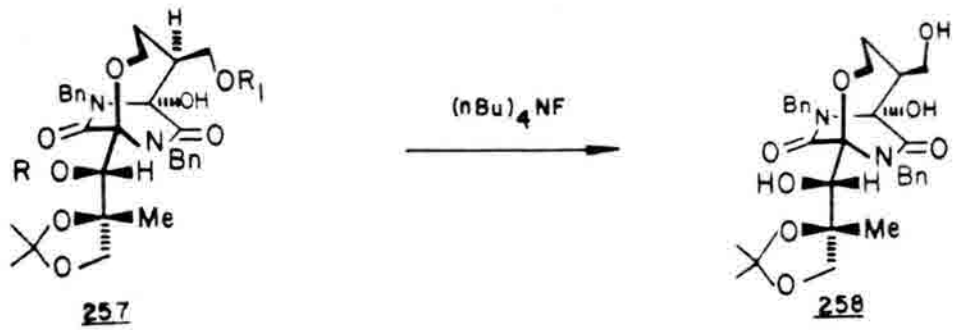
8,10-Dibenzyl-8,10-diaza-1-[1'-O-tert-butyldimethylsilyl)-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (257)

To a stirred solution of 256 (15 mg, 0.021 mmol, 1.0 equiv) in THF (1 mL) at -100°C was added tert-butyllithium (0.005 mL, 0.023 mmol, 1.1 equiv) and the resulting dark enolate was stirred at -100°C for 2 min. A steady stream of $O_2$ was bubbled through the mixture for 10 min. The mixture was stirred 10 min at -100°C, allowed to warm to room temperature; diluted with $CH_2Cl_2$, poured into $H_2O$ and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 12 mg (78%) of 257 as an oil.

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 0.03(6H, s), 0.10(6H, s), 0.85(9H, s), 0.92(9H, s), 1.02(3H, s), 1.20(3H, s), 1.30(3H, s), 2.15(2H, m), 3.32(1H, dd, J=5.95Hz, J=10.13Hz), 3.60(2H, m), 3.67(1H, 1/2ABq, J=8.60Hz), 3.70(2H, m), 3.76(1H, 1/2ABq, J=14.48Hz), 4.11(1H, 1/2ABq, J=8.60Hz), 4.13(1H, s), 4.65(1H, 1/2ABq, J=15.24Hz), 4.74(1H, s, $D_2O$ exch), 4.91(1H, 1/2ABq, J=15.24Hz), 5.34(1H, 1/2ABq, J=14.48Hz), 7.20-7.50(10H, m).

IR(NaCl, neat): 3500-3200, 1670, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 754($M^+-CH_3$, 1.3), 712($M^+-C_4H_9$, 0.9), 638($M^+-C_4H_9S$, 11.2), 581(33), 437(43.8), 129(3), 91(100).




257

Bn = $CH_2Ph$
$R_1$ = TBDMS

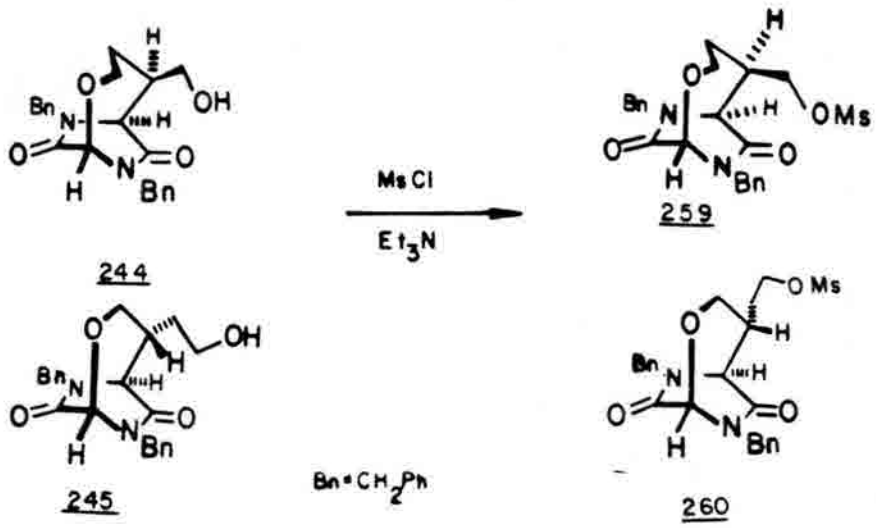
258

8,10-Dibenzyl-8,10-diaza-1-[(1'-hydroxy)-2',3'-O-isopropylidene]-5-hydroxymethyl-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (258)

To a stirred solution of 257 (22 mg, 0.03 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added solid tetra-n-butylammonium fluoride (37.38 mg, 0.143 mmol, 5.0 equiv). The mixture was stirred for 2 h, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:9:89 $NH_4OH$/MeOH/$CH_2Cl_2$) to afford 11 mg (71%) of 258 as an oil.

$^1H$ NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 1.28(3H, s), 1.33(3H, s), 1.39(3H, s), 2.00-2.15(3H, m), 2.40(1H, m, $D_2O$ exch), 3.23-3.39(5H, m), 3.56(1H, 1/2ABq, J=15.98Hz), 3.90(1H, d, J=9.12Hz), 4.18(1H, d, J=9.12Hz), 4.65(1H, d, J=10.24Hz), 4.68(1H, 1/2ABq, J=15.98Hz), 5.01(1H, 1/2ABq, J=14.98Hz), 6.26(1H, d, J=10.24Hz, $D_2O$ exch), 6.31(1H, s, $D_2O$ exch), 7.40(10H, m).

IR(NaCl, neat): 3600-3200, 1650, 1050 $cm^{-1}$.




244

245

259

260

8,10-Dibenzyl-8,10-diaza-5-[(methanesulfonyl)methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (259) and 7,9-Dibenzyl-7,9-diaza-4-[[2'-(methanesulfonyl)oxy]ethyl]-2-oxabicyclo[3.2.2]nonane-6,8-dione (260)

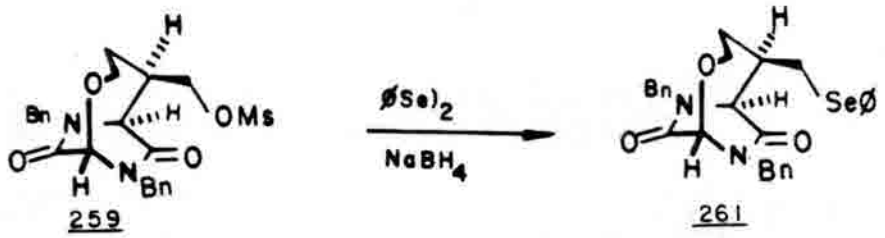
To a stirred solution of 244 and 245 (54 mg, 0.142 mmol, 1.0 equiv) in THF (2 mL) at 0°C was added triethylamine (0.02 mL, 0.156 mmol, 1.1 equiv) and the mixture was stirred at 0°C. After 10 min, mesyl chloride (0.018 ml, 0.156 mmol, 1.1 equiv) was added and the mixture was stirred an additional 10 min at 0°C, diluted with ether, filtered, concentrated, and separated by PTLC silica gel (eluted with 4:1 EtOAc/hexanes) to afford 57 mg (87.5%) of 259 and 260 as a mixture of oils. Note: Pure 259 was obtained by recovery from the subsequent selenide displacement on the mixture of mesylates.

Compound 259

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 1.50-1.60(1H, m), 1.79-1.89(1H, m), 2.36-2.44(1H, m), 2.98(3H, s), 3.77(1H, dd, $J_{vic}$=9.14Hz, $J_{gem}$=13.82Hz), 3.95(1H, dd, $J_{vic}$=7.33Hz, $J_{gem}$=13.82Hz), 4.09(1H, dd, $J_{vic}$=5.66Hz, $J_{gem}$=10.53Hz), 4.13-4.16(1H, m), 4.19(1H, d, J=2.29Hz), 5.06(2H, twice, 1/2ABq, J=15.05Hz), 5.10(2H, twice 1/2ABq, J=14.88Hz), 5.21(1H, s), 7.20-7.38(10H, m).

IR(NaCl, neat): 1672, 1450, 1150 $cm^{-1}$.

Mass spectrum, m/e: 458($M^+$, 4.7), 363(1.3), 353(9.2), 261(1.9), 218(4.1), 167(52.8), 121(21.1), 91(100).




259 261

Bn = $CH_2Ph$

8,10-Dibenzyl-8,10-diaza-5-[(phenylselenyl)methyl]-2-oxabicyclo[4.2.2]-decane-7,9-dione (261)

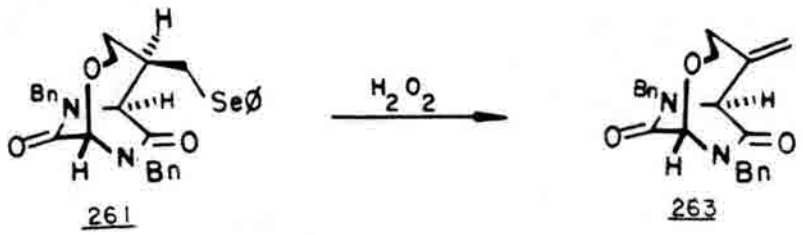
To a stirred solution of diphenyl diselenide (18 mg, 0.057 mmol, 1.05 equiv) in EtOH (1 mL) at room temperature was added solid sodium borohydride (43 mg, 0.115 mmol, 2.1 equiv) and the mixture was stirred until $H_2$ evolution had stopped. After 30 min, the selenide salt was transferred to a stirred solution of 259 (25 mg, 0.055 mmol, 1.0 equiv) in EtOH (1 mL) at room temperature and the mixture was warmed to 45°C. After 20 min, it was cooled to room temperature, evaporated to dryness and separated by PTLC silica gel (1:1 EtOAc/hexanes) to afford 22 mg (78%) of 261 as an oil.

$^{1}H$ NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.60-1.78(1H, m), 1.90-2.01(1H, m), 2.00-2.17(1H, m), 2.80-2.94(1H, m), 3.00-3.11(1H, m), 3.66(1H, dd, J=10.81Hz, J=14.41Hz), 3.69(1H, dd, J=7.20Hz, J=14.41Hz), 4.32(1H, d, J=2.50Hz), 3.88(1H, 1/2ABq, J=16.73Hz), 4.18(1H, 1/2ABq, J=16.73Hz), 5.02(1H, 1/2ABq, J=16.73Hz), 5.06(1H, 1/2ABq, J=16.73Hz), 5.17(1H, s), 7.2-7.6(15H, m).

IR(NaCl, neat): 1670, 1430, 1050 $cm^{-1}$.

Mass spectrum, m/e: 520(6.3), 429(0.2), 363(8.9), 292(4.3), 91(100).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 30.46(t), 32.92(t), 43.89(d), 47.28(t), 47.58(t), 61.57(d), 64.10(t), 83.36(d), 127.04(d), 127.80(d), 127.97(d), 128.20, 128.55(d), 128.67(d), 129.14(d), 129.47(d), 132.17(s), 135.03(s), 162.36(s), 166.62(s).




261 $\xrightarrow{H_2O_2}$ 263

Bn = $CH_2Ph$

8,10-Dibenzyl-8,10-diaza-5-(methylene)-2-oxabicyclo[4.2.2]decane-7,9-dione (263)

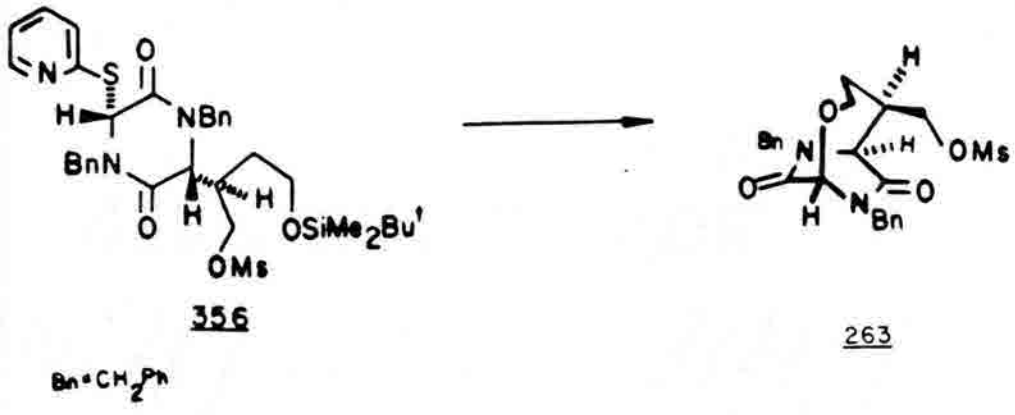
To a stirred solution of 261 (154 mg, 0.291 mmol, 1.0 equiv) in THF (3.5 mL) at room temperature was added 30% hydrogen peroxide (0.045 mL, 1.48 mmol, 5.0 equiv) and the temperature was brought to reflux. After 45 min, the mixture was cooled to room temperture, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 96 mg (90%) of 263 as an oil.

$^1H$ NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 2.18-2.28(1H, m), 2.35(1H, dd, $J_{gem}$=16.38Hz, $J_{vic}$=6.87Hz), 3.28(1H, dd, $J_{gem}$=13.40Hz, $J_{vic}$=9.05Hz), 3.77(1H, dd, $J_{gem}$=13.40Hz, $J_{vic}$=6.87Hz), 3.84(1H, 1/2ABq, J=14.62Hz), 4.13(1H, 1/2ABq, J=14.51Hz), 4.35(1H, s), 4.92(1H, 1/2ABq, J=14.62Hz), 5.01(1H, s), 5.09(1H, 1/2ABq, J=14.51Hz), 5.10(1H, s), 5.20(1H, s), 7.12-7.32(10H, m).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) δ: 34.92(t), 47.51(t), 47.98(t), 63.40(t), 65.32(d), 83.89(d), 119.68(t), 128.61(d), 128.50(d), 127.95(d), 134.33(s), 134.68(s), 142.86(s), 166.97(s), 164.23(s).

IR(NaCl, neat): 1675, 1660, 1150 $cm^{-1}$.

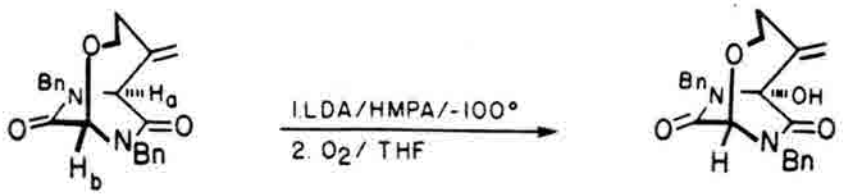
Mass spectrum, m/e: 362($M^+$, 11.5), 271(2.3), 91(100).



356 263

8,10-Dibenzyl-8,10-diaza-5-(methylene)-2-oxabicyclo[4.2.2]decane-7,9-dione (263)

To a stirred solution of mesylate (356) (18 mg, 0.026 mmol, 1.0 equiv) in THF (1 mL) was added a solution of $PhHgClO_4$ (0.058 mmol, 2.2 equiv) in THF (2 mL) and the mixture was stirred for 22 min at room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and passed through a silica plug. The crude was dissolved in THF (1.5 mL) at room temperature and $BH_3PhSeNa$ (0.03 mmol, 1.1 equiv, 1 mL EtOH) was added and the mixture was stirred 12 h, concentrated to dryness diluted with THF (5 mL). Hydrogen peroxide 30% (0.03 ml, 1.0 equiv) was added and the mixture was heated to reflux. After 20 min, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 4.1 mg (37% overall ) of 263 as an oil which was identical in every respect to that obtained from 261.




263 266

Bn = $CH_2Ph$

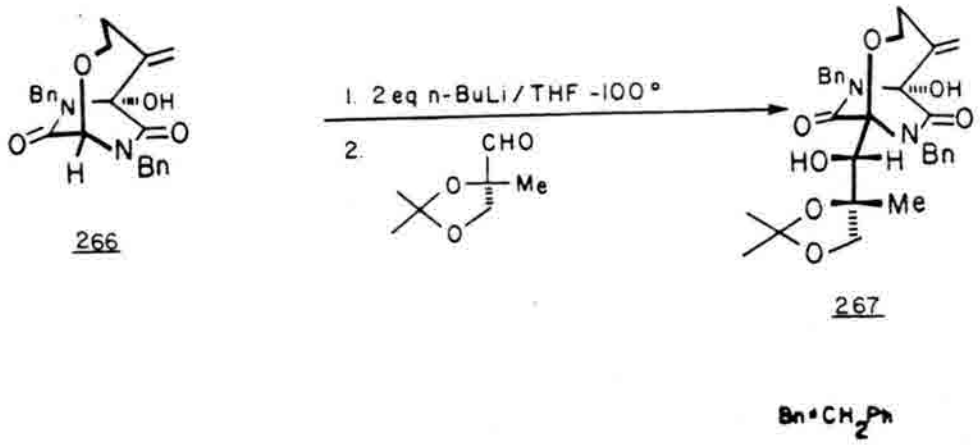
8,10-Dibenzyl-8,10-diaza-5-methylene-6-hydroxy-2-oxabicyclo[4.2.2]-decane-7,9-dione (266)

To a stirred solution of 263 (54 mg, 0.149 mmol, 1.0 equiv) in THF (2 mL) at -100°C was added HMPA (0.54 mL, 0.298 mmol, 2.0 equiv) followed by n-butyllithium (0.09 mL, 0.179 mmol, 1.2 equiv) and the dark brown anion was stirred at -100°C for 15 min. A steady flow of $O_2$ was bubbled through the mixture for 15 min at -100°C, then it was warmed to room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 20 mg (35.5%, 63.7% based on recovered starting material) of 266 as an oil.

$^1$H NMR (360 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 2.12(1H, dd, $J_{vic}$=9.83Hz, $J_{gem}$=16.58Hz), 2.31(1H, dd, $J_{gem}$=16.58Hz, $J_{vic}$=7.21Hz), 3.31(1H, dd, $J_{gem}$=13.09Hz, $J_{vic}$=9.83Hz), 3.84(1H, dd, $J_{gem}$=13.09Hz, $J_{vic}$=7.21Hz), 4.27(1H, 1/2ABq, J=14.13Hz), 4.47(1H, 1/2ABq, J=14.40Hz), 4.64(1H, 1/2ABq, J=14.13Hz), 4.94(1H, s, $D_2O$ exch), 4.99(1H, 1/2ABq, J=14.40Hz), 5.09(1H, s), 5.24(1H, s), 5.60(1H, s), 7.20-7.50(10H, m).

IR(NaCl, neat): 3600-3200, 1670, 1660, 1250 $cm^{-1}$.

Mass spectrum, m/e: 378($M^+$, 1.0), 294(2.2), 133(12.1), 111(24.1), 91(72.6), 57(100).




