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SYNTHETIC APPROACHES TO BICYCLOMYCIN

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SYNTHETIC APPROACHES TO BICYCLOMYCIN

by

BARRY DOUGLAS ROBINS

A THESIS SUBMITTED
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HOUSTON, TEXAS

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Abstract

Synthetic Approaches to Bicyclomycin

by

Barry Douglas Robins

Bicyclomycin 1 is an antibiotic that is isolated from a culture filtrate of *Streptomyces sapporonensis* and *Streptomyces aizunensis*. Bicyclomycin exhibits a low toxicity and also possesses a unique chemical structure. Model studies of the synthesis are presented, however the total synthesis was not realized.

![Chemical Structure](image)

The critical reaction involves oxidative cyclization of a methylideneipiperazinedione to the bicyclo[4.4.2] system under basic conditions. This is then elaborated to include the carbon framework of the side chain. The two amides are protected throughout the model synthesis and possible protecting groups are described for an eventual total synthesis of bicyclomycin.
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I. Introduction

Bicyclomycin, a new antibiotic, was isolated independently by two Japanese groups.\textsuperscript{1,2} It was found to be active against Gram-negative bacteria\textsuperscript{3} and showed a low toxicity in mice.\textsuperscript{2b} The structure of bicyclomycin was determined mainly by spectroscopic means and was confirmed by X-ray diffraction analysis.\textsuperscript{4} Recently, the absolute configuration\textsuperscript{5} was established as 6R-hydroxy-5-methylene-1S-(1'S,2'S,3'-trihydroxy-2'S-methylpropyl)-2-oxa-7,9-diazabicyclo[4.2.2]decan-8,10-dione.

![Chemical Structure of Bicyclomycin]

Bicyclomycin is unique in its chemical structure, a highly oxidized piperazinedione, and its mechanism of anti-
bacterial action which bears no relation to any group of known antibiotics. Work was done to investigate how the activity is related to the structure. Müller et al. found that the antibacterial activity was very sensitive to structural modifications in the molecule. Iseki et al. have shown that the methylene is necessary for activity in the binding to membrane proteins of E. coli.

Due to bicyclomycin's unique structure and interesting profile of antibacterial activity, it has received considerable interest in the past few years as a synthetic target. As of yet, no reported total synthesis has appeared in the literature.

The first reported synthetic study was by Maag et al. in 1978. In examining the acidic stability of bicyclomycin they found that it rearranged to a mixture (~1:1) of two diastereomers 2a and 2b (0.1N HClO₄, 100°C, 15 min.). This mixture was converted to the mono-p-bromobenzoates 3a and 3b which were separated (Scheme 1). The absolute configuration of isomer 3a was determined by single-crystal x-ray diffractions analysis. These results were used to also establish the absolute configuration of bicyclomycin.
In addition to determining the absolute configuration, these rearrangement products $2a$ and $2b$ were prepared in racemic form by total synthesis (Scheme 2). Condensation of aldehyde $4$ with $N,N'$-diacetylglucose anhydride gave $5$. Hydrazinolysis and trans ketalization with ethylene glycol and $p$-toluenesulfonic acid led to $6$. This spiro system was di-acetylated and condensed with a ketone to give $7$. This was transformed to the diol $8$ in three steps then converted to $2a$ and $2b$ in two more steps. This rearranged
bis-spiro system appears to be thermodynamically more stable than the bicyclic system. Hence any attempts to synthesize bicyclomycin should avoid its formation.

Williams et al.\textsuperscript{11} have found a way to avoid the formation of the spiro system by introducing the 6-hydroxy group after formation of the bicyclic system. In an
efficient three-step sequence sarcosine anhydride 2 was converted to the bicyclo[4.2.2]system 12 (Scheme 3). The key reaction was the metal-mediated intramolecular cyclization. It was found that the cyclization occurred with either the silyl ether 11a or the alcohol 11b but was
highly dependant upon the metal and the counterion. Functionalization of this bicyclic system was first achieved by regiospecific formation of the bridgehead alcohol 13a with lithium diisopropylamide (LDA) and MoOPH.\textsuperscript{17}

\textbf{Scheme 4}

\[ 12 \xrightarrow{\text{1. LDA}} \xrightarrow{\text{2. CHO}} 14a \quad \text{R=H} \\
\quad \text{14b} \quad \text{R=SiMe}_2(t-\text{Bu}) \]

\[ 13a \quad \text{R=H} \\
\quad 13b \quad \text{R=SiMe}_2(t-\text{Bu}) \]
Conversion to N,N'-dimethyl-5-desmethylenebicyclomycin 15 was accomplished by two similar pathways (Scheme 4). Aldol condensation of 13a with aldehyde 4 yielded 14a as a mixture of all four isomers. One isomer was slightly favored (ratio of isomers was 4:3:3:2) and this contained the identical stereochemistry as bicyclomycin. Deprotection of the acetonide gave the tetraol 15. In an improved procedure, alcohol 13a was protected as a silyl ether 13b. The aldol condensation with aldehyde 4 proved to be stereospecific in that only three of the four isomers of 14b were formed. The ratio of the three isomers was 4:1:1 with the major isomer being converted to 15. While the second route involved more steps, it produced 15 in a higher isolated yield (34% to 16%).

Nakatsuka 13 also utilizes a stereocontrolled aldol condensation for the introduction of the trihydroxy side chain. Conversion of sarcosine anhydride 9 to the 3,6-dimethoxy compound 16 followed by alkylation and elimination led to benzoate 17a (Scheme 5). Selective activation of the piperazinedione nucleus was required to insure formation of the bicyclic system and not the spiro system. First the benzoate 17a was hydrolyzed to the alcohol 17b and protected as the trifluoroacetate 17c. Activation of the piperazinedione was accomplished with acetic anhydride and trifluoroacetic acid to give the monoacetoxy compound
**Scheme 5**

16 → 17a \( R = \text{COPh} \)  
17b \( R = \text{H} \)  
17c \( R = \text{COCF}_3 \)

18a \( R = \text{COCF}_3 \)  
18b \( R = \text{H} \)  

18a. Mild hydrolysis of the trifluoroacetate gave 18b which was cyclized with pyridinium tosylate to give the bicyclic compound 19. Stereospecific aldol condensation with aldehyde 4 led to a 9:3:3:1 ratio of isomers of 20 (Scheme 6). The major isomer was converted to N,N,O-
trimethylbicyclomycin 21 by deprotection of the acetonide. Recently the total synthesis of (±)-bicyclomycin was presented by Nakatsuka at the IUPAC Symposium on Organic Synthesis in Tokyo, Japan in August, 1982 but the details have yet to appear in print.
II. Retrosynthetic Analysis

Bicyclomycin is a unique, highly oxidized piperazinedione. Biosynthetic studies have shown (L)-leucine and (L)-isoleucine to be precursors for the piperazinedione nucleus. We felt that the most advantageous route toward the synthesis of bicyclomycin was by first forming a suitably protected piperazinedione. Next would be cyclization to the bicyclo[4.2.2] system. Finally elaboration of the side chain and removal of the amide protecting groups would yield bicyclomycin. This is similar to the routes used by Williams and Nakatsuka but obvious differences will be seen.

As shown in Scheme 7, the first key retrosynthetic intermediate is the bicyclic aldehyde. Since numerous methods for carbon-carbon bond formation to an aldehyde are known, completion of the side chain could be readily realized. The aldehyde or its equivalent could be formed by oxidative cyclization of the alkylidene piperazinedione. As previously mentioned, bicyclomycin will rearrange under acidic conditions to the bis-spiro system. Therefore it would be advantageous to conduct this cyclization under neutral or basic conditions.
The piperazinedione 25 was the second key intermediate and its convenient synthesis should be devised (Scheme 8). Ring opening to an acyclic precursor would give the β-methylene-α-keto amide 26. Due to its expected instability, this functionality could arise from two possible systems.
27a or 27b (with protection of the terminal alcohol). Oxidation of 27b or ozonolysis of 27a followed by elimination of R"'OH then elimination of HX would give 26. Both of these intermediates 27a and 27b are highly functionalized N-acyl-α-amino acid amides. N-acyl-α-amino acid amides can be prepared by a wide variety of methods. The easiest and the most versatile method to make a large number of highly diversified and substituted compounds is that of Ugi's four-component condensation.19 By simply mixing an appropriate carboxylic acid, a primary amine, an isonitrile, and a carbonyl compound (aldehyde or ketone), a variety of N-acyl-α-amino acid amides can be obtained. Therefore, a judicious choice of the four components is necessary.

Each of the four components had to meet certain criteria for the synthesis. The carbonyl component must be an aldehyde. Also there should be a leaving group in the α-position so elimination of HX from 27a or 27b would give the α,β-unsaturated amide. The isonitrile and the amine required functionalities (R' and R respectively) that could be removed at a later stage in the synthesis to give the secondary amide. For the carboxylic acid, there are two possibilities (28a or 28b). Which one is used would depend upon the functionalities present in the other three components. The following section will deal with how Ugi's four-component condensation was utilized for the attempted synthesis of bicyclomycin.
III. Synthesis

Bicyclomycin presents a serious challenge to the synthetic chemist for many reasons. It is known\textsuperscript{1,5} that bicyclomycin will decompose under acidic or basic conditions to a biologically inactive compound. Therefore mild reaction conditions must be employed in the final stages of the synthesis. Another consideration is the trihydroxy side chain. Any reasonable synthesis should exercise high control of the relative stereochemistry. Both Williams\textsuperscript{11} and Nakatsuka\textsuperscript{13} utilize an aldol condensation with an already functionalized aldehyde (see Schemes 4 and 6). Our approach differs in that stereospecific hydroxylation is incorporated after the carbon framework has been assembled.

Although the method for introduction and elaboration of the side chain varies, all reported approaches start in approximately the same way. First there is construction of a piperazinedione where the amides are suitably protected. Next the bicyclic system is formed in some manner that either minimizes or eliminates the formation of a spiro system. Finally the side chain is introduced and the amides deprotected. Although the routes are similar, there is a large degree of flexibility in many of the transformation.
The most critical choice is what to use as the protecting groups for the amides. The deprotection will occur towards the end of the synthesis when the system will be sensitive to harsh conditions.

While this thesis does not deal with the total synthesis, many possible protecting groups have been considered. For model studies, an \textit{n}-propyl group was used because it is sterically similar to a potential protecting group while being chemically inert. The major part of this section deals with model systems for the construction of the bicyclic framework and elaboration of the side chain. In addition, there is a discussion of potential protecting groups and their manner of deprotection.

As explained in the retrosynthetic analysis, the first key intermediate is a suitable methylidenepiperazinedione (see Scheme 7). This could be prepared by ring closure of an acyclic precursor. This precursor, and a wide variety of them, could easily be prepared by Ugi's four-component condensation.\textsuperscript{19} By virtue of this condensation, any part of the molecule could be modified with a minimum amount of difficulty.

