INFORMATION TO USERS

This reproduction was made from a copy of a manuscript sent to us for publication and microfilming. While the most advanced technology has been used to photograph and reproduce this manuscript, the quality of the reproduction is heavily dependent upon the quality of the material submitted. Pages in any manuscript may have indistinct print. In all cases the best available copy has been filmed.

The following explanation of techniques is provided to help clarify notations which may appear on this reproduction.

1. Manuscripts may not always be complete. When it is not possible to obtain missing pages, a note appears to indicate this.

2. When copyrighted materials are removed from the manuscript, a note appears to indicate this.

3. Oversize materials (maps, drawings, and charts) are photographed by sectioning the original, beginning at the upper left hand corner and continuing from left to right in equal sections with small overlaps. Each oversize page is also filmed as one exposure and is available, for an additional charge, as a standard 35mm slide or in black and white paper format.*

4. Most photographs reproduce acceptably on positive microfilm or microfiche but lack clarity on xerographic copies made from the microfilm. For an additional charge, all photographs are available in black and white standard 35mm slide format.*

*For more information about black and white slides or enlarged paper reproductions, please contact the Dissertations Customer Services Department.

UMI Dissertation Information Service

University Microfilms International
A Bell & Howell Information Company
300 N. Zeeb Road, Ann Arbor, Michigan 48106
Laird, Alison Ann

SYNTHETIC STUDIES FOR THE TOTAL SYNTHESIS OF
NAPHTHYRIDINOMYCIN

Rice University

Ph.D. 1985

University
Microfilms
International

300 N. Zeeb Road, Ann Arbor, MI 48106
PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark ☑.

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages ☑
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _________ lacking when material received, and not available from school or author.
12. Page(s) _________ seem to be missing in numbering only as text follows.
13. Two pages numbered _______. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received _______
16. Other ___________________________________________________________
    ______________________________________________________________
    ______________________________________________________________

University Microfilms International
RICE UNIVERSITY

SYNTHETIC STUDIES FOR THE
TOTAL SYNTHESIS OF NAPHTHYRIDINOMYCIN

by

ALISON ANN LAIRD

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

APPROVED, THESIS COMMITTEE:

T. Furuyama, Associate Professor, Chairman

W. E. Billups, Professor and
Department Chairman, Chemistry

R. L. Sass, Professor and
Department Chairman, Biology

Houston, Texas
September, 1985
SYNTHETIC STUDIES FOR THE TOTAL SYNTHESIS OF NAPHTHYRIDINOMYCIN

by

Alison Ann Laird

Abstract

Development of a synthetic route led to the synthesis of the tetracyclic compound 76a, a key intermediate for continued studies on the total synthesis of naphthyridinomycin.
Acknowledgements

I wish to thank Dr. Tohru Fukuyama for his guidance, patience, and wonderful example of perseverance in the laboratory. My research efforts were constantly encouraged by his sincere interest and synthetic collaboration during the project.

I am grateful to Dr. John Partridge of Hoffmann-La Roche for kindly providing an x-ray analysis of phenol 76a for structure confirmation.

Finally, I would like to thank the Department of Chemistry, Rice University, and the National Institute of Health for financial support during the course of my graduate research.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter I</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Chapter II</td>
<td>Synthetic Studies For The Total Synthesis of Naphthyridinomycin</td>
<td>7</td>
</tr>
<tr>
<td>Chapter III</td>
<td>Experimental Results</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>202</td>
</tr>
</tbody>
</table>
Chapter I

INTRODUCTION
Naphthyridinomycin is a novel heterocyclic quinone antibiotic first isolated from *Streptomyces lusitanus*. The pure compound was obtained as ruby red crystals with high resolution mass spectrometry indicating a molecular formula of $C_{11}H_{17}N_3O_6$. Structure elucidation by x-ray crystallography gave the molecular structure 1, with intramolecular hydrogen bonding observed between the hydroxyl group and the tertiary amine of the oxazolidine. As shown by Zmijewski and Nikolajczak the biosynthesis of naphthyridinomycin incorporates $^{14}$C-labelled tyrosine at carbon atoms 6 and 7 with the aromatic ring of tyrosine serving as the precursor for the quinone system. Carbon enrichment also occurs with incorporation of $^{14}$C-labelled glycine at the two carbons of the oxazolidine and incorporation of $^{14}$C-labelled methionine in the O-, N-, and C-methyl groups at carbons 2', 3', and 8'. Biological studies indicate that the antibiotic is a potent, but highly toxic antimicrobial and antitumor agent, inhibiting DNA synthesis and DNA template activity by binding to dG•dC base pairs.
In addition to naphthyridinomycin, three other structurally similar compounds are known. Cyanocycline A (cyanonaphthyridinomycin), 2, is produced by substitution of cyanide at the aminal of naphthyridinomycin. Like the parent compound, it exhibits significant antimicrobial activity against Gram-positive and Gram-negative bacteria and cytotoxicity against cultured tumor cells and ascites tumors in mice. In 1976 Itoh and his co-workers reported the isolation of SF-1739 HP 3 from a culture of Streptomyces griseoplanus. Reaction of SF-1739 HP with potassium cyanide in methanol afforded naphthocyanidine 4. Both compounds have antibacterial activities against Gram-negative bacteria, accompanied by marked activity against leukemia P388.

Various structural features of naphthyridinomycin such as, most importantly, the presence of eight chiral centers (including five contiguous chiral carbons), embedded in the skeleton of a very sterically crowded hexacyclic system, add complexity to any synthetic attempts of the antibiotic. In addition, construction of a labile aminal, an oxazolidine and a quinone ring while maintaining
stereochemical control increases the difficulties expected in a stereoselective synthesis. Presently only two groups have published significant work on naphthyridinomycin. The approach of Danishefsky, O’Neill and Springer features a convergent synthesis with amide bond formation between the tetrahydroisoquinolinol 5 and the carboxyglutamyl derivative 6, followed by Collins oxidation to give the ketoamide 7 as a mixture of diastereomers at C(12) and C(9). Unfortunately, cyclization of the ketoamide in the presence of excess boron trifluoride etherate in refluxing methylene chloride gave two products, 8 and 9, corresponding to N-formylation of the isomer with the undesired configuration at C(12) and ring closure of an iminium-enol intermediate yielding a tetracyclic product having the correct stereochemistry at C(12) and C(9), but the incorrect stereochemistry at C(6). Attempts to obtain the desired epimer at C(6) by varying cyclization conditions failed. Evans and
Biller\textsuperscript{7} have published a stereoselective synthesis of a pentacyclic intermediate featuring an intermolecular amidalkylation reaction and a Friedel-Crafts ring closure as key steps in the synthetic scheme. A tricyclic lactam 10 was condensed with methyl glyoxylate and then treated with thionyl chloride to yield the chloride 11. Amidalkylation occurred in the presence of phenol 12 promoted by tin tetrachloride to give the desired isomer 13 in 56% yield. Ozonolysis of the corresponding benzoate 14 followed by reductive workup produced a mixture of tetrahydropyranols with 15a and 15b as the major isomers. The crude reaction mixture was then treated with hexamethyldiphosphorous triamide and carbon tetrachloride to convert the tetrahydropyranols to the chloride 16 which was reacted directly with stannic chloride to effect cyclization into the aromatic nucleus yielding compound 17.
Comparison of the pentacyclic intermediate 17 with naphthyridinomycin shows that Evans and Biller have successfully constructed a quinone precursor, lacking only the oxazolidine found in the naphthyridinomycin ring skeleton, with correct stereochemistry at seven of the eight chiral centers present in the target antibiotic. As evidenced by the work already published on naphthyridinomycin, a total synthesis with its inherent difficulties is of great interest to synthetic chemists and certainly any successful synthesis will require extensive stereochemical control throughout the process. To date, no total syntheses for naphthyridinomycin, cyanocycline A, SF-1739 HP, or naphthocyanidine have been published.
Chapter II

SYNTHETIC STUDIES FOR THE

TOTAL SYNTHESIS OF NAPHTHYRIDINOMYCIN
Naphthyrindinomycin presents a formidable challenge synthetically, requiring control of stereochemistry at eight chiral centers in a sterically crowded hexacyclic system that includes an aromatic ring serving as the protected quinone. Previous work done in our laboratory pursued a route dependent upon a key oxidative cyclization to complete five of the six rings constituting the naphthyrindinomycin skeleton. Specifically, the phenol 18 was oxidized to a quinone intermediate 19 which slowly reacted by photolysis to give a 1,3-dioxolane 20 instead of the desired ring closure 21. Allowing quinone 19 to stand at room
temperature in the dark resulted in decomposition with no major reaction product formed. Treatment under basic, neutral and acidic conditions with heat also proved futile with no observed reaction. Further attempts to cyclize the corresponding acyl derivative 22, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene were unsuccessful with oxidation occurring only at the benzylic position next to the lactam, to yield alcohol 23.\(^\text{10}\) Disappointed by these results as well as hampered by a tedious synthetic route, we decided to focus on forming a lactam intermediate capable of electrophilic cyclization into the aromatic system.\(^\text{11}\)

Upon reevaluating the synthetic approach, it was decided that a model compound was required containing three of the skeletal rings found
in naphthyridinomycin with four established chiral centers. In addition, a synthetic precursor should be available for future elaboration into either a tetracyclic or pentacyclic system. Based on these considerations, compound I appeared to be the desired synthetic target. Retrosynthetic analysis suggested that amine I might be synthesized by cyclization into the aromatic system using an appropriate leaving group adjacent to the lactam nitrogen represented by intermediate II. Prior introduction of the aromatic system could occur by in situ reduction of the imine formed from condensation of an aromatic aldehyde III and a bicyclic amine such as compound IV. The cyclobutane portion of the bicyclic intermediate IV could be later expanded into a γ-lactam by manipulation of the methyl ester into an oxime intermediate V followed by a Beckmann rearrangement to form the desired ring system VI. It was the bicyclic amine intermediate IV, with cis stereochemistry, which became the immediate synthetic target and, we hoped, would test the feasibility of aromatic cyclization to complete four rings by a stereocontrolled synthesis.
A \([2 + 2]\) photoaddition product of 2-hydroxypyridine and methyl acrylate served as starting material with the stereochemistry published as shown in compound \(24a\).\(^{14}\) In retrospect, we believe that the correct stereochemistry instead has all hydrogens cis and it is this isomer, compound \(24b\), which will be used during discussion of the synthetic route. Analysis of the stereochemistry and our conclusions will follow.

\[
\begin{align*}
24a & \quad \quad \quad \quad \quad \quad 24b
\end{align*}
\]

To introduce a nitrogen functional group, the bicyclic lactam \(25b\), a model compound with an N-\(\text{N}\)-propyl group on the original lactam \(24b\), was reacted with nitrosyl chloride followed by addition of methanol to give the dimer of the corresponding nitroso compound.\(^{15}\) Refluxing in methanol cracked the dimer to the oxime \(26b\). Catalytic hydrogenation of the oxime over rhodium on alumina\(^{16}\) produced an unexpected 1:1 mixture of compounds, apparently with nonselective reduction initially giving both amine isomers. However, the isomer with the amine and the carbomethoxy group on the same face of the molecule cyclized into a lactam, as evidenced by loss of the signal for the methyl ester in the \(^1H\) nmr (Figure 1), while the other reduction product still had a methyl ester proton signal at 3.70 ppm as shown in Figure 2. It quickly became
evident that the configuration of the carbon bearing the methyl ester was extremely important since this stereochemistry determined which amine isomer was inactivated through lactam formation. Because of these results, it was crucial to know the stereochemistry of the original
Figure 1.

Figure 2.
bicyclic lactam with certainty, and thus establish which amine cyclized during hydrogenation.