266 267

Bn = $CH_2Ph$

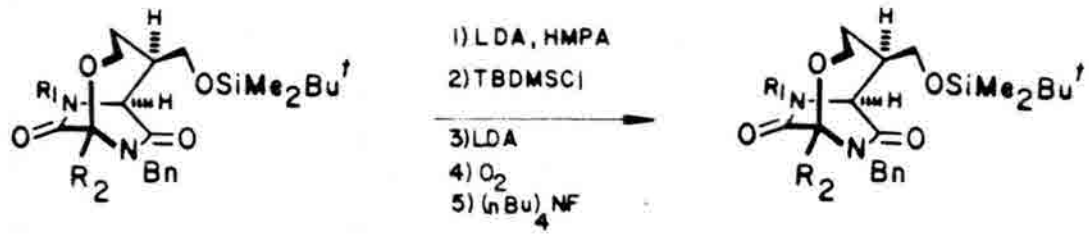
N,N'-Dibenzyl-2',3'-O-(isopropylidene)bicyclomycin (267)

To a stirred solution of 266 (24 mg, 0.063 mmol, 1.0 equiv) in THF (2 mL) at -100°C was added n-BuLi (0.08 mL, 0.152 mmol, 2.4 equiv) and the dark enolate was stirred at -100°C. After 10 min, (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.045 mL, 0.317 mmol, 1.5 equiv) was added and the mixture was allowed to warm to room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 16 mg (48.2%, 67.7% based on recovered starting material) of 267 as an oil.

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 1.34(3H, s), 1.35(3H, s), 1.54(3H, s), 1.98-2.12(2H, m), 2.79(1H, dd, $J_{gem}$=13.71Hz, $J_{vic}$=1.80Hz), 3.53(1H, dd, $J_{gem}$=13.71, $J_{vic}$=7.14Hz), 3.77(1H, 1/2ABq, J=9.31Hz), 4.10(1H, 1/2ABq, J=9.31Hz), 4.32(1H, 1/2ABq, J=13.55Hz), 4.58(1H, 1/2ABq, J=13.55Hz), 4.62(1H, d, J=9.91Hz), 4.68(1H, 1/2ABq, J=15.32Hz), 5.00(1H, s, $D_2O$ exch), 5.13(1H, s), 5.17(1H, 1/2ABq, J=15.32Hz), 5.56(1H, s), 6.50(1H, d, J=9.91Hz, $D_2O$ exch), 7.20-7.58(10H, s).

IR(NaCl, neat): 3600-3200, 1675, 1660, 1250 $cm^{-1}$.

Mass spectrum, m/e: 465($M^+$-58, 0.2), 244(1.2), 179(2.1), 91(100).




252 $R_1$ = $CH_2Ph$, $R_2$ = H

268 $R_1$ = CH(SiMe$_3$)Ph, $R_2$ = H

Bn = $CH_2Ph$

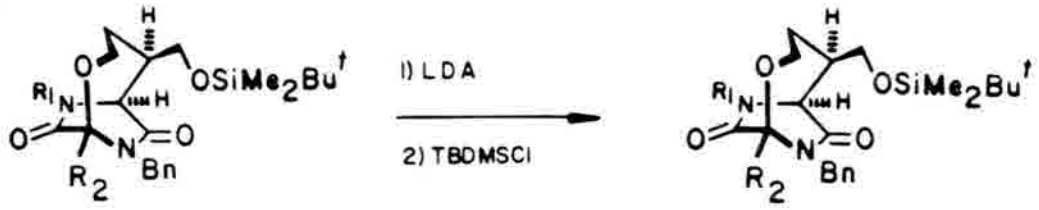
8-Benzyl-10-[(tert-butyldimethylsilyl)benzyl]-8,10-diaza-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (268)

To a stirred solution of 252 (21 mg, 0.045 mmol, 1.0 equiv) in THF (2.5 mL) at -78°C was added a solution of LDA (0.049 mmol, 1.1 equiv) in THF (1.5 mL), the dark yellow solution was stirred for 5 min at -78°C, then solid trimethylsilyl chloride (6 mg, 0.049 mmol, 1.1 equiv) was added and the mixture was warmed to room temperature. The mixture was then cooled to -78°C, a solution of LDA (0.049 mmol, 1.1 equiv) in THF (0.5 mL) was added followed by solid MoOPh (97 mg, 0.224 mmol, 5.0 equiv), the mixture was stirred 10 min at -78°C, warmed to room temperature over 20 min, then solid $(n\text{-}Bu)_4NF$ (11.7 mg, 0.049 mmol, 1.0 equiv) was added. After 1 h at room temperature the mixture was concentrated to dryness and separated by PTLC silica gel (eluted with 1:2 hexanes/EtOAc) to afford 12 mg (41.2%, 54.7% based on recovered starting material) of 268 as an oil.

$^1H$ NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 0.007(3H, s), 0.12(12H, s), 0.86(9H, s), 1.42-1.60(2H, m), 1.77(1H, m), 3.21(1H, dd, $J_{vic}$=9.79Hz, $J_{gem}$=9.79Hz), 3.37(1H, s), 3.50(1H, dd, $J_{vic}$=9.79Hz, $J_{gem}$=9.79Hz), 3.83(2H, dd, J=4.52Hz), 4.06(1H, 1/2ABq, J=14.86Hz), 4.42(1H, d, J=1.76Hz), 5.09(1H, s), 5.24(1H, 1/2ABq, J=14.86Hz), 7.18-7.38(10H, m).

IR(NaCl, neat): 1670, 1450 $cm^{-1}$.

Mass spectrum, m/e: 566($M^+$, 22.4), 509(22.1), 475(11.8), 449(18.3), 437(18.3), 260(10.1), 91(100), 57(35.3).




252 $R_1 = CH_2Ph$, $R_2 = H$

Bn = $CH_2Ph$

270 $R_1 = CH_2Ph$, $R_2 = SiMe_2Bu^t$

269 $R_1 = R_2 = H$

8-Benzyl-8,10-diaza-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxobicyclo[4.2.2]decane-7,9-dione (269) and 8,10-Dibenzyl-8,10-diaza-1-[tert-butyldimethylsilyl]-5[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (270)

To a stirred solution of 252 (109 mg, 0.233 mmol, 1.0 equiv) in THF (2 mL) at -78°C was added a solution of LDA (0.267 mmol, 1.1 equiv) in THF (1 mL) and the dark brown enolate was stirred for 15 min. Solid tert-butyldimethylsilyl chloride (175.5 mg, 1.16 mmol, 5.0 equiv) was added, and the mixture was stirred at -78°C. After 20 min, the mixture was warmed to room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$ and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:4 EtOAc/hexanes) to afford 32 mg (27%, 42% based on starting material) of 270 and 19 mg (22%, 41.26% based on recovered starting material) of 269 as an oil.

Compound 269

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 0.012 (3H, s), 0.014(3H, s), 0.821(9H, s), 1.48-1.58(1H, m), 1.78-1.87(1H, m), 2.02-2.16(1H, m), 3.39(1H, dd, $J_{vic}$=6.59Hz, $J_{gem}$=9.84Hz), 3.62(1H, dd, $J_{vic}$=$J_{gem}$=9.84Hz), 3.81(1H, dd, $J_{vic}$=8.86Hz, $J_{gem}$=13.63Hz), 3.90(1H, dd, $J_{vic}$=7.41Hz, $J_{gem}$=13.63Hz), 4.06(1H, 1/2ABq, J=14.70Hz), 4.23(1H, dd, J=2.51Hz, J=4.29Hz), 4.98(1H, s), 5.09(1H, 1/2ABq, J=14.70Hz), 6.57(1H, bs), 7.19-7.29(5H, m).

IR(NaCl, neat): 3400, 1670, 1050 $cm^{-1}$.

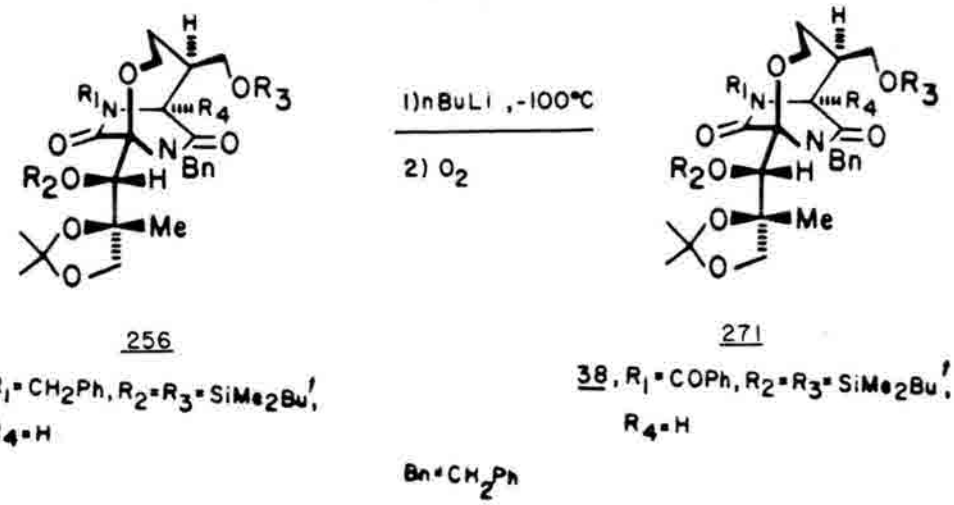
Mass spectrum, m/e: 389($M^+$-$CH_3$, 0.9), 347(10.3), 317(0.3), 241(0.3), 179(28.2), 135(100), 91(36.8).

Compound 270

$^1$H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.11(3H, s), 0.025(3H, s), 0.054(6H, s), 0.57(9H, s), 0.924(9H, s), 1.74(2H, m), 1.95(1H, m), 3.43(1H, m), 3.53(1H, m), 3.63(1H, m), 3.73(1H, bs), 3.80(1H, m), 4.20(1H, 1/2ABq, J=14.41Hz), 4.40(1H, 1/2ABq, J=15.14Hz), 4.77(1H, 1/2ABq, J=15.14Hz), 5.34(1H, 1/2ABq, J=14.41Hz), 7.20-7.30(10H, m).

IR(NaCl, neat): 1670, 1450, 1020 $cm^{-1}$.

Mass spectrum, m/e: 609($M^+$, 609), 567(19.0), 213(1.6), 179(3.4), 149(25.5), 91(83.1), 75(100).




256

$R_1 = CH_2Ph$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$

271

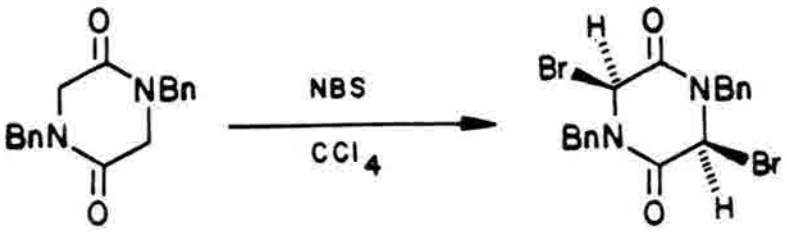
38, $R_1 = COPh$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$

8-Benzyl-10-benzoyl-8,10-diaza-[(1'-O-tert-butyldimethylsilyl)-2',3'-O-isopropylidene]-5-[[(tert-butyldimethylsilyl)oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (271)

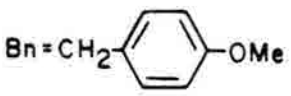
To a stirred solution of 256 (62 mg, 0.085 mmol, 1.0 equiv) in THF (5 mL) at -100°C was added tert-butyllithium (0.04 mL, 0.0941 mmol, 1.1 equiv) and the resulting yellow enolate was stirred for 10 min at -100°C. A steady stream of $O_2$ was bubbled through the mixture for 30 min at -100°C and 30 min at room temperature. The mixture was then diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:5 EtOAc/hexanes) to afford 22 mg (35%, 68% based on starting material) of 271 as an oil. (NOTE: It is difficult by NMR to establish which of the two N-benzyl groups was oxidized. The structure chosen corresponds to the least hindered approach of the base.)

$^1$H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$: 0.092(3H, s), 0.067(3H, s), 0.056(3H, s), 0.116(3H, s), 0.079(9H, s), 0.932(9H, s), 1.26(3H, s), 1.350(3H, s), 1.33(3H, s), 1.50-2.00(2H, m), 2.56-2.70(1H, m), 2.99(1H, dd, $J_{vic}$=9.12Hz, $J_{gem}$=9.83Hz), 3.19(1H, dd, $J_{vic}$=10.02Hz, $J_{gem}$=9.83Hz), 3.45-3.70(2H, m), 3.82(1H, 1/2ABq, J=8.60Hz), 4.08(1H, 1/2ABq, J=8.60Hz), 4.36(1H, d, J=1.91Hz), 4.62(1H, 1/2ABq, J=15.17Hz), 4.80(1H, s), 5.03(1H, 1/2ABq, J=15.17Hz), 7.15-7.56(10, m).

IR(NaCl, neat): 1680, 1400, 1250, 1100 $cm^{-1}$.




273 274

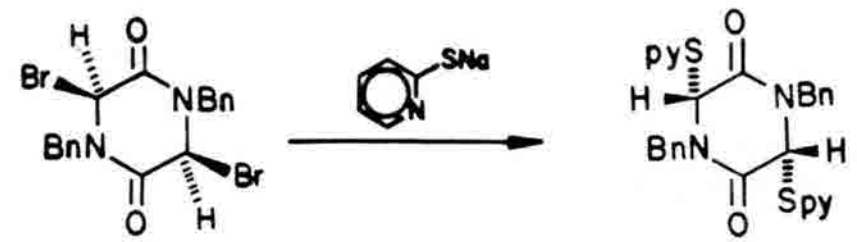



1,4-Di-para-methoxybenzyl-3,6-bis-bromo-2,5-piperazinedione (274)

To a stirred solution of 273 (5.0 g, 14.1 mmol, 1.0 equiv) in $CCl_4$ (350 mL) was added N-bromosuccinamide (5.28 g, 29.66 mmol, 2.1 equiv) and a catalytic amount (1 mol %) of benzoyl peroxide. The mixture was brought to reflux temperature for 1 h, cooled to ambient temperature, filtered, and concentrated to give 6.72 g (93%) of 274 as pale yellow crystals, mp 164-165°C (recryst. EtOAc/hexanes).

$^1H$ NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 4.23(6H, s), 4.44(2H, 1/2ABq, J=13.48Hz), 5.66(2H, 1/2ABq, J=13.48Hz), 6.37(2H, s), 7.36(4H, 1/2ABq, J=8.68Hz), 7.68(4H, 1/2ABq, J=8.68Hz).

IR(NaCl, neat): 1695, 1520 $cm^{-1}$.




274 275

Bn=$CH_2$Ph-p-OMe

1,4-Di-para-methoxybenzyl-3,6-bis-(2'-thiopyridyl)-2,5-piperazinedione (275)

To a stirred suspension of sodium hydride (577 mg, 14.43 mmol, 1.0 equiv) in THF (100 mL) was added solid 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 room temperature and was then transferred via cannula into a stirred solution of 274 (3.52 g, 6.87 mmol, 1.0 equiv) in THF (100 mL). The mixture was allowed to stir for 30 min, poured into $H_2O$ and thoroughly extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to afford 275 (3.81 g, 97%) as white crystals, mp 174-175°C (recryst. EtOAc/hexanes).

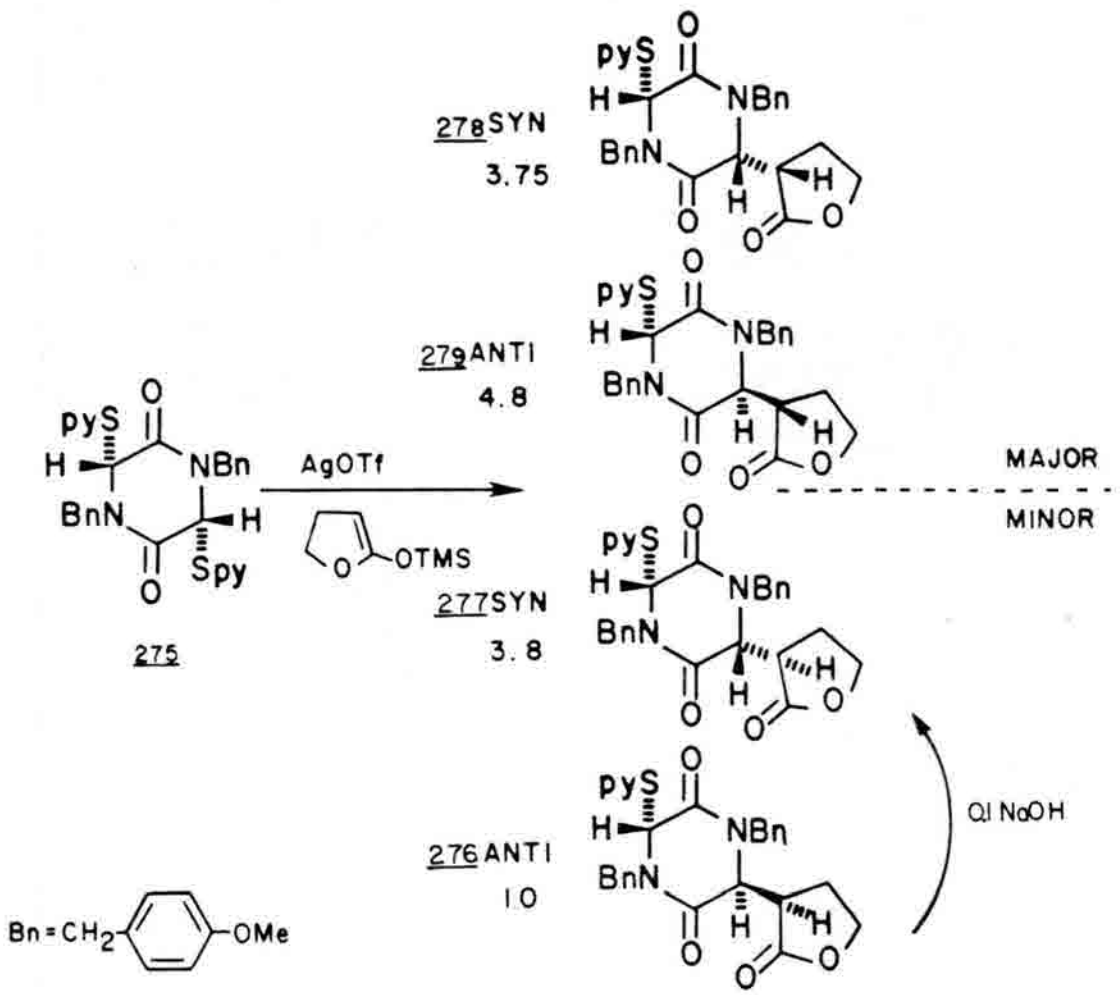
$^1H$ NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 3.85(6H, s), 4.17(2H, 1/2ABq, J=14.47Hz), 5.22(2H, 1/2ABq, J=14.47Hz), 6.73(2H, s), 6.89(4H, 1/2ABq, J=8.58Hz), 7.17(2H, m), 7.31(4H, 1/2ABq, J=8.58Hz), 7.32(2H, m), 7.61(2H, m), 8.57(2H, d, J=4.76Hz).

IR(NaCl, neat): 1670, 1505, 1405, 1240 1112 $cm^{-1}$.

Mass spectrum, m/e: 592($M^+$+$H_2O$+1.0, 0.4), 574($M^+$+1.0, 0.4), 543(0.5), 219(8.0), 121(29.6), 111(84.4), 57(100).