The four-component condensation combines an amine, an isonitrile, a carboxylic acid, and a carbonyl compound (aldehyde or ketone) to form an N-acyl-\(\alpha\)-amino acid amide. By varying any one or all of the components, a large variety of compounds could be made. For this synthesis, certain
restrictions would have to be placed on all of the components. Both amides would be protected with the \( n \)-propyl group for model systems so \( n \)-propylamine and \( n \)-propylisonitrile would be used. The carbonyl compound must be an aldehyde and required a leaving group in the \( \alpha \) position. Finally, the carboxylic acid needed a functional group on the \( \alpha \)-carbon that could be converted to an \( \alpha \)-keto group.

The aldehyde proved to be easy to prepare. Allyl alcohol was converted into either an ester (benzoate)\(^{39} \) or a carbonate (methyl or ethyl). Ozonolysis of the double bond led to the desired aldehyde.

The carboxylic acid had to be a polyfunctional compound where the \( \alpha \)-carbon would bear either an alcohol or a methylene. In this way either standard oxidation of the alcohol or ozonolysis of the methylene would yield the \( \alpha \)-keto compound. The \( \beta \)-position should bear a methylene or its equivalent (a protected hydroxymethyl group). Finally there would be a protected alcohol in the \( \delta \)-position. These functionalities could be combined to yield two possible structures for the carboxylic acid A and B.

![Structures A and B](image-url)
In the initial studies, simple carboxylic acids such as methacrylic acid or lactic acid were employed. Both worked well and the choice depended on functional groups present in the other components. In a typical experiment, methacrylic acid (1 eq.), aldehyde 30 (1.1 eq.), n-propylamine (1.1 eq.), and n-propylisonitrile (1.2 eq.) were combined in methanol and heated to give the N-acyl-α-amino acid amide 31 (scheme 9). Ozonolysis of 31 followed by cyclization and elimination with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) gave the piperazinedione 32.
With the methylidenepiperazinedione nucleus now in hand, attention turned to formation of the bicyclic system (Scheme 10). Oxidation of the methylidenepiperazinedione 33 would accomplish this by formation of a nitrogen-stabilized carbonium ion intermediate 34. Attack by the terminal alcohol on the carbonium ion would yield the desired bicyclo [4.2.2] system.
The methylidene piperazinedione 33 (R=n-propyl) could be prepared as seen in Scheme 11. For the four-component condensation, carboxylic acid 36 was prepared in three steps from 4-pentenal; 1) cyanohydrin formation with sodium cyanide and HCl, 2) methanolysis of the nitrile to the methyl ester with methanol, trimethyl orthoformate and HCl and 3) hydrolysis of the ester with NaOH. This was condensed with aldehyde 30, \( \text{n-propylamine} \), and \( \text{n-propyl-isonitirile} \) to give the N-acyl-\( \alpha \)-amino acid 37. Oxidation of the alcohol followed by acidic cyclization gave the piperazinedione 38 as a mixture of isomers. Ozonolysis followed by reductive cleavage of the ozonide gave the alcohol 39 from which benzoic acid was eliminated by treatment with DBU to give the methylidene piperazinedione 40.
Scheme 11

\[
\begin{align*}
\text{MeOH} & \quad \Delta \\
\text{CHO} & \quad \text{H}_2\text{N} - \text{n-Pr} \\
\text{n-PrN=C} & \quad \text{MeOH} \\
\text{CHO} & \quad \text{H}_2\text{N} - \text{n-Pr} \\
\text{CHO} & \quad \text{CHO} \\
\end{align*}
\]

1) Jones oxid.  
2) MeOH  
CSA

\[
\begin{align*}
\text{MeO} & \quad \text{PrN} \quad \text{CHO} \\
\text{CHO} & \quad \text{CHO} \\
\text{CHO} & \quad \text{CHO} \\
\end{align*}
\]

1) O$_3$  
2) NaBH$_4$

DBU

\[
\begin{align*}
\text{MeO} & \quad \text{PrN} \quad \text{CHO} \\
\text{CHO} & \quad \text{CHO} \\
\text{CHO} & \quad \text{CHO} \\
\end{align*}
\]
The stage is now set for the cyclization. The presence of the methyl ether, as opposed to an alcohol, should not affect the course of the reaction. Treatment of compound 40 with bromine in dichloromethane led to a mixture of isomeric bromohydrins 41a and 41b along with a minor amount of the desired bicyclic compound 42 (Scheme 12).

Scheme 12

As stated previously, it is known that bicyclomycin is unstable under acidic conditions. Therefore, trace amounts of HBr could catalyze the rearrangement of the desired bicyclic system 42 to the more stable spiro system 41. Varying the conditions with bromine still led to a mixture of 41 and 42. Other brominating reagents were tried under a wide variety of conditions. It appears that a mild brominating reagent was required to avoid the facile rearrangement to the spiro system. Fortunately it was found that treatment of 40 with pyridinium bromide perbromide (Py·HBr₂) in the presence of excess pyridine at room temperature gave the bicyclic bromide 42 as the exclusive product.
With the bicyclo[4.2.2] system now secured, a fully functionalized carboxylic acid was desired. Scheme 13 shows the procedure for preparation of a carboxylic acid of type A (page 16). This was accomplished in five steps from the available γ-phenylallylsuccinic anhydride\(^\text{20}\) \(^{43}\). Lithium aluminum hydride (LiAlH\(_4\)) reduction to the diol and acetylation with acetic anhydride and pyridine gave the Scheme 13
diacetate 44. Ozonolysis of the double bond gave the aldehyde 45. A Mannich reaction 21 with dimethylamine hydrochloride, formaldehyde and triethylamine yielded the unsaturated aldehyde 46. Oxidation with selenium dioxide and 30% hydrogen peroxide 22 gave the carboxylic acid 47.

Carboxylic acid 47 was now used in the four-component condensation with aldehyde 48, n-propylamine and n-propylisonitrile (Scheme 14a). The aldehyde was changed from 30 to 48 because it was found that elimination of the carbonate proceeded smoother then elimination of the benzoate with DBU. The N-acyl-α-amino acid formed 49 was then oxidized with ozone to yield the α-ketoamide 50. Treatment with DBU affected three successive transformations; 1) elimination of acetic acid to 51, 2) cyclization to piperazinedione 52 and 3) elimination of the carbonate to form the methylidene piperazinedione 53. Hydrolysis of the acetate 53 with NaOH gave the desired diol 54 (Scheme 14b).
Scheme 14a

\[ \text{AcO} \quad \text{CHO} \quad \text{PrNH} \quad \text{Pr} \quad \text{MeOH} \quad \Delta \quad \text{PrNH} \quad \text{Pr} \quad \text{OCO}_2\text{Et} \]

1) O$_3$

2) Me$_2$S

\[ \text{AcO} \quad \text{CHO} \quad \text{PrNH} \quad \text{Pr} \quad \text{OCO}_2\text{Et} \quad \text{PrNH} \quad \text{Pr} \quad \text{OCO}_2\text{Et} \]

\[ \text{HO} \quad \text{PrN} \quad \text{NPr} \quad \text{PrN} \quad \text{NPr} \quad \text{OCO}_2\text{Et} \]

\[ \text{HO} \quad \text{PrN} \quad \text{NPr} \quad \text{OCO}_2\text{Et} \]

\[ \text{HO} \quad \text{PrN} \quad \text{NPr} \quad \text{OCO}_2\text{Et} \]

\[ \text{HO} \quad \text{PrN} \quad \text{NPr} \quad \text{OCO}_2\text{Et} \]
As expected, this diol was very unstable under acidic conditions. Brief treatment with HCl in dichloromethane at room temperature gave the spiro compound 55 as the only product (Scheme 15). Cyclization with pyridinium bromide
perbromide and excess pyridine in dichloromethane successfully gave the bicyclic bromide 56. Unfortunately, bromide 56 proved to be unreactive. All attempts at $S_N^2$ displacement of the bromine failed. This failure is probably due to the poor reactivity for $S_N^2$ reactions in the neopentyl position.

Consequently other oxidizing agents besides halogenating reagents were explored. The major requirement was that the bicyclic system formed contained an aldehyde equivalent. A sulfide would be acceptable on this basis because oxidation to the sulfoxide followed by Pummerer rearrangement would give an $\alpha$-acetoxy sulfide. Hydrolysis of an $\alpha$-acetoxy sulfide should yield an aldehyde. It is known that addition of sulfenyl halides to olefins proceeds through an episulfonium intermediate. Attack of the sulfenyl halide with the more reactive olefin should lead to the bicyclic system. Unfortunately neither benzene-sulfenyl chloride or benzenesulfenyl bromide under a variety of conditions produced the desired bicyclic system. Another possibility is the use of selenium reagents.

In this case, treatment of diol 54 with benzenselenyl chloride and excess pyridine in dichloroethane gave the bicyclic selenide 57 (Scheme 16). Subsequent oxidation with m-chloroperoxybenzoic acid (mCPBA) to the selenoxide and Pummerer rearrangement with acetic anhydride and triethylamine gave the $\alpha$-acetoxy selenide 58. Basic hydrolysis
with NaOH in methanol gave the aldehyde 59. Unfortunately this aldehyde, which is a key intermediate in the

Scheme 16

retrosynthetic analysis, could not be obtained in a pure form. This is presumably due to its ease of hydration or hemiacetal formation (60a or 60b). The three substituents α to the aldehyde are all electron withdrawing so as to leave the carbonyl electron deficient and susceptible to nucleophilic attack.
Attempts were made to use the aldehyde 59 in further reactions without purification. In this regard, alkyl-lithium and Grignard reagents proved to be unsuccessful for alkylations. Treatment with triethyl 2-phosphono-propionate and LDA in tetrahydrofuran gave no desired product but instead the deformylated compound 61 (Scheme 17).

Scheme 17

\[
\begin{align*}
\text{(EtO)}_2P\text{CH(Me)CO}_2\text{Et} & \xrightarrow{\text{LDA}} \text{61} \\
\text{59} & \xrightarrow{\text{Ph}_3\text{P}=\text{C(Me)CO}_2\text{Et}} \text{toluene} \quad \text{62}
\end{align*}
\]
This is in agreement with the results of Williams.\textsuperscript{11a} The Wittig reaction with ethyl 2-(triphenylphosphoranylidene) propionate in toluene gave the desired product \textsuperscript{62} but with some problems. The reaction proceeded slowly and there was significant decomposition of the starting material with prolonged heating. This contributed to the low yield (\textasciitilde 30\%) for the reaction.

The configuration of the double bond also remains a problem. Both isomers were formed and separated with E> Z but the exact ratio was not determined (\textsuperscript{1H-NMR of olefin proton Z=5.96\&, E=6.8\&). In order to insure the correct stereochemistry for the side chain, a different scheme would be needed for each isomer. Because of these complications, other methods to obtain the aldehyde \textsuperscript{52} were examined.