Upon examination of the two possible structures given previously for the bicyclic lactam, one finds that compound 24h has an inherent symmetry the other isomer lacks. If, assuming that the ring junction is sig, compound 24h can be opened at the lactam carbonyl by methoxide, then the cyclobutane ring possesses a plane of symmetry with only seven different carbon atoms instead of ten found in a cyclobutane ring with no plane of symmetry. Therefore, it seemed reasonable that ring opening on the activated lactam intermediate 29 to the biscalbomethoxy
derivative 30 would indicate what the original stereochemistry was. If a $^{13}$C nmr of compound 30 showed twelve carbon signals, then the original lactam had the stereochemistry assigned to compound 24a. If, instead, the $^{13}$C nmr showed only nine carbon peaks, then this product contained a plane of symmetry, possible only with the original stereochemistry assigned to compound 24b.

Treatment of the original lactam with acetic anhydride at 140°C cleanly afforded the N-acyl derivative 29. Ring opening with sodium methoxide in methanol at 25°C gave two compounds. The major product was formed by attack of methoxide at the lactam carbonyl with introduction of a methoxy group as shown by $^1$H nmr (Figure 3). The proton noise-decoupled $^{13}$C nmr spectrum had nine signals, supporting structure 30b and an off-resonance $^{13}$C nmr agreed with this same structure (Figures 4 and 5). Based on our earlier argument, compound 30b can only
be a derivative of lactam 24b. However, epimerization under basic conditions at the chiral center in question is a possibility, rendering the $^{13}$C nmr results inconclusive. Isolation of the minor reaction product after treatment with methoxide showed it to be identical to the lactam before acylation with acetic anhydride. The presence of only these two products strongly suggests that epimerization, although possible, occurred at a negligible rate during ring opening. As further confirmation the unsaturated bis-carbomethoxy compound was reduced with palladium on carbon in ethanol under a hydrogen atmosphere of 1000 psi to the saturated cyclobutane 31b. The proton noise-decoupled $^{13}$C nmr

Figure 3.
Figure 6.
spectrum of this derivative also showed only nine carbon signals with a trace amount of ethanol present (Figure 6). With $^{13}$C nmr data supporting structures 30b and 31b, thus establishing compound 24b as the initial lactam, it followed that the mixture of products from catalytic reduction was compounds 27b and 28b. Unfortunately the amine of the desired configuration cyclized, preferentially forming a lactam.

To corroborate our conclusions regarding the stereochemistry of lactam 27b, we decided to synthesize the lactam by exploiting a route that, throughout the synthesis, featured stereochemical control. While working on model studies, an unusual rearrangement was observed that altered a six-membered lactam to a five-membered ring. Treatment of the unprotected lactam 24b with iodine in methanol gave the iodide 32 as one major isomer. When this compound was heated in methanol with silver nitrate to facilitate loss of the iodide ion, methanol attacked at the carbon bearing the methyl ether and not at the carbon originally bearing the iodide. This phenomenon resulted in ring contraction to $\gamma$-lactam 33, accompanied by a shift in the IR carbonyl absorption from 1677 cm$^{-1}$ to 1700 cm$^{-1}$ for lactam 33. Apparently the lone pair of
electrons on nitrogen participated with neighboring group assistance during loss of the iodide to form a five-membered lactam intermediate stabilized by the methoxy group. $S_N$1 attack by methanol yielded the rearrangement product. This stereospecific ring contraction offered a promising route for the synthesis of lactam 27b with unambiguous stereochemistry.
Conversion of γ-lactam 33 to the carbobenzoxy derivative 34 activated the lactam carbonyl for subsequent ring opening by n-propylamine to the cyclobutane 35. This intermediate, if cyclized, would have the desired stereochemistry at the chiral center bearing the benzylurethane as found in the lactam 27b structure. Cyclization

\[ \text{33} \rightarrow \text{34} \]

\[ \text{35} \]

unfortunately did not occur under various conditions, including heating both the urethane 35 and its deprotected amine analogue in acidic methanol and acidic THF up to reflux temperatures. Not until the thioacetal 36 was formed, using ethyl mercaptan and boron trifluoride etherate, was cyclization possible with mercuric chloride in wet acetonitrile to give an epimeric mixture of alcohols. Substitution by methanol in the presence of a catalytic amount of camphorsulfonic acid
(CSA), followed by hydrogenolysis of the carbobenzoxyurethane resulted in a product identical to lactam 27b by tlc behavior, 1H nmr, IR and mass spectroscopy. With cyclization of the target bicyclic amine and the proximal methyl ester favored, modifications to avert lactam formation were necessary.

With the cyclobutane ring possibly limiting the desired bicyclic amine to a rigid conformation favoring lactam closure, and, considering that extensive synthetic changes were needed to get a five-membered
cyclic amine from the cyclobutane system, a bicyclo[4.3.0] lactam urethane 38, already having the desired ring skeleton, was used to synthesize the key amine intermediate. (Synthesis of the lactam urethane 38 is described in the experimental section on pages 89-104.) Again rearrangement with ring contraction indirectly established the stereochemistry of the latent amino group. Addition of iodine monochloride \(^{32}\) to the double bond in methanol to give compound 39 preceded the skeletal rearrangement in methanol which yielded lactam 40.

\[
\begin{align*}
\text{38} & \xrightarrow{\text{ICl, MeOH}} \text{39} \\
\text{40} & \xrightarrow{\text{AgNO}_3, \text{MeOH}}
\end{align*}
\]

Anion formation using lithium diisopropylamide (LDA) \(^{23}\) followed by addition of 2-(tert-butoxycarbonyl-oxyimino)-2-phenylacetonitrile (BOC-ON) \(^{23}\) activated the lactam carbonyl for ring opening by \(n\)-propylamine to afford the dimethyl acetal 42a. Heating compound 42a
in tetrahydrofuran with hydrochloric acid effected ring closure and deprotection of the t-butylurethane producing an epimeric mixture of the amine alcohols. Refluxing in acidic methanol converted to a single methyl ether. Unlike the cyclobutane analogue, compound showed no lactam formation, remaining uncyclized during the stereoccontrolled synthesis of an amine functionality.
As mentioned in the retrosynthetic analysis (page 10), the next step involved introduction of an aromatic system to attempt a cyclization, thus completing the tetracyclic system. Condensation of amine 44 with the substituted benzaldehyde 45 followed by reduction with sodium cyanoborohydride in situ gave compound 46a. Unfortunately treatment of methyl ether 46a or the corresponding

\[
\begin{align*}
\text{45} & \quad + \quad \text{44} \\
\end{align*}
\]

N-trifluoroacetamide 46b with Lewis acids, camphorsulfonic acid, hydrochloric acid and trifluoroacetic acid showed only decomposition with some alcohol formation. Refluxing compound 46b in formic acid for several minutes yielded a very uv-active product characterized as
pyridone 47, formed by loss of methanol with ring opening. The desired kinetic cyclization product 48 was not detected, indicating that ring closure into the aromatic nucleus was unfavorable in this system.

With the failure of kinetic cyclization into the aromatic ring, a new approach, focusing on initial formation of the carbon-carbon bond linking the aromatic ring to a precursor of the bicyclic lactam, was
taken. Examination of naphthyridinomycin indicated that breaking the aminal bond and opening the oxazolidine would give intermediate VII. A reverse Pictet-Spengler cyclization suggested the use of intermediate VIII which might be synthesized from olefin IX. The olefin, in turn, could be synthesized by cyclization of a ketoamide such as compound X.
A possible precursor for compound X is the alcohol XI, a product of either a Grignard reaction between the aromatic bromide XII and aldehyde XIII or an aldol-type reaction between the aromatic aldehyde XIV and the unsaturated ester XV. In the outlined analysis, it is the Grignard
reaction or, alternatively, the aldol-type reaction, that represents the key synthetic step with early formation of the carbon-carbon bond which failed to occur in the aforementioned approach.

To investigate the possibilities of a Grignard reaction, the Grignard reagent was made from the corresponding aromatic bromide in refluxing tetrahydrofuran. Addition of Grignard reagent to a solution of aldehyde in THF, under argon, yielded a 1:1 mixture of the epimeric alcohols.

With a fairly clean reaction using a simpler aromatic ring, the desired substituted aromatic bromide was employed similarly. Making the Grignard reagent with a benzyl ether present, however, created difficulties with self-destruction of the reagent by attacking the benzyl ether to release the phenoxide. Under standard conditions (Mg, THF, reflux) formation of the highly substituted Grignard reagent proceeded with much decomposition. Grignard formation at room temperature was very slow. Modifying the conditions by first generating the aryllithium using n-butyllithium at −78°C, followed by addition of anhydrous magnesium bromide in THF, produced a cleaner reactant upon
warming to room temperature. Addition of this Grignard reagent to aldehyde 50 gave two isomeric alcohols 52, accompanied by decomposition.

Despite poor yields, the synthesis was continued to the enamide 56 to check the feasibility of the synthetic scheme beyond the critical coupling reaction. After isolation, the two alcohols were oxidized with Jones reagent \(^{32}\) to the ketone 54. Deprotection of the t-butyl ester to the carboxylic acid in trifluoroacetic acid \(^{33}\) followed by mixed anhydride formation \(^{34}\) with ethyl chloroformate and subsequent amide formation upon addition of ammonia yielded the ketoamide 55.

Cyclization to the enamide 56 went very cleanly while heating 55 in toluene with camphorsulfonic acid and quinoline present. Fortunately the reaction sequence beyond the Grignard reaction up to formation of lactam 56 proved to be very feasible with no foreseeable synthetic problems. However, faced with such poor yields from the Grignard reaction, which were exacerbated by self-destruction of the reagent, we instead considered coupling an aromatic aldehyde with a metal dienolate to effect carbon-carbon bond formation—the alternate reaction route considered in the retrosynthetic analysis on page 29.
Interest shifted to the possibility of alkylating the \(\alpha,\beta\)-unsaturated ester 57 in a \(\gamma\)-addition of the substituted benzaldehyde 58. Studies by Majewski and his co-workers suggested that, by varying reaction conditions, \(\gamma\)-alkylation could be favored. It was determined that, in reactions of metalated senecioamides with carbonyl compounds, kinetic control gave \(\alpha\)-substituted products with
thermodynamic control favoring formation of the γ-substituted products. Furthermore, the α-substituted products could dissociatively equilibrate to the thermodynamically favored isomers at room temperature. We thought perhaps alkylation of ester 57 could be controlled similarly to give the desired γ-alkylation product.

\[
\begin{align*}
\text{Me}_3\text{N} & \quad \text{Me}_3\text{N} \\
\text{O} & \quad \text{OH} \\
\text{CHO} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

N,N-dimethyl-senecioamide \hspace{1cm} \alpha\text{-alkylation} \hspace{1cm} \gamma\text{-alkylation}

To conduct preliminary studies, various metalated dianions of ester 57 were treated with anisaldehyde. The ester was first prepared from a Michael reaction between t-butyl acetoacetate and the unsaturated urethane 59\textsuperscript{7} followed by cyclization and preferential reduction of the ethyl ester with Super Hydride (lithium triethylborohydride).\textsuperscript{38}
Generation of the dienolate at -78°C, using lithium diisopropylamide,\textsuperscript{39} followed by addition of anisaldehyde yielded a very messy reaction with formation of a cyclic urethane 62 apparently arising from attack of
the alkoxide of the desired γ-alkylation product on the ethyl urethane.
The desired alcohol was never isolated although its presence as a
reaction intermediate seemed certain with the existence of the cyclic
urethane 62. Reaction of ester 57 with LDA at -78°C, followed by metal
exchange with anhydrous magnesium bromide in THF recovered only starting
material upon workup. Repeating the conditions, but with warming of the
reaction mixture to 0°C after addition of anisaldehyde paralleled the
results using just LDA. Only the cyclic urethane was seen, implicating
the desired γ-alkylation product as a reaction intermediate, but with
the rate of cyclization into the ethyl urethane being too fast to
control under the reaction conditions. Altering anion formation,
however, using LDA followed by addition of zinc chloride in THF40 at
-78°C yielded, upon reaction with anisaldehyde at room temperature,
isomerization of the α-addition product to the desired isomer 63,
accompanied by some cyclization to form the urethane byproduct 62.
These conditions with dienolate formation in the presence of zinc
chloride looked very promising, giving a fairly clean reaction
proceeding at a rate easily monitored by analytical tlc. It was decided
then to pursue this route, using a highly substituted aromatic aldehyde.