Analysis (recrystallized from EtOAc/hexanes):

| | | | | |
|---|---|---|---|---|
| Calcd for $C_{30}H_{28}N_4O_4S_2$ | C=62.91%; | H=4.93%; | N=9.78%; | S=11.19% |
| Found | 63.21 | 4.95 | 11.24 | 11.24 |




1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-({2"-γ-butyrolactonyl)-2,5-piperazinediones (276), (277), (278), and (279)

To a THF (200 mL) solution of 275 (9.25 g, 16.88 mmol, 1.0 equiv) was added AgOTf (4.55 g, 17.72 mmol, 1.05 mmol) at room temperature. The solution was stirred 10 min until it turned milky white. Immediately, the ketene silyl acetal of γ-butyrolactone (4.91 mL, 21.94 mmol, 1.3 equiv) was added and the mxiture was stirred for 2 h at room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on flash column silica gel to afford 370 mg (2.46% yield) of anti-minor 276, 1.415 g (13.2% yield) of syn-minor 277, 1.750 g (16.38% yield) of syn-major 278, and 1.378 g (12.89% yield) of anti-major 279 lactones in an overall 1.75:1 ratio of major to minor lactones (45% combined). (NOTE: higher yields (71%) could be obtained on smaller scale (1 g)).

Major Anti Lactone 279 mp 168-168.5°C (recryst. EtOAc/hexanes)

$^1H$ NMR (270 MHz) ($CDCl_3$) δ TMS: 1.80-2.05(2H, m), 3.19(1H, dd, $J_{vic}=J_{vic}=8.13Hz$), 3.77(3H, s), 3.81(3H, s), 4.08(1H, 1/2ABq, J=14.48Hz), 4.20-4.40(3H, m), 4.85(1H, s), 5.09(1H, 1/2ABq, J=15.35Hz), 5.28(1H, 1/2ABq, J=14.48Hz), 5.86(1H, s), 6.82(2H, d, J=8.40Hz), 6.84(2H, d, J=8.66Hz), 7.06(1H, t), 7.17(2H, d, J=8.40Hz), 7.17-7.20(1H, m), 7.19(2H, d, J=8.66Hz), 7.56(1H, t, J=6.42Hz), 8.27(1H, d, J=3.86Hz).

IR(NaCl, neat): 1765, 1670, 1512, 1245, 1025 $cm^{-1}$.

Mass spectrum, m/e: 467(0.9), 347(3.4), 257(5.8), 167(7.1), 121(5.5), 111(19.1), 57(100).

Analysis (recrystallized from EtOAc/hexanes):

| | | | | |
|---|---|---|---|---|
| Calcd for $C_{29}H_{29}N_3O_6S$: | C=63.60%; | H=5.33%; | N-7.67%; | S= 5.85% |
| Found | 63.40 | 5.52 | 7.50 | 5.85 |

Minor Anti Lactone 276 mp 136-138°C (recryst. EtOAc/hexanes)

$^1$H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.20-1.40(1H, m), 1.80-1.90(1H, m), 3.75-3.98(2H, m), 3.78(3H, s), 3.80(3H, s), 4.17(1H, 1/2ABq, J=14.30Hz), 4.20(1H, 1/2ABq, J=13.92Hz), 4.32(1H, d, J=2.28Hz), 5.14(1H, d, J=2.28Hz), 5.23(1H, 1/2ABq, J=13.92Hz), 5.28(1H, 1/2ABq, J=14.30Hz), 5.62(1H, s), 6.68(2H, d, J=8.64Hz), 6.76(2H, d, J=8.59Hz), 6.88-6.94(1H, m), 7.12-7.16(1H, m), 7.24(2H, d, J=8.64Hz), 7.29(2H, d, J=8.59Hz), 7.49(1H, t), 7.87(1H, d, J=4.23Hz).

IR(NaCl, neat): 1770, 1678, 1520, 1251, 1031 $cm^{-1}$.

Mass spectrum, m/e: 400(0.3), 368(0.7), 191(3.1), 149(13.8), 121(27.4), 91(4.9), 57(100).

Minor Syn Lactone 277 mp 194-195°C (recryst. EtOAc/hexanes)

$^1$H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.30-2.44(2H, m), 3.31(1H, dd, $J_{vic}$=$J_{vic}$=10.86Hz), 3.80(6H, s), 3.99(2H, twice, 1/2ABq, J=14.52Hz), 4.17-4.27(1H, m), 4.34(1H, dd, $J_{vic}$=$J_{gem}$=8.65Hz), 4.81(1H, s), 4.99(1H, 1/2ABq, J=14.62Hz), 5.28(1H, 1/2ABq, J=14.50Hz), 6.64(1H, s), 6.80(2H, d, J=7.58Hz), 6.83(2H, d, J=7.43Hz), 7.15(2H, d, J=4.3Hz), 7.26(2H, d, J=7.58Hz), 7.20-7.30(2H, m), 7.59(1H, t, J=7.70Hz), 8.48(1H, d, J=4.23Hz).

IR(NaCl, neat): 1768, 1670, 1512, 1450, 1242, 1020 $cm^{-1}$.

Analysis (recrystallized from EtOAc/hexanes):

| | | | | |
|---|---|---|---|---|
| Calcd for $C_{29}H_{29}N_3O_6S$: | C=63.60%; | H=5.33%; | N=7.67%; | S= 5.85% |
| Found | 63.44 | 5.17 | 7.55 | 5.75 |

Major Syn Lactone 276 mp 138-140°C (recryst. EtOAc/hexanes)

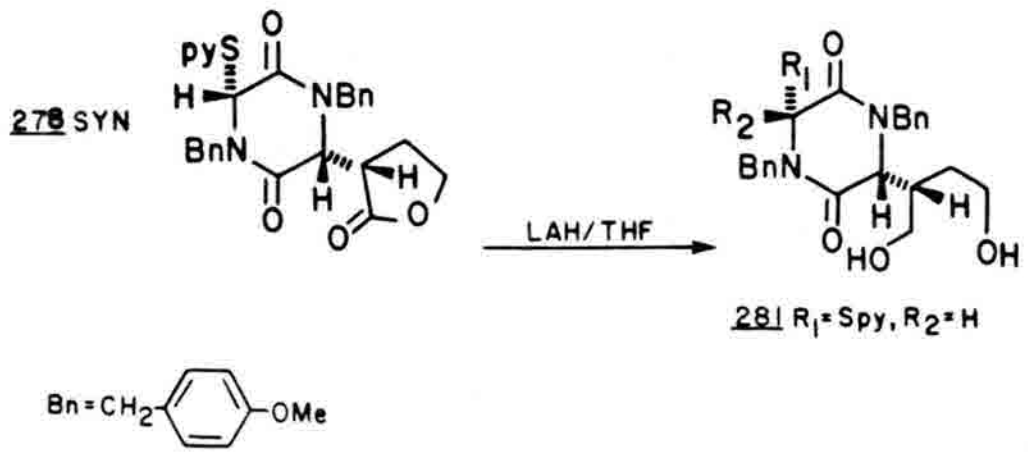
$^1$H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.80-2.10(2H, m), 3.14(1H, ddd, $J_{vic}$=4.06Hz, $J_{vic}$=10.81Hz, $J_{vic}$=10.81Hz), 3.91(3H, s), 3.92(3H, s), 4.12(1H, 1/2ABq, J=14.34Hz), 4.25-4.32(1H, m), 4.50(1H, ddd, $J_{vic}$=14.34Hz, $J_{gem}$=$J_{vic}$=9.80Hz), 4.59(1H, 1/2ABq, J=14.83Hz), 4.73(1H, d J=4.06Hz), 5.07(1H, 1/2ABq, J=14.83Hz), 5.29(1H, 1/2ABq, J=14.34Hz), 6.67(1H, s), 6.92(2H, d, J=8.88Hz), 6.96(2H, d, J=8.88Hz), 7.27-7.40(2H, m), 7.31(2H, d, J=8.88Hz), 7.32(2H, d, J=8.88Hz), 7.72(1H, m), 8.63(1H, d, J=4.19Hz).

IR(NaCl, neat): 1772, 1672, 1513, 1265, 1025 $cm^{-1}$.

Mass spectrum, m/e: 438(0.2), 316(0.2), 163(3.9), 136(5.5), 121(100). 111(12.3).

Epimerization Results: Treatment of a THF (2 mL) solution of minor anti-lactone with 1 equivalent of 0.1N NaOH resulted in a 1:1

mixture of syn and anti minor lactones as well as a small amount of an unidentified compound. The weight recovery for the epimerization was low (20%).



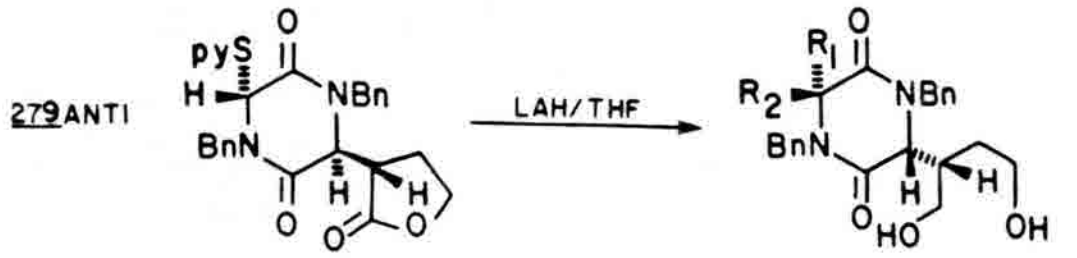

syn1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-[(1"-hydroxymethyl)-3"-hydroxypropyl]-2,5-piperazinedione (281)

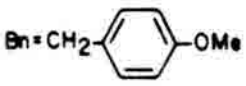
to a stirred solution of major syn lactone 278 (600 mg, 1.09 mmol, 1.0 equiv) in THF (60 mL) at 0°C equipped with a constant $N_2$ flow, was added all at once solid $LiAlH_4$ (20.85 mg, 0.549 mmol, 2.0 equiv). Immediately following addition the mixture was quenched with excess $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature and stirred for 1 hr. The suspension was then filtered, concentrated, and separated on PTLC silica gel using a chromatron (eluted with EtOAc) to afford 197 mg (33%, 40% by conversion) of 281 as an oil.

$^1H$ NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.72(1H, m), 1.91(1H, m), 2.36(1H, m), 3.58-3.76(6H, m), 3.78(3H, s), 3.80(3H, s), 4.02(1H, 1/2ABq, J=14.39Hz), 4.12(1H, 1/2ABq, J=15.35Hz), 4.25(1H, d, J=6.90Hz), 5.18(1H, 1/2ABq, J=14.39Hz), 5.28(1H, 1/2ABq, J=15.35Hz), 6.70(1H, s), 6.83(4H, d, J=8.65Hz), 7.16(4H, d, J=8.65Hz), 7.26(2H, m), 7.60(1H, m), 8.52(1H, d, J=3.41Hz).

IR(NaCl, neat): 3600-3100-1660, 1510, 1240, 1025 $cm^{-1}$.

Mass spectrum, m/e: 503($M^+$-48, 0.5), 429(0.7), 198(11.9), 121(100), 111(25.8).




Anti-1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-[(1"-hydroxymethyl)-3"-hydroxypropyl]-2,5-piperazinedione (282)

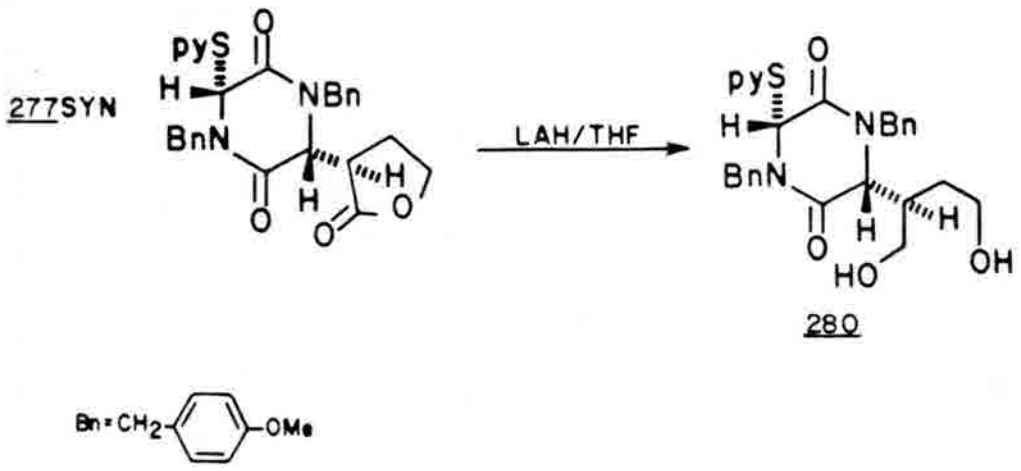
To a stirred solution of 279 (850 mg, 1.58 mmol, 1.0 equiv) in THF (180 mL) at 0°C was added solid $LiAlH_4$ (30.14 mg, 0.79 mmol, 0.5 equiv), the mixture was stirred for 30 min at 0°C, quenched with $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature, filtered, concentrated, and separated by silica gel flash column to afford 128 mg (15%, 21% based on recovered starting material) of 282 as an oil. NOTE: An alternate procedure was utilized in which the $LiAlH_4$ was added in 0.25 equivalent portions over a period of an hour at 0°C, resulting in substantial increase in the yield (51%).

Treatment of 279 with 1 N NaOH resulted in a mixture of 278 and 279.

$^1$H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.80-1.90(1H, m), 1.90-1.92(1H, m, $D_2O$ exch), 1.90-1.93(1H, m), 2.36-2.40(1H, m), 3.79(3H, s), 3.80(3H, s), 3.80-3.95(4H, m), 4.02(1H, 1/2ABq, J=14.31Hz), 4.13(1H, 1/2ABq, J=14.50Hz), 4.24(1H, d, J=5.81Hz), 4.25(1H, m, $D_2O$ exch), 5.17(1H, 1/2ABq, J=14.31Hz), 5.22(1H, 1/2ABq, J=14.81Hz), 6.79(1H, s), 6.79(2H, d, J=8.86Hz), 6.82(2H, d, J=8.86Hz), 7.05-7.15(2H, m), 7.13(2H, d, J=8.86Hz), 7.17(2H, d, J=8.86Hz), 7.56(1H, m), 8.52(1H, m).

IR(NaCl, neat): 3600-3100, 1660 $cm^{-1}$.

Mass spectrum, m/e: 440($M^+$-111, 0.6), 198(5.7), 111(13.1), 84(100).







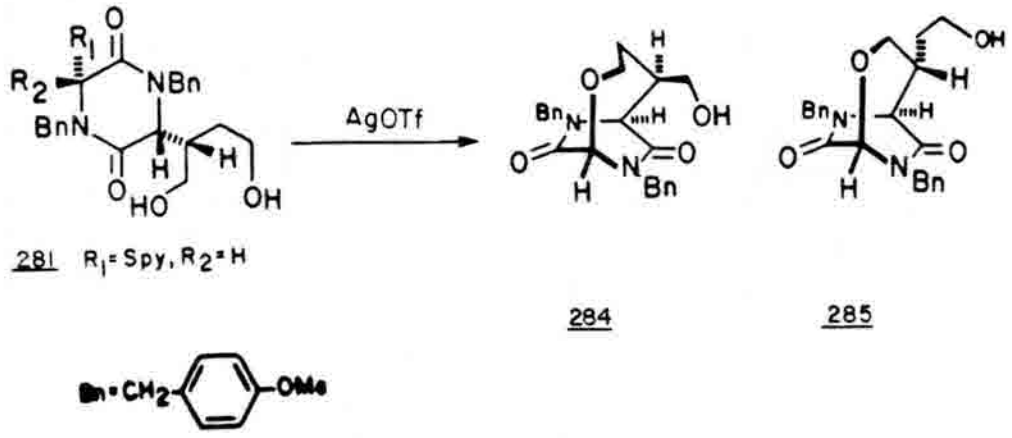
syn1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-[(1"-hydroxymethyl)-3"-hydroxypropyl]-2,5-piperazinedione (280)

To a stirred solution of 277 (1.102 g, 2.014 mmol, 1.0 equiv) in THF (100 mL) at 0°C was added solid $LiAlH_4$ (38.2 mg, 1.0 mmol, 0.5 equiv) and the solution was stirred for 15 min at 0°C, quenched with excess $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature, filtered, concentrated, and separated by silica gel flash column (eluted with 100% EtOAc) to afford 185 mg (17%, 19% based on recovered starting material) of 280 as an oil.

$^1H$ NMR (270 MHz) ($CDCl_3$) δ TMS: 2.18-2.28(2H, m), 2.95-3.01(1H, m), 3.20-3.40(1H, m), 3.50-3.90(5H, m), 3.77(3H, s), 3.79(3H, s), 3.92(1H, 1/2ABq, J=14.81Hz), 4.00(1H, 1/2ABq, J=14.48Hz), 4.10(1H, d, J=6.93Hz), 5.11(1H, 1/2ABq, J=14.48Hz), 5.34(1H, 1/2ABq, J=14.81Hz), 6.65(1H, s), 6.79(2H, d, J=8.65Hz), 6.80(2H, d, J=8.65Hz), 7.11(2H, d, J=8.65Hz), 7.10(2H, d, J=8.65Hz), 7.20-7.32(2H, m), 7.55(1H, m), 8.46(1H, d, J=4.19Hz).

IR(NaCl, neat): 3600-3100, 1670, 1420, 1050 $cm^{-1}$.

Mass spectrum, m/e: 441($M^+$-110, 0.8), 426(2.1), 354(0.9), 121(100), 110(43.2).






8,10-Di-para-methoxybenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo-[4.2.2]decane-7,9-dione (284) and 7,9-Di-para-methoxybenzyl-7,9-diaza-4-(2'-hydroxyethyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (285)

To a stirred solution of major syn diol 281 (316 mg, 0.573 mmol, 1.0 equiv) in THF (5 mL) at 25°C was added AgOTf (294.7 mg, 1.147 mmol, 2.0 equiv) in one portion. The milky white solution was stirred for 15 min, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with EtOAc) to afford 198 mg (78% yield) of a 3:2 mixture of eight 284 and seven 285 membered ring alcohols.

Compound 284

$^1$H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.80(1H, m), 2.08(1H, m), 3.70-3.90(6H, m), 3.79(6H, s), 4.16(1H, 1/2ABq, J=14.47Hz), 4.21(1H, 1/2ABq, J=14.60Hz), 4.28(1H, d, J=3.24Hz), 4.88(1H, 1/2ABq, J=14.47Hz), 4.93(1H, 1/2ABq, J=14.60Hz), 5.20(1H, s), 6.83(4H, d, J=8.53Hz), 7.18(2H, d, J=3.53Hz), 7.20(2H, d, J=8.53Hz).

IR(NaCl, neat): 3600-3200, 1668, 1510, 1230 $cm^{-1}$.