Perhaps the aldehyde was not inherently unstable but just under the harsh conditions used in the hydrolysis. Therefore milder conditions were needed for this transformation. Reduction of the $\alpha$-acetoxyselenide \textsuperscript{58} with diisobutylaluminum hydride (DIBAL-H) gave the desired aldehyde \textsuperscript{59}. The aldehyde seemed to partially decompose during purification so it was used without purification. While the Wittig reaction still proceeded slowly and in low yield, alkylation of the aldehyde with alkyl lithium reagents was successful. This was somewhat encouraging in that the
desired alcohol 63 could be isolated (Scheme 18). Unfortunately the yields were low and some of the unreacted aldehyde 59 was also recovered.

Scheme 18

Another possibility considered was a two step process. First the α-acetoxyxelenide 58 would be hydrolyzed and reduced to the alcohol 64 with NaOH and sodium borohydride in one pot. Mild oxidation of the alcohol 64 under the aprotic conditions of Swern;\(^\text{28}\) (oxalyl chloride, DMSO, Et\(_3\)N in dichloromethane), would give the aldehyde 59 (Scheme 19). While the alkylation proceeded slightly better than before, the yields were still not acceptable. The reaction was difficult to control and the combined yield for oxidation and alkylation ranged from ~15 to 30\%.
These disappointing results warranted a modification of the strategy. If the carbon side chain were attached before the formation of the bicyclic system, these problems would possibly be avoided. This could be done at the very beginning of the synthesis by changing the aldehyde used in the four-component condensation. Depending on the functionalization desired, many possibilities existed for the aldehyde. One basic structure is shown below.

If this route were to be successful, R=CH₃ would lead to bicyclomycin. Since this would introduce a chiral center at the beginning, R=H was used for a model system. This might not be a useful model for steric reasons but the greater ease in interpretation of the results would be more
beneficial. For $X$, it has been shown that carbonates are better than esters for the elimination. The main choice then is what protecting group to use for $R'$. This will depend on the stability of the system to the deprotection conditions. Scheme 20 shows a general procedure for the preparation of the aldehydes of this basic structure.

**Scheme 20**

\[
\begin{align*}
\text{Ph} \quad \text{OHC} & \quad \text{LDA} \quad \text{HO} \quad \text{CO}_2\text{Et} \\
\text{R} & \quad \text{CO}_2\text{Et} & \\
\end{align*}
\]

1) $\text{OEt H}$
2) LiAlH$_4$
3) protection

\[
\begin{align*}
\text{Ph} \quad \text{R} & \quad \text{CO}_2\text{Et} \\
\text{65} & \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO} \quad \text{O} \quad \text{R} & \quad \text{O} \quad \text{R}' \\
\text{1)} \text{AcOH: H}_2\text{O} & \quad \text{2)} \text{ClCO}_2\text{Et-Py} \\
\text{3)} \text{O}_3 & \quad \text{4)} \text{Me}_2\text{S} \\
\text{66} & \quad \text{CHO} \\
\text{EtO}_2\text{CO} & \quad \text{R} \\
\text{R'} & \\
\text{67} & \\
\end{align*}
\]
For R=H, condensation of ethyl acetate anion (generated from ethyl acetate and LDA) with cinnamaldehyde gave 65. Protection of the alcohol 65 with ethyl vinyl ether, reduction of the ester with LiAlH₄ and protection of the terminal alcohol gave 66. Many possible groups were used for protecting this alcohol, with methoxyethoxymethyl ether 29 (MEM) appearing to be the best. Deprotection of the secondary alcohol, conversion to the ethyl carbonate and finally ozonolysis gave the aldehyde 67. In order for some of these aldehydes to be used in the four-component condensation, it was necessary to also change the carboxylic acid.

This is not obvious unless past experimental observations are examined. Ozonolysis of compound 49 to form the α-keto amide 50 was very slow so any protecting group that was somewhat sensitive to ozone could not be used. Also, hydrolysis of the acetate 53 would prohibit use of any base sensitive protecting group. With these restrictions, a carboxylic acid of type B (see page 16) would be more useful. As the number of protecting groups being used increases, care must be taken to insure selectivity in their removal. The protecting group chosen for the carboxylic acid was a p-methoxyphenyl ether. Oxidation with ceric ammonium nitrate 30 (CAN) would lead to the desired alcohol and p-benzoquinone as a by-product. Synthesis of a carboxylic acid of this type is shown in Scheme 21.
Scheme 21

1) \text{OMs} \\
\text{NaOH} \\
2) \text{O}_3 \\
3) \text{Me}_2\text{S} \\

\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{H} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{CHO} & \quad \text{CHO} \\
\text{68} & \quad \text{68}
\end{align*}

\text{Mannich reaction}

\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{OMe} & \quad \text{OMe} \\
\text{69} & \quad \text{69}
\end{align*}

1) \text{TMS-CN} \\
\text{TiCl}_4 \\
2) \text{HCl, EtOH} \\

\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{Et} & \quad \text{Et} \\
\text{CO}_2 & \quad \text{CO}_2 \\
\text{70} & \quad \text{71}
\end{align*}

\text{NaOH} \\
\text{MeOH} \\

\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{70} & \quad \text{71}
\end{align*}
Condensation of p-methoxyphenol with NaOH and 4-pentenyl mesylate followed by ozonolysis gave the aldehyde 68. A Mannich reaction21 as before gave the unsaturated aldehyde 69. Treatment with trimethylsilyl cyanide (TMS-CN) and titanium tetrachloride31 gave the cyanohydrin trimethylsilyl ether which was converted directly to the α-hydroxy ester 70 with HCl in ethanol. Hydrolysis with NaOH gave the carboxylic acid 71.

The carboxylic acid 71 was mixed with aldehyde 67 (R=H, R'=MEM), n-propylamine and n-propylisonitrile in the four-component condensation (Scheme 22). The N-acyl-α-amino acid amide 72 formed was oxidized with N,N-dicyclohexylcarbodiimide (DCC), DMSO and dichloroacetic acid32 under mild conditions to give the α-keto amide 73. Cyclization and elimination with DBU gave the alkyldenepiperazinedione 74 as a mixture of isomers. Oxidation of the aromatic system with ceric ammonium nitrate provided the diol 75 which is ready for cyclization. In the previous route, two reagents were found useful for cyclization to the bicyclic system and both were tested for this system. While treatment of 75 with pyridinium bromide perbromide and excess pyridine led to the bicyclic bromide 76a, benzene-selenyl chloride in the presence of excess pyridine gave none of the desired bicyclic product 76b and only a small amount of the possible spiro system 77 was obtained (Scheme 23).
Scheme 22

\[
\begin{align*}
&\text{n-PrN} = C + \text{H}_2\text{N} \, \text{n-Pr} \\
&\xrightarrow{\text{MeOH} \quad \Delta} \\
&\text{CHO} \\
&\text{EtOCO}_2 \text{CHO} \\
&\text{OMEM}
\end{align*}
\]

71

\[
\begin{align*}
&\text{OAr} \\
&\text{PrNH} \text{NPr} \\
&\text{EtOCO}_2 \text{OMEM}
\end{align*}
\]

72

\[
\begin{align*}
&D\text{CC, DMSO} \\
&\text{OAr} \\
&\text{PrNH} \text{NPr} \\
&\text{EtOCO}_2 \text{OMEM}
\end{align*}
\]

73

\[
\begin{align*}
&\text{DBU} \\
&\text{HO} \\
&\text{PrN} \text{NPr} \\
&\text{OMEM}
\end{align*}
\]

74

\[
\begin{align*}
&\text{CAN} \\
&\text{HO} \\
&\text{PrN} \text{NPr} \\
&\text{OMEM}
\end{align*}
\]

75
This was an unexpected result. It was planned that the selenide 76b could be converted to the olefin and then stereospecifically dihydroxylated. The lack of cyclization is possibly due to steric hindrance. With addition of substituents on the olefin, formation of the intermediate carbonium ion would be retarded (see Scheme 10). Also, intramolecular attack by the alcohol could be retarded by these same substituents.

To verify if the protected alcohol functionalization was interfering with the cyclization, compound 78 was prepared (Scheme 24). Cyclization of 78 with pyridinium bromide perbromide and excess pyridine gave the bicyclic bromide 79a, treatment with benzeneselenenyI chloride and excess pyridine failed to yield the selenide 79b. Thus
this reagent was excluded for the cyclization of any substituted system. Therefore, attention was now directed towards the use of the bromide \(76a\).

Scheme 24

\[
\begin{align*}
\text{78} & \rightarrow \text{79a} \quad x = \text{Br} \\
\text{79b} & \quad x = \text{SePh}
\end{align*}
\]

Deprotection of the MEM ether\(^{29}\) \(76a\) was effected with titanium tetrachloride at \(0^\circ\) to give the alcohol \(80\) (Scheme 25). Oxidation with pyridinium chlorochromate\(^{33}\) (PCC) to the aldehyde followed by elimination of hydrogen bromide with DBU gave the \(\alpha,\beta\)-unsaturated aldehyde \(81\). The configuration of the double bond remains unknown but is believed to be trans for steric reasons (the coupling constant \(J_{AB}\) could not be determined).
Scheme 25

\[ \text{76a} \xrightarrow{\text{TiCl}_4} \text{80} \xrightarrow{1)\text{PCC}} 2)\text{DBU} \rightarrow \text{81} \]

The sequence was now repeated using aldehyde 67 (R=CH\text{3}, R'=\text{CO}_2\text{Me}). Cyclization of the alkylidene-piperazine-dione 82 with pyridinium bromide perbromide and excess pyridine gave the bicyclic bromide 83a (Scheme 26). Hydrolysis of the carbonate 83a gave the alcohol 83b which was oxidized with pyridinium chlorochromate to yield the aldehyde 84. Elimination with DBU gave the α,β-unsaturated aldehyde 85 as a single compound. The configuration of the olefin could not be confirmed but is believed to be the E isomer. While the aldehyde 85 could be obtained, some problems were associated with this route. Formation of compound 83 was difficult because of further reaction of the product under the reaction conditions. Cyclization to the bicyclic bromide 83a proceeded slowly and with low yield.
For these reasons, the first idea of addition of the carbon side chain at a later stage must be reexamined. Aldehyde 52 had already been prepared and was used in attempted alkylations. A more thorough study of this alkylation was undertaken along with other possible methods for carbon-carbon bond formation. In the course of these studies, it was found that direct treatment of the α-acetoxyoxyselenide with alkyllithium reagents led to the alkylated
products. The aldehyde 59 is generated "in situ" and reacts with excess alkyllithium.

In this manner the α-acetoxyxyseleneide 58 was treated with excess 2-propenyllithium, prepared from 2-bromopropene and lithium wire34 at -78° in THF, to give a diastereomeric mixture of the allyl alcohols 86 (Scheme 27).