Proceeding to the coupling reaction of interest, benzaldehyde 58
next served as the carbonyl component, reacting with the zinc dienolate
at 0°C. Despite incomplete reaction of ester 57, two products were
formed—one being the desired alcohol 64 and the second product
resulting from further reaction of the newly formed alkoxide to give
urethane 65. Yields of alcohol 64 were moderate, ranging from 40-50%,
but, when considering the simplification of the synthesis and the crucial carbon-carbon bond formation between an aromatic system and a bicyclic lactam precursor, the reaction opened a viable synthetic route.
Alcohol 64 proved to be a valuable synthetic intermediate, eventually leading to construction of a pentacyclic skeleton having correct stereochemistry at five of the eight chiral centers present in naphthyridinomycin. Having solved the problem of introducing the aromatic system, the immediate concern was synthesis of the 6-lactam with subsequent introduction of an amine with stereochemical control. Hydrogenolysis of the benzyl ether and hydrogenation of the double bond over rhodium on carbon converted alcohol 64 to the saturated phenol 66, which was then reprotection as the benzyl ether 67. At this point, it was decided that protection of the primary alcohol preceding oxidation of the secondary alcohol would be a preferred synthetic sequence since
oxidation to a carbonyl functional group at the primary alcohol position might pose problems with reaction selectivity later in the synthesis. Attempts, however, to convert diol 67 to the monobenzoate ester, pivaloate ester or the triphenylmethyl ether were unsuccessful with either no reaction, as in the cases of pivaloate ester and triphenylmethyl ether formation, or simultaneous reaction at both alcohol sites with benzoyl chloride to give the dibenzoate ester.

Thwarted by the unselectivity encountered with benzoate ester formation under a variety of reaction conditions, we tried to selectively oxidize the secondary alcohol to the ketone in the presence of the primary alcohol. Reacting diol 67 with DDQ\(^{41}\) showed no selectivity with a complex mixture of oxidation products forming, oxidation with pyridinium chlorochromate\(^{42}\) gave the aldehyde, Jones
oxidation produced the ketoacid and only chromium trioxide, either in the presence of acetic acid or in the form of Collin’s reagent, yielded mixtures of the desired ketoalcohol with the ketoaldehyde at a very slow oxidation rate. Unable to form the ketoalcohol cleanly in good yield, both alcohols were finally oxidized with Jones reagent, yielding the ketoacid, followed by methylation, to give ketoester. After deprotecting the t-butyl ester with trifluoroacetic acid (TFA), the carboxylic acid was activated as a mixed anhydride for conversion.
in the presence of ammonia, to the amide 70. Cyclization to the olefin 71 went smoothly with catalytic amounts of CSA and quinoline in
refluxing benzene. Treatment of the enamide 71 with nitrosyl chloride followed by \textit{in situ} reduction of the \(\alpha\)-chloro oxime using sodium cyanoborohydride yielded the single oxime isomer 72. The stereochemical outcome of the reduction, predicted by model studies performed in our laboratory, resulted from preferential delivery of a hydride to the less hindered face of the molecule, thus favoring formation of the desired isomer at the benzylic position of oxime 72. Proton nmr data for compounds synthesized from the oxime support the proposed stereochemistry and will be discussed in detail later in the text.

Continuing the synthesis, reduction of oxime 72 with hydrogen over Raney nickel catalyst (W-2)\(^{45}\) cleanly afforded one amine isomer 73. As expected, catalytic reduction occurred from the less hindered side to
establish the correct stereochemistry at the amine functionality. Phenolic cyclization of 73 with formaldehyde in refluxing methanol gave the tetrahydroisoquinoline 74, which, upon heating in acetonitrile, led to a second cyclization to yield the pentacyclic lactam 75.

Comparison of structure 75 with naphthyridinomycin reveals that the model lactam has intact the ring skeleton found in the target molecule with only the oxazolidine missing. Five of the eight chiral centers have been established with the correct configuration, including the four contiguous chiral centers at C(5), C(6), C(7) and C(18). The major synthetic modifications now required to complete the synthesis include introduction of an appropriate side chain at C(12), construction of the
oxazolidine, conversion of the ethyl urethane to an N-methylamine, oxidation to the quinone and finally, reduction of the lactam at C(10) to an aminal.

Since the amine 73 so readily cyclized with formaldehyde, we were anxious to try the cyclization with a glyoxylate which would allow introduction of a hydroxymethyl precursor at the newly formed benzylic position. Stereochemistry at that center could not be predicted from models since it was not apparent what transition state would be favored during nitrogen-carbon bond formation. Reaction of compound 73 with hydrated methyl glyoxylate produced exclusive formation of one isomer of compound 76. Acylation of this product gave compound 77 for further characterization and structure confirmation. However, it was not
immediately evident what configuration existed at the benzylic carbon bearing the methyl ester.

Now an appropriately substituted tetracyclic skeleton was synthetically available for elaboration into naphthyridinomycin, but the stereochemistry of two chiral centers was either uncertain or unknown. As mentioned in the oxime synthesis, the benzylic proton at C(5) was assumed to be delivered from the less hindered face. Studies of nmr data provide support for the presence of the desired isomer in compounds 74, 76 and 77, with the chiral center being initially established in oxime 72. Models of these tetracyclic products show that, if the

benzylic proton at C(5) is cis to the adjacent proton, the dihedral angle would approximate 45° to 60°, and the proton should experience coupling of 6 to 4 Hz respectively. If, in the other case, the benzylic proton is trans, the angle between the two protons should be very close to 180°, consequently showing coupling of 12 to 13 Hz. Proton nmr spectra for the tetracyclic amines 74, 76 and 77 (Figures 7, 8 and 9) show coupling for the benzylic proton at C(5) ranging from 2 to 4 Hz.
Figure 7.

Figure 8.
There is no indication of any larger coupling, thus supporting a structure with the protons cis at C(5) and C(6) as established in the oxime precursor 72. Furthermore, when the signal for the amine proton at N(11) in amine 77 was irradiated (Figure 10), the benzylic signal for the proton at C(5) collapsed to a doublet showing coupling of 2 Hz with the proton at C(6). The splitting of the benzylic proton signal, lost upon irradiation of the amine proton signal, is believed to be due to long-range W coupling with the proton at N(11).49 This phenomenon implies that the molecular conformation is limited to a planar structure across five atoms, with N(11), C(6) and C(5) as the three center atoms,
which is only possible with the desired stereochemistry at the benzylic position in question. If the benzylic proton at C(5) in lactam 77 is trans to the adjacent proton at C(6), then the planar relationship between the amine proton and the benzylic proton necessary for W coupling does not exist.

Finally, the presence of W coupling severely limits the possible orientations of the molecule to one conformation. Examination of molecular models of the desired isomer of compound 77 reveals that the dihedral angle between the benzylic proton at C(12) and the amine proton at N(11) is close to 40°, which should result in splitting of

Figure 10.
approximately 7 Hz for the proton at C(12). The undesired isomer of 77, with the methyl ester on the α face, would have a dihedral angle close to 90°, resulting in very little splitting of the benzylic proton signal at C(12). In fact, coupling of 4 to 5 Hz has been observed for this proton signal in compounds 76 and 77, supporting a structure with the methyl ester on the β face. Based on these observations, it is thought that the compound formed from phenolic cyclization of amine 73 and methyl glyoxylate is the desired isomer 76a. To further verify the stereochemistry at C(5) and C(12), an x-ray analysis of 76 was performed by Hoffmann-La Roche. The x-ray structure, shown in Figure 11, agrees with structure 76a.

Cyclization of compound 77a to the lactam, analogous to ring closure on the unsubstituted amine 74 to give compound 75, would nearly complete construction of the naphthyridinomycin skeleton, lacking only the oxazolidine. However, heating amine 77a from 120–180°C resulted in no reaction, nor did attempts to activate the amine with trimethylaluminum produce lactam 78. These results seem to indicate

![Chemical structure images]

77a  78
that the conformation of amine 77a precludes facile cyclization and that it may be necessary to continue with other synthetic steps before this particular ring closure is possible.

Completing a total synthesis of naphthyridinomycin based on the synthetic work presented here still requires several major steps, with construction of the oxazolidine probably being the most problematic elaboration. Possibly a modification of compound 76a, such as preferential reduction of the methyl ester at C(12) or phenolic cyclization of 73 with glycolaldehyde, followed by protection of the resulting alcohol, would change the molecular conformation enough to favor cyclization to the pentacyclic lactam 80. Or, delaying lactam formation until later in the synthesis, alkylation of the existing lactam nitrogen using LDA would yield the tertiary lactam 81 in preparation for oxazolidine formation. Treatment of 81 either under acidic conditions or with Meerwein's reagent to give an imino ether intermediate may favor cyclization of the N-alkyl side chain to an imino ether salt 82 which, after reduction of the imine and the methyl ester would yield the desired oxazolidine 83. Protection of the alcohol side chain prior to hydrolysis of the ethyl urethane, followed by N-methylation of the newly generated amine, should give methylamine 84 which, after deprotection to the phenol, could be oxidized to yield quinone 85. Removal of the alcohol protecting group to release the monoalcohol at C(10) would enable selective oxidation to an intermediate aldehyde which may spontaneously cyclize to the protected
naphthyridinomycin derivative 86. Deprotection to the alcohol would yield naphthyridinomycin. Currently synthetic work towards this end is continuing in the laboratory of Dr. Tohru Fukuyama at the Chemistry Department of William Marsh Rice University.
Chapter III

EXPERIMENTAL RESULTS
TECHNICAL NOTES

Melting points (mp), determined on a Mel-Temp, are uncorrected.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1320 Infrared Spectrophotometer and are reported in wave numbers (cm\(^{-1}\)).

Nuclear magnetic resonance (NMR) spectra were determined on a JEOL FX-90Q instrument in the Fourier Transform mode. Chemical shifts are reported in parts per million down field from tetramethylsilane (8) as the internal standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole at 70 eV using direct probe insertion at temperatures of 150 to 300°C. High resolution mass spectra were obtained under similar conditions using a CEC 21-110B instrument.

Analytical thin layer chromatography (tlc) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F-254. Preparative tlc separations were made on plates (20 x 20 cm) prepared with a 2 mm layer of Merck silica gel 60 PF-254. Compounds were eluted from the adsorbent with 10% methanol in methylene chloride.

Column chromatography was performed on Woelm silica gel, 32-63 mesh, packed in Altex columns on an mplc system.

Hydrogenations and high temperature reactions were carried out in a stainless steel Parr general purpose bomb.
Reagents and solvents were commercial grades and were used as supplied with the following exceptions:

Methylene chloride: distilled and stored over aluminum oxide.

Ether: distilled through a 24-inch Snyder column.

Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl.

Dimethylformamide: dried over 4Å molecular sieves.

Pyridine: dried over potassium hydroxide pellets.

Diisopropylamine: distilled from sodium hydride and stored over potassium hydroxide pellets.

Lithium diisopropylamide (LDA) was prepared by dropwise addition of n-butyllithium in hexanes to a stirred solution of diisopropylamine in tetrahydrofuran at 0°C and was used after stirring for 5 minutes.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
N-n-propyl enamide (25b)

Sodium hydride (50% in mineral oil, 12.7 mmol) was added to a solution of 2.109 g (11.7 mmol) of enamide 24b and 2.11 ml (18.67 mmol) of n-propyl iodide stirring in 20 ml of dimethyl sulfoxide at 25°C. After completion of the reaction in seven minutes, 1 ml of acetic acid was added to neutralize any excess base. The mixture was poured over ice and partitioned between ether and a dilute sodium chloride solution. After thoroughly extracting the aqueous layer with ether, the ether solution was dried over anhydrous magnesium sulfate and evaporated. Chromatography on a silica gel column, using 80% ether in hexanes, yielded 2.352 g (90.5%) of 25b as a clear oil.