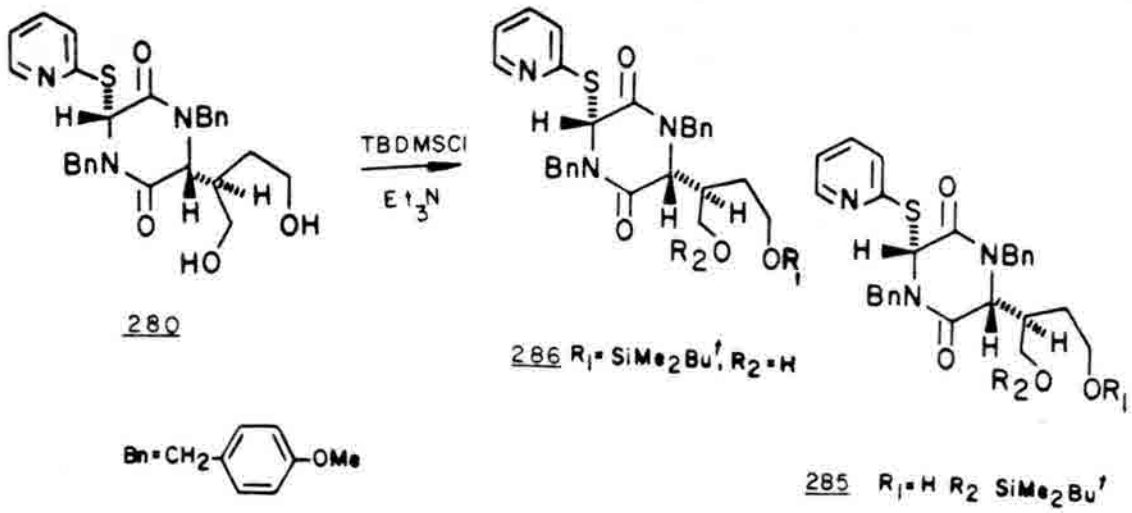
Mass spectrum, m/e: 440($M^+$, 1.9), 389(2.0), 352(1.6), 319(1.7), 198(1.4), 121(100).

Compound 285

$^1$H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.40-1.75(2H, m), 1.80-1.90(1H, m), 2.50(1H, m), 3.27(1H, dd, $J_{vic}$=8.51Hz, $J_{gem}$=13.16Hz), 3.53(2H, t, J=6.58Hz), 3.77(1H, dd, $J_{vic}$=4.64Hz, $J_{gem}$=13.16Hz), 3.78(6H, s), 3.94(1H, d, J=3.02Hz), 4.43(1H, 1/2ABq, J=14.48Hz), 4.45(1H, 1/2ABq, J=14.45Hz), 4.59(1H, 1/2ABq, J=14.45Hz), 4.63(1H, 1/2ABq, J=14.48Hz), 5.09(1H, s), 6.85(2H, d, J=8.48Hz), 6.86(2H, d, J=8.48Hz), 7.18(2H, d J=8.48Hz), 7.21(2H, d, J=8.48Hz).

IR(NaCl, neat): 3600-3200, 1668, 1510, 1230 $cm^{-1}$.

Mass spectrum, m/e: 440($M^+$, 2.1), 389(0.7), 121(100).




1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-[[1"-(hydroxymethyl)]-3"-'(tert-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (286) and 1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-[[1"-[(tert-butyldimethylsilyl)oxy]methyl]-3"-(hydroxypropyl)]-2,5-piperazinedione (285)

To a stirred solution of 280 (298 mg, 0.541 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added $Et_3N$ (0.750 mL, 0.541 mmol, 1.0 equiv) followed by tert-butyldimethylsilyl chloride (89.23 mg, 0.594 mmol, 1.15 equiv) and the mixture was stirred at room temperature. After 14 h, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by flash column silica gel (eluted wtih 1:1 EtOAc/hexanes) to afford 96 mg (27.0%, 35% based on recovered starting material) of 286 and 45 mg (12.6%, 16.2% based on recovered starting material) of 285 as oils.

Compound 286

$^1$H NMR (270 MHz) ($CDCl_3$) δ TMS: 0.11(3H, s), 0.12(3H, s), 0.92(9H, s), 1.3(1H, m), 1.98(2H, m), 2.40(1H, m), 3.70-4.00(4H, m), 3.80(3H, s), 3.80(3H, s), 3.94(1H, 1/2ABq, J=14.67Hz), 3.96(1H, 1/2ABq, J=14.33Hz), 4.14(1H, d, J=6.57Hz), 5.12(1H, 1/2ABq, J=14.32Hz), 5.31(1H, 1/2ABq, J=14.67Hz), 6.62(1H, s), 6.79(2H, d, J=8.52Hz), 6.82(2H, d, J=8.52Hz), 7.12(2H, d, J=8.52Hz), 7.12-7.16(2H, m), 7.14(2H, 1/2ABq, J=8.52Hz), 7.60(1H, dd, J=10.80Hz, J=8.18Hz), 8.48(1H, d, J=8.48Hz).

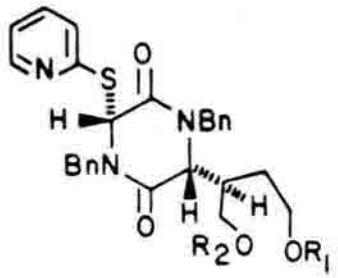
IR(NaCl, neat): 3600-3200, 1671, 1248, 1030 $cm^{-1}$.

Mass spectrum, m/e: 540(0.1), 497(24.2), 231(2.4), 149(3.0), 121(100).

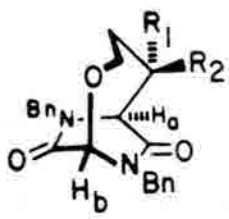
Compound 285

$^1$H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 0.06(6H, s), 0.89(9H, s), 1.87(1H, m), 1.89(1H, m), 2.28-2.35(1H, m), 2.86-2.98(1H, m), 3.74(3H, s), 3.75(3H, s), 3.75-3.85(4H, m), 3.81(1H, 1/2ABq, J=14.74Hz), 3.94(1H, 1/2ABq, J=14.49Hz), 3.97(1H, d, J=7.24Hz), 5.09(1H, 1/2ABq, J=14.49Hz), 5.33(1H, 1/2ABq, J=14.74Hz), 6.61(1H, s), 6.75(2H, d, J=8.60Hz), 6.76(2H, d, J=8.60Hz), 7.05(2H, d, J=8.60Hz), 7.10(2H, d, J=8.60Hz), 7.10-7.20(2H, m), 7.51(1H, bt, J=1.71Hz, J=8.129Hz), 8.40(1H, bd, J=4.7Hz).

IR(NaCl, neat): 3700-3200, 1665, 1240, 1030 $cm^{-1}$.

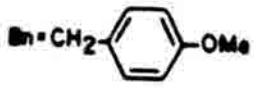


AgOTf



285 $R_1$ = H $R_2$ $SiMe_2Bu^t$

287 $R_1$ = $CH_2OH$, $R_2$ = H



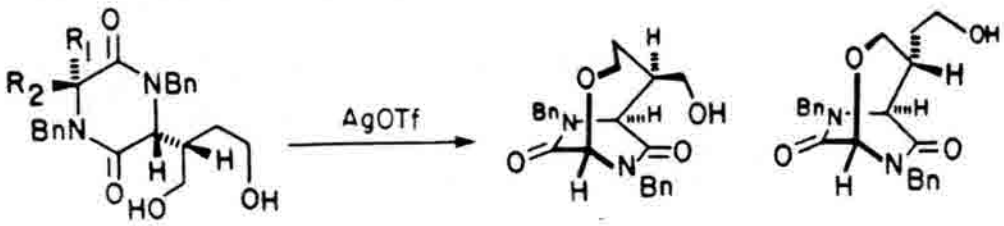
8,10-Di-para-methoxybenzyl-8,10-diaza-5-[[(tert-butyldimethylsilyl)-oxy]methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (287)

To a stirred solution of 285 (20 mg, 0.03 mmol, 1.0 equiv) in THF (1.2 mL) at room temperature was added solid silver triflate (15 mg, 0.06 mmol, 2.0 equiv) and the mixture was stirred at room temperature. After 22 min, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$, the combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 11 mg (66%) of 287 as an oil.

$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ TMS: 0.09(3H, s), 0.10(3H, s), 0.92(9H, s), 1.60-1.80(2H, m), 2.20-2.40(1H, m), 3.38-3.48(2H, m), 3.56(1H, dd, $J_{vic}$=6.35Hz, $J_{gem}$=10.72Hz), 3.80(6H, s), 3.80-3.90(1H, m), 3.86(1H, 1/2ABq, J=14.15Hz), 4.03(1H, 1/2ABq, J=14.64Hz), 4.44(1H, d, J=0.97Hz), 4.96(1H, 1/2ABq, J=14.156Hz), 5.17(1H, s), 5.23(1H, 1/2ABq, J=14.64Hz), 6.82(2H, d, J=8.78Hz), 6.83(2H, d, J=8.75Hz), 7.11(2H, d, J=8.78Hz), 7.14(2H, d, J=8.75Hz).

IR(NaCl, neat): 1680, 1515, 1247, 1030 $cm^{-1}$.

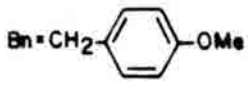
Mass spectrum, m/e: 503($M^+$-48, 0.5), 429(0.7), 198(11.9), 121(100), 111(25.8).




282 $R_1$ = H, $R_2$ = Spy

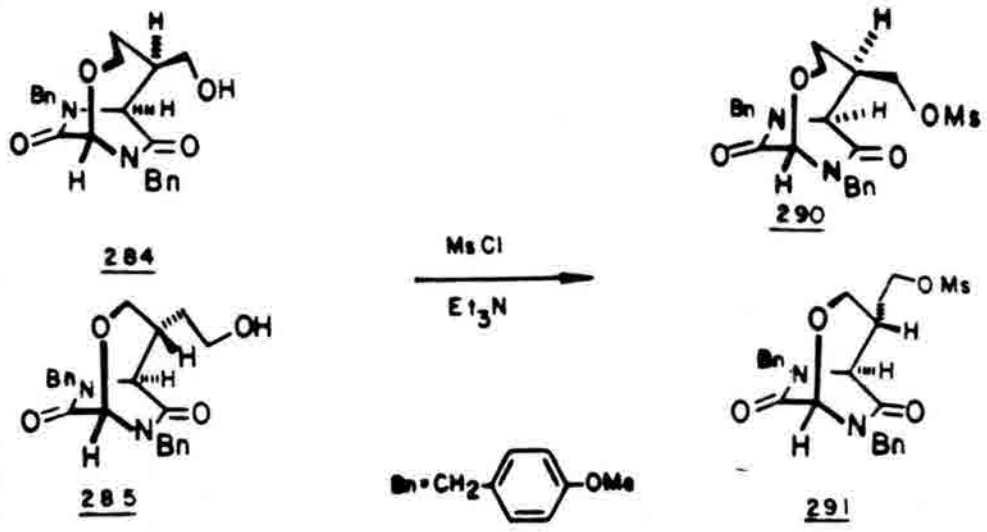
284

285




8,10-Di-*para*-methoxybenzyl-8,10-diaza-5-hydroxymethyl-2-oxabicyclo-[4.2.2]decane-7,9-dione (284) and 7,9-Di-*para*-methoxybenzyl-7,9-diaza-4-(2'-hydroxyethyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (284)

To a stirred solution of major *anti* diol 282 (128 mg, 0.232 mmol, 1.0 equiv) in THF (2 mL) was added AgOTf (119 mg, 0.464 mmol, 2.0 equiv) at 25°C. The milky white solution was stirred for 15 min, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with EtOAc) to afford a mixture of the bicyclic alcohols (82 mg, 80% yield, 10:1 ratio of the eight-membered:seven-membered ring alcohols 284 and 285 respectively; (calculated by NMR integration of bridgehead methine's adjacent to the bridging oxygen atom).




8,10-Di-*para*-methoxybenzyl-8,10-diaza-5-[(methanesulfonyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (290) and 7,9-Di-*para*-methoxybenzyl-7,9-diaza-4-[2'-(methanesulfonyl)ethyl]-2-oxabicyclo[3.2.2]nonane-6,8-dione (291)

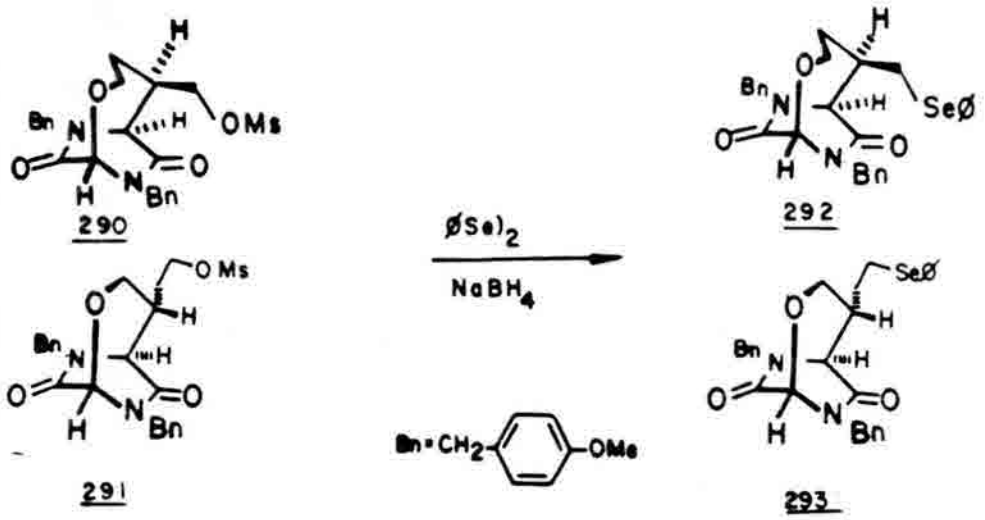
To a stirred solution of the alcohols 284 and 285 (obtained above as a 2:1 mixture) (198 mg, 0.45 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added $Et_3N$ (0.157 mL, 1.125 mmol, 2.5 equiv) followed by mesyl chloride (0.087 ml, 1.125 mmol, 2.5 equiv). The solution was stirred for 12 h, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with 2:1 EtOAc/hexanes) to afford 208 mg (85% yield) of the mixture of mesylates 290 and 291 in the same ratio of ring sizes as the starting material mixture.

Compound 290:

$^1$H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.50-1.70(1H, m), 1.78-1.96(1H, m), 2.32-2.46(1H, m), 3.03(3H, s), 3.80-4.30(4H, m), 3.80(3H, s), 3.81(3H, s), 4.08(1H, 1/2ABq, J=14.51Hz), 4.13(1H, 1/2ABq, J=14.44Hz), 4.22(1H, m), 4.96(1H, lab, J=14.51Hz), 4.97(1H, 1/2ABq, J-14.44Hz), 5.20(1H, s), 6.84(2H, d, J=8.63Hz), 6.80(2H, J=8.59Hz), 7.17(2H, d, J=8.63Hz), 7.23(2H, d, J=8.59Hz).

IR(NaCl, neat): 1675, 1510, 1460, 1240 $cm^{-1}$.

Mass spectrum, m/e: 518($M^+$, 3.5), 422(1.9), 397(3.1), 352(0.7), 301(2.7), 232(0.1), 121(100).




8,10-Di-para-methoxybenzyl-8,10-diaza-5-[(phenylselenyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (292) and 7,9-Di-para-methoxybenzyl-7,9-diaza-4-[2'-(phenylselenyl)ethyl]-2-oxabicyclo[3.2.2]nonane-6,8-dione (293)

To a stirred solution of diphenyl diselenide (137.9 mg, 0.442 mmol, 1.1 equiv) in EtOH (2.2 mL) was added solid $NaBH_4$ (33.4 mg, 0.883 mmol, 2.2 equiv) at 25°C and the solution was stirred for 20 min until $H_2$ evolution ceased. This solution was added to a THF (3.5 mL) solution of mesylates 290 and 291 (208 mg, 0.401 mmol, 1.0 equiv) and the mixture was refluxed for 2.2 h. After cooling, the reaction mixture was poured into $H_2O$ and exhaustively extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on a small silica gel flash column (eluted with 33% EtOAc/hexanes) to afford 81 mg (35% yield) of the seven-membered ring selenide 293 and 162 mg (70% yield) of the eight-membered ring selenide 292 as oils.

Compound 292

$^1$H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.60-1.78(1H, m), 1.82-1.96(1H, m), 2.00-2.07(1H, m), 2.84(1H, dd, $J_{bic}$=5.54Hz, $J_{gem}$=13.26Hz), 3.06(1H, dd, $J_{vic}$=8.96Hz, $J_{gem}$=13.26Hz), 3.66(1H, dd, $J_{vic}$=8.85Hz, $J_{gem}$=13.81Hz), 3.78-3.92(1H, m), 3.79(6H, s), 3.95(1H, 1/2ABq, J=14.48Hz), 4.15(1H, 1/2ABq, J=14.58Hz), 4.31(1H, d, J=2.42Hz), 4.88(1H, 1/2ABq, J=14.58Hz), 4.88(1H, 1/2ABq, J=14.48Hz), 5.16(1H, s), 6.79(2H, d, J=8.64Hz), 6.84(2H, d, J=8.57Hz), 7.15(2H, d, J=8.57Hz), 7.17(2H, d, J=8.64Hz), 7.28-7.45(3H, m), 7.51-7.58(2H, m).

IR(NaCl, neat): 1675, 1515, 1460, 1250, 1070, 1030 $cm^{-1}$.

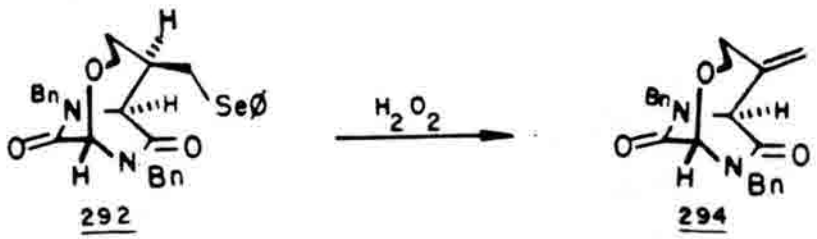
Mass spectrum, m/e: 580($M^+$, 15.2), 423(6.7), 314(8.2), 234(6.8), 210(10.3), 157(20.0), 121(100).

Compound 293

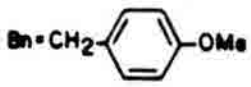
$^1$H NMR ($CDCl_3$) δ TMS: 1.20-1.40(2H, m), 2.20-2.38(1H, m), 2.72(2H, t, J=7.80Hz), 3.51(1H, dd, $J_{vic}$=10.31Hz, $J_{gem}$=12.59Hz), 3.75(1H, s), 3.78-3.88(1H, m), 3.79(3H, s), 3.80(3H, s), 4.19(1H, 1/2ABq, J=14.61Hz), 4.29(1H, 1/2ABq, J=14.86Hz), 4.74(1H, 1/2ABq, J=14.86Hz), 4.74(1H, 1/2ABq, J=14.61Hz), 5.02(1H, s), 6.83(2H, d, J=8.64Hz), 6.83(2H, d, J=8.68Hz), 7.05(2H, d, J=8.68Hz), 7.10(2H, d, J=8.64Hz), 7.26-7.30(3H, m), 7.45-7.49(2H, m).

IR(NaCl, neat): 1691, 1612, 1515, 1247, 1030 $cm^{-1}$.

Mass spectrum, m/e: 580($M^+$, 5.2), 459(3.5), 423(2.4), 121(100).




292 294




8,10-Di-*para*-methoxybenzyl-8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]-decane-7,9-dione (294)

To a stirred solution of the selenide 292 (2.10 mg, 0.405 mmol, 1.0 equiv) in THF (4.2 mL) was added 30% hydrogen peroxide (0.124 mL, 0.405 mmol, 10 equiv). The solution was refluxed for 20 min, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The organic extracts were combined, dried over anhydrous $Na_2SO_4$, concentrated, and separated by PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 162 mg (95.5%) of the desired olefin 294, mp 112-113°C (recryst. $Et_2O$/hexanes).