Instead of separating the isomers at this stage, the mixture was oxidized to the enone 87 with Jones reagent35 (CrO3, H2SO4, H2O) in acetone at 0°. This was done for two reasons; it avoids the separation of the alcohols and it helps to distinguish the two double bonds for subsequent reactions. The enone 87 was cis-dihydroxylated with osmium tetroxide in THF followed by hydrogen sulfide to give the triol 88. This reaction appears to be not only regiospecific but also stereospecific in that only one compound is formed based on NMR and tlc analysis. Protec-
tion of the diol 88 with 2,2-dimethoxypropane and camphor-
sulfonic acid (CSA) gave the acetonide 89.
The entire framework of bicyclomycin is now complete. All that remains is reduction of the ketone and deprotection of the amides (when not using model compounds). Attempted reduction of the ketone 89 failed but only a few reagents were used. The system might be too crowded sterically (quaternary carbons on both sides of the carbonyl group) for attack by the reducing agent. Perhaps deprotection of the amide first would improve the possibility for the reduction.

Bicyclomycin is interesting as a synthetic target in that the task of devising suitable protecting groups for the amides is very challenging. Both Williams\textsuperscript{11} and Nakatsuka\textsuperscript{13} have presented papers using N,N'-dimethylamides but neither have mentioned the use of protecting groups. Few examples for protecting groups for amides exist in the literature but previous work in our group on other projects\textsuperscript{36} has proven useful.

One approach that was successful was the utilization of a retro-Michael addition. Frank\textsuperscript{36} found that elimination of acrylonitrile from a 2-cyanoethyl amide failed when treated with a base. In our studies, the reaction proceeded but was dependent on the base used. The bicyclic selenide 90 was prepared in the same manner as the selenide 57 (page 27) was with the substitution of 2-cyanoethylisonitrile for \textit{n}-propylisonitrile. Treatment of the nitrile 90 with
three equivalents of \( n \)-butyllithium at \(-78^\circ\) gave the deprotected compound 91 cleanly (Scheme 28). Other bases gave Scheme 28

\[\begin{align*}
\text{NC} & \quad \text{N} & \quad \text{Pr} \\
\text{OH} & \quad \text{O} & \quad \text{SePh} \\
\text{O} & \quad \text{O} & \quad \text{SePh} \\
\text{n-BuLi} & \quad & \quad 91
\end{align*}\]

90

either incomplete reactions or no reaction at all. Fortunately, the deprotection failed when 2-propenyllithium was used. This means that the protecting group would survive the conditions for elaboration of the carbon side chain. Because of the mode of deprotection, this protecting group could not be utilized for both amides but only the one shown, compound 90. If it were used on the other amide, 92, the bicyclic system could be destroyed by rearrangement of anion 93 to 94 (Scheme 29).
For protection of this amide, a different approach is needed. One possibility is the decomposition of the amidal 96 which would yield the secondary amide 97 and the aldehyde 98 (Scheme 30). The amidal 96 could be seen to arise from the enamide 95. For the cyclization to the bicyclic system, an enamide is oxidized with intramolecular attack of an alcohol (see Scheme 10). If the reaction were carried out in the presence of water, the amidal 96 would be formed. This series of reactions has been successful for the formation of secondary amides 97 where N-bromosuccinimide (NBS) in THF:H₂O (3:1) was used for the oxidation to the amidal 96 and sodium bicarbonate for its decomposition. Another
possible deprotection of the enamide 95 would be ozonolysis to the formimide 99 then methanolysis with MeOH and triethylamine to give the deprotected amide 97. This scheme is not usable because of the presence of another olefin. Obviously, the enamide 95 must be masked until time for its deprotection.

Closer examination of the piperazinedione system reveals that the amide nitrogen for this deprotection arises from the amine component in the initial condensation. A suitable amine would be one that had a substituent in the β-position and that could be converted to the enamide. This
substituent must also survive all of the previous reaction conditions. Two routes are considered to be useful that utilize available starting materials.

The first route involves the use of aminoacetaldehyde diethylacetal (Scheme 31). Acid hydrolysis of the acetal 100 would give the aldehyde 101. Treatment with acetic anhydride and sodium acetate would give the enol acetal-enamide 102. Deprotection as mentioned before (Scheme 30) would give the deprotected amide 97. The second route provides more flexibility. In this case, a protected ethanolamine is used (Scheme 32). At the proper time, this is deprotected to the terminal alcohol 103b. Conversion to the selenide 104 can be accomplished in either one step (ArSeCN, n-Bu$_3$P$_3$ or N-PSP, n-Bu$_3$P$_3$) or two steps (1. MsCl/TEA 2. (PhSe)$_2$/NaBH$_4$). The selenide 104 can now be
oxidized to the selenoxide and eliminated to give the desired enamide 95. Final deprotection to the secondary amide 97 is done as before (Scheme 30).

Scheme 32

\[ \text{Scheme 32} \]

\[ 103a \quad R=\text{any protecting group} \]

\[ 103b \quad R=H \]

\[ \rightarrow \]

\[ 95 \]

\[ \rightarrow \]

\[ 97 \]

A wide variety of protecting groups for the alcohol 103b could be used in this second route. The decision will depend upon which protecting groups are used in other parts of the molecule. It should be noted that this route, oxidation of an enamide, could be used for both amides. This leaves open the possibility for simultaneous deprotection of both amides.

In this attempt of the total synthesis of bicyclomycin, a large number of routes have been examined. Most have been
unsuccessful but their failures have led to other ideas. The major route discussed appears most likely to eventually yield the final product. Attempts at finding the right combination of protecting groups and conditions for some of the reactions are still in progress in our group.
IV. Experimental

General Procedure

Medium pressure liquid chromatography (MPLC) purification was carried out with a Fluid Metering Inc. pump attached to Altex glass columns filled with Woelm silica gel, 32-63 mesh. High performance liquid chromatography (HPLC) was carried out with a Waters 6000 solvent delivery system attached to Altex glass columns filled with Woelm silica gel, 32-63 mesh. Reactions were followed by thin-layer chromatography (tlc) using Merck 60 F-254 precoated silica gel plates, 0.25 mm thick.

Reactions requiring an inert atmosphere were run under a blanket of argon. Ozonolysis was carried out using a Welsbach Corp. Ozonator.

$^1$H-NMR spectra were recorded on either a Varian EM-390 or a JEOL FX-90Q spectrometer at 90 MHz and are reported as downfield in ppm from tetramethylsilane ($\delta=0$). Coupling constants are reported in Hz and multiplicity is reported as follows: s=singlet, brs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet. $^{13}$C-NMR were recorded on a JEOL FX-90Q spectrometer at 22.49 MHz and are reported as downfield from tetramethylsilane with deuteriochloroform as an internal standard $\left[\delta_{(TMS)}=\delta_{(CDCl_3)}+77.1\text{ ppm}\right]$. All
$^{13}$C-NMR spectra were recorded with the protons completely decoupled.

Low resolution mass spectra (MS) were obtained on a Finnigan 3300 quadrupole mass spectrometer attached to a Finnigan 6100 data system. High resolution mass spectra for exact mass determination were obtained on a CEC/Dupont 21-110B double focusing high resolution mass spectrometer.

Elemental analysis was performed by Galbraith Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected. Melting points were obtained with a Meltemp melting point apparatus.

Solvents and reagents were purified prior to use when deemed necessary; tetrahydrofuran and ether (distilled from benzophenone ketone); dichloromethane (stored over Al₂O₃); 1,2-dichloroethane (distilled and stored over Al₂O₃); DMSO (stored over 4A molecular sieve). Other reagents were either commercially available or were prepared according to published procedures.
Reduction of Anhydride 43

γ-Phenylallylsuccinic anhydride was prepared\textsuperscript{20} on a 0.5 mole scale and used without purification. A solution of the anhydride 43 in THF (200 ml) was added dropwise to a slurry of lithium aluminum hydride (28.5 g, 0.75 mole) in THF (600 ml). When the addition was complete, the reaction was quenched by careful addition of water (30 ml), 3N sodium hydroxide (30 ml), and water (90 ml) successively. Magnesium sulfate (150 g) was added and the slurry was filtered through celite, washed with ether and evaporated. The residue was used without purification. \textsuperscript{1}H-NMR: 1.6-1.8 (m, 3 H), 2.1-2.3 (t, J=6 Hz, 2 H), 3.5-3.8 (m, 4 H), 6.2 (dt, J=7 Hz, 16 Hz, 1 H), 6.4 (d, J=16 Hz, 1 H), 7.1-7.4 (m, 5 H).

Diacetate 44

Acetic anhydride (141 ml, 1.5 mole) was added to a solution of the crude diol in pyridine (121 ml, 1.5 mole) and the reaction mixture was stirred at room temperature for 45 minutes. The solvent was evaporated under vacuum then toluene (75 ml) was added to the residue and again the solvent was evaporated under vacuum. The residue was used without purification. A small sample was purified by MPLC (ether:hexane gradient). \textsuperscript{1}H-NMR: 1.6-1.9 (m, 3 H), 2.04 (s, 3 H), 2.06 (s, 3 H), 2.3 (t, J=6 Hz, 2 H), 4.05
(d, J=6 Hz, 2 H), 4.16 (t, J=6 Hz, 2 H), 6.2 (dt, J=7, 16 Hz, 1 H), 6.5 (d, J=16 Hz, 1 H), 7.2-7.4 (m, 5 H). MS: 290 (M⁺), 230 (-C₂H₄O₂), 170 (-C₄H₈O₄) exact mass: calculated m/e 290.1518 found 290.1524.

**Aldehyde 45**

Ozone was bubbled through a solution of the crude acetate **44** in methanol:dichloromethane (25%, 200 ml), at -78°C for 1.5 hours. The solution was flushed with argon to remove excess ozone then dimethyl sulfide (81 ml, 1.1 mole) was added. The reaction mixture was slowly warmed to room temperature and then set for 30 minutes. Triethylamine (2 ml) was added and the solvent was carefully evaporated. The residue was used without purification. A small sample was purified by MPLC (ether:hexane gradient).

**¹H-NMR:** 1.6-1.9 (m, 3 H), 2.08 (s, 6 H), 2.5 (brs, 2 H), 4.0-4.25 (m, 4 H), 9.8 (t, J=1.3 Hz, 1 H) MS: 216 (M⁺), 187 (-CHO), 173 (-C₂H₃O) exact mass: calculated m/e 216.0997 found 216.1002.

**Aldehyde 46**

A solution of the crude aldehyde **45**, dimethylamine hydrochloride (80.5 g, 1 mole), formaldehyde (38%, 118 ml, 1.5 mole), and triethylamine (14 ml, 0.1 mole) in
ethanol:water (60%, 100 ml) was stirred at 60°C for 1.5 hours. The reaction mixture was evaporated to a small volume and then partitioned between ether and dilute sodium chloride. The aqueous layer was washed with ether and the ether layers were combined and washed with brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by distillation under reduced pressure (bp 135°C/7 mm) to yield 29 g (25% overall). \(^1\)H-NMR: 1.7-2.2 (m, 2H), 2.04 (s, 6 H), 3.1 (m, 1 H), 4.0 (d, J=6 Hz, 2 H), 4.1 (t, J=6 Hz, 2 H), 6.2 (s, 1 H), 6.38 (s, 1 H), 9.57 (s, 1 H) MS: 228 (M\(^+\))

exact mass: calculated m/e 228.0997 found 228.0992.