IR (CH₂Cl₂): 1729, 1655, 1194, 1100, 1045

NMR (CDCl₃): 0.91 (3H, t, J = 7 Hz), 1.57 (2H, m), 2.32 - 3.04 (4H, m), 3.39 (2H, t, J = 7 Hz), 3.70 (3H, s), 4.80 (1H, d, J = 8 Hz), 6.02 (1H, d of d, J = 8 Hz, J = 1 Hz)

MS: 223 (32, M⁺), 191 (11), 136 (100)

Exact Mass: Calcd. for C₁₂H₁₇NO₃ 223.1208
          Found 223.1211
Methoxy oxime lactam (26b)

A solution of nitrosyl chloride in methylene chloride was added dropwise at -15°C to 2.172 g (9.74 mmol) of enamide 25b in 40 ml of dry methylene chloride under argon. When the uv-activity of the olefin disappeared by analytical tlc, 20 ml of methanol and 2.71 ml (19.5 mmol) of triethylamine were added. The reaction mixture was warmed to room temperature and stirred for an additional 30 minutes, followed by evaporation to obtain the nitroso dimer. Refluxing in methanol for 2 hours cracked the dimer to the desired oxime. After removing the methanol by evaporation, a column separation using 80% ether in hexanes gave 2.175 g (77.6%) of white crystals, mp 110°C (ether).

IR (CH₂Cl₂): 3560, 3290, 1727, 1650, 1362, 1058

NMR (CDCl₃): 0.97 (3H, t, J = 7 Hz), 1.69 (2H, m), 2.44 (1H, d of t, J = 13 Hz, J = 3 Hz), 2.77 (1H, d of d, J = 10 Hz, J = 13 Hz), 3.28 (3H, s), 3.60 (3H, s), 3.79 (1H, t, J = 7 Hz), 4.79 (1H, s), 8.08 (1H, s)

MS: 284 (1, M+), 267 (79), 253 (55), 102 (100)

Exact Mass: Cacl. for C₁₃H₂₀N₄O₅ 284.1372
Found 284.1368
Tricyclic methoxy lactam (27b) and Methoxyamino lactam (28b)

Reduction of 705.0 mg (2.48 mmol) of oxime 26b was carried out in 30 ml of ethyl acetate, using 466.9 mg of 5% rhodium on alumina under 1350 psi of hydrogen for one hour at 130°C. After filtering the reaction mixture through celite and evaporating, the two products were separated on a preparative silica gel tlc, eluting with 3% methanol in methylene chloride. Recovery yielded 310.1 mg (52.5%) of the lactam 27b and 313.6 mg (46.8%) of the amine 28b.

Characterization of lactam 27b:

IR (CH$_2$Cl$_2$): 3420, 1704, 1650, 1083

NMR (CDCl$_3$): 0.90 (3H, t, J = 7Hz), 1.52 (2H, m), 2.28 (1H, m), 2.64 - 3.16 (5H, m), 3.38 (3H, s), 3.88 - 4.20 (1H, m), 4.64 (1H, d, J = 3 Hz), 8.04 (1H, br s)

MS: 238 (1, M$^+$), 223 (3), 207 (66), 104 (100)

Exact Mass: Calcd. for C$_{12}$H$_{18}$N$_2$O$_3$ 238.1317
               Found                     238.1315
Characterization of amine 28b:

IR (CH$_2$Cl$_2$): 1725, 1642

NMR (CDCl$_3$): 0.92 (3H, t, J = 7 Hz), 1.40 - 1.91 (4H, m), 2.48 (1H, AB, J = 11 Hz), 2.57 (1H, d of d, J = 6 Hz, J = 2 Hz), 2.76 (1H, d, J = 6 Hz), 2.92 (1H, AB, J = 11 Hz), 3.12 - 3.50 (2H, m), 3.42 (3H, s), 3.70 (3H, s), 3.84 - 4.28 (1H, m), 4.40 (1H, d, J = 2 Hz)

MS: 270 (<1, M+), 267 (2), 156 (100)

Exact Mass: Calc'd. for C$_{14}$H$_{23}$N$_3$O$_4$ 270.1579
Found 270.1572
**Methoxyiodo lactam (32)**

Iodine, 4.21 g (16.57 mmol), was added portionwise at room temperature to 3.00 g (16.57 mmol) of enamide 24b in 50 ml of methanol buffered with 6.96 g (82.87 mmol) of sodium bicarbonate. When the reaction was completed, 3 ml of a saturated sodium bisulfite solution was added with stirring, followed by partitioning between methylene chloride and a dilute sodium chloride solution. After thoroughly extracting the aqueous layer with methylene chloride, the methylene chloride solution was dried over anhydrous magnesium sulfate, filtered and evaporated. The product was separated by chromatography using ether as the eluent to afford the desired iodide as white crystals, 5.48 g (97.6%), with a mp 171°C, dec. (methanol).

**IR (CH₂Cl₂):** 3403, 1728, 1675, 1072

**NMR (CDCl₃):** 2.64 (1H, d, J = 10 Hz), 3.04 – 3.56 (3H, m), 3.40 (3H, s), 3.70 (3H, s), 4.76 (1H, m), 7.05 (1H, br s)

**MS:** 339 (<1, M+), 308 (8), 212 (97), 127 (100)

**Exact Mass:**
Calcd. for C₁₆H₁₄NO₄I 338.9967
Found 338.9968
Carbomethoxy lactam dimethyl acetal (33)

The methoxyiodo lactam 32 (2.19 g, 6.45 mmol) was heated in 60 ml of methanol at 120°C in the presence of 1.32 g (7.76 mmol) of silver nitrate and 1.07 g (13.0 mmol) of sodium acetate for 30 minutes. After cooling the reaction mixture, 5 ml of a saturated sodium chloride solution was added with stirring, followed by filtration through a column of celite. The mixture was partitioned between ether and a dilute sodium chloride solution and the ether layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The crude reaction products were dissolved in 60 ml of methanol and the mixture was heated in the presence of camphorsulfonic acid (200 mg) for 50 minutes to convert the acetoxy derivative, a minor reaction product, to the desired dimethyl acetal. When all the acetoxy compound had reacted, the solution was neutralized with triethylamine and evaporated to a small volume. The crude product was partitioned between methylene chloride and a saturated sodium bicarbonate solution, thoroughly extracting the aqueous layer with methylene chloride. The methylene chloride solution was dried over anhydrous magnesium sulfate, filtered
and evaporated. Separation on a silica gel column using 3% methanol in ether yielded 1.31 g (83.5%) of the desired acetal. Crystallization from ether gave white crystals, mp 119°C.

IR (CH₂Cl₂): 3428, 1729, 1700, 1192, 1076

NMR (CDCl₃): 2.66 (1H, d, J = 7 Hz), 2.96 (1H, d of d, J = 7 Hz, J = 7 Hz), 3.28 (1H, d, J = 6 Hz), 3.37 (3H, s), 3.41 (3H, s), 3.71 (3H, s), 4.06 (1H, d, J = 6 Hz), 6.03 (1H, br s)
Carbobenzoxyurethane dimethyl acetal (34)

Anion formation was carried out at -78°C under argon, using 5.84 mmol of LDA in 5 ml of THF added dropwise to 1.18 g (4.87 mmol) of the lactam in 20 ml of THF. After 10 minutes of stirring to ensure complete proton abstraction, benzyl chloroformate (1.39 ml, 9.74 mmol) was added. The reaction mixture was warmed to -10°C, stirred for 20 minutes and then neutralized with 1 ml of acetic acid. After partitioning the reaction mixture between ether and a saturated sodium bicarbonate solution followed by drying the ether layer over anhydrous magnesium sulfate, the ether solution was filtered and evaporated. A column separation with 50% ether in hexanes gave 1.37 g (74.5%) of the activated lactam.

IR (CH₂Cl₂): 1789, 1725, 1076

NMR (CDCl₃): 2.44 - 2.76 (2H, m), 2.97 - 3.24 (1H, m), 3.31 (3H, s), 3.39 (3H, s), 3.54 (3H, s), 4.30 (1H, d of d, J = 18 Hz, J = 2 Hz), 5.33 (2H, s), 7.30 - 7.57 (5H, m)
N-n-propylamide carbobenzyxurethane dimethyl acetal (35)

Heating the activated lactam 34 (1.26 g, 3.34 mmol) for 20 minutes in 12 ml of toluene at 130° with 2.74 ml (33.4 mmol) of n-propylamine and 636 mg (6.68 mmol) of 2-hydroxypyridine opened the ring to yield the desired n-propylamide. When the reaction was complete, the excess amine and toluene were removed by evaporation. Separation by medium pressure liquid chromatography gave 756 mg (51.9%) of the desired amide.

IR (CH₂Cl₂): 3438, 1730, 1657, 1509, 1200, 1058

NMR (CDCl₃): 0.92 (3H, t, J = 7 Hz), 1.50 (2H, m), 2.24 (1H, d of d, J = 15 Hz, J = 9 Hz), 2.68 – 3.20 (3H, m), 3.31 (3H, s), 3.34 (3H, s), 3.59 (3H, s), 4.20 (1H, d, J = 1 Hz), 4.24 (1H, m), 5.10 (2H, s), 5.96 (1H, br s), 7.15 – 7.42 (5H, m)

MS: 436 (<1, M+), 405 (2), 290 (78), 210 (97), 90 (100)

Exact Mass: Calcd. for C₂₂H₂₂N₂O₇, 436.2209
Found 436.2200
35
N-\text{\textit{n}}-\text{propylamide carbobenzoxyurethane dithiocetal (36)}

The dimethyl acetal (471 mg, 1.08 mmol) was converted at room temperature to the thioacetal by reaction with 0.40 ml (5.40 mmol) of ethanethiol in the presence of 0.66 ml (5.40 mmol) of boron trifluoride etherate, using methylene chloride as the solvent. The reaction mixture was then partitioned between methylene chloride and a saturated solution of sodium bicarbonate. The methylene chloride layer was dried through a sodium sulfate column and evaporated under reduced pressure. Column separation with 75% ether in hexanes gave 419 mg (78.2%) of the thioacetal.

IR (CH$_2$Cl$_2$): 3440, 3300, 1728, 1653, 1509, 1051

NMR (CDCl$_3$): 0.91 (3H, t, J = 7 Hz), 1.17 (3H, t, J = 7 Hz), 1.21 (3H, t, J = 7 Hz), 1.32 (2H, m), 2.24 (1H, d of d, J = 17 Hz, J = 11 Hz), 2.36 - 2.82 (2H, m), 2.64 (2H, q, J = 7 Hz), 3.20 (2H, m), 3.60 (3H, s), 3.78 (1H, d of d, J = 11 Hz, J = 4 Hz), 4.31 (1H, t of d, J = 10 Hz, J = 5 Hz), 5.15 (2H, d, J = 1 Hz), 6.00 (1H, br t, J = 6 Hz), 7.12 (1H, d, J = 11 Hz), 7.23 - 7.46 (5H, m)

MS: 496 (<1, M+), 467 (1), 465 (1), 362 (70), 316 (61), 137 (100)

Exact Mass: Calcd. for C$_{24}$H$_{34}$N$_2$O$_2$S$_2$ 496.2065
               Found 496.2068
Carbobenzoxyurethane methoxy N-n-propyl lactam (37)

Deprotection of the thioacetal (323 mg, 0.65 mmol) was carried out in a 1:4 acetonitrile-water mixture (8 mL) using 716 mg (2.64 mmol) of mercuric chloride with 331 mg (3.94 mmol) of sodium bicarbonate. Stirring the reaction mixture at 25°C for five minutes yielded the aldehyde which cyclized to the epimeric alcohols upon heating to 50°C for 20 minutes. After filtering the solution through celite, the organic layer was partitioned between ether and water. The ether layer was dried over anhydrous magnesium sulfate, filtered and evaporated to recover the crude alcohol mixture. The alcohols, dissolved in 8 mL of methanol, were refluxed for 10 minutes in the presence of 49 mg (0.21 mmol) of camphorsulfonic acid to yield the methyl ether 37. The reaction mixture was evaporated to a small volume and partitioned between ether and a saturated solution of sodium bicarbonate. The ether layer was dried over magnesium sulfate and evaporated to dryness. A chromatographic separation with ether as the eluent gave 125 mg (47.6%) of the single methyl ether isomer.
IR (CH$_2$Cl$_2$): 3420, 3330, 1731, 1650, 1505, 1061