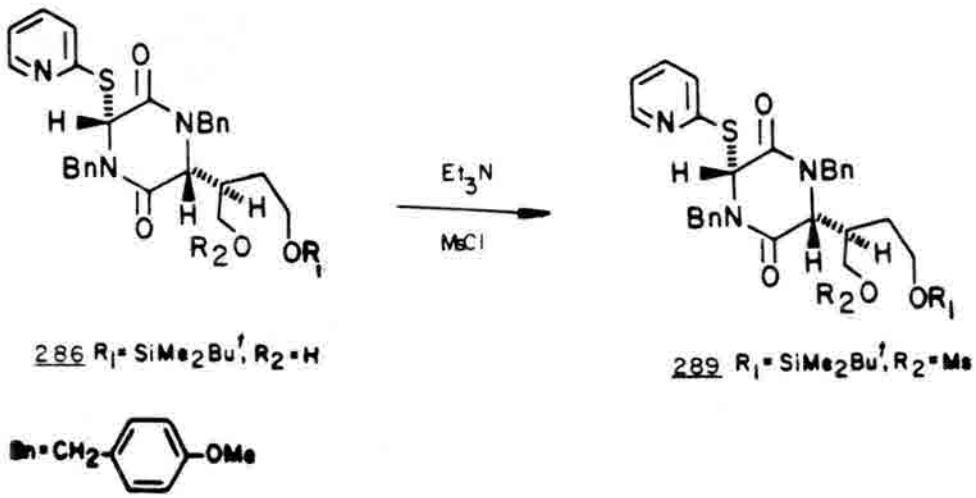
$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ TMS: 2.27(1H, dd, $J_{gem}$=16.29Hz, $J_{vic}$=6.82Hz), 2.40(1H, dd, $J_{gem}$=16.29Hz, $J_{vic}$=8.97Hz), 3.30(1H, dd, $J_{gem}$=13.22Hz, $J_{vic}$=8.97Hz), 3.78-3.82(1H, m), 3.79(6H, s), 3.87(1H, 1/2ABq, J=14.41Hz), 4.39(1H, s), 4.16(1H, 1/2ABq, J=14.42Hz), 4.88(1H, 1/2ABq, J=14.42Hz), 4.97(1H, 1/2ABq, J=14.41Hz), 5.07(1H, s), 5.16(1H, s), 5.24(1H, s), 6.85(4H, d, J=8.08Hz), 7.15(2H, d, J=8.08Hz), 7.22(2H, d, J=8.08Hz).

IR(NaCl, neat): 1682, 1615, 1518, 1250, 1031 $cm^{-1}$.

Mass spectrum, m/e: 422($M^+$, 3.6), 301(2.7), 149(4.1), 121(100).

Analysis (recrystallized from $Et_2O$/hexanes):

| | | | |
|---|---|---|---|
| Calcd for $C_{24}H_{26}N_2O_5$: | C=68.23%; | H=6.20%; | N=6.63 |
| Found | 68.26 | 6.30 | 6.65 |




286 $R_1$ = $SiMe_2Bu^t$, $R_2$ = H

289 $R_1$ = $SiMe_2Bu^t$, $R_2$ = Ms



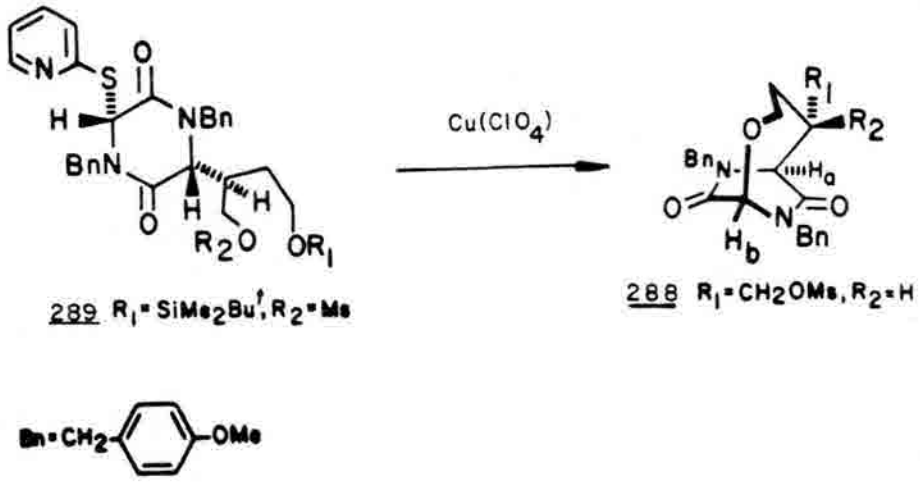

1,4-Di-para-methoxybenzyl-3-(2'-thiopyridyl)-6-[[1"-(methanesulfonyl)-methyl]-3"-[(tert-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (289)

To a stirred solution of 286 (154 mg, 0.231 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added $Et_3N$ (0.035 mL, 0.254 mmol, 1.1 equiv) followed by mesyl chloride (0.019 mL, 0.254 mmol, 1.1 equiv). The mixture was stirred at room temperature. for 35 min, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 117 mg (68%, 75% based on recovered starting material) of 289 as an oil.

$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.056(3H, s), 0.06(3H, s), 0.885(9H, s), 1.78-1.91(1H, m), 1.93-2.04(1H, m), 2.63-2.78(1H, m), 2.97(3H, s), 3.73(3H, s), 3.73(3H, s), 3.73-3.93(4H, m), 4.02-4.12(2H, m), 4.39(1H, d, J=2.90Hz), 5.05(1H, 1/2ABq, J=14.44Hz), 5.32(1H, 1/2ABq, J=14.72Hz), 6.74(1H, s), 6.74(2H, d, J=8.62Hz), 6.77(2H, d, J=8.62Hz), 7.05(2H, d, J=8.62Hz), 7.08(2H, d, J=8.62Hz), 7.08-7.20(2H, m), 7.50(1H, dd, J=1.5Hz, J=7.79Hz), 8.56(1H, bd, J=4.0Hz).

IR(NaCl, neat): 1680, 1510, 1250, 1170 $cm^{-1}$.

Mass spectrum, m/e: 566(0.1), 471(0.5), 187(100), 121(88).







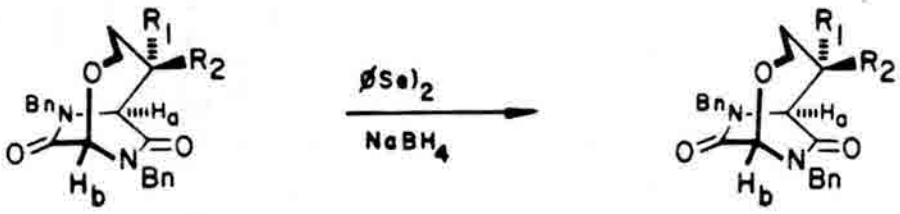
8,10-Di-para-methoxybenzyl-8,10-diaza-5-[(methanesulfonyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (288)

To a stirred solution of 289 (16 mg, 0.23 mmol, 1.0 equiv) in THF (1 mL) at room temperature was added solid $Cu(ClO_4)_2$ (6.0 mg, 0.023 mmol, 1.0 equiv) and the mixture was stirred at room temperature. After 16 h, the mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 9.8 mg (83%) of 288 as an oil.

$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 1.78-1.94(2H, m), 1.48-1.62(1H, m), 3.07(3H, m), 3.31(1H, dd, $J_{vic}$=6.93Hz, $J_{gem}$=12.39Hz), 3.80-4.01(3H, m), 3.81(3H, s), 3.82(4H, s), 4.12(1H, 1/2ABq, J=14.30Hz), 4.19(1H, bs), 4.97(1H, 1/2ABq, J=14.48Hz), 5.16(1H, 1/2ABq, J=14.30Hz), 5.23(1H, s), 6.86(4H, d, J=8.58Hz), 7.16(2H, d, J=8.58Hz), 7.20(2H, 1/2ABq, J=8.58Hz).

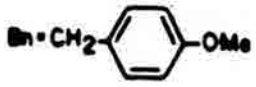
IR(NaCl, neat): 1670, 1608, 1512, 1240 $cm^{-1}$.

Mass spectrum, m/e: 518($M^+$, 7.8), 422(5.9), 397(9.4), 301(7.9), 136(20.5), 121(100).




288 $R_1$ = $CH_2OMs$, $R_2$ = H

292a $R_1$ = $CH_2SeØ$ $R_2$ = H



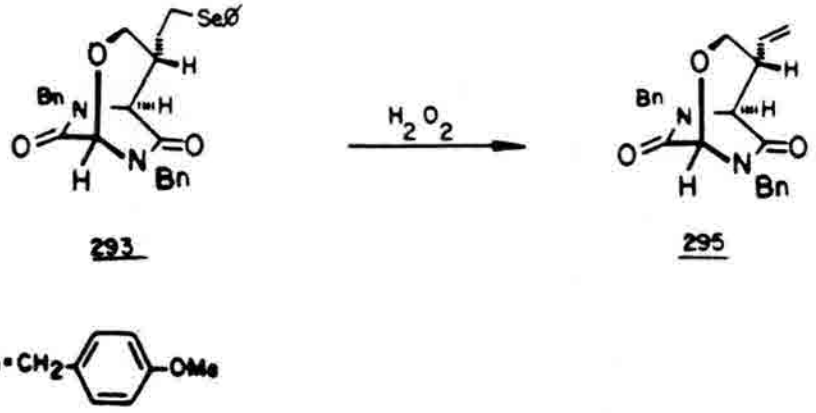

8,10-Di-*para*-methoxybenzyl-8,10-diaza-5-[(phenylselenyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (292a)

To a stirred solution of 288 (80 mg, 0.154 mmol, 1.0 equiv) in THF (2.5 mL) at room temperature was added a solution of $PhSeNaBH_3$ (0.169 mmol, 1.1 equiv) in EtOH (1.5 mL) and the mixture was heated to reflux. After 20 min, the mixture was cooled, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 82 mg (99%) of 292a as an oil.

$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 2.48-2.69(1H, m), 2.85-3.04(1H, m), 3.18-3.35(1H, m), 2.00(1H, d, $J_{vic}$=8.58Hz, $J_{gem}$=12.59Hz), 2.79(1H, dd, $J_{vic}$=7.16Hz, $J_{gem}$=12.59Hz), 3.24(1H, dd, $J_{vic}$=9.39Hz, $J_{gem}$=13.66Hz), 3.78(6H, s), 3.84(1H, dd, $J_{vic}$=7.31Hz, $J_{gem}$=13.66Hz), 4.01(1H, 1/2ABq, J=14.46Hz), 4.03(1H, 1/2ABq, J=14.73Hz), 4.54(1H, s), 4.94(1H, 1/2ABq, J=14.46Hz), 5.05(1H, 1/2ABq, J-14.73Hz), 5.17(1H, s), 6.83(2H, d, J=8.05Hz), 6.84(2H, d, J=8.05Hz), 7.12(2H, d, J=8.05Hz), 7.15(2H, d, J=8.05Hz), 7.27-7.29(3H, m), 7.50-7.53(2H, m).

IR(NaCl, neat): 1725, 1670, 1608, 1512, 1240 $cm^{-1}$.

Mass spectrum, m/e: 518($M^+$, 1.8), 422(4.8), 397(1.4), 382(2.1), 301(3.7), 121(100).




293 295




7,9-Di-para-methoxybenzyl-7,9-diaza-4-(vinyl)-2-oxabicyclo[3.2.2]-nonane-6,8-dione (295)

To a stirred solution of 293 (80 mg, 0.138 mmol, 1.0 equiv) in THF (4 mL) at room temperature was added 30% $H_2O_2$ (0.02 ml, 0.691 mmol, 5.0 equiv) and the mixture was heated to reflux. AFter 20 min, the mixture was cooled to room temperature, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$, the combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel to afford 47 mg (81%) of 295 as a solid, mp 115-116°C (recryst. $CH_2Cl_2$).

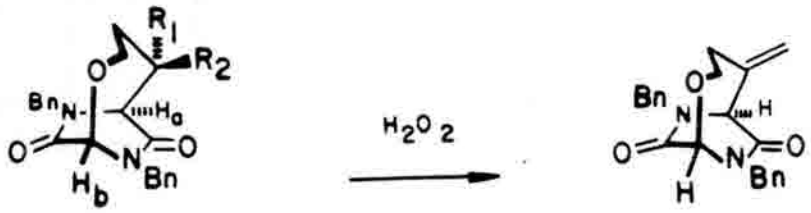
$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ TMS: 2.85(1H, dd, $J_{vic}$=7.52Hz, $J_{vic}$=7.12Hc, $J_{vic}$=7.12Hz), 3.69-3.89(2H, m), 3.79(6H, s), 3.88(1H, s), 4.10(1H, 1/2ABq, J=14.64Hz), 4.29(1H, 1/2ABq, J=14.74Hz), 4.77(1H, 1/2ABq, J=14.64Hz), 4.96(1H, 1/2ABq, J=14.74Hz), 5.07(1H, s), 5.11(1H, d, $J_{cis}$=9.55Hz), 5.15(1H, d, $J_{trans}$=17.05Hz), 5.23(1H, ddd, $J_{cis}$=9.55Hz, $J_{trans}$=17.05Hz, $J_{vic}$=7.52Hz), 6.85(4H, d, J=8.47Hz), 7.12(4H, d, J=8.47Hz).

IR(NaCl, neat): 1690, 1612, 1513, 1240, 1030 $cm^{-1}$.

Mass spectrum, m/e: 422($M^+$, 7.1), 301(11.2), 217(2.5), 121(100).

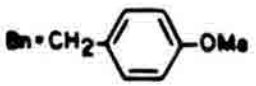
Analysis (recrystallized from $CH_2Cl_2$):

| | | | |
|---|---|---|---|
| Calcd for $C_{24}H_{26}N_2O_5$: | C=68.23; | H=6.20; | N=6.63 |
| Found | 68.14 | 6.29 | 6.40 |



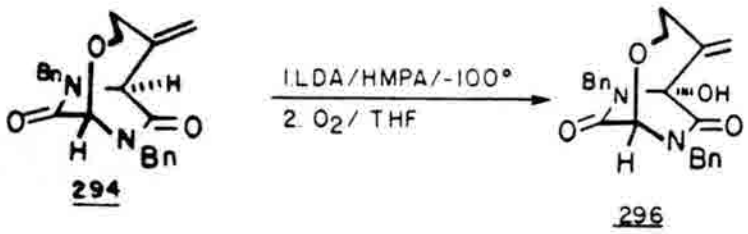

292a $R_1$ = $CH_2SeØ$ $R_2$ = H

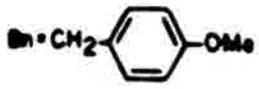
294




8,10-Di-para-methoxybenzyl-8,10-diaza-5-(methylene)-2-oxabicyclo-[4.2.2]decane-7,9-dione (294)

To a stirred solution of 292a (80 mg, 0.154 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added 30% $H_2O_2$ (0.047 mL, 1.54 mmol, 10.0 equiv) and the mixture was heated to reflux. After 15 min, the mixture was cooled, diluted with $CH_2Cl_2$, poured into $H_2O$, exhaustively extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by silica gel flash column (eluted with 1:1 EtOAc/hexanes) to afford 54 mg (83%) of 294 as a crystalline solid identical to that obtained from 292.




8,10-Di-*para*-methoxybenzyl-8,10-diaza-5-methylene-6-hydroxy-2-oxa-bicyclo[4.2.2]decane-7,9-dione (296)

To a stirred solution of 294 (80 mg, 0.213 mmol, 1.0 equiv) at -78°C in THF (1 mL) was added HMPA (0.07 mL, 0.42 mmol, 2.0 equiv) hexamethylphosphorous triamide (0.077 mL, 0.42 mmol, 2.0 equiv) followed by n-BuLi (0.33 ml, 0.32 mmol, 1.5 equiv). The dark brown anion was stirred for 7 min and $O_2$ was bubbled through the solution for 10 min at -78°C, warmed to 0°C over 3 min, and quenched with $H_2O$ (50 mL). The mixture was diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 41 mg (49% yield, 52% by conversion) of the alcohol 296, mp 199-199.5°C (recryst. THF/ether).

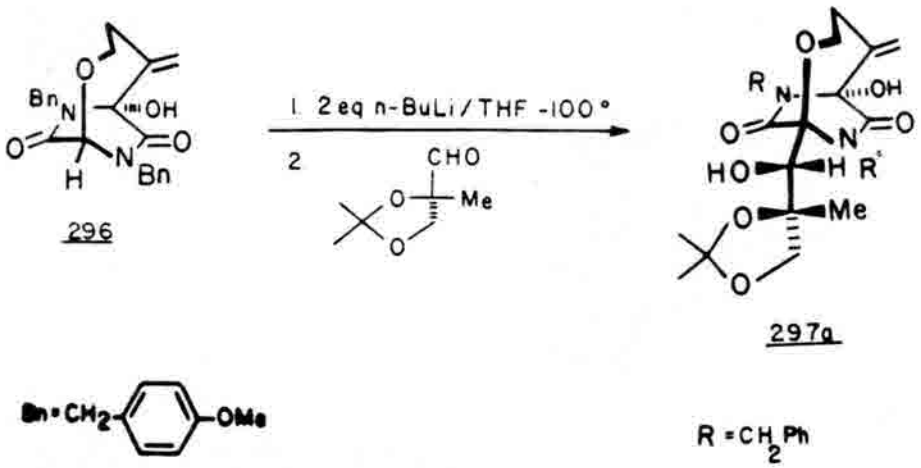
$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ TMS: 2.27(1H, dd, $J_{vic}$=9.21Hz, $J_{gem}$=16.63Hz), 2.41(1H, dd, $J_{vic}$=7.03Hz, $J_{gem}$=16.63Hz), 3.31(1H, dd, $J_{vic}$=9.21Hz, $J_{gem}$=13.62Hz), 3.80(3H, s), 3.80-3.85(1H, m), 3.81(3H, s), 3.88(1H, 1/2ABq, J=14.45Hz0, 4.16(1H, 1/2ABq, J=14.37Hz), 4.39(1H, s, $D_2O$ exch), 4.89(1H, 1/2ABq, J=14.37Hz), 4.97(1H, 1/2ABq, J=14.45Hz), 5.07(1H, bs), 5.16(1H, bs), 5.23(1H, s), 6.85(2H, d, J=8.53Hz), 6.86(2H, d, J=8.53Hz), 7.15(2H, d, J=8.53Hz), 7.22(2H, d, J=8.53Hz).

IR(NaCl, neat): 3500-3100, 1673, 1610, 1513, 1246, 1083 $cm^{-1}$.

Mass spectrum, m/e: 438($M^+$, 0.9), 421(0.5), 317(1.2), 301(0.6), 177(5.0), 149(2.0), 121(100).

Exact Mass: Calcd for $C_{24}H_{26}N_2O_6$: 438.17918

Found 438.1793




N,N'-Di-para-methoxybenzyl-(2',3'-O-isopropylidene)bicyclomycin (297a)

To a THF (2 mL) solution of 296 (13 mg, 0.029 mmol, 1.0 equiv) at -98°C was added n-butyllithium (0.31 mL, 0.68 mmol, 2.3 equiv). The slightly yellow anion was stirred for 3 min, and quenched with (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.021 mL, 0.148 mmol, 5.0 equiv). The mixture was stirred for 10 min at -98°C, warmed to -50°C, quenched with 50% $H_2O$/MeOH (0.2 mL), evaporated to dryness and separated on PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 6 mg of the desired diol 297a (42% yield, 95% by conversion) plus 9 mg of the starting material 296.