**Carboxylic Acid 47**

A solution of the aldehyde \(\text{46} \) (29 g, 0.13 mole) and selenium dioxide (1.45 g, 5% by weight) in \(\text{t-butanol} \) (145 ml) was heated to 60°C. Slowly, hydrogen peroxide (30%, 29 ml, 1 ml/g) was added with stirring and the reaction mixture was heated for 3 hours. The reaction mixture was then partitioned between ether, saturated sodium bicarbonate and brine. The organic layer was then washed two times with saturated sodium bicarbonate and brine. The aqueous layers were combined, washed with ether and the combined ether extracts were discarded. The aqueous layer was then acidified with concentrated hydrochloric acid and
washed two times with ether. The ether layers were combined and washed with brine. The organic layer was dried over magnesium sulfate and evaporated to yield 22.65 g (73%). No further purification was necessary. $^1$H-NMR: 1.8-2.1 (m, 2 H), 2.04 (s, 6 H), 3.04 (m, 1 H), 4.04 (d, J=6 Hz, 2 H), 4.16 (t, J=6 Hz, 2 H), 5.78 (s, 1 H), 6.44 (s, 1 H), 7.0-7.6 (brs, 1 H). MS: 244 (M$^+$), 199 (-CO$_2$H), 185 (-OAc), 184 (-C$_2$H$_4$O$_2$) exact mass: calculated m/e (M$^+$-CO$_2$H) 199.0970 found 199.0970.

Aldehyde 48

Ozone was bubbled through a solution of allyl ethyl carbonate$^{40}$ (42.85 g, 0.33 mole) in methanol (250 ml) at -78$^\circ$ for 3 hours. The solution was flushed with argon then dimethyl sulfide (47 ml, 0.64 mole) was added. The reaction mixture was slowly warmed to room temperature and more dimethyl sulfide (23 ml, 0.31 mole) was added. The reaction mixture was set for 30 minutes then the solvent was carefully evaporated to a small volume. The residue was partitioned between ether and dilute sodium chloride. The aqueous layer was washed two times with ether and the ether layers were combined and washed with dilute sodium chloride. The organic phase was dried with magnesium sulfate and evaporated. The residue was purified by
distillation under reduced pressure (bp 75^0/10 mm) to yield 34.81 g (80 %). \(^1^H\)-NMR: 1.36 (t, J=7 Hz, 3 H), 4.25 (q, J=7 Hz, 2 H), 4.7 (s, 2 H), 9.6 (s, 1 H) MS: 132 (M\(^+\)) exact mass: calculated m/e 132.0422 found 132.0426.

**Four-Component Condensation Product 49**

\(n\)-Propylamine (1.81 ml, 0.022 mole) was added to a solution of aldehyde 48 (2.65 g, 0.02 mole) in methanol (15 ml) at 0\(^\circ\) and stirred for 10 minutes. Carboxylic acid 47 (4.88 g, 0.02 mole) in methanol (10 ml) was then added and the mixture was stirred for 5 minutes. Finally, \(n\)-propylisonitrile (2.15 ml, 0.024 mole) was added and the reaction mixture was stirred for 1 hour at 0\(^\circ\) then 6 hours at room temperature. The solvent was evaporated and the residue was purified by MPLC (ether: hexane gradient) to yield 7.29 g (75 %). \(^1^H\)-NMR: 0.8-1.0 (m, 6 H), 1.3 (t, J=7 Hz, 3 H), 1.2-2.1 (m, 6 H), 2.05 (s, 6 H), 2.6-3.8 (m, 5 H), 3.9-4.4 (m, 6 H), 4.5-4.9 (m, 2 H), 5.4 (brs, 2 H), 6.6-7.0 (brs, 1 H); MS: 486 (M\(^+\)), 400 (-C\(_4\)H\(_8\)NO) exact mass: calculated m/e 486.2024 found 486.2021.

**Methylidenepiperazinedione 53**

Ozone was bubbled through a solution of compound 49 (6.2 g, 0.013 mole) in ethyl acetate (200 ml) at -78\(^\circ\) for
2 hours. The solution was flushed with argon and dimethyl sulfide (9 ml, 0.127 mole) was added. The reaction mixture was slowly warmed to room temperature then partitioned between ethyl acetate, saturated sodium bicarbonate and brine. The aqueous layer was washed with ethyl acetate and the combined organic layers were washed with brine. The organic layer was dried with magnesium sulfate and evaporated to yield compound 50 which was used quickly and without purification.

DBU (3.8 ml, 0.026 mole) was added to the impure material 50 in benzene (50 ml) and the solution was stirred at 50° for 15 minutes. The reaction mixture was partitioned between ether, brine and 3N hydrochloric acid and then the aqueous layer was washed with ether. The organic layers were combined and washed with brine followed by saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by MPLC (ether:hexane gradient) to yield 2.37 g (55%). $^1$H-NMR: 0.89 (t, J=7.5 Hz, 3 H), 0.92 (t, J=7.5 Hz, 3 H), 1.4-1.9 (m, 4 H), 2.03 (s, 3 H), 2.33 (m, 2 H), 2.88-3.20 (m, 1 H), 3.37-3.98 (m, 3 H), 4.2 (t, J=7 Hz, 2 H), 4.6 (s, 1 H), 5.04 (d, J=1.3 Hz, 1 H), 5.18 (s, 1 H), 5.22 (s, 1 H), 5.98 (d, J=1.3 Hz, 1 H). $^{13}$C-NMR: 170.0, 165.2, 158.7, 143.3, 136.0, 115.3, 103.9, 86.1, 62.7, 45.7, 44.9, 29.2, 22.1, 20.7, 19.4, 11.4, 10.9
MS: 338 (M⁺), 321 (-OH), 295 (-C₂H₅O), 225 (-C₆H₉O₂)  
exact mass: calculated m/e 338.1841 found 338.1844.

Diol 54

Sodium hydroxide (3N, 2 ml, 0.006 mole) was added to a solution of the acetate 53 (2.02 g, 0.006 mole) in methanol (25 ml) at room temperature and the reaction mixture was set for 15 minutes. Dry ice was added and the solvent was evaporated. The residue was partitioned between ethyl acetate and brine then the aqueous layer was washed with ethyl acetate. The organic layers were combined and washed with brine. The organic layer was dried with magnesium sulfate and evaporated to yield 1.63 g (92%). The residue was used without further purification. ¹H-NMR: 0.92 (t, J=7.5 Hz, 3 H), 0.98 (t, J=7.5 Hz, 3 H), 1.4-2.0 (m, 4 H), 2.3 (m, 2 H), 2.8-3.3 (m, 1 H), 3.4-4.0 (m, 5 H), 5.0 (d, J=1.3 Hz, 1 H), 5.2 (s, 2 H), 5.96 (d, J=1.3 Hz, 1 H) ¹³C-NMR: 164.7, 158.2, 144.6, 135.3, 114.9, 102.7, 86.0, 61.2, 44.7, 32.9, 21.6, 18.8, 10.9, 10.4 MS: 296 (M⁺), 279 (-OH), 225 (-C₄H₇O)  exact mass: calculated m/e 296.1736 found 296.1739.
Spiro System 55

Hydrochloric acid gas was bubbled through a solution of the diol 54 (303 mg, 1.02 mmole) in dichloromethane (10 ml) at room temperature for 10 minutes. The solvent was evaporated and the residue was purified by MPLC (ether: hexane gradient) to yield 196 mg (67%). $^1$H-NMR: 0.89 (t, $J=7.2$ Hz, 3 H), 0.93 (t, $J=7.2$ Hz, 3 H), 1.4-1.9 (m, 4 H), 2.64-3.08 (m, 3 H), 3.32-3.88 (m, 3 H), 4.08-4.56 (m, 2 H), 4.95 (d, $J=1.3$ Hz, 1 H), 5.03 (m, 1 H), 5.28 (m, 1 H), 5.92 (d, $J=1.3$ Hz, 1 H). $^{13}$C-NMR: 164.0, 157.6, 148.2, 134.7, 109.3, 101.9, 93.3, 67.7, 45.7, 44.0, 31.0, 21.6, 18.8, 11.3, 10.7 MS: 278 (M$^+$), 208 (-C$_4$H$_6$O) exact mass: calculated m/e 278.1630 found 278.1629.

Bicyclic Bromide 56

Pyridinium bromide perbromide (358 mg, 1.19 mmole) was added to a solution of the diol 54 (301 mg, 1.02 mmole) and pyridine (411 µl, 5.08 mmole) in dichloromethane (5 ml) at room temperature under an atmosphere of argon. The mixture was stirred for 15 minutes then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by MPLC (ether:
hexane gradient) to yield 248 mg (65%). Crystallization from ether:hexane (1:3) gave white crystals, mp 88°-90°.

$^1$H-NMR: 0.91 (t, J=7 Hz, 3 H), 0.97 (t, J=7 Hz, 3 H), 1.4-2.0 (m, 4 H), 2.12-2.72 (m, 2 H), 2.88-4.10 (m, 6 H), 3.48 (d, J=11 Hz, 1 H), 4.36 (d, J=11 Hz, 1 H), 4.88 (brs, 1 H), 5.17 (s, 1 H), 5.62 (s, 1 H) $^{13}$C-NMR: 169.8, 163.1, 147.1, 118.5, 89.3, 84.1, 65.9, 45.5, 43.7, 34.6, 32.5, 21.8, 21.5, 11.5, 11.2 MS: 376/374 (M$^+$), 295 (-Br), 210 (-C$_2$H$_9$BrO) exact mass: calculated m/e 376.0821 found 376.0821, calculated m/e 374.0841 found 374.0846 analyzed for C$_{15}$H$_{23}$BrN$_2$O$_4$ (calculated: C 48.01, H 6.18) found: C 48.13, H 6.30.

**Bicyclic Selenide 57**

Benzeneselenenyl chloride (810 mg, 4.24 mmole) was added to a solution of the diol 54 (1.14 g, 3.85 mmole) and pyridine (1.55 ml, 19.3 mmole) in dichloroethane (6 ml) at room temperature under an atmosphere of argon. The mixture was stirred for 30 minutes at 70° then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (ether:hexane gradient) to yield 1.16 g (67%). Crystallization from ether:hexane (1:4) gave pale yellow crystals,
mp 114°-115°. \(^1\)H-NMR: 0.82 (t, J=7 Hz, 3 H), 0.92 (t, J=7 Hz, 3 H), 1.4-1.9 (m, 4 H), 2.1-2.7 (m, 2 H), 2.82-4.08 (m, 6 H), 3.4 (d, J=12.3 Hz, 1 H), 3.99 (d, J=12.3 Hz, 1 H), 4.9 (s, 1 H), 5.18 (s, 1 H), 5.6 (s, 1 H), 7.12-7.68 (m, 5 H). \(^13\)C-NMR: 169.8, 164.1, 147.3, 133.1, 130.1, 128.9, 127.3, 118.2, 90.4, 84.0, 65.4, 45.8, 43.7, 34.7, 33.8, 21.8, 21.3, 11.4 MS: 452/450 (M\(^+\)), 381/379 (\(\text{C}_{4}\text{H}_{7}\text{O}\)) exact mass: calculated m/e 452.1214 found 452.1203, calculated m/e 450.1222 found 450.1225 analyzed for \(\text{C}_{21}\text{H}_{28}\text{N}_{2}\text{O}_{4}\text{Se}\) (calculated: C 55.87, H 6.25) found: C 55.93, H 6.11.