NMR (CDCl$_3$): 0.85 (3H, t, $J = 7$ Hz), 1.17 - 1.73 (2H, m), 2.45 (1H, d of d, $J = 18$ Hz, $J = 11$ Hz), 3.01 (1H, d of d, $J = 18$ Hz, $J = 11$ Hz), 3.38 (3H, s), 3.46 (3H, s), 3.75 - 4.13 (1H, m), 4.43 (1H, d, $J = 2$ Hz), 4.43 - 4.93 (1H, m), 5.11 (2H, s), 7.35 (5H, s)

MS: 404 (1, M$^+$), 373 (1), 287 (35), 253 (40), 204 (100)

Exact Mass: Calcd. for C$_{22}$H$_{38}$N$_2$O$_6$ 404.1947
Found 404.1949
Tricyclic methoxy lactam (27b)

The carbobenzoxyurethane (67.5 mg, 0.17 mmol) was subjected to hydrogenolysis conditions, requiring 24.5 mg of 10% palladium on carbon and 1300 psi of hydrogen in 4 ml of absolute ethanol at 100°C for two hours. After filtering the reaction mixture through celite and removing ethanol under reduced pressure, the crude product was separated on a preparative silica gel tlc, eluting with 5% methanol in methylene chloride. Hydrogenolysis followed by in situ cyclization gave 24.0 mg (60.4%) of the lactam 27b.

IR (CHCl₃): 3420, 1704, 1650, 1080

NMR (CDCl₃): 0.90 (3H, t, J = 7 Hz), 1.57 (2H, m), 2.30 (1H, d of d, J = 11 Hz, J = 8 Hz), 2.69 - 3.21 (5H, m), 3.38 (3H, s), 3.89 - 4.21 (1H, m), 4.67 (1H, d, J = 4 Hz), 8.20 (1H, br s)

MS: 238 (1, M+), 207 (68), 158 (100)

Exact Mass: Calcd. for C₁₂H₁₃N₂O₃, 238.1317
Found 238.1326
4-(4-methoxyphenoxy)butyric acid (38a)

Potassium hydroxide pellets (34.6 g, 0.62 mol) were added slowly to a melt of 62.1 g (0.50 mol) of 4-methoxyphenol, followed by addition of 77 ml (1.00 mol) of $\gamma$-butyrolactone. The mixture was heated with vigorous stirring at 210°C under argon for 17 hours at which time 100 ml of water was added with heating to dissolve the potassium salts. The reaction mixture was poured into a dilute HCl solution, cooled for 3 hours and filtered to collect crystals of the desired acid. The crystals were washed with ice water and dried to yield 65.9 g (62.7%) of product.
\textit{t-Butyl 8-ketoester (38b)}^{54}

The acid chloride was prepared by heating 10.67 g (50.8 mmol) of the corresponding carboxylic acid 38a in 20.0 ml (274 mmol) of thionyl chloride at 70°C for 1 hour. After evaporation to dryness, the crude acid chloride, dissolved in 10 ml of methylene chloride, was added to a solution of Meldrum's acid (7.69 g, 53.4 mmol) and pyridine (8.22 ml, 102 mmol) in 80 ml of methylene chloride at 0°C. The solution was warmed to room temperature and stirred for an additional 20 minutes to complete alkylation. The reaction mixture was partitioned between methylene chloride and a dilute HCl solution and the aqueous layer was thoroughly extracted with methylene chloride. The combined methylene chloride layers were washed with a saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was refluxed for 30 minutes in a mixture of 25 ml of \textit{t}-butyl alcohol and 25 ml of toluene to yield the desired ketoester.
A solution of 35.4 g (115 mmol) of ketoester 38b, 21.5 g (114 mmol) of unsaturated urethane 59 and 20.7 ml (45.2 mmol) of a 40% solution of Triton B in 200 ml of ethanol was stirred for 16 hours at 25°C to afford the 1,4-adduct 38c. After quenching the reaction with dry ice, the solution was evaporated to a small volume, partitioned between ether and a saturated sodium chloride solution and the ether layer was dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column yielded 18.9 g (34.3%) of the desired product.
Unsaturated cyclic urethane (38d)

Cyclization of 18.9 g (39.3 mmol) of ketoester 38c in the presence of camphorsulfonic acid (914 mg, 3.93 mmol) and quinoline (0.511 ml, 4.33 mmol) in refluxing benzene (50 ml) yielded the desired unsaturated urethane. The reaction mixture was partitioned between ether and a dilute solution of HCl and the ether layer was washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and evaporated. The crude product was used without further purification.
**Saturated cyclic urethane (38e)**

Subjecting 18.2 g (39.3 mmol) of the urethane 38d to 1100 psi of hydrogen with a catalyst mix of 2.0 g of 5% rhodium on alumina and excess Raney nickel in 100 ml of ethyl acetate hydrogenated the double bond after heating at 140°C for 4 hours. Filtration through celite, followed by evaporation gave the crude desired product 38e.
Ethylurethane alcohol (38f)

Deprotection to the alcohol was carried out by oxidizing 18.3 g (39.3 mmol) of cyclic urethane 38e with 40.0 g (72.8 mmol) of ceric ammonium nitrate, added portionwise, in a solvent mix of acetonitrile (80 ml) and water (20 ml) at 0°C. When oxidative removal of the aromatic ring was complete, the reaction mixture was partitioned between ether and a saturated solution of sodium chloride. The ether layer was washed twice with sodium chloride solutions and then the combined ether extracts were washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. A separation by column chromatography (solvent gradient up to 80% ether in hexanes) yielded 10.9 g (73.9% from compound 38g) of alcohol 38f.
Urethane phenyl selenide (38g)

Addition of methanesulfonyl chloride (3.5 ml, 45.2 mmol) to a solution of 10.9 g (29.1 mmol) of alcohol 38f and 12.1 ml (87.2 mmol) of triethylamine in 60 ml of methylene chloride at 0°C afforded the mesylate. The reaction mixture was partitioned between methylene chloride and a dilute solution of HCl and the ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. The crude mesylate was dissolved in 100 ml of absolute ethanol with 5.45 g (17.4 mmol) of diphenyl diselenide to which sodium borohydride (325 mg, 8.6 mmol) was added at room temperature. The reaction was heated at 50°C for 10 minutes to complete selenide formation and then partitioned between ether and a dilute solution of HCl. The ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated.
Olefin (38h)

Ozonolysis of the crude selenide 38g (14.9 g, 29.1 mmol) dissolved in 100 ml of ethyl acetate was performed at 0°C to give the selenoxide. After oxidation was complete, 4.45 ml (31.9 mmol) of triethylamine was added and the reaction was heated for 20 minutes at 80°C. The solution was partitioned between ether and a saturated solution of sodium bicarbonate and the ether layer was dried over anhydrous magnesium sulfate, filtered and evaporated. Purification by liquid chromatography with a solvent gradient up to 60% ether in hexanes yielded 8.25 g (79.8% from compound 38f) of the desired olefin 38h.
Ethylurethane amide (38i)

The t-butyl ester 38h (7.44 g, 20.9 mmol) was deprotected to the carboxylic acid in 12 ml of trifluoroacetic acid when allowed to stand at room temperature for 1 hour. After evaporation to dryness, the carboxylic acid was activated as the mixed anhydride by reaction with 6.00 ml (62.8 mmol) of ethyl chloroformate and 5.84 ml (41.9 mmol) of triethylamine in 60 ml of methylene chloride at 0°C. When mixed anhydride formation was complete by analytical tlc, ammonia was passed through the reaction mixture to afford the desired amide. The reaction was partitioned between methylene chloride and a saturated solution of sodium bicarbonate. The aqueous layer was thoroughly washed with methylene chloride and the combined methylene chloride extracts were dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column with 5% methanol in ether gave 5.89 g (94.3%) of the amide 38i.
IR (CH₂Cl₂): 3519, 3400, 1746, 1690

NMR (CDCl₃): 1.24 (3H, t, J = 7 Hz), 1.29 (3H, t, J = 7 Hz),
2.45 (2H, t, J = 10 Hz), 3.01 (1H, d of d, J = 18 Hz, J = 10 Hz), 4.01 - 4.48 (4H, m), 4.93 - 5.29 (2H, m),
5.50 - 6.15 (3H, m)

MS: 298 (18, M⁺), 281 (46), 258 (75), 144 (100)

Exact Mass: Calcd. for C₁₄H₂₂N₂O₅ 298.1528
Found 298.1533
Ethylurethane enamide (38)

Ozonolysis of the olefin 38i (5.89 g, 19.8 mmol) was carried out at -78°C in a solvent mix of methanol (35 ml) and methylene chloride (35 ml). Upon completion, the flask was flushed with argon, dimethyl sulfide (14.5 ml, 198 mmol) was added and the solution was allowed to warm slowly to room temperature. Evaporation to dryness yielded the crude aldehyde which was used without further purification. A solution of the aldehyde, camphorsulfonic acid (459 mg, 1.98 mmol) and quinoline (0.466 ml, 3.95 mmol) in 120 ml of toluene was refluxed for 15 minutes with removal of water via a Dean-Stark trap to effect cyclization to the enamide 38. The reaction mixture was cooled and partitioned between ether and a dilute solution of HCl. The ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Purification by liquid chromatography using ether as the eluent gave 2.82 g (50.5%) of the desired enamide.
IR (CDCl₃): 3418, 1743, 1691, 1183

NMR (CDCl₃): 1.26 (6H, t, J = 7 Hz), 2.55 (1H, m), 3.00 (1H, m),
4.15 (4H, q, J = 7 Hz), 4.34 (1H, t, J = 7 Hz),
4.75 (1H, d of d, J = 10 Hz, J = 2 Hz), 5.30 (1H, br s),
6.03 (1H, d of d, J = 10 Hz, J = 4 Hz), 6.91 (1H, br s)

MS: 282 (70, M+), 236 (53), 210 (72), 208 (72), 31 (100)

Exact Mass:
Calcd. for C₁₃H₁₈N₄O₅: 282.1215
Found: 282.1212
Methoxyiodo lactam (39)

Iodine monochloride (1.60 g, 9.84 mmol) was added dropwise with vigorous stirring to a mixture of 2.72 g (9.63 mmol) of the enamide 38 and pyridine (3.11 ml, 38.5 mmol) in 40 ml of methanol. On completion of the reaction, an aqueous solution of sodium sulfite was added at 0°C to reduce any remaining oxidizing agent. The reaction mixture was partitioned between methylene chloride and a saturated solution of sodium bicarbonate. The methylene chloride layer was dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column with ether yielded 2.36 g (55.7%) of the desired iodide.