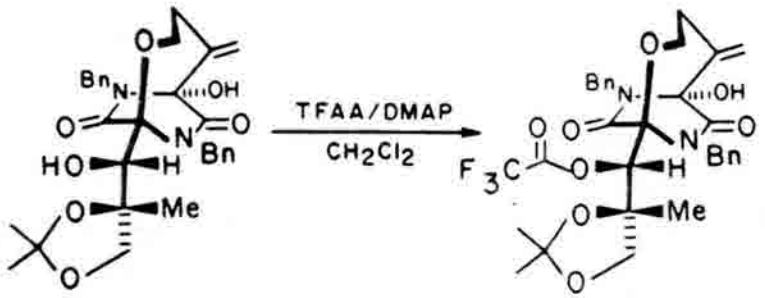
$^1$H NMR (360 MHz) ($CDCl_3$) δ TMS: 0.841(3H, s), 1.36(3H, s), 1.37(3H, s), 2.00-2.10(1H, m), 2.80-2.89(1H, m), 3.55-3.62(1H, m), 3.78-3.85(1H, m), 3.78(6H, s), 3.82(1H, 1/2ABq, J=9.26Hz), 4.11(1H, 1/2ABq, J=9.26Hz), 4.31(1H, 1/2ABq, J=13.52Hz), 4.53(1H, 1/2ABq, J=13.52Hz), 4.61(1H, d, J=9.86Hz), 4.64(1H, 1/2ABq, J=15.26Hz), 4.99(1H, s), 5.08(1H, 1/2ABq, J=15.26Hz), 5.15(1H, s), 5.56(1H, s), 6.59(1H, d, J=9.86Hz, $D_2O$ exch), 6.79(4H, d, J=8.47Hz), 7.39(2H, d, J=8.47Hz), 7.44(2H, d, J=8.47Hz).

IR(NaCl, neat): 3600-3150, 1670, 1660, 1612, 1515, 1245 $cm^{-1}$.

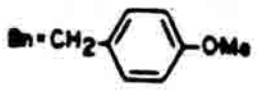
Mass spectrum, m/e: 582($M^+$, 0.8), 468(0.4), 451(0.4), 408(2.0), 241(1.0), 149(3.3), 121(100).

Exact mass: Calcd for $C_{31}H_{38}N_2O_9$: 582.25784

Found 582.257100




297a 318




N,N'-Di-para-methoxybenzyl-[1'-O-(trifluoroacetyl)]-(2',3'-O-isopropylidene)bicyclomycin (318)

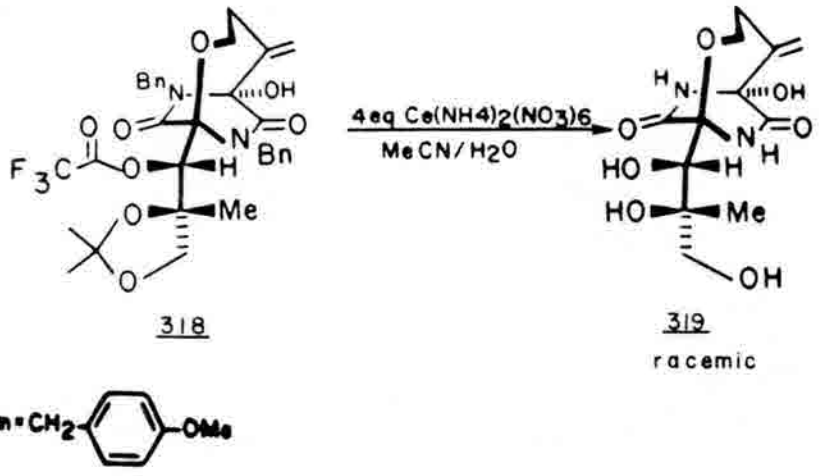
To a stirred solution of 297a (9 mg, 0.154 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) at room temperature was added solid N,N-dimethyl-amino pyridine (20 mg, 0.169 mmol, 11.0 equiv) followed by trifluoroacetic anhydride (0.02 mL, 0.15 mmol, 10.0 equiv) and the mixture was stirred at room temperature. After 25 min, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 10 mg (95%) of 318 as an oil.

$^1$H NMR (270 MHz) ($CDCl_3$) $\delta$ TMS: 0.41(3H, s), 1.12(3H, s), 1.15(3H, s), 2.30(1H, dd, $J_{vic}$=8.87Hz, $J_{gem}$=16.60Hz), 2.40(1H, dd, $J_{vic}$=7.30Hz, $J_{gem}$=16.60Hz), 3.05(1H, d, J=9.56Hz), 3.24(1H, dd, $J_{vic}$=8.87, $J_{gem}$=13.64Hz), 3.76(3H, s), 3.78(3H, s), 3.86(1H, dd, $J_{vic}$=7.30Hz, $J_{gem}$=13.64Hz), 4.22(1H, d, J=9.56Hz), 4.22(1H, 1/2ABq, J=13.81Hz), 4.55(1H, 1/2ABq, J=13.61Hz), 4.55(1H, 1/2ABq, J=13.81Hz), 4.94(1H, s), 4.95(1H, 1/2ABq, J=13.61Hz), 5.19(1H, s), 5.67(1H, bs), 6.09(1H, s, $D_2O$ exch), 6.78(2H, d, J=7.60Hz), 6.83(2H, d, J=7.92Hz), 7.86(2H, d, J=7.60Hz), 8.184(2H, d, J=7.92Hz).

IR(NaCl, neat): 3600-3200, 1790, 1680, 1665, 1660, 1510, 1250 $cm^{-1}$.

Exact mass: Calcd for $C_{33}H_{37}F_3N_2O_{10}$: 678.24011

Found 678.24290



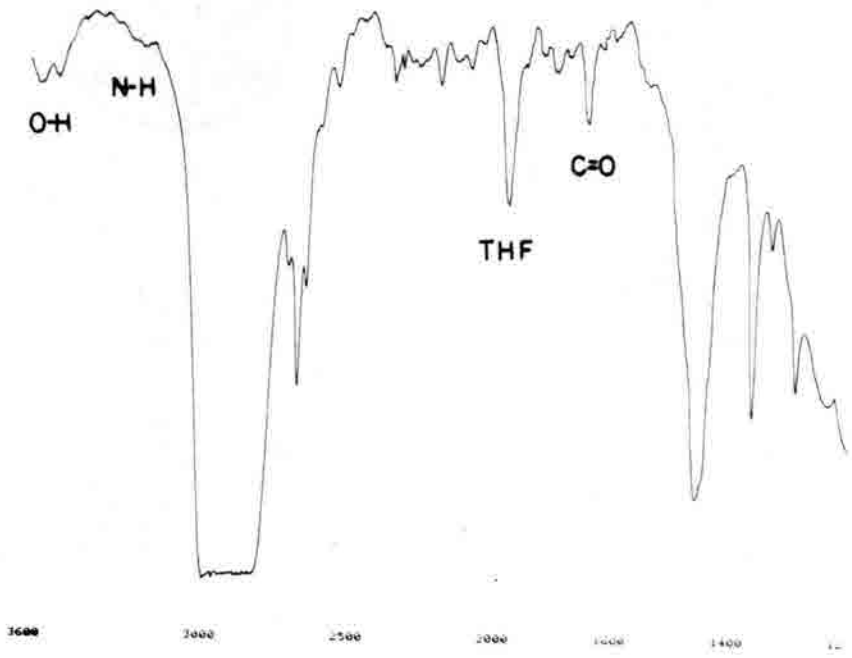

318

319
racemic



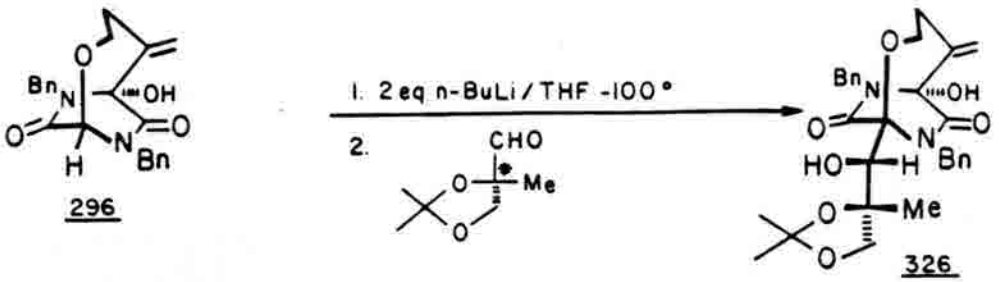
(+)-Bicyclomycin (319)

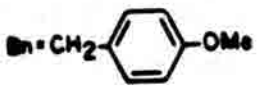
To a stirred solution of 318 (18 mg, 0.026 mmol, 1.0 equiv) in acetonitile/$H_2O$ (0.2 M) was added solid ceric ammonium nitrate (58.2 mg, 0.106 mmol, 4.0 equiv) and the mixture was stirred at room temperature. After 40 min, the mixture was diluted with MeOH and separated by PTLC silica gel (eluted with 1:1 MeOH/THF) to afford 2.6 mg (32%, 35% based on recovered starting material) of racemic bicyclomycin 319.




SOLUTION (THF) IR OF SYNTHETIC BICYCLOMYCIN

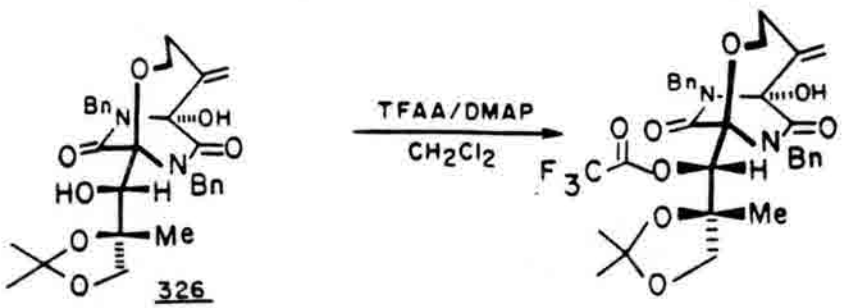
**Optically Active Series:**

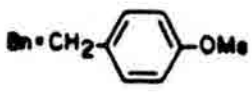



(+)-N,N'-Di-para-methoxybenzyl-(2',3'-O-isopropylidene)bicyclomycin (326)

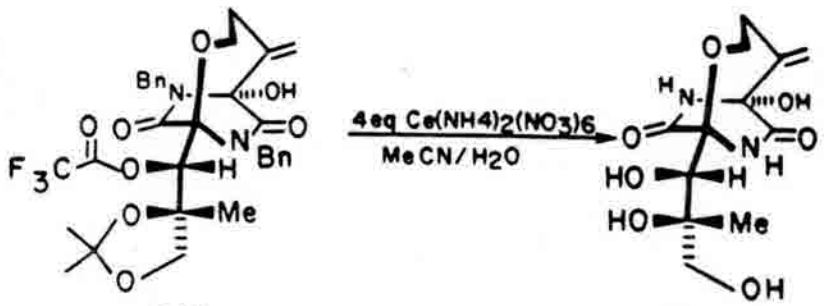
To a stirred solution of 296 (40 mg, 0.091 mmol, 1.0 equiv) in THF (1 mL) at -100°C was added n-BuLi (0.095 mL, 0.228 mmol, 2.5 equiv), the yellow enolate was stirred for 10 min, then optically active aldehyde 18 (0.008 ml, 0.059 mmol, 0.65 equiv) and the mixture was stirred at -100°C. After 20 min, the mixture was warmed to -50°C, methanol (10 equiv) was added, and the mixture was warmed to room temperature, diluted wtih $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:2 EtOAc/hexanes) to afford 5 mg [9%, 49% based on recovered starting material, $[\alpha]_D^{25}$ = -4.60 (c=2.5, $CH_2Cl_2$)] of 326 as an oil, $[\alpha]_D^{25}$ = +74.80 (c=5, $CH_2Cl_2$). 326 was identical to racemic diol 297a by NMR, IR, and TLC.



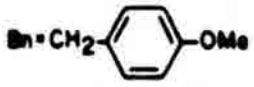




(+)-N,N'-Di-para-methoxybenzyl-[1'-O-(trifluoroacetyl)]-(2',3'-O-isopropylidene)bicyclomycin (327)

To a stirred solution of 326 (6 mg, 0.01 mmol, 1.0 equiv) in $CH_2Cl_2$ (1 mL) at room temperature was added DMAP (14.4 mg, 0.11 mmol, 11.0 equiv) followed by trifluoroacetic anhydride (0.014 mL, 0.1 mmol, 10.0 equiv) and the mixture was stirred at room temperature. After 20 min, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 1:2 EtOAc/hexanes) to afford 7 mg (99%) of 327 as an oil, $[\ ]_D^{24}$ = +41.18 (c=6, $CH_2Cl_2$). Compound 327 was found to be identical by NMR and TLC with 318 (the racemic material).

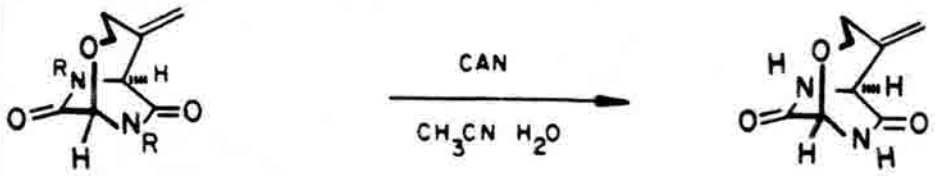



327 328



(+)-Bicyclomycin (Synthetic) (328)

To a stirred solution of (+)-327 (7 mg, 0.01 mmol, 1.0 equiv) in $CH_3CN$ (0.3 mL) and $H_2O$ (0.1 mL) at room temperature was added CAN (33.9 mg, 0.06 mmol, 6.0 equiv), the mixture was stirred 42 min, diluted with MeOH, and separated by PTLC silica gel (eluted with 1:5 MeOH/$CHCl_3$) to afford 1 mg (32.07%) of 1 as a white powder, $[\alpha]_D^{24} = +49.0^{\circ}$ (c-0.1, $CH_3OH$), 78% enantiomeric excess. The synthetic material was identical by NMR and TLC with an authentic sample of naturally occurring bicyclomycin.




294 304

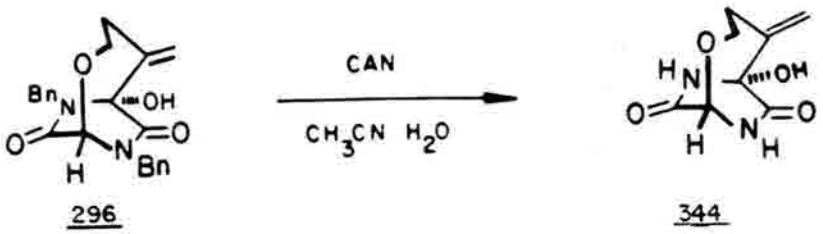
R=$CH_2$pPh OMe

8,10-Diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione (304)

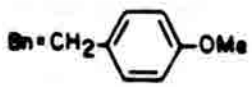
To a stirred solution of 294 (14 mg, 0.03 mmol, 1.0 equiv) in MeCN (0.1 mL) was added CAN (72.75 mg, 0.133 mmol, 4.0 equiv). The mixture was stirred for 1.2 hr, diluted with MeOH (1 mL) and separated by PTLC silica gel (eluted with 20% MeOH in $CHCl_3$) to afford 5.5 mg (91%) of the fully deprotected bicyclic piperazinedione 304 plus 1 mg (ca 8%) of a mixture of mono-N-p-methoxybenzylpiperazinediones.

$^1H$ NMR (270 MHz) (DMSO-$d_6$) $\delta$ DMSO: 2.35-2.60(2H, m), 3.78(1H, dd, J=1.46Hz, J=6.84Hz), 3.83(1H, dd, J=1.46Hz, J=6.84Hz), 4.26(1H, s), 4.87(1H, s), 5.00(1H, s), 5.06(1H, s), 8.68(1H, $D_2O$ exch), 9.02(1H, $D_2O$ exch).

IR(NaCl, neat): 3300-3200, 1680, 1620, 1250 $cm^{-1}$.




296 344

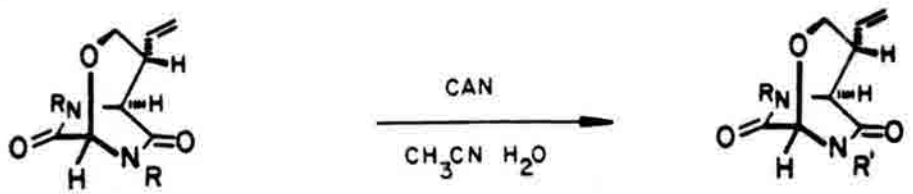



8,10-Diaza-5-methylene-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (344)

To a solution of 296 (14.6 mg, 0.03 mmol, 1.0 equiv) in $CH_3CN/H_2O$ (80 1:30 mL) was added solid cerric ammonium nitrate (100 mg, 0.10 mmol, 5.5 equiv) and the reaction was stirred at room temperture. After 1.2 hr, the mixture was diluted with $CH_3OH$ and separated by PTLC silica gel (eluted with 1:5 $MeOH/CHCl_3$) to afford mg (61%) of 344 as well as a small amount of the mixture of monodeprotected compounds.

$^1H$ NMR (270 MHz) (DMSO-$d_6$) $\delta$ DMSO: 2.50-2.70(2H, m), 3.56(1H, dd, $J_{gem}$=9.10Hz, $J_{vic}$=2.5Hz), 3.78(1H, dd, $J_{vic}$=2.5Hz, $J_{gem}$=11.1Hz), 4.89(1H, s), 5.06(1H, s), 5.39(1H, s), 6.95(1H, s, $D_2O$ exch), 8.89(1H, bs, $D_2O$ exch), 9.14(1H, bs, $D_2O$ exch).

IR(NaCl, neat): 3600-3200, 1690, 1620, 1250 $cm^{-1}$.




295 R=$CH_2$pPh OMe

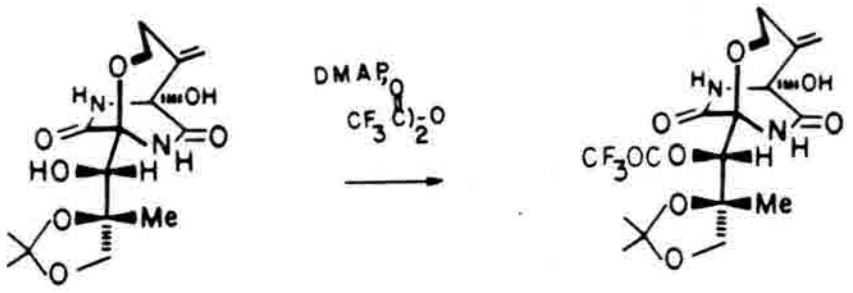
303 R=H R'=H

7,9-Diaza-4-(vinyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (303)

To a stirred solution of 295 (28 mg, 0.066 mmol, 1.0 equiv) in $CH_3CN/H_2O$ (80 1:30 mL) was added ceric ammonium nitrate (163 mg, 0.298 mmol, 4.5 equiv) and the mixture was stirred at room temperature. AFter 40 min, the mixture was dissolved in MeOH and separated by PTLC silica gel (eluted with 10% MeOH in $CH_2Cl_2$) to afford 7.5 mg (62.4%) of 303 and 1.2 mg (9.9%) of the mixture of monodeprotected compounds .