\(\alpha\)-Acetoxy selenide 58

mCPBA (80 %) was added to a solution of the selenide 57 (1.12 g, 2.48 mmole) in dichloromethane (15 ml) at 0° with good stirring until the reaction was complete. Excess dimethyl sulfide (2 ml) was added and the reaction mixture was partitioned between dichloromethane, saturated sodium bicarbonate and brine. The aqueous layer was washed with dichloromethane and the organic layers were combined. The organic layer was then dried with sodium sulfate and evaporated. The crude selenoxide was used without purification.

Triethylamine (0.37 ml, 2.48 mmole) was added to a solution of the selenoxide and acetic anhydride (1.26 ml,
12.4 mmole) in dichloromethane (10 ml) at room temperature. The mixture was stirred for 1 hour then partitioned between ether, brine, and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by MPLC (ether: hexane gradient) to yield 1.15 g (91%). $^1$H-NMR: 0.7-1.2 (m, 6 H), 1.4-2.0 (m, 4 H), 2.1 (s, 3 H), 2.2-2.7 (m, 2 H), 2.8-4.3 (m, 9 H), 4.9 (brs, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H), 7.2-8.4 (m, 5 H) MS: 510/508 (M⁺), 353 ($-\text{C}_6\text{H}_5\text{Se}$) exact mass: calculated m/e 510.1269 found 510.1275, calculated m/e 508.1277 found 508.1285 analyzed for C$_{23}$H$_{30}$N$_2$O$_6$Se (calculated: C 54.22; H 5.93) found: C 54.19, H 5.98.

**Basic Hydrolysis of 58**

Sodium hydroxide (3N, 49 µl, 0.05 mmole) was added to a solution of the $\alpha$-acetoxyselelenide 58 (25 mg, 0.05 mmole) in methanol (3 ml) at room temperature and the reaction mixture was set for 20 minutes. Dry ice was added and the solvent was evaporated. The residue was partitioned between ether and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue obtained was impure
and could not be purified without decomposition. See oxidation of alcohol 64 for characterization of the aldehyde 59.

**Horner-Emmons Reaction on Aldehyde 59**

\(\alpha\)-Acetoxyselenide 58 (16 mg, 0.03 mmole) was hydrolyzed as above and used immediately. Triethyl 2-phosphonopropionate (77 mg, 0.32 mmole) was added to lithium diisopropylamide (0.32 mmole, freshly prepared from diisopropylamine and \(\eta\)-BuLi) in THF (2 ml) at \(-78^\circ\) under an atmosphere of argon. The solution was stirred for 10 minutes then the impure aldehyde 59 in THF (0.5 ml) was added. The mixture was stirred for 5 minutes then warmed to room temperature. The reaction mixture was partitioned between ethyl acetate, brine, and 3N hydrochloric acid. The organic layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (60% ether:hexane) to yield 6 mg (66%). \(^1\)H-NMR: 0.88 (t, \(J=7\) Hz, 3 H), 0.92 (t, \(J=7\) Hz, 3 H), 1.2-2.0 (m, 4 H), 2.2-2.6 (m, 2 H), 2.8-4.2 (m, 6 H), 4.85 (brs, 1 H), 5.16 (s, 1 H), 5.24 (s, 1 H), 5.60 (s, 1 H) MS: 282 (M\(^+\)).
Wittig Reaction on Aldehyde 59

α-Acetoxyiselenide 58 (20 mg, 0.04 mmole) was hydrolyzed as before. The residue was dissolved in toluene (5 ml) and ethyl 2-(triphenylphosphoranylidene) propionate (142 mg, 0.39 mmole) was added. The reaction mixture was refluxed for 4.5 hours with azeotropic removal of water. The solvent was then evaporated and the residue was purified by HPLC (60 % ether:hexane) to yield both isomers. The first product was the E isomer, 4 mg (26 %). The second product was the Z isomer, 2 mg (13 %). $^1$H-NMR of the E isomer: 0.88 (t, J=7 Hz, 3 H), 0.92 (t, J=7 Hz, 3 H), 1.3 (t, J=7.5 Hz, 3 H), 1.4-1.8 (m, 4 H), 1.8 (d, J=1.5 Hz, 3 H), 2.3-2.6 (m, 2 H), 2.8-3.3 (m, 5 H), 3.9-4.0 (m, 1 H), 4.2 (q, J=7.5 Hz, 2 H), 4.8 (s, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H), 6.8 (d, J=1.5 Hz, 1 H). $^1$H-NMR of Z isomer: 0.88 (t, J=7 Hz, 3 H), 0.92 (t, J=7 Hz, 3 H), 1.2 (t, J=7.5 Hz, 3 H), 1.4-1.8 (m, 4 H), 2.05 (d, J=2 Hz, 3 H); reduced to singlet on irradiation at 5.98), 2.2-2.6 (m, 2 H), 2.8-3.7 (m, 5 H), 3.8-4.0 (m, 1 H), 4.1 (q, J=7.5 Hz, 2 H), 4.9 (s, 1 H), 5.18 (s, 1 H), 5.6 (s, 1 H), 5.98 (d, J=2 Hz, 1 H); reduced to singlet on irradiation at 2.05).
Partial Reduction of 58

Diisobutylaluminum hydride (20% in hexanes) was added to a solution of the α-acetoxysele
ride 58 (20 mg, 0.04 mmole) in dichloromethane (2 ml) at -78°C under an atmosphere of argon until complete. The reaction was quenched by addition of brine and 3N hydrochloric acid then the mixture was warmed to room temperature. The reaction mixture was partitioned between dichloromethane and brine and then the aqueous layer was washed with dichloromethane. The combined organic layers were dried with sodium sulfate and evaporated. The residue obtained could not be purified without decomposition. See oxidation of alcohol 64 for characterization of aldehyde 59.

Bicyclic Alcohol 64

Sodium Borohydride (350 mg, 9.2 mmole) was added to a solution of the α-acetoxysele
ride 58 (350 mg, 0.69 mmole) in ethanol (6 ml) at 0°C. Sodium hydroxide (3N, 0.69 ml, 0.69 mmole) was then added and the solution was stirred for 35 minutes. Ether was added and the reaction mixture was first acidified with 3N hydrochloric acid then basified with saturated sodium bicarbonate. The solvent was evaporated and the residue was partitioned between ether, brine and hydrochloric acid. The aqueous layer was washed with ether
and the combined ether layers were washed with brine and then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by MPLC (ether:hexane gradient) to yield 188 mg (88%). Crystallization from isopropyl ether: dichloromethane (2:1) gave white crystals, mp 112°-113°. 

^1H-NMR: 0.89 (t, J=7 Hz, 3 H), 0.95 (t, J=7 Hz, 3 H), 1.4-2.0 (m, 4 H), 2.2-2.6 (m, 2 H), 2.7-4.1 (m, 6 H), 4.38 (d, J=12 Hz, 1 H), 4.44 (d, J=12 Hz, 1 H), 5.0 (s, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H). ^13C-NMR: 170.6, 164.8, 147.1, 118.4, 88.8, 84.2, 64.5, 62.9, 45.4, 44.0, 35.2, 21.8, 21.3, 11.4 MS: 312 (M+), 295 (-OH), 281 (-CH=O) exact mass: calculated m/e 312.1685 found 312.1679 analyzed for C_{15}H_{24}N_{2}O_{5} (calculated: C 57.68, H 7.74) found: C 57.53, H 7.74.

**Oxidation of Alcohol 64**

Dimethyl sulfoxide (303 μl, 3.85 mmole) was added to a solution of oxalyl chloride (187 μl, 1.92 mmole) in dichloromethane (2 ml) at -78° under an atmosphere of argon. The solution was stirred for 10 minutes then alcohol 64 (150 mg, 0.48 mmole) in dichloromethane (1 ml) was added. The solution was stirred for 15 minutes then triethylamine (1.19 ml, 7.69 mmole) was added. The reaction mixture was then stirred for 10 minutes at -78° and then warmed to 0°.
The reaction mixture was quenched with water and then partitioned between ethyl acetate, brine and 3N hydrochloric acid. The organic layer was washed with brine and then saturated sodium bicarbonate and brine. The organic layer was then dried with magnesium sulfate and evaporated. The residue obtained was not further purified. $^1$H-NMR: 0.87 (t, J=7 Hz, 3 H), 0.89 (t, J=7 Hz, 3 H), 1.4-1.9 (m, 4 H), 2.3-2.6 (m, 2 H), 3.0-3.8 (m, 6 H), 4.9 (brs, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H), 9.5 (s, 1 H). $^{13}$C-NMR: 191.0, 170.1, 163.6, 146.4, 119.0, 87.5, 84.2, 65.2, 46.7, 43.3, 34.7, 21.4, 21.0, 11.1 MS: 310 (M$^+$), 281 (-CHO), 239 (-C$_4$H$_7$O) exact mass: calculated m/e: 310.1528 found 310.1520.

Aldehyde 67 (R=H, R'=-MEM)

CSA (80 mg, 0.23 mmole) was added to a solution of the alcohol 65 (1.0 g, 4.5 mmole) and ethyl vinyl ether (0.5 ml, 5.4 mmole) in dichloromethane (10 ml) at room temperature. The reaction mixture was set for 15 minutes then excess triethylamine was added. The solvent was evaporated and the residue was used without characterization.

The residue in ether (10 ml) was added to a slurry of LiAlH$_4$ (172 mg, 4.5 mmole) in ether (15 ml) slowly at 0$^\circ$. The reaction mixture was warmed to room temperature and then hydrolyzed by addition of water (0.2 ml), 3N sodium
hydroxide (0.2 ml), and water (0.6 ml) successively. Magnesium sulfate (1.0 g) was added then the slurry was filtered through celite and washed with ether. The filtrate was evaporated; the residue was used without characterization.

MEM-Cl\(^{29}\) (0.62 ml, 5.4 mmole) was added to a solution of the residue and diisopropylethylamine (1.58 ml, 9.1 mmole) in dichloroethane (8 ml) at room temperature under an atmosphere of argon. The mixture was stirred at 60\(^\circ\) for 2 hours and then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was used without characterization.