IR (CH₂Cl₂): 3395, 1738, 1684, 1181, 1071

NMR (CDCl₃): 1.27 (6H, t, J = 7 Hz), 2.34 - 2.88 (1H, m), 3.13 (1H, t, J = 7 Hz), 3.39 (3H, s), 4.21 (4H, q, J = 7 Hz), 4.39 (1H, t, J = 10 Hz), 4.54 - 4.74 (1H, m), 4.86 (1H, m), 6.90 (1H, br s)

MS: 440 (1, M+), 368 (73), 336 (73), 208 (100)

Exact Mass: Calcd. for C_{14}H_{21}IN₂O₆ 440.0444
Found 440.0449
**Lactam dimethyl acetal (40)**

A solution of the methoxyiodo lactam 39 (2.29 g, 5.20 mmol), sodium acetate (850 mg, 10.4 mmol) and silver nitrate (1.07 g, 6.23 mmol) in 50 ml of methanol was heated at 120°C for 1 hour to afford rearrangement to the dimethyl acetal. When the starting material was gone, 5 ml of a saturated solution of sodium chloride was added with stirring, followed by filtration through a celite column. Upon addition of camphorsulfonic acid (1.82 g, 7.83 mmol) traces of an acetoxy byproduct converted cleanly to the desired dimethyl acetal when the solution was heated to 60°C for 1 hour. The reaction mixture was worked up by evaporation to a small volume, followed by partitioning between methylene chloride and a saturated sodium bicarbonate solution. After drying the organic layer over magnesium sulfate and evaporating the solvent, chromatographic separation with 5% methanol in ether as the solvent yielded 1.56 g (87.5%) of the dimethyl acetal.
IR (CH$_2$Cl$_2$): 3428, 1741, 1700, 1189, 1076

NMR (CDCl$_3$): 1.25 (6H, t, $J = 7$ Hz), 2.31 (1H, m), 3.09 (1H, t of d, $J = 8$ Hz, $J = 2$ Hz), 3.46 (6H, s), 4.17 (4H, q, $J = 7$ Hz), 4.29 - 4.47 (1H, m), 4.51 (1H, m), 5.77 (1H, br s)

MS: 344 (26, M+), 312 (60), 271 (71), 241 (100)

Exact Mass: Calcd. for C$_{14}$H$_{14}$N$_2$O, 344.1583
Found 344.1579
acetone
t-Butylurethane dimethyl acetal (41)

Urethane formation proceeded by first forming the lactam anion using 4.80 mmol of LDA in 5 ml of THF which was added by syringe, with stirring at -78°C, to 1.50 g (4.36 mmol) of the dimethyl acetal 40 dissolved in 20 ml of THF under argon. After stirring for 10 minutes, 1.62 g (6.54 mmol) of BOC-ON dissolved in 3 ml of THF was added. The solution was allowed to warm to 0°C and stirred at this temperature for 15 minutes to complete the reaction. When no starting material remained by analytical tlc, 1 ml of acetic acid was added to neutralize excess base, followed by partitioning between ether and dilute hydrochloric acid solution. The organic layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column with a solvent gradient up to 40% ether in hexanes gave 1.42 g (73.5%) of the desired t-butylurethane.
IR (CH$_2$Cl$_2$): 1781, 1743, 1702

NMR (CDCl$_3$): 1.22 (6H, t, J = 7 Hz), 1.55 (9H, s), 2.49 (1H, m),
3.27 (1H, m), 3.40 (6H, s), 4.09 (2H, q, J = 7 Hz),
4.14 (2H, q, J = 7 Hz), 4.52 (1H, m)

MS: 444 (17, M$^+$), 371 (70), 343 (55), 48 (100)

Exact Mass: Calcd. for C$_{26}$H$_{32}$N$_2$O$_5$, 444.2107
Found 444.2102
N-n-Propylamide dimethyl acetal (42a) and N-n-Propylbisamide (42b)

Ring opening of 1.37 g (3.07 mmol) of t-butylurethane 41 was performed by heating the starting material at 130°C for 30 minutes with 3.0 ml of n-propylamine and 29.2 mg (0.307 mmol) of 2-hydroxyypyridine. Evaporation followed by column separation with 80% ether in hexanes gave 751 mg (48.6%) of the desired compound 42a, and 306 mg (19.3%) of the bisamide 42b.

Characterization of amide 42a:

IR (CH\textsubscript{3}Cl\textsubscript{2}): 3438, 3360, 1700, 1502, 1161

NMR (CDCl\textsubscript{3}): 0.93 \text{ (3H, t, J = 7 Hz)}, 1.27 \text{ (6H, t, J = 7 Hz)}, 1.43 \text{ (9H, s)}, 1.50 \text{ (2H, m)}, 2.48 \text{ (1H, m)}, 2.80 \text{ (1H, m)}, 3.22 \text{ (1H, m)}, 3.35 \text{ (3H, s)}, 3.40 \text{ (3H, s)}, 4.00 - 4.44 \text{ (5H, m)}, 5.54 - 6.00 \text{ (2H, br s)}

Characterization of bisamide 42b:

IR (CH\textsubscript{3}Cl\textsubscript{2}): 3438, 1705, 1664

NMR (CDCl\textsubscript{3}): 0.88 \text{ (3H, t, J = 7 Hz)}, 0.94 \text{ (3H, t, J = 7 Hz)}, 1.25 \text{ (3H, t, J = 7 Hz)}, 1.43 \text{ (9H, s)}, 1.50 - 1.74 \text{ (4H, m)}, 2.48 \text{ (1H, m)}, 2.98 - 3.65 \text{ (5H, m)}, 3.33 \text{ (3H, s)}, 3.35 \text{ (3H, s)}, 4.16 \text{ (2H, q, J = 7 Hz)}, 4.56 \text{ (1H, br d, J = 6 Hz)}, 5.96 \text{ (1H, t, J = 5 Hz)}, 6.22 \text{ (1H, d, J = 8 Hz)}, 6.67 \text{ (1H, br s)}
42a
Methoxyamino N-n-propyl lactam (44)

Cyclization of the dimethyl acetal 42a (384 mg, 0.76 mmol) was carried out by heating the compound at 55°C for 5 minutes in a mixture of 1 ml of 3 N HCl and 20 ml of THF. The resulting mixture of epimeric alcohols was partitioned between ethyl acetate and a saturated solution of sodium bicarbonate. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered and evaporated. After dissolving the crude product mixture in 10 ml of methanol, the t-butylurethane was deprotected by heating the solution at 55°C in the presence of 4 ml of methanol saturated with HCl for 70 minutes. During the deprotection the alcohols were converted to a single methyl ether isomer. When the reaction was complete, the methanol was evaporated with low heat under reduced pressure followed by addition of triethylamine to neutralize the acid. Filtration through a celite column to remove the amine hydrochloride salts, evaporation and separation on a preparative silica gel tlc gave 141 mg (49.8%) of the lactam product 44.
IR (CH$_2$Cl$_2$): 3380, 3210, 1698, 1650, 1190, 1071

NMR (CDCl$_3$): 0.92 (3H, t, J = 7 Hz), 1.28 (6H, t, J = 7 Hz), 1.44 - 1.90 (2H, m), 2.39 (1H, m), 2.62 (1H, t, J = 7 Hz), 2.82 - 3.26 (2H, m), 3.42 (3H, s), 3.66 (1H, m), 3.86 (1H, m), 4.19 (4H, q, J = 7 Hz), 4.48 (1H, d, J = 4 Hz)

MS: 371 (58, M+), 338 (70), 325 (70), 323 (70), 269 (94), 104 (100)

Exact Mass: Caled. for C$_{17}$H$_{20}$N$_2$O$_6$ 371.2056
Found 371.2066
N-n-propyl lactam methoxybenzyl amine (46a)

The corresponding imine of the bicyclic amine 44 (101 mg, 0.27 mmol) and the aromatic aldehyde 45 (94 mg, 0.33 mmol) was formed when the two reactants were heated in 4 ml of methanol at 60°C for 1 hour. Upon addition of acetic acid (0.005 ml, 0.08 mmol) and sodium cyanoborohydride (9 mg, 0.14 mmol), the imine was reduced in situ after heating for 40 minutes. The condensation product was partitioned between ether and dilute HCl and the ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation of the crude reaction mixture on a preparative silica gel tlc (5% methanol in methylene chloride) yielded 152 mg (86.8%) of benzylamine 46a.
IR (CH₂Cl₂): 3310, 1736, 1697, 1645, 1122

NMR (CDCl₃): 0.87 (3H, t, J = 7 Hz), 0.94 (3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 2.14 (3H, s), 2.32 (1H, m), 2.68 (1H, d of d, J = 7 Hz, J = 6 Hz), 2.96 (1H, t, J = 7 Hz), 3.63 (2H, m), 3.77 (3H, s), 3.84 (3H, s), 3.98 (1H, d of d, J = 7 Hz, J = 5 Hz), 4.18 (1H, t, J = 7 Hz), 4.46 (1H, d, J = 2 Hz), 4.75 (1H, AB, J = 11 Hz), 5.07 (1H, AB, J = 11 Hz), 6.76 (1H, s), 7.22 - 7.60 (5H, m)

MS: 641 (<1, M+), 551 (2), 287 (97), 19 (100)

Exact Mass: Calculated for C₆H₄N₂O₉ 641.3312
Found 641.3313
Trifluoroacetamide N-n-propyl pyridone (47)

Amine 46a (43 mg, 0.067 mmol) was first protected as the trifluoroacetamide 46b by reacting it with 0.20 ml of trifluoroacetic anhydride in the presence of 0.40 ml of triethylamine in 4 ml of dry methylene chloride under argon for 64 hours. The resultant amide was partitioned between ether and dilute HCl and the ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. The crude product was then heated in 2 ml of formic acid for 7 minutes, followed by evaporation of the solvent. Separation on a preparative silica gel tlc plate (60% ether in hexanes) yielded 14 mg (31%) of the pyridone 47.

IR (CH₃Cl₂): 3428, 3300, 1704, 1600, 1155, 1126

NMR (CDCl₃): 0.78 (3H, t, J = 7 Hz), 1.19 (3H, t, J = 7 Hz), 1.24 (3H, t, J = 7 Hz), 1.54 (2H, m), 2.13 (3H, s), 2.83 (1H, m), 3.68 (2H, m), 3.72 (3H, s), 3.76 (3H, s), 4.05 (2H, q, J = 7 Hz), 4.13 (2H, q, J = 7 Hz), 4.43 (1H, m), 4.68 (1H, br s), 4.79 (2H, s), 6.02 (1H, br s), 6.50 (1H, s), 6.81 (1H, d of d, J = 11 Hz, J = 2 Hz), 7.14 - 7.44 (5H, m)

MS: 705 ([M+], 614 (1), 388 (22), 271 (78), 34 (100)

Exact Mass: Calcd. for C₃₅H₄₂F₆N₇O₃ 705.2872
Found 705.2872
t-buty1 ester aldehyde (50)

Ozonolysis of olefin \(38h\) (537 mg, 1.51 mmol) was performed at \(-78^\circ C\) in 10% methanol in methylene chloride (7 ml). After flushing the solution with argon, 0.80 ml (10.9 mmol) of dimethyl sulfide was added and the reaction was warmed slowly to room temperature. The solution was partitioned with methylene chloride and a saturated solution of sodium bicarbonate and sodium bisulfite, followed by thorough extraction of the aqueous layer with methylene chloride. The combined methylene chloride layers were dried through an anhydrous sodium sulfate column and evaporated to yield 606 mg of the crude aldehyde 50.