$^1H$ NMR (270 MHz) ($CDCl_3/CD_3OD$) $\delta$ TMS: 2.75(1H, m), 3.54(1H, s), 3.60(1H, dd, $J_{vic}$=9.76Hz, $J_{gem}$=12.76Hz), 3.85(1H, dd, $J_{vic}$=5.44Hz, $J_{gem}$=12.76Hz), 4.70(1H, s), 5.13(1H, dd, $J_{cis}$=10.43Hz, $J_{gem}$=1.13Hz), 5.20(1H, dd, $J_{trans}$=17.51Hz, $J_{gem}$=1.13Hz), 5.65(1H, ddd, $J_{cis}$=10.43Hz, $J_{trans}$=17.51Hz, $J_{gem}$=7.23Hz). No amide hydrogens due to small amount of $CD_3OD$ as NMR cosolvent

IR(NaCl, neat): 3250, 1690, 1615, 1518, 1245, 1050 $cm^{-1}$.



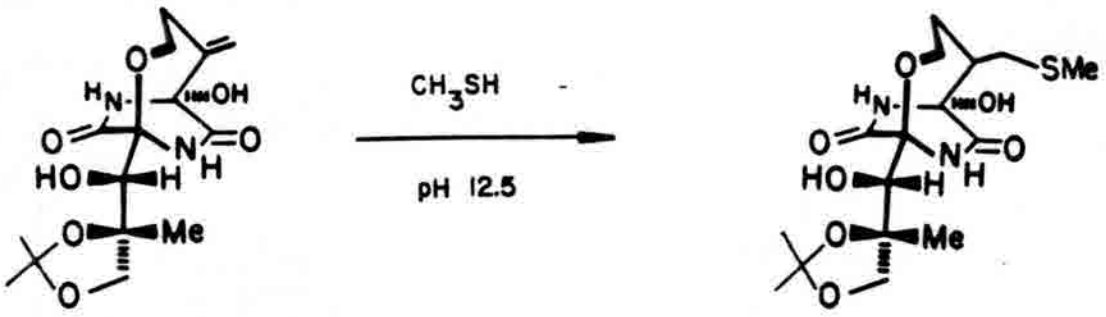

305 316

(+)-1'-O-(Trifluoroacetyl)-(2',3'-O-isopropylidene)-bicyclomycin (316)

To a stirred solution of 305 (36 mg, 0.105 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) at room temperature was added DMAP (29.4 mg, 0.231 mmol, 2.2 equiv) followed by trifluoroacetic anhydride (0.03 mL, 0.21 mmol, 2.0 equiv) and the mixture was stirred at room temperature. AFter 25 min, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 17 mg (37%) of 316 as a white solid, mp 188-190°C (recryst. EtOAc/hexanes).

$^1H$ NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.30(3H, s), 1.45(3H, s), 1.49(3H, s), 2.61-2.63(2H, m), 3.84(1H, 1/2ABq, J=8.52Hz), 3.89(1H, m), 4.03(1H, dd, $J_{gem}$=5.80Hz, $J_{vic}$=13.50Hz), 4.53(1H, 1/2ABq, J=8.52Hz), 4.71(1H, s, $D_2O$ exch), 5.19(1H, s), 5.63(1H, s), 5.79(1H, s), 6.50(1H, s, $D_2O$ exch), 8.72(1H, s, $D_2O$ exch).

IR(NaCl, neat): 3600-3200, 1730, 1080 $cm^{-1}$.



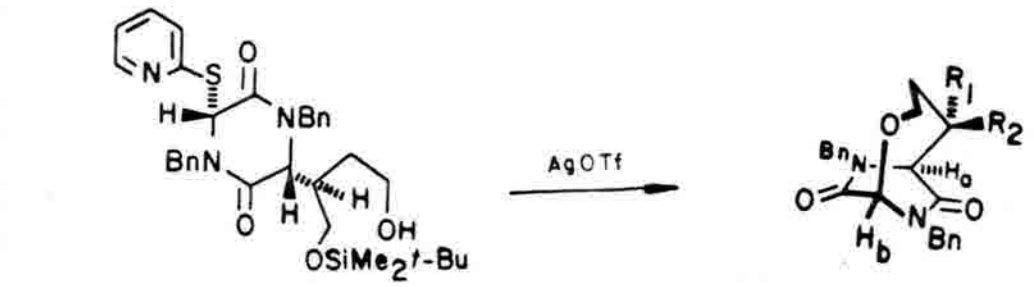

305 347

Thiolate Addition to Bicyclomycin acetonide 305 (347)

To a stirred solution of 305 (8 mg, 0.023 mmol, 1.0 equiv) in THF (0.1 mL) at room temeprature was added MeSNa (0.1 ml, 0.0208 mmol, 0.88 equiv, pH 12.5 ca. 0.208 M) and the mixture was stirred for 30 min, diluted with $CH_3OH$, anhydrous sodium sulfate was added, the solution was filtered, concentrated, and separated by PTLC silica gel (eluted with 10% MeOH/$CH_2Cl_2$) to afford 7 mg (76%) of 347 as a glass.

$^1H$ NMR (270 MHz) ($CD_3OD$) $\delta$ TMS: 1.38(3H, s), 1.40(3H, s), 1.50(3H, s), 2.10(3H, s), 2.10-2.40(5H, m), 3.39(1H, s), 3.79(1H, d, J=9.20Hz), 3.90-4.20(3H, m).

IR(NaCl, neat): 3600-3200, 1640 $cm^{-1}$.

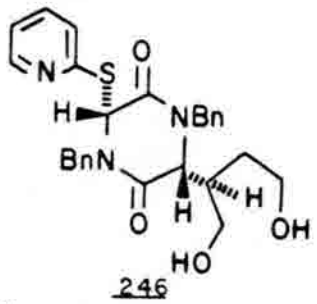



355

357 $R_1 = CH_2OH$, $R_2 = H$

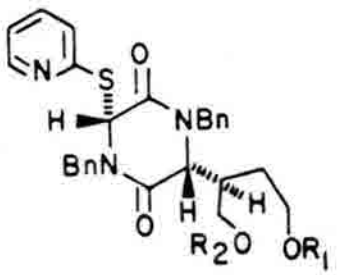
8,10-Dibenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]-decane-7,9-dione (357)

To a stirred solution of 355 (82 mg, 0.135 mmol, 1.0 equiv) in $CHCl_3$ (1.5 mL) at room temperature was added solid AgOTf (34.8 mg, 0.135 mmol, 1.0 equiv) and the mixture was stirred at room temperature. After 35 min, the mixture was diluted with THF (1 mL) and solid tetra-n-butyl ammonium fluoride (102 mg, 0.337 mmol, 5.0 equiv) was added. The mixture was stirred for 10 min, diluted with $CH_2Cl_2$, poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous $Na_2SO_4$, filtered, concentrated, and poured through a silica plug to afford 41.2 mg (80%) of 357 as an oil. This was carried on to the next step without further purification. The structure of the alcohol was established by conversion to the selenide via the mesylate. The selenide was then oxidized to give the exomethylene 263 which was identical to that obtained from the major diastereomeric lactone.



246

Bn = $CH_2Ph$



351 $R_1$ = $SiPh_2Bu^t$ $R_2$ = H

355 $R_1$ = H $R_2$ = $SiPh_2Bu^t$

357 $R_1$ = $R_2$ = $SiPh_2Bu^t$

1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1"-[(tert-butyldimethylsilyl)oxymethyl]-3"-hydroxypropyl]-2,5-piperazinedione 355; 1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1"-hydroxymethyl-3"-[(tert-butyldimethylsilyl)oxypropyl]]-2,5-piperazinedione 351; and 1,4-Dibenzyl-3-(2'-thiopyridyl)-6-[1"-[(tert-butyldimethylsilyl)oxymethyl]-3"-[(tert-butyldimethylsilyl)oxypropyl]-2,5-piperazinedione 357

To a stirred solution of 246 (564 mg, 1.15 mmol, 1.0 equiv) in $CH_2Cl_2$ (1 mL) at room temperature was added solid DMAP (2 mg), triethylamine (0.162 mL, 1.15 mmol, 1.0 equiv) and tert-butyldimethylsilyl-chloride (174.6 mg, 1.15 mmol, 1.0 equiv) and the mixture was stirred at room temperature. After 24 h, the mixture was poured into $H_2O$, and exhaustively extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous $Na_2SO_4$, filtered, and separated by radial chromatography on silica gel (eluted with 1:3 EtOAc/hexanes) to afford 87 mg (12.4%) of 355, 318 mg (46%) of 351, and 132 mg (19.1%) of 357 as oils.

Compound 355

$^{1}H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.11(6H, s), 0.91(9H, s), 1.8(2H, m), 2.35(1H, m), 3.60-3.75(5H, m), 4.05(1H, 1/2ABq, J=15.14Hz), 4.12(1H, 1/2ABq, J=14.75Hz), 4.15(1H, d, 2Hz), 5.19(1H, 1/2ABq, J=14.75Hz), 5.35(1H, 1/2ABq, J=15.14Hz), 6.65(1H, s), 7.20(11H, m), 7.35(2H, m), 8.40(1H, m).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 5.15(q), 18.3(s), 26.03(q), 31.22(t), 42.55(d), 46.87(t), 49.73(t), 60.50(t), 61.62(t), 120.96(d), 122.77(d), 127.79(d), 128.32(d), 128.67(d), 129.02(d), 135.56(s), 135.91(s), 136.31(s), 149.22(d), 155.23(s), 164.46(s), 166.68(s).

IR(NaCl, neat): 3600-3200, 1670, 1260 $cm^{-1}$.

Compound 351

$^{1}H$ NMR (100 MHz) ($CDCl_3$) $\delta$ $CHCl_3$: 0.14(6H, s), 0.97(9H, s), 1.80(2H, m), 2.30(1H, m), 3.01(1H, m), 3.65-3.75(4H, m), 4.10(2H, m), 4.17(1H, bs), 5.24(1H, 1/2ABq, J=14.65Hz), 5.43(1H, 1/2ABq, J=14.89Hz), 6.75(1H, s), 7.25(11H, m), 7.35(2H, m), 8.42(1H, d, J=4.64Hz).

$^{13}C$ NMR (25 MHz) ($CDCl_3$) δ $CHCl_3$: -5.382(q), 18.14(s), 25.85(q), 30.93(t), 42.20(d), 46.52(t), 49.62(t), 60.47(t), 60.94(t), 120.73(d), 122.19(d), 127.44(d), 128.09(d), 128.43(d), 135.27(s), 135.62(s), 136.44(d), 148.87(d), 154.87(s), 164.40(s), 167.15(s).

IR(NaCl, neat): 3600-3200, 1670, 1260 $cm^{-1}$.

Compound 357

$^{1}H$ NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$: 0.081(12H, s), 0.90(9H, s), 0.92(9H, s), 1.89(2H, m), 2.15(1H, m), 3.78-3.82(4H, m), 4.07(2H, m), 4.17(1H, d, J=7.20Hz), 5.18(1H, 1/2ABq, J=14.65Hz), 5.38(1H, 1/2ABq, J=14.89Hz), 6.63(1H, s), 7.20-7.30(12H, m), 7.35(1H, m), 8.43(1H, m).

IR(NaCl, neat): 1670, 1250 $cm^{-1}$.

# APPENDIX 2

## X-RAY ANALYSIS DATA FOR 237

Table 1. Atom Coordinates ($\times 10^4$) and Temperature Factors ($\mathring{A}^2 \times 10^3$)

| atom | x | y | z | U |
|---|---|---|---|---|
| S | 4770(1) | 9023(1) | 7511(1) | 47(1)* |
| C(1) | 4674(4) | 9643(2) | 6637(2) | 34(1)* |
| C(2) | 6258(4) | 10083(2) | 6637(2) | 35(1)* |
| C(3) | 4595(4) | 11077(2) | 7194(2) | 32(1)* |
| C(4) | 2997(4) | 10695(2) | 6943(2) | 33(1)* |
| C(5) | 4645(4) | 11214(2) | 8133(2) | 38(1)* |
| C(6) | 4137(6) | 10628(2) | 8720(2) | 52(1)* |
| C(7) | 3614(6) | 11025(2) | 9480(3) | 65(2)* |
| C(8) | 3519(5) | 11825(2) | 8416(2) | 49(1)* |
| C(9) | 4418(4) | 8192(2) | 7028(2) | 40(1)* |
| C(10) | 4332(6) | 6951(2) | 7176(3) | 71(2)* |
| C(11) | 3715(6) | 6910(2) | 6385(3) | 67(2)* |
| C(12) | 3526(6) | 7520(2) | 5945(3) | 66(2)* |
| N(3) | 3880(4) | 8169(2) | 6260(2) | 51(1)* |
| C(14) | 7601(4) | 11229(2) | 6783(2) | 36(1)* |
| C(15) | 7463(4) | 11634(2) | 5985(3) | 44(1)* |
| C(16) | 6972(6) | 12337(2) | 5995(4) | 68(2)* |
| C(17) | 6822(8) | 12713(3) | 5280(5) | 102(3)* |
| C(18) | 7167(9) | 12414(4) | 4546(4) | 114(3)* |
| C(19) | 7594(8) | 11713(4) | 4493(4) | 106(3)* |
| C(20) | 7767(6) | 11312(3) | 5231(3) | 69(2)* |
| C(21) | 1658(4) | 9681(2) | 6261(2) | 42(1)* |
| C(22) | 1587(4) | 9728(2) | 5325(3) | 45(1)* |
| C(23) | 1959(8) | 10348(3) | 4914(3) | 80(2)* |
| C(24) | 1743(9) | 10399(3) | 4060(3) | 99(2)* |
| C(25) | 1197(7) | 9841(4) | 3615(3) | 88(2)* |
| C(26) | 911(7) | 9210(4) | 4002(3) | 85(2)* |
| C(27) | 1111(5) | 9155(3) | 4856(3) | 66(2)* |
| N(1) | 3142(3) | 10045(1) | 6608(2) | 36(1)* |
| N(2) | 6141(3) | 10748(1) | 6894(2) | 32(1)* |
| C(13) | 4727(5) | 7602(2) | 7509(3) | 58(1)* |
| O(1) | 7567(3) | 9810(1) | 6383(2) | 53(1)* |
| O(2) | 1642(3) | 10996(1) | 7036(2) | 53(1)* |
| O(3) | 2947(4) | 11685(2) | 9181(2) | 67(1)* |
| O(4) | 3234(4) | 12357(1) | 8062(2) | 71(1)* |

*Equivalent isotropic U defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

Table 2. Bond Lengths (Å)

| | | | |
|---|---|---|---|
| S-C(1) | 1.831(3) | S-C(9) | 1.773(3) |
| C(1)-C(2) | 1.507(4) | C(1)-N(1) | 1.433(4) |
| C(2)-N(2) | 1.326(4) | C(2)-O(1) | 1.229(4) |
| C(3)-C(4) | 1.513(4) | C(3)-C(5) | 1.532(5) |
| C(3)-N(2) | 1.457(4) | C(4)-N(1) | 1.346(4) |
| C(4)-O(2) | 1.225(4) | C(5)-C(6) | 1.511(5) |
| C(5)-C(8) | 1.529(5) | C(6)-C(7) | 1.493(6) |
| C(7)-O(3) | 1.438(5) | C(8)-O(3) | 1.338(5) |
| C(8)-O(4) | 1.177(5) | C(9)-N(3) | 1.308(5) |
| C(9)-C(13) | 1.378(5) | C(10)-C(11) | 1.367(7) |
| C(10)-C(13) | 1.377(6) | C(11)-C(12) | 1.360(6) |
| C(12)-N(3) | 1.356(5) | C(14)-C(15) | 1.499(5) |
| C(14)-N(2) | 1.482(4) | C(15)-C(16) | 1.385(5) |
| C(15)-C(20) | 1.379(6) | C(16)-C(17) | 1.357(9) |
| C(17)-C(18) | 1.338(10) | C(18)-C(19) | 1.368(11) |
| C(19)-C(20) | 1.417(8) | C(21)-C(22) | 1.510(6) |
| C(21)-N(1) | 1.474(4) | C(22)-C(23) | 1.378(6) |
| C(22)-C(27) | 1.372(6) | C(23)-C(24) | 1.387(7) |
| C(24)-C(25) | 1.347(9) | C(25)-C(26) | 1.364(10) |
| C(26)-C(27) | 1.387(7) | | |

Table 3. Bond Angles (deg.)

| | | | |
|---|---|---|---|
| C(1)-S-C(9) | 102.9(2) | S-C(1)-C(2) | 108.6(2) |
| S-C(1)-N(1) | 113.5(2) | C(2)-C(1)-N(1) | 114.4(3) |
| C(1)-C(2)-N(2) | 117.7(3) | C(1)-C(2)-O(1) | 118.1(3) |
| N(2)-C(2)-O(1) | 124.1(3) | C(4)-C(3)-C(5) | 111.4(3) |
| C(4)-C(3)-N(2) | 114.4(3) | C(5)-C(3)-N(2) | 112.1(3) |
| C(3)-C(4)-N(1) | 118.1(3) | C(3)-C(4)-O(2) | 118.7(3) |
| N(1)-C(4)-O(2) | 123.2(3) | C(3)-C(5)-C(6) | 119.1(3) |
| C(3)-C(5)-C(8) | 114.0(3) | C(6)-C(5)-C(8) | 102.1(3) |
| C(5)-C(6)-C(7) | 102.7(3) | C(6)-C(7)-O(3) | 105.2(3) |
| C(5)-C(8)-O(3) | 108.8(3) | C(5)-C(8)-O(4) | 127.7(4) |
| O(3)-C(8)-O(4) | 123.3(4) | S-C(9)-N(3) | 119.7(3) |
| S-C(9)-C(13) | 116.2(3) | N(3)-C(9)-C(13) | 124.1(3) |
| C(11)-C(10)-C(13) | 119.6(4) | C(10)-C(11)-C(12) | 118.4(4) |
| C(11)-C(12)-N(3) | 123.3(5) | C(9)-N(3)-C(12) | 116.8(3) |
| C(15)-C(14)-N(2) | 111.0(3) | C(14)-C(15)-C(16) | 120.0(4) |
| C(14)-C(15)-C(20) | 121.1(4) | C(16)-C(15)-C(20) | 118.8(4) |
| C(15)-C(16)-C(17) | 121.1(5) | C(16)-C(17)-C(18) | 120.7(6) |
| C(17)-C(18)-C(19) | 120.9(6) | C(18)-C(19)-C(20) | 119.3(6) |
| C(15)-C(20)-C(19) | 119.0(5) | C(22)-C(21)-N(1) | 112.4(3) |
| C(21)-C(22)-C(23) | 121.4(4) | C(21)-C(22)-C(27) | 120.8(4) |
| C(23)-C(22)-C(27) | 117.8(4) | C(22)-C(23)-C(24) | 120.6(5) |
| C(23)-C(24)-C(25) | 120.8(5) | C(24)-C(25)-C(26) | 119.6(5) |
| C(25)-C(26)-C(27) | 120.0(6) | C(22)-C(27)-C(26) | 121.1(5) |
| C(1)-N(1)-C(4) | 122.9(3) | C(1)-N(1)-C(21) | 116.2(3) |
| C(4)-N(1)-C(21) | 120.7(3) | C(2)-N(2)-C(3) | 124.5(3) |
| C(2)-N(2)-C(14) | 119.2(3) | C(3)-N(2)-C(14) | 115.8(2) |
| C(9)-C(13)-C(10) | 117.6(5) | C(7)-O(3)-C(8) | 110.8(3) |