The residue was dissolved in acetic acid:water (4:1, 10 ml) and heated at 60\(^\circ\) for 15 minutes. The solvent was evaporated and then the residue was purified by MPLC (ether:hexane gradient) to yield 913 mg (76 \%) of the alcohol. \(^1\)H NMR: 1.4-2.1 (m, 2 H), 3.4 (s, 3 H), 3.3-4.0 (m, 6 H), 4.4-4.6 (m, 1 H), 4.7 (s, 2 H), 6.2 (dd, J=16.7, 5.1 Hz, 1 H), 6.65 (d, J=16.7 Hz, 1 H), 7.1-7.5 (m, 5 H).

Ethyl chloroformate (0.5 ml, 5.1 mmole) was added to a solution of the secondary alcohol (913 mg, 3.4 mmole) and triethylamine (2.4 ml, 17.2 mmole) in dichloromethane (10 ml) at 0\(^\circ\). The reaction mixture was warmed to room temperature and then partitioned between ether, brine and 3N
hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was used without characterization.

Ozone was bubbled through a solution of the residue in methanol:dichloromethane (10 %, 25 ml) at -78$^\circ$ for 20 minutes. The solution was flushed with argon and then dimethyl sulfide (2.5 ml, 34.3 mmole) was added. The reaction mixture was slowly warmed to room temperature and then set for 15 minutes. The solvent was evaporated and the residue was partitioned between ether and brine. The aqueous layer was washed with ether and the combined organic layers were dried with magnesium sulfate and evaporated. The residue was purified by MPLC (ether:hexane gradient) to yield 504 mg (56 %). $^1$H-NMR: 1.2 (t, J=6 Hz, 3 H), 1.9-2.4 (m, 2 H), 3.4 (s, 3 H), 3.3-4.0 (m, 6 H), 4.0-4.3 (m, 1 H), 4.6-4.9 (m, 4 H), 9.5 (d, J=2.5 Hz, 1 H).

Aldehyde 69

Methanesulfonyl chloride (50 ml, 0.65 mole) was added to a solution of 4-pentenol (51.6 ml, 0.5 mole) and triethylamine (209 ml, 1.5 mole) in dichloromethane (150 ml) dropwise at 0$^\circ$. After the addition was complete, the mixture was warmed to room temperature and then partitioned between ether, brine and concentrated hydrochloric acid.
The ether layer was washed with brine and then dried with magnesium sulfate. The solvent was carefully evaporated and the residue was used without characterization.

Sodium hydroxide (26 g, 0.65 mole) in water (26 ml) was added to a solution of p-methoxyphenol (80.6 g, 0.65 mole) in dimethylformamide (50 ml) at room temperature. The solution was stirred for 10 minutes and then the crude mesylate in dimethylformamide (50 ml) was added. The reaction mixture was heated at 80\(^\circ\) for 20 minutes then ice was added. The reaction mixture was partitioned between ether and dilute sodium chloride. The aqueous layer was washed with ether and then the combined ether layers were washed with 3N sodium hydroxide and brine. The organic layer was then washed with brine, dried with magnesium sulfate and evaporated. The residue was used without characterization.

Ozone was bubbled through a solution of the residue in methanol:dichloromethane (15 %, 600 ml) at -78\(^\circ\) for 4 hours. The solution was flushed with argon and dimethyl sulfide (73 ml, 1.9 mole) was added. The reaction mixture was slowly warmed to room temperature then set for 1 hour. The solvent was evaporated and the residue was used without characterization.

A solution of the residue, dimethylamine hydrochloride (81.5 g, 1.0 mole), formaldehyde (37 %, 121 ml, 1.5 mole) and triethylamine (14 ml, 0.1 mole) in ethanol:water (60 %, 300 ml) was refluxed for 2 hours. The reaction mixture was
evaporated to a small volume and then partitioned between ether, brine and concentrated hydrochloric acid. The aqueous layer was washed with ether and then the combined ether layers were washed with brine. The organic layer was washed with saturated sodium bicarbonate and brine, dried with magnesium sulfate and evaporated. $^1$H-NMR: 2.7 (t, J=6.5 Hz, 2 H), 3.8 (s, 3 H), 4.05 (t, J=6.5 Hz, 2 H), 6.1 (s, 1 H), 6.4 (s, 1 H), 6.8 (s, 4 H), 9.6 (s, 1 H). exact mass: calculated 206.0942 found 206.0937.

**Ethyl Ester 70**

Titanium tetrachloride was added to a solution of the aldehyde 69 (5.0 g, 0.024 mole) and trimethylsilyl chloride (3.9 ml, 0.029 mole) in dichloromethane (10 ml) dropwise until the reaction was complete. The reaction mixture was used without any work-up or isolation of the product.

Ethanol (75 ml) was added and then hydrochloric acid gas was bubbled through the solution for 15 minutes. The reaction mixture was refluxed for 2.5 hours then evaporated to a small volume. The residue was partitioned between ether and brine. The aqueous layer was washed with ether and then the combined ether layers were washed with brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was used without purification. $^1$H-NMR: 1.25 (t, J=7 Hz, 3 H), 2.6 (t, J=6.5 Hz, 2 H), 3.3 (d, J=5 Hz, 1 H), 3.8 (s, 3 H), 4.05 (t, J=6.5 Hz, 2 H),
4.2 (q, J=7 Hz, 2 H), 4.6 (d, J=5 Hz, 1 H), 5.2 (s, 1 H),
5.3 (s, 1 H), 6.8 (s 4 H).

**Carboxylic Acid 71**

Sodium hydroxide (3N, 12 ml, 36.4 mmole) was added to a solution of the ester 70 in ethanol (50 ml) at room
temperature and the solution was set for 20 minutes. Dry ice was added then the solvent was evaporated. The residue
was partitioned between ether, brine and 3N sodium hydroxide. The ether layer was washed with brine and the combined aqueous layers were washed with ether. The ether layers were discarded and the aqueous layer was acidified with 3 N hydrochloric acid. The aqueous layer was washed two times with ether and the ether layers were combined. The organic layer was washed with brine and dried with magnesium sulfate. The solvent was evaporated to yield 5.34 g (87 %). The residue was used without further purification. \(^1^H\)-NMR:

2.6 (t, J=6.5 Hz, 2 H), 3.3-4.0 (m, 1 H), 3.7 (s, 3 H),
4.1 (t, J=6.5 Hz, 2 H), 4.7 (s, 1 H), 5.2 (s, 1 H), 5.3 (s, 1 H), 5.9 (brs, 1 H), 6.8 (s, 4 H) exact mass:
calculated m/e 252.0997 found 252.1000.
Alkylidenepiperazinedione 74

Carboxylic acid 71 (253 mg, 1.0 mmole), aldehyde 67 (R=H, R'=MEM) (290 mg, 1.1 mmole), n-propylamine (90 µl, 1.1 mmole) and n-propylisonitrile (107 µl, 1.2 mmole) were combined in methanol (4 ml) and heated at 60° for 30 minutes. The solvent was evaporated and the residue was purified by MPLC (ether:hexane gradient) to yield 306 mg (49%). The product 72 was used without characterization.

Dichloroacetic acid was added to a solution of the product 72, DCC (201 mg, 0.98 mmole) and DMSO (0.5 ml) in dichloromethane (5 ml) dropwise until the reaction was complete. Acetic acid (0.2 ml) was added and then the solvent was evaporated. The residue was filtered through celite and washed with ether. The filtrate was partitioned between ether and brine and then the ether layer was washed with saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was used quickly without purification.

DBU (146 µl, 0.98 mmole) was added to a solution of the residue in benzene (3 ml) and the reaction mixture was heated at 60° for 1 hour. The mixture was partitioned between ether, brine and 3N hydrochloric acid. The aqueous layer was washed with ether and the ether layers combined. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with
magnesium sulfate and evaporated. The residue was purified to yield 117 mg (45%) of both isomers. $^1$H-NMR of the Z isomer: 0.7-1.0 (m, 6 H), 1.2-2.1 (m, 4 H), 2.3-2.6 (m, 2 H), 2.8-3.2 (m, 2 H), 3.2-4.2 (m, 12 H), 3.4 (s, 3 H), 3.8 (s, 3 H), 4.5 (s, 2 H), 4.9 (s, 1 H), 5.0 (s, 1 H), 5.1 (s, 1 H), 5.8 (s, 1 H), 6.8 (s, 4 H), 6.9 (s, 1 H). $^1$H-NMR of E isomer: 5.8 shifted to 6.2 (t, J=7.7 Hz, 1 H).

Diol 75

Ceric ammonium nitrate was added to a solution of compound 74 (117 mg, 0.22 mmole) in THF:H$_2$O (3:1, 3 ml) at 0°C until the reaction was complete. The reaction mixture was partitioned between ethyl acetate and brine then washed with saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (ether) to yield 51 mg (54%). The diol 75 was not characterized.

Bicyclic Bromide 76a

Pyridinium bromide perbromide (42 mg, 0.13 mmole) was added to a solution of the diol 75 (51 mg, 0.12 mmole) and pyridine (48 µl, 0.59 mmole) in dichloromethane (2 ml) at room temperature under an atmosphere of argon. The reaction mixture was stirred for 20 minutes then partitioned
between ethyl acetate, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (50 % ether:hexane) to yield 34 mg (57 %). \textsuperscript{1}H-NMR: 0.7-1.2 (m, 6 H), 1.4-2.2 (m, 8 H), 3.0-4.1 (m, 12 H), 3.4 (s, 3 H), 4.3-4.5 (dd, J=9, 4 Hz, 1 H), 4.6 (s, 1 H), 4.7 (s, 2 H), 5.2 (s, 1 H), 5.6 (s, 1 H) MS: 508/506 (M\textsuperscript{+}), 427 (-Br).

Alcohol 80

Titanium tetrachloride (1 drop) was added to a solution of the bromide 76a (20 mg, 0.04 mmole) in dichloromethane (2 ml) at 0\textdegree. The reaction mixture was stirred for 10 minutes then quenched with concentrated ammonium hydroxide (0.2 ml). The reaction mixture was partitioned between ether and brine then the ether layer was washed with brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (60 % ether:hexane) to yield 14 mg (85 %). \textsuperscript{1}H-NMR: 0.7-1.1 (m, 6 H), 1.4-2.1 (m, 6 H), 2.6-3.0 (m, 2 H), 3.0-4.1 (m, 8 H), 4.4-4.6 (m, 1 H), 4.7 (s, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H) MS: 420/418 (M\textsuperscript{+}), 403/401 (-OH), 389/387 (-CH\textsubscript{3}O).
Aldehyde 81

Pyridinium chlorochromate (excess) was added to a solution of the alcohol 80 (3 mg, 0.007 mmole) in dichloromethane (1 ml) at room temperature and the reaction mixture was stirred for 1.5 hours. The reaction mixture was diluted with hexanes and then passed through a short silica gel column (~2 cm x 20 mm diameter) with ether. The solvent was evaporated and the residue was used with only partial characterization. Crude $^1$H-NMR: 9.8 (s).