NMR (CDCl3): 1.30 (6H, t, \(J = 7\) Hz), 1.46 (9H, s), 2.16 - 2.74 (1H, m), 2.94 - 3.32 (1H, m), 4.23 (4H, q, \(J = 7\) Hz), 9.78 (1H, br s)
t-Butyl ester 2,4-dimethoxy-3-methylbenzyl alcohols (51)

The Grignard reagent was prepared by refluxing the aromatic bromide 49 (743 mg, 3.21 mmol) with magnesium turnings (88 mg, 3.63 mmol) in 5 ml of THF under argon. The reaction was initially started with only one fourth of the bromide, requiring 0.40 ml of 1.51 N n-butyllithium to scavenge water in the solvent. Once started, the remaining bromide was added dropwise in THF, maintaining a reflux for 20 minutes. A solution of the prepared Grignard reagent (0.60 ml) was carefully added to 115 mg (0.32 mmol) of aldehyde 50 dissolved in 5 ml of THF under argon at room temperature. The reaction mixture was worked up by partitioning between ether and dilute HCl. The ether layer was washed with brine followed by a saturated sodium bicarbonate wash, dried over anhydrous magnesium sulfate, filtered and evaporated. The two diastereomeric alcohols were obtained by separation on a preparative silica gel tlc plate using 80% ether in hexanes. The Grignard reaction gave 66 mg of the top alcohol isomer and 26 mg of the bottom alcohol isomer (56% overall yield).
Characterization of the top alcohol isomer:

NMR (CDCl₃): 1.26 (3H, t, J = 7 Hz), 1.30 (3H, t, J = 7 Hz), 1.44 (9H, s), 2.16 (3H, s), 2.40 (1H, m), 2.71 (1H, m), 3.16 (1H, d of t, J = 13 Hz, J = 7 Hz), 3.79 (3H, s), 3.83 (3H, s), 4.23 (4H, q, J = 7 Hz), 4.23 (1H, t, J = 11 Hz), 4.72 (1H, m), 5.10 (1H, m), 6.68 (1H, d, J = 11 Hz), 7.25 (1H, d, J = 10 Hz)

MS: 509 (2, M⁺), 491 (3), 435 (12), 200 (100)

Characterization of the bottom alcohol isomer:

NMR (CDCl₃): 1.11 - 1.28 (6H, m), 1.40 (9H, s), 1.53 - 2.00 (2H, m), 2.13 (3H, s), 2.36 (1H, m), 3.08 (1H, d of d, J = 18 Hz, J = 7 Hz), 3.78 (3H, s), 3.82 (3H, s), 4.00 - 4.37 (4H, m), 4.62 (1H, m), 5.23 (1H, t, J = 6 Hz), 6.63 (1H, d, J = 8 Hz), 7.29 (1H, d, J = 8 Hz)

MS: 509 (3, M⁺), 478 (1), 273 (19), 200 (81), 29 (100)
51 top isomer
51 bottom isomer
**t-Butyl ester 2,4-dimethoxy-3-methyl-5-benzylxy benzyl alcohols (53)**

The Grignard reagent was prepared from the lithiated aromatic bromide which was formed by addition of 12.9 mmol of n-butyllithium at -78°C to bromide 52 (4.50 g, 13.3 mmol) in 10 ml of THF under argon. Addition of anhydrous magnesium bromide in THF (16.2 mmol) effected metal exchange to form the Grignard reagent. The arylmagnesium bromide was added to aldehyde 50 (2.31 g, 6.47 mmol) dissolved in 10 ml of THF at room temperature. The resulting product mixture was partitioned between ether and dilute HCl and the ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column with 20% ether in hexanes gave 1.35 g (33.9%) of a mixture of the epimeric alcohols.
Characterization of the top alcohol isomer:

IR (CH$_2$Cl$_2$): 1725, 1677, 1148, 1113

NMR (CDCl$_3$): 1.26 (6H, t, J = 7 Hz), 1.44 (9H, s), 1.52 - 1.82 (2H, m), 2.21 (3H, s), 2.39 (1H, m), 3.10 (1H, m), 3.73 (3H, s), 3.80 (3H, s), 4.20 (1H, t, J = 8 Hz), 4.22 (4H, q, J = 7 Hz), 4.66 (1H, m), 5.02 (2H, d, J = 2 Hz), 5.14 (1H, m), 6.96 (1H, s), 7.25 - 7.46 (5H, m)

MS: 615 (<1, M+), 541 (<1), 300 (96), 34 (100)

Exact Mass: Calcd. for C$_{33}$H$_{44}$NO$_{10}$ 615.3043
          Found 615.3032

Characterization of the bottom alcohol isomer:

IR (CH$_2$Cl$_2$): 1724, 1695, 1146, 1112

NMR (CDCl$_3$): 1.14 - 1.35 (6H, m), 1.40 (9H, s), 2.18 (3H, s), 2.37 (1H, AB, J = 11 Hz), 2.71 (1H, m), 3.06 (1H, d of d, J = 11 Hz, J = 5 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.01 - 4.43 (4H, m), 5.07 (2H, s), 5.25 (1H, m), 7.08 (1H, s), 7.28 - 7.54 (5H, m)

MS: 615 (<1, M+), 541 (<1), 468 (13), 450 (10), 300 (94), 34 (100)

Exact Mass: Calcd. for C$_{33}$H$_{44}$NO$_{10}$ 615.3043
          Found 615.3032
53 top isomer
53 top isomer

>530 x 50
53 bottom isomer
t-Butyl ketoester (54)

The epimeric alcohols (220.6 mg, 0.359 mmol) were oxidized with 0.150 ml of 2.7 M Jones reagent in 5 ml of acetone at 0°C. Upon completion of the reaction, the solution was partitioned between ether and a dilute sodium chloride solution. The ether layer was subsequently washed with a solution of sodium bicarbonate and sodium bisulfite, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a preparative silica gel tlc (5% ether in methylene chloride) yielded 149.4 mg (67.9%) of the desired ketoester.

NMR (CDCl₃): 1.09 - 1.46 (6H, m), 1.39 (9H, s), 2.24 (3H, s), 2.39 (1H, d of d, J = 13 Hz, J = 7 Hz), 3.17 (1H, d of d, J = 13 Hz, J = 7 Hz), 3.54 (1H, br s), 3.77 (3H, s), 3.89 (3H, s), 4.09 (2H, q, J = 7 Hz), 4.22 (2H, q, J = 7 Hz), 5.07 (2H, s), 7.22 - 7.55 (6H, m)
**Ketoamide (55)**

The $t$-butyl ester 54 (188.3 mg, 0.307 mmol) was deprotected to the carboxylic acid in 4 ml of trifluoroacetic acid (TFA) at room temperature. After evaporating the TFA with low heat, the crude acid was activated as the mixed anhydride with 0.150 ml (1.57 mmol) of ethyl chloroformate and 0.130 ml (0.933 mmol) of triethylamine in 4 ml of dry methylene chloride at 0°C. Upon mixed anhydride formation, 0.50 ml of ethanol saturated with ammonia was added to afford the desired amide when warmed to room temperature. The reaction mixture was partitioned between methylene chloride and a solution of saturated sodium bicarbonate. After thoroughly washing the aqueous layer with methylene chloride, the organic layer was dried through an anhydrous sodium sulfate column and evaporated. The crude amide was used directly for cyclization to the enamide 56 without further purification.
Enamide (56)

A solution of the amide 55 (171 mg, 0.307 mmol), camphorsulfonic acid (36 mg, 0.155 mmol) and quinoline (0.018 ml, 0.153 mmol) was heated to 80°C in 5 ml of toluene for 1 hour to effect cyclization to the desired enamide 56. The reaction mixture was partitioned between ether and dilute HCl after cooling. The ether was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation on a silica gel column eluting with 80% ether in hexanes yielded 88.8 mg (53.7%) of enamide 56.

NMR (CDCl₃): 1.25 (6H, t, J = 7 Hz), 2.20 (3H, s), 2.65 (1H, m), 3.06 (1H, m), 3.67 (3H, s), 3.86 (3H, s), 4.17 (4H, q, J = 7 Hz), 4.40 (1H, t, J = 7 Hz), 4.92 (1H, br d, J = 10 Hz), 5.11 (2H, s), 5.43 (1H, br d, J = 17 Hz), 6.90 (1H, s), 7.29 - 7.57 (5H, m), 7.92 (1H, br s)
t-Butyl ester diol (63) and Cyclic 4-methoxybenzyl urethane (62)

The zinc dienolate was generated by first treating 100 mg (0.35 mmol) of the unsaturated ester with 0.81 mmol of LDA in 5 ml of THF at -78°C under argon, followed by addition of anhydrous zinc chloride in THF (0.82 mmol). The reaction mixture was stirred for 5 minutes at -78°C to ensure complete dienolate formation. Addition of 0.051 ml (0.42 mmol) of anisaldehyde at low temperature with subsequent warming to 25°C for 3 minutes gave two products. The reaction mixture was partitioned between ether and dilute HCl and the ether layer was washed with brine, washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation by liquid chromatography using 80% ether in hexanes as the eluent yielded 62 mg (42%) of the desired diol 63 and 34 mg (26%) of the cyclic urethane 62.
Characterization of diol 63:

IR (CH_{2}Cl_{2}): 3440, 1709, 1675, 1165

NMR (CDCl_{3}): 1.31 (3H, t, J = 7 Hz), 1.49 (9H, s), 1.66 (1H, br s), 2.64 (1H, d of d, J = 16 Hz, J = 2 Hz), 2.96 (1H, d of d, J = 16 Hz, J = 10 Hz), 3.60 (2H, d, J = 8 Hz), 3.80 (3H, s), 4.26 (2H, q, J = 7 Hz), 4.91 (1H, br d, J = 7 Hz), 6.91 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz)

MS: 421 (<1, M+), 348 (51), 286 (100)

Characterization of cyclic urethane 62:

NMR (CDCl_{3}): 1.48 (9H, s), 2.76 (1H, m), 3.02 (1H, d of d, J = 14 Hz, J = 2 Hz), 3.40 (2H, d, J = 17 Hz), 3.81 (3H, s), 5.28 (1H, d of d, J = 11 Hz, J = 4 Hz), 6.91 (2H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz)
α,β-Unsaturated cyclic t-butyl ester (60)

The Michael acceptor 59 (39.6 g, 212 mmol) and 53 ml (318 mmol) of t-butyl acetoacetate were dissolved in 120 ml of absolute ethanol. After addition of 2.00 g (42 mmol) of sodium hydride (50% in mineral oil), the reaction mixture was heated at 70°C for 15 minutes. The flask was cooled and dry ice was added to quench the reaction. The mixture was then partitioned between ether and a dilute sodium chloride solution and the ether layer was dried over magnesium sulfate, filtered and evaporated. The crude product was dissolved in 200 ml of toluene and cyclized while refluxing for 20 minutes in the presence of 8.4 g (42 mmol) of p-toluenesulfonic acid and 6.0 ml (51 mmol) of quinoline. During the cyclization water was removed by use of a Dean-Stark trap. Upon completion of the reaction, the mixture was partitioned between ether and dilute HCl and the organic layer was washed with brine and a
saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The desired product was crystallized from hexanes, rinsing with 20% ether in hexanes to yield 44.1 g (63.6%) of the t-butyl ester 60 with mp 87°C.

IR (CH₂Cl₂): 1728, 1685, 1166

NMR (CDCl₃): 1.26 (3H, t, J = 7 Hz), 1.29 (3H, t, J = 7 Hz), 1.48 (9H, s), 2.61 (3H, s), 2.83 (1H, AB, J = 14 Hz), 3.13 (1H, AB, J = 14 Hz), 4.19 (2H, q, J = 7 Hz), 4.23 (2H, q, J = 7 Hz), 4.67 (1H, d of d, J = 11 Hz, J = 5 Hz)

MS: 327 (73, M⁺), 272 (73), 270 (74), 200 (100)

Exact Mass: Calcd. for C₁₄H₂₂NO₆ 327.1682
Found 327.1675
a,β-Unsaturated t-butyl ester alcohol (61)

Selective reduction of the ethyl ester 60 was performed by dropwise addition of 70 ml of a 1 M solution of Super Hydride (lithium triethylborohydride) in THF at 0°C to 10.0 g (30.6 mmol) of 60 in 40 ml of THF under argon. The reaction mixture was partitioned between ether and a dilute sodium chloride solution and the ether layer was washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and evaporated. Separation with 80% ether in hexanes on a silica gel column gave 8.7 g (100%) of alcohol 61.