Table 4. Anisotropic Temperature Factors ($\AA^2 \times 10^3$)

| atom | U | U | U | U | U | U |
|---|---|---|---|---|---|---|
| S | 62(1) | 36(1) | 42(1) | -0(1) | -7(1) | -6(1) |
| C(1) | 32(2) | 34(2) | 35(2) | -3(1) | 1(1) | -2(1) |
| C(2) | 28(2) | 35(2) | 40(2) | -1(1) | -1(1) | 3(1) |
| C(3) | 29(2) | 29(2) | 37(2) | -2(1) | -3(1) | 4(1) |
| C(4) | 23(1) | 43(2) | 35(2) | 1(2) | -0(1) | 3(1) |
| C(5) | 32(2) | 44(2) | 38(2) | -5(2) | -2(2) | 9(2) |
| C(6) | 62(2) | 52(2) | 43(2) | 3(2) | 1(2) | 12(2) |
| C(7) | 78(3) | 78(3) | 39(2) | 1(2) | 1(2) | 12(2) |
| C(8) | 53(2) | 52(2) | 42(2) | -13(2) | -4(2) | 8(2) |
| C(9) | 37(2) | 35(2) | 49(2) | -1(2) | 8(2) | -5(1) |
| C(10) | 85(3) | 34(2) | 94(4) | 9(2) | 30(3) | 0(2) |
| C(11) | 63(3) | 39(2) | 99(4) | -18(2) | 26(3) | -13(2) |
| C(12) | 65(3) | 52(2) | 82(3) | -25(2) | -0(3) | -7(2) |
| N(3) | 59(2) | 39(2) | 57(2) | -10(1) | -6(2) | -3(1) |
| C(14) | 27(2) | 37(2) | 44(2) | -5(2) | -1(1) | -5(1) |
| C(15) | 28(2) | 49(2) | 54(2) | 1(2) | -4(2) | -10(2) |
| C(16) | 64(3) | 49(2) | 92(4) | 17(2) | -1(3) | -5(2) |
| C(17) | 97(4) | 91(4) | 119(5) | 55(4) | -18(4) | -11(3) |
| C(18) | 115(5) | 139(5) | 87(4) | 63(4) | -27(4) | -45(4) |
| C(19) | 108(5) | 159(7) | 51(3) | -4(4) | 1(3) | -55(5) |
| C(20) | 73(3) | 82(3) | 53(3) | -3(2) | 5(2) | -20(3) |
| C(21) | 21(2) | 51(2) | 53(2) | -5(2) | -1(2) | -7(1) |
| C(22) | 28(2) | 56(2) | 49(2) | -10(2) | -3(2) | 5(2) |
| C(23) | 125(5) | 65(3) | 51(3) | -3(2) | -5(3) | 17(3) |
| C(24) | 153(6) | 89(4) | 55(3) | 1(3) | -1(3) | 36(4) |
| C(25) | 62(3) | 151(5) | 50(3) | -21(3) | -4(3) | 32(4) |
| C(26) | 63(3) | 136(5) | 57(3) | -42(3) | 11(2) | -21(3) |
| C(27) | 48(3) | 86(3) | 64(3) | -23(3) | 7(2) | -23(2) |
| N(1) | 25(1) | 38(1) | 46(2) | -8(1) | -1(1) | 0(1) |
| N(2) | 26(1) | 29(1) | 41(1) | -1(1) | 1(1) | -1(1) |
| C(13) | 67(3) | 42(2) | 64(2) | 4(2) | 6(2) | 2(2) |
| O(1) | 31(1) | 41(1) | 87(2) | -14(1) | 8(1) | 2(1) |
| O(2) | 25(1) | 59(2) | 74(2) | -15(1) | -1(1) | 9(1) |
| O(3) | 80(2) | 74(2) | 45(2) | -11(1) | 14(2) | 22(2) |
| O(4) | 100(2) | 45(2) | 67(2) | -7(1) | -3(2) | 20(2) |

The anisotropic temperature factor exponent takes the form:
$-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + \ldots + 2hka^*b^*U_{12})$

Table 5. Hydrogen Coordinates ($\times 10^4$) and Temperature Factors ($\text{Å}^2 \times 10^3$)

| atom | x | y | z | U |
|---|---|---|---|---|
| H(1) | 4635 | 9381 | 6126 | 34 |
| H(3) | 4549 | 11526 | 6916 | 37 |
| H(5) | 5836 | 11298 | 8172 | 41 |
| H(6a) | 5069 | 10319 | 8836 | 63 |
| H(6b) | 3217 | 10357 | 8499 | 63 |
| H(7a) | 4566 | 11106 | 9836 | 82 |
| H(7b) | 2764 | 10767 | 9779 | 82 |
| H(10) | 4488 | 6529 | 7498 | 85 |
| H(11) | 3421 | 6462 | 6144 | 79 |
| H(12) | 3121 | 7490 | 5384 | 81 |
| H(14a) | 7636 | 11557 | 7238 | 43 |
| H(14b) | 8620 | 10954 | 6777 | 43 |
| H(16) | 6736 | 12563 | 6517 | 79 |
| H(17) | 6460 | 13197 | 5301 | 111 |
| H(18) | 7120 | 12696 | 4050 | 124 |
| H(19) | 7770 | 11497 | 3960 | 114 |
| H(20) | 8092 | 10822 | 5207 | 80 |
| H(21a) | 1701 | 9191 | 6418 | 53 |
| H(21b) | 658 | 9894 | 6486 | 53 |
| H(23) | 2375 | 10747 | 5220 | 96 |
| H(24) | 1984 | 10838 | 3784 | 118 |
| H(25) | 1009 | 9887 | 3028 | 99 |
| H(26) | 573 | 8805 | 3684 | 96 |
| H(27) | 913 | 8708 | 5123 | 73 |
| H(13) | 5203 | 7643 | 8055 | 101 |

# APPENDIX 3

## X-RAY ANALYSIS DATA FOR 323

Table 1. Atom Coordinates ($x10^4$) and Temperature Factors ($Å^2 \times 10^3$)

| atom | x | u | z | U* |
|---|---|---|---|---|
| O(1) | 8203(4) | 3951(2) | 7811(1) | 61(1) |
| O(2) | 6796(5) | 4568(3) | 6985(2) | 90(1) |
| O(3) | 9990(5) | 1780(3) | 8834(2) | 92(2) |
| O(4) | 11041(5) | 3574(3) | 8510(2) | 92(1) |
| O(5) | 12684(5) | 623(3) | 10039(1) | 77(1) |
| O(6) | 12064(7) | -1283(3) | 9716(2) | 117(2) |
| C(1) | 8280(6) | 2767(4) | 8125(2) | 48(1) |
| C(2) | 8184(6) | 1813(4) | 7617(2) | 52(1) |
| C(3) | 6471(7) | 2432(4) | 7361(2) | 60(2) |
| C(4) | 5220(7) | 2450(5) | 7903(3) | 78(2) |
| C(5) | 6463(7) | 2647(4) | 8427(2) | 71(2) |
| C(6) | 7120(7) | 3752(4) | 7334(2) | 64(2) |
| C(7) | 9814(7) | 1887(5) | 7208(2) | 77(2) |
| C(8) | 5696(9) | 1956(6) | 6797(3) | 107(3) |
| C(9) | 7927(7) | 466(4) | 7813(2) | 70(2) |
| C(10) | 9927(7) | 2795(4) | 8503(2) | 63(2) |
| C(11) | 11590(8) | 1627(6) | 9198(2) | 104(3) |
| C(12) | 11105(7) | 724(4) | 9681(2) | 61(2) |
| C(13) | 10848(9) | -559(5) | 9455(3) | 99(3) |
| C(14) | 13298(8) | -624(5) | 10047(2) | 75(2) |
| C(15) | 15031(10) | -676(10) | 9753(6) | 204(6) |
| C(16) | 9613(9) | 1199(9) | 10058(3) | 133(4) |
| C(17) | 13274(15) | -1103(7) | 10661(3) | 152(4) |

Equivalent isotropic $\underline{U}$ defined as one third of the trace of the orthogonalized $\underline{U}_{ij}$ tensor.

Table 2. Bond Lengths (Å)

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.460(5) | O(1)-C(6) | 1.364(6) |
| O(2)-C(6) | 1.207(6) | O(3)-C(10) | 1.327(6) |
| O(3)-C(11) | 1.458(7) | O(4)-C(10) | 1.181(6) |
| O(5)-C(12) | 1.433(6) | O(5)-C(14) | 1.420(6) |
| O(6)-C(13) | 1.333(8) | O(6)-C(14) | 1.382(7) |
| C(1)-C(2) | 1.541(6) | C(1)-C(5) | 1.524(7) |
| C(1)-C(10) | 1.497(7) | C(2)-C(3) | 1.553(7) |
| C(2)-C(7) | 1.529(7) | C(2)-C(9) | 1.530(6) |
| C(3)-C(4) | 1.539(7) | C(3)-C(6) | 1.504(7) |
| C(3)-C(8) | 1.490(8) | C(4)-C(5) | 1.520(7) |
| C(11)-C(12) | 1.507(8) | C(12)-C(13) | 1.486(7) |
| C(12)-C(16) | 1.492(8) | C(14)-C(15) | 1.454(11) |
| C(14)-C(17) | 1.480(8) | | |

Table 3. Bond Angles (deg.)

| | | | |
|---|---|---|---|
| C(1)-O(1)-C(6) | 105.6(3) | C(10)-O(3)-C(11) | 116.1(4) |
| C(12)-O(5)-C(14) | 110.1(4) | C(13)-O(6)-C(14) | 113.1(4) |
| O(1)-C(1)-C(2) | 102.8(3) | O(1)-C(1)-C(5) | 104.9(3) |
| C(2)-C(1)-C(5) | 103.6(4) | O(1)-C(1)-C(10) | 106.9(3) |
| C(2)-C(1)-C(10) | 118.4(4) | C(5)-C(1)-C(10) | 118.4(4) |
| C(1)-C(2)-C(3) | 91.7(3) | C(1)-C(2)-C(7) | 112.2(4) |
| C(3)-C(2)-C(7) | 114.0(4) | C(1)-C(2)-C(9) | 115.1(4) |
| C(3)-C(2)-C(9) | 114.3(4) | C(7)-C(2)-C(9) | 108.9(4) |
| C(2)-C(3)-C(4) | 102.0(4) | C(2)-C(3)-C(6) | 99.0(4) |
| C(4)-C(3)-C(6) | 102.5(4) | C(2)-C(3)-C(8) | 119.4(4) |
| C(4)-C(3)-C(8) | 116.7(5) | C(6)-C(3)-C(8) | 114.6(4) |
| C(3)-C(4)-C(5) | 104.6(4) | C(1)-C(5)-C(4) | 101.8(4) |
| O(1)-C(6)-O(2) | 121.4(4) | O(1)-C(6)-C(3) | 107.9(4) |
| O(2)-C(6)-C(3) | 130.7(4) | O(3)-C(10)-O(4) | 123.6(5) |
| O(3)-C(10)-C(1) | 109.5(4) | O(4)-C(10)-C(1) | 126.9(4) |
| O(3)-C(11)-C(12) | 106.5(5) | O(5)-C(12)-C(11) | 105.1(4) |
| O(5)-C(12)-C(13) | 103.3(4) | C(11)-C(12)-C(13) | 112.5(4) |
| O(5)-C(12)-C(16) | 108.5(4) | C(11)-C(12)-C(16) | 111.8(5) |
| C(13)-C(12)-C(16) | 114.8(5) | O(6)-C(13)-C(12) | 107.7(5) |
| O(5)-C(14)-O(6) | 105.3(4) | O(5)-C(14)-C(15) | 108.5(6) |
| O(6)-C(14)-C(15) | 109.0(6) | )(5)-C(14)-C(17) | 109.8(5) |
| O(6)-C(14)-C(17) | 108.7(5) | C(15)-C(14)-C(17) | 115.2(7) |

Table 4. Anisotropic Temperature Factors ($\AA^2 \times 10^3$)

| atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{12}$ | $U_{13}$ |
|---|---|---|---|---|---|---|
| O(1) | 77(2) | 37(1) | 70(2) | 6(1) | 5(2) | -0(2) |
| O(2) | 96(3) | 80(2) | 94(2) | 36(2) | 3(3) | 16(2) |
| O(3) | 105(3) | 67(2) | 104(3) | 30(2) | -52(2) | -29(2) |
| O(4) | 90(3) | 71(2) | 116(3) | 21(2) | -26(3) | -29(2) |
| O(5) | 90(3) | 51(2) | 89(2) | -7(2) | -33(2) | 5(2) |
| O(6) | 157(4) | 51(2) | 144(4) | -12(2) | -59(4) | 10(3) |
| C(1) | 53(3) | 40(2) | 52(2) | 8(2) | 2(2) | 0(2) |
| C(2) | 52(3) | 45(2) | 60(2) | -2(2) | -2(3) | -1(2) |
| C(3) | 63(3) | 55(3) | 61(3) | 4(2) | -9(3) | -2(3) |
| C(4) | 58(3) | 67(3) | 108(4) | 21(3) | 13(4) | 4(3) |
| C(5) | 83(4) | 57(3) | 72(3) | 5(3) | 22(3) | 8(3) |
| C(6) | 59(3) | 66(3) | 67(3) | 8(3) | 9(3) | 7(3) |
| C(7) | 78(4) | 67(3) | 85(4) | -6(3) | 19(3) | 11(3) |
| C(8) | 107(5) | 118(5) | 97(4) | 5(4) | -44(4) | -12(4) |
| C(9) | 77(3) | 46(2) | 88(3) | -0(3) | -10(3) | -2(3) |
| C(10) | 77(3) | 46(3) | 66(3) | 2(3) | -5(3) | -8(3) |
| C(11) | 106(5) | 109(5) | 97(4) | 35(4) | -53(4) | -32(4) |
| C(12) | 64(3) | 60(3) | 60(3) | -7(2) | -22(3) | 12(3) |
| C(13) | 112(5) | 66(3) | 119(5) | -4(4) | -43(5) | -6(4) |
| C(14) | 83(4) | 57(3) | 86(4) | 2(3) | -21(4) | 8(3) |
| C(15) | 117(7) | 148(8) | 346(15) | 27(9) | 67(9) | 49(6) |
| C(16) | 106(6) | 202(8) | 91(5) | -29(5) | -14(4) | 66(6) |
| C(17) | 259(10) | 100(5) | 98(5) | 18(4) | -38(7) | 39(7) |

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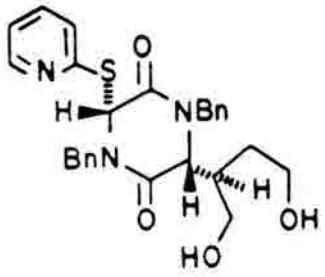
The anisotropic temperature factor exponent takes the form:
$-2\pi^2 (\underline{h}^2\underline{a}^{*2}\underline{U}_{11} + \underline{k}^2\underline{b}^{*2}\underline{U}_{22} + \ldots + 2\underline{hka}^*\underline{b}^*\underline{U}_{12})$

Table 5. Hydrogen Coordinates ($x10^4$) and Temperature Factors ($\mathring{A}^2 \times 10^3$)

| atom | x | y | z | U |
|---|---|---|---|---|
| H(4a) | 4592 | 1676 | 7938 | 79 |
| H(4b) | 4371 | 3116 | 7873 | 79 |
| H(5a) | 6158 | 3387 | 8641 | 71 |
| H(5b) | 6437 | 1949 | 8692 | 71 |
| H(7a) | 10069 | 2714 | 7075 | 85 |
| H(7b) | 9607 | 1360 | 6873 | 85 |
| H(7c) | 10814 | 1578 | 7431 | 85 |
| H(8a) | 5315 | 1117 | 6866 | 109 |
| H(8b) | 6641 | 1961 | 6508 | 109 |
| H(8c) | 4703 | 2436 | 6653 | 109 |
| H(9a) | 6947 | 337 | 8081 | 76 |
| H(9b) | 9002 | 122 | 7979 | 76 |
| H(9c) | 7671 | 66 | 7443 | 76 |
| H(11a) | 12558 | 1305 | 8964 | 104 |
| H(11b) | 11937 | 2409 | 9366 | 104 |
| H(13a) | 11007 | -576 | 9033 | 106 |
| H(13b) | 9664 | -844 | 9551 | 106 |
| H(15a) | 15793 | -440 | 10076 | 176 |
| H(15b) | 15281 | -159 | 9417 | 176 |
| H(15c) | 15251 | -1528 | 9651 | 176 |
| H(16a) | 8521 | 1301 | 9839 | 134 |
| H(16b) | 9958 | 1980 | 10228 | 134 |
| H(16c) | 9433 | 602 | 10368 | 134 |
| H(17a) | 13315 | -1992 | 10684 | 142 |
| H(17b) | 12410 | -793 | 10938 | 142 |
| H(17c) | 14434 | -769 | 10753 | 142 |

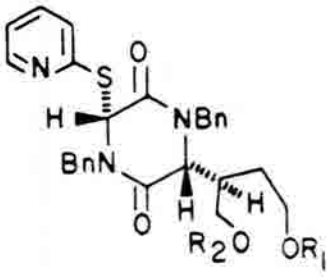
# APPENDIX 4

## SELECTIVE FUNCTIONALIZATION OF MINOR DIOL 246

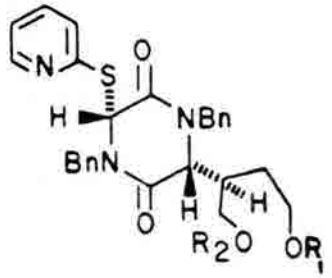


246

$Et_3N$ | TBDMSCl

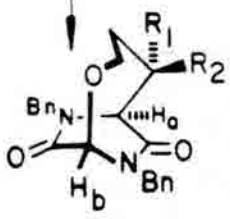


355 $R_1$ = H $R_2$ $SiMe_2Bu^t$



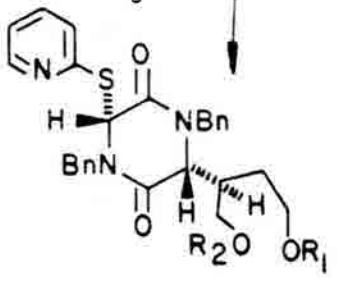
351 $R_1$ = $SiMe_2Bu^t$, $R_2$ = H

AgOTf



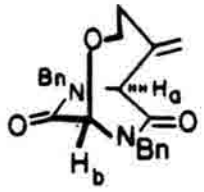
357 $R_1$ = $CH_2OH$, $R_2$ = H

$Et_3N$ | MsCl



356 $R_1$ = $SiMe_2Bu^t$, $R_2$ = Ms

1. $Cu(ClO_4)$
2. NaSePh, THF
3. $H_2O_2$



263 $R_1$ = $CH_2OMs$, $R_2$ = H