DBU (2 μl, 0.014 mmole) was added to a solution of the impure aldehyde in benzene (1 ml) at room temperature. The reaction mixture was stirred for 15 minutes then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (60% ether:hexane) to yield the desired aldehyde. $^1$H-NMR: 0.7-1.1 (m, 6 H), 1.4-2.6 (m, 6 H), 3.0-4.0 (m, 6 H), 4.6 (s, 1 H), 5.2 (s, 1 H), 6.6 (s, 1 H), 6.8 (m, 1 H), 7.2 (m, 1 H), 9.6 (m, 1 H); reduced to singlet on irradiation at 6.8. MS: 336 (M$^+$), 307 (-CHO).
Dicyclic Bromide 83a

Diol 82 was prepared in an analogous manner to diol 75 (\(^1H\)-NMR data to follow). Pyridinium bromide perbromide (6 mg, 0.019 mmole) was added to a solution of the diol 82 (7 mg, 0.017 mmole) and pyridine (7 l, 0.085 mmole) at room temperature under an atmosphere of argon. The reaction mixture was stirred for 20 minutes then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (50 % ether:hexane) to yield the desired product. \(^1H\)-NMR of diol 82: 0.7-1.1 (m, 6 H), 1.1-1.4 (m, 3 H), 1.4-2.1 (m, 4 H), 2.1-2.6 (m, 3 H), 2.6-4.4 (m, 8 H), 3.8 (s, 3 H), 5.0 (s, 1 H), 5.1-5.4 (m, 2 H), 5.9-6.1 (m, 1 H) \(^1H\)-NMR of product 83a: 0.7-1.1 (m, 6 H), 1.1-1.4 (m, 3 H), 1.4-2.1 (m, 5 H), 2.3-2.6 (m, 2 H), 2.8-4.6 (m, 9 H), 3.8 (s, 3 H), 4.8 (s, 1 H), 5.1 (s, 1 H), 5.6 (s, 1 H) MS: 492/490 (M), 411 (-Br).

Aldehyde 85

Sodium hydroxide (3N, 30 \(\mu l\), 0.01 mmole) was added to a solution of the bromide 83a in methanol (1 ml) at room temperature and the reaction mixture was stirred for 4 hours. Dry ice was added and then the solvent was evaporated. The
residue was filtered through celite and magnesium sulfate with ether and then the filtrate was evaporated. The residue was used without characterization.

Dichloroacetic acid (1 drop) was added to a solution of the alcohol \( \text{83b} \), DCC (10 mg, 0.048 mmole) and DMF (10 \( \mu l \), 0.14 mmole) in dichloromethane (2 ml) at room temperature and the reaction mixture was stirred for 10 minutes. Acetic acid (2 drops) was added and then the solvent was evaporated. The residue was partitioned between ether and brine then the ether layer was washed with saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was used without characterization.

DBU (5 \( \mu l \), 0.03 mmole) was added to a solution of the aldehyde \( \text{84} \) in dichloromethane (1 ml) at room temperature and the reaction mixture was stirred for 10 minutes. The reaction mixture was then partitioned between ether, brine and 3N hydrochloric acid. The ether layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by HPLC (10% ether: dichloromethane) to yield the desired aldehyde. \( ^1H\text{-NMR:} \)

\[
\begin{align*}
0.7-1.1 (m, 6 H), & \quad 1.1-2.0 (m, 4 H), & \quad 1.8 (d, J=1 Hz, 3 H), \\
2.3-2.6 (m, 2 H), & \quad 2.8-4.2 (m, 6 H), & \quad 4.8 (s, 1 H), \\
5.2 (s, 1 H), & \quad 5.6 (s, 1 H), & \quad 6.5 (d, J=1 Hz, 1 H), \\
9.6 (s, 1 H).
\end{align*}
\]
Bicyclic Enone 87

2-Propenyllithium (1.44 N) was added to a solution of the \( \alpha \)-acetoxyselenide 58 (604 mg, 1.19 mmole) in THF (5 ml) at \(-78^\circ\) under an atmosphere of argon until the reaction was complete. The reaction mixture was stirred for 15 minutes then quenched with acetic acid:methanol (1:1, 2 ml). The mixture was warmed to room temperature and partitioned between ether and brine. The ether layer was washed with brine then dried with magnesium sulfate and evaporated. The residue was used without purification or characterization.

Jones Reagent was added to a solution of the alcohol 86 in acetone (6 ml) at 0\(^\circ\) until the reaction was complete. Isopropanol was added and the mixture was evaporated to a small volume. The residue was partitioned between ether and dilute sodium chloride and then the aqueous layer was washed with ether. The ether layers were combined and washed with brine then saturated sodium bicarbonate, sodium sulfite and brine. The organic layer was dried with magnesium sulfate and evaporated. The residue was purified by MPLC (ether:hexane gradient) to yield 166 mg (40 %).

\(^1\)H-NMR: 0.84 (t, J=7 Hz, 3 H), 0.89 (t, J=7 Hz, 3 H), 1.4-1.9 (m, 4 H), 2.0 (s, 3 H), 2.3-2.6 (m, 2 H), 2.7-3.8 (m, 6 H), 4.9 (s, 1 H), 5.2 (brs, 2 H), 5.6 (brs, 1 H), 5.8 (brs, 1 H). \(^13\)C-NMR: 190.9, 168.7, 164.2, 146.7, 141.6,
124.9, 119.1, 98.2, 84.3, 65.0, 47.6, 43.4, 34.7, 21.6, 20.6, 19.1, 11.3, 11.2 MS: 350 (M⁺), 281 (-C₄H₅O), 264 (-C₄H₆O₂) exact mass: calculated m/e 350.1841 found 350.1836.

Triol 88

Osmium tetroxide (0.5 M in THF) was added to a solution of the enone 87 (100 mg, 0.29 mmole) in THF (2 ml) until the reaction was complete. Hydrogen sulfide was bubbled through the solution for 5 minutes and then the mixture was stirred for 10 minutes. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was partitioned between ethyl acetate and brine. The organic layer was washed with brine and then dried with magnesium sulfate and evaporated. The residue was purified by HPLC (80 % ether:hexane) to yield 55 mg (50 %).

¹H-NMR: 0.85 (t, J=7 Hz, 3 H), 0.88 (t, J=7 Hz, 3 H), 1.3-1.9 (m, 4 H), 1.5 (s, 3 H), 2.3-2.6 (m, 2 H), 2.7-4.5 (m, 10 H), 5.0 (s, 1 H), 5.2 (s, 1 H), 5.7 (s, 1 H) ¹³C-NMR:

203.9, 168.9, 164.9, 146.1, 119.1, 93.1, 84.1, 82.2, 68.4, 65.5, 43.1, 43.5, 37.5, 21.5, 20.5, 11.2 MS: 384 (M⁺), 367 (-OH), 354 (-CH₂O), 353 (-CH₃O), 281 (-C₄H₇O₂) exact mass: calculated m/e 384.1896 found 384.1896.
Acetonide 89

CSA (2 mg, 0.006 mmole) was added to a solution of the triol 88 (44 mg, 0.11 mmole) and 2,2-dimethoxypropane (5 drops) in dichloromethane (2 ml) at room temperature. The reaction mixture was heated at 35° for 45 minutes. Excess triethylamine was added and then the solvent was evaporated. The residue was purified by HPLC (60% ether:hexane) to yield 46 mg (95%). ^1H-NMR: 0.84 (t, J=7 Hz, 3 H), 0.92 (t, J=7 Hz, 3 H), 1.3 (s, 3 H), 1.35 (s, 3 H), 1.4-1.9 (m, 4 H), 1.7 (s, 3 H), 2.3-2.6 (m, 2 H), 2.7-3.2 (m, 2 H), 3.3-4.4 (m, 6 H), 4.9 (s, 1 H), 5.2 (s, 1 H), 5.6 (s, 1 H) ^13C-NMR: 201.9, 168.8, 163.5, 147.1, 118.5, 110.9, 87.2, 84.1, 74.5, 65.5, 65.3, 47.9, 43.5, 34.9, 34.8, 26.1, 21.9, 20.5, 11.5 MS: 424 (M^+), 409 (-CH_3), 367 (-C_3H_7N) exact mass: calculated m/e 424.2209 found 424.2206 analyzed for C_{21}H_{32}N_2O_7 (calculated: C 59.42, H 7.60) found: C 59.24, H 7.46.

Deprotected Amide 91

n-Butyllithium (1.64 N, 1.33 ml, 2.19 mmole) was added to a solution of the nitrile 90 (537 mg, 0.73 mmole) in THF (5 ml) at -78° under an atmosphere of argon. Methanol (1 ml) was added and the solution was warmed to room temperature. The reaction mixture was partitioned between
ethyl acetate, brine and 3N hydrochloric acid. The organic layer was washed with brine then saturated sodium bicarbonate and brine. The organic layer was dried with magnesium sulfate and evaporated. Crystallization from cold ether gave 194 mg (65%) of pale yellow crystals, mp 165°-166°. Recrystallization of the filtrate gave an additional 45 mg (80% total). Characterization of the nitrile 90: $^1$H-NMR: 0.84 (t, J=7.5 Hz, 3 H), 1.4-2.0 (m, 2 H), 2.2-4.2 (m, 10 H), 3.4 (d, J=12.7 Hz, 1 H), 3.98 (d, J=12.7 Hz, 1 H), 4.99 (s, 1 H), 5.2 (s, 1 H), 5.65 (s, 1 H), 7.2-7.7 (m, 5 H) $^{13}$C-NMR: 169.0, 164.7, 146.2, 119.1, 117.3, 90.5, 84.1, 65.4, 45.9, 37.7, 34.7, 33.5, 21.3, 17.2, 11.4 MS: 463/461 (M$^+$) exact mass: calculated m/e: 463.1010 found 463.1016, calculated m/e: 461.1018 found 461.1016 analyzed for C$_{21}$H$_{25}$N$_3$O$_4$Se (calculated: C 54.55, H 5.45) found C 54.41, H 5.39. Characterization of product 91. $^1$H-NMR: 0.84 (t, J=7.5 Hz, 3 H), 1.2-2.1 (m, 2 H), 2.4-2.8 (m, 2 H), 2.8-4.1 (m, 4 H), 3.4 (d, J=12.7 Hz, 1 H), 3.9 (d, J=12.7 Hz, 1 H), 5.12 (s, 1 H), 5.60 (s, 1 H), 7.2-7.7 (m, 5 H) $^{13}$C-NMR: 170.3, 164.9, 148.1, 117.1, 91.3, 81.4, 66.0, 46.0, 35.1, 33.3, 21.7, 11.6 MS: 410/408 (M$^+$) exact mass: calculated m/e: 410.0745 found 410.0747, calculated m/e: 408.0752 found 408.0742 analyzed for C$_{18}$H$_{22}$N$_2$O$_4$Se (calculated: C 52.82, H 5.42) found C 52.79, H 5.48.
V. References


23. (a) R. Pummerer, Ber., 43, 1401 (1910).


VI. Selected Spectra

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\begin{align*}
\text{AcO} & \quad \text{AcO} \\
\text{CHO} & \quad \text{O}_{\text{Et}}
\end{align*}
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