IR (CH₂Cl₂): 1719, 1680, 1627, 1166, 1138

NMR (CDCl₃): 1.32 (3H, t, J = 7 Hz), 1.48 (9H, s), 2.51 (3H, m), 2.66 (1H, AB, J = 17 Hz), 2.94 (1H, AB, J = 17 Hz), 3.66 (2H, d, J = 6 Hz), 4.23 (2H, q, J = 7 Hz)

MS: 285 (M⁺), 254 (52), 230 (95), 200 (98), 75 (100)

Exact Mass: Calcd. for C₁₄H₂₃NO₅ 285.1576
Found 285.1579
t-Butyl ester diol (64) and t-Butyl ester cyclic urethane (65)

Alcohol 57 (7.42 g, 26.0 mmol) in 30 ml of THF was added by syringe to 65.1 mmol of LDA in 90 ml of THF with vigorous stirring at -78°C under argon. After stirring for 5 minutes, 65.1 mmol of anhydrous zinc chloride in THF was added and the solution was stirred for an additional 5 minutes. The aromatic aldehyde 58 (6.7 g, 23.4 mmol) was dissolved in 15 ml of THF and transferred to the zinc enolate under argon at -78°C. Warming the flask to 0°C, the coupling reaction was allowed to proceed for 25 minutes while monitoring by analytical tlc and then quenched with 5 ml of acetic acid. The reaction mixture was partitioned between ether and dilute HCl. The ether layer was washed with dilute brine, washed with a saturated solution of sodium bicarbonate, dried over magnesium
sulfate, filtered and evaporated. Column separation with a solvent
gradient up to 60% ether in hexanes gave 7.3 g (49%) of a mixture of two
compounds. A second separation of 22.5 mg of the mixture on a
preparative silica gel tlc with 3% methanol in methylene chloride gave
12.7 mg (56.3 wgt. %) of the desired diol 64 and 9.7 mg (43 wgt. %) of
the cyclic urethane 65.

Characterization of diol 64:

IR (CH₂Cl₂): 3444, 1720, 1674, 1163

NMR (CDCl₃): 1.29 (3H, t, J = 7 Hz), 1.49 (9H, s), 2.22 (3H, s),
2.64 (1H, d of d, J = 16 Hz, J = 4 Hz), 2.95 (1H,
d of d, J = 16 Hz, J = 7 Hz), 3.57 (2H, d,
J = 14 Hz), 3.76 (3H, s), 3.83 (3H, s), 4.23 (2H,
q, J = 7 Hz), 4.32 (1H, m), 5.11 (2H, s), 5.20
(1H, d, J = 4 Hz), 7.00 (1H, s), 7.28 - 7.27 (5H, m)

MS: 571 (<1, M+), 525 (<1), 394 (74), 334 (100)

Exact Mass: Calcd. for C₃₄H₆₄NO₉ 571.2781
             Found 571.2775

Characterization of cyclic urethane 65:

IR (CH₂Cl₂): 3400, 1685, 1650, 1128, 1070

NMR (CDCl₃): 1.47 (9H, s), 2.23 (3H, s), 2.30 - 3.18 (2H, m),
3.72 (3H, s), 3.86 (3H, s), 5.07 (2H, s), 5.54 (1H,
d of d, J = 12 Hz, J = 4 Hz), 6.90 (1H, s), 7.29 -
7.50 (5H, m)

MS: 525 (1, M+), 469 (17), 394 (64), 334 (100)

Exact Mass: Calcd. for C₂₉H₃₂NO₈ 525.2362
             Found 525.2357
t-Butyl ester diol (66)

Hydrogenolysis of the benzyl ether occurred by subjecting 7.08 g of the mixture of compounds containing the desired diol to 1 atmosphere of hydrogen in the presence of 1.13 g of 10% palladium on carbon for 1 hour, using 80 ml of absolute ethanol as the solvent. Filtration through a celite column with subsequent evaporation gave the crude phenol. Reduction of the double bond was done on a series of 500-800 mg batches of crude phenol. Typical reaction conditions involved heating 705 mg of the crude phenol in 50 ml of absolute ethanol with 695 mg of 5% rhodium on carbon under 1100 psi hydrogen for 30 minutes at 110°C. The reaction mixture was then filtered through celite and the catalyst was rinsed twice with ethanol. A silica gel column separation of the combined rhodium on carbon reduction products yielded 2.68 g (44.7%) of the desired saturated phenol diol 66.
IR (CH$_2$Cl$_2$): 3524, 3420, 1721, 1684, 1147, 1105, 1080

NMR (CDCl$_3$): 1.28 (3H, t, J = 7 Hz), 1.38 (9H, s), 1.69 - 2.11 (2H, m), 2.18 (3H, s), 2.43 (1H, AB, J = 13 Hz), 2.93 (1H, d of d, J = 13 Hz, J = 6 Hz), 3.41 (1H, d, J = 11 Hz), 3.68 (3H, s), 3.77 (3H, s), 4.17 (2H, q, J = 7 Hz), 4.44 - 4.79 (1H, br m), 5.33 (1H, d, J = 8 Hz), 6.82 (1H, s)

MS: 483 (10, M+), 409 (73), 378 (47), 216 (100)

Exact Mass: Calculated for C$_2$H$_7$NO, 483.2468
          Found             483.2471
t-Butyl ester diol (67)

The phenol was reprotected as the benzyl ether by reacting 2.66 g (5.5 mmol) of the saturated diol at 70°C for 90 minutes with 1.3 ml (11.0 mmol) of benzyl bromide and 4.56 g (33.0 mmol) of pulverized potassium carbonate in a solvent mixture of 5:1 acetone-DMF. Upon completion of benzyl ether formation, the reaction mixture was filtered through celite, evaporated with heat under reduced pressure, and separated on a silica gel column with 80% ether in hexanes to give 3.04 g (96.5%) of the saturated diol 67.

IR (CH₂Cl₂): 3430, 1723, 1684, 1148, 1109, 1080

NMR (CDCl₃): 1.30 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.92 (2H, d, J = 14 Hz), 2.19 (3H, s), 2.46 (1H, d of d, J = 23 Hz, J = 10 Hz), 2.96 (1H, d of d, J = 10 Hz, J = 5 Hz), 3.48 (1H, d, J = 12 Hz), 3.71 (3H, s), 3.81 (3H, s), 4.02 (1H, d, J = 7 Hz), 4.20 (2H, q, J = 7 Hz), 4.48 - 4.79 (1H, br m), 5.05 (2H, s), 5.38 (1H, d, J = 7 Hz), 6.90 (1H, s), 7.28 - 7.52 (5H, m)

MS: 573 (1, M+), 542 (1), 500 (32), 426 (40), 92 (100)

Exact Mass: Calcd. for C₃₁H₄₃NO₈ 573.2937
Found 573.2951
Methyl ketoester (69)

Diol 67 (3.02 g, 5.27 mmol), dissolved in 50 ml of acetone, was oxidized to the ketoacid with 4 ml of Jones reagent (2.7 M) added at 0°C followed by warming to room temperature with stirring for 1 hour. Excess Jones reagent was quenched with 2 ml of isopropanol. Equal volumes of ether (20 ml) and water (20 ml) were added and the reaction mixture was partitioned between ether and a dilute sodium chloride solution. After washing the ether layer twice with dilute brine, 40 ml of hexanes was added and the organic layer was partitioned with a saturated solution of sodium bicarbonate, pulling the carboxylate into the aqueous layer. The aqueous layer was carefully acidified with concentrated HCl and a partition with ethyl acetate extracted the desired ketoacid into the organic layer. Drying the ethyl acetate solution over magnesium sulfate followed by evaporation gave 2.41 g (78.1%) of the crude ketoacid.

Continuing without further purification, the carboxylic acid was converted to the methyl ester by reacting it at 50°C with 0.96 ml (16.5 mmol) of methyl iodide in the presence of 2.84 g (20.6 mmol) of
pulverized potassium carbonate in 40 ml of acetone. When methylation was complete, the cooled reaction mixture was filtered through celite, evaporated to a small volume and partitioned between ether and water. The ether layer was dried over magnesium sulfate, filtered and evaporated. Separation by column chromatography with a solvent gradient up to 40% ether in hexanes yielded 2.13 g (86.4%) of the methyl ester.

IR (CH₂Cl₂): 1750, 1719, 1691, 1136

NMR (CDCl₃): 1.17 (3H, t, J = 7 Hz), 1.36 (9H, s), 2.23 (3H, s), 2.37 (1H, d of d, J = 17 Hz, J = 7 Hz), 3.10 (1H, d of t, J = 13 Hz, J = 7 Hz), 3.41 - 3.64 (2H, br s), 3.76 (6H, s), 3.88 (3H, s), 4.08 (2H, q, J = 7 Hz), 4.30 (1H, t, J = 10 Hz), 4.99 (1H, m), 5.07 (2H, s), 7.29 (1H, s), 7.30 - 7.50 (5H, m)

MS: 599 (2, M+), 542 (22), 526 (29), 508 (72), 126 (100)

Exact Mass: Calcd. for C₃₂H₄₁N₂O₁₀ 599.2730
Found 599.2724
Ketoamide (70)

The t-butyl ester (2.08 g, 3.48 mmol) was deprotected to the carboxylic acid by reacting with 6 ml of trifluoroacetic acid at room temperature for 10 minutes. The reagent was evaporated and the crude acid was taken up in toluene and evaporated to remove any trace amounts of trifluoroacetic acid. The acid was activated by conversion to the mixed anhydride with 1.66 ml (17.4 mmol) of ethyl chloroformate and 1.45 ml (10.4 mmol) of triethylamine in 40 ml of dry methylene chloride at 0°C. When mixed anhydride formation was complete as indicated by analytical TLC, 6 ml of ethanol saturated with ammonia was added and the reaction mixture was warmed to room temperature. The resultant amide was partitioned between methylene chloride and dilute HCl, the methylene chloride layer was washed with brine followed by a wash with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Separation by liquid chromatography using 5% methanol in ether gave 1.85 g (98.1%) of the desired ketoamide.
IR (CH$_2$Cl$_2$): 3508, 3400, 1740, 1700, 1683

NMR (CDCl$_3$): 1.17 (3H, t, J = 7 Hz), 2.21 (3H, s), 2.45 (2H, d, J = 7 Hz), 2.47 (1H, m), 3.11 (1H, m), 3.55 (2H, br d, J = 5 Hz), 3.74 (3H, s), 3.76 (3H, s), 3.88 (3H, s), 4.07 (2H, q, J = 7 Hz), 4.32 (1H, t, J = 7 Hz), 4.97 (1H, m), 5.09 (2H, s), 5.41 (1H, br s), 5.97 (1H, br s), 7.19 (1H, s), 7.29 - 7.52 (5H, m)

MS: 542 (13, M$^+$), 451 (72), 419 (46), 92 (100)

Exact Mass: Caled. for C$_{24}$H$_{34}$N$_2$O$_3$ 542.2264
Found 542.2256
Enamide methyl ester (71)

Cyclization of 1.79 g (3.31 mmol) of the ketoamide was performed at reflux temperature in 40 ml of benzene with 307 mg (1.32 mmol) of camphorsulfonic acid and 0.195 ml (1.65 mmol) of quinoline, using a Dean-Stark trap to remove water. Upon completion of the reaction the solution was partitioned between ether and dilute HCl. The ether layer was washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated. Purification by liquid chromatography with ether as the eluent gave 1.37 g (78.8%) of the desired enamide.

IR (CH₂Cl₂): 3390, 1750, 1698, 1685, 1081, 1063

NMR (CDCl₃): 1.23 (3H, t, J = 7 Hz), 2.19 (3H, s), 2.57 (1H, m), 2.62 (2H, d, J = 7 Hz), 3.03 (1H, m), 3.65 (3H, s), 3.71 (3H, s), 3.85 (3H, s), 4.15 (2H, q, J = 7 Hz), 4.41 (1H, t, J = 6 Hz), 4.90 (1H, d of d, J = 7 Hz, J = 4 Hz), 5.10 (2H, s), 5.39 (1H, br d, J = 18 Hz), 6.89 (1H, s), 7.27 - 7.51 (5H, m), 7.91 (1H, br s)

MS: 524 (74, M⁺), 451 (71), 433 (72), 92 (100)

Exact Mass: Calcd. for C₂₈H₃₂N₂O₄ 524.2158
             Found 524.2161
**Oxime Lactam (72)**

Dropwise addition of nitrosyl chloride in methylene chloride at 
-30°C to 974 mg (1.86 mmol) of the enamide in a 2:1 mixture of 
acetonitrile-methylene chloride (24 ml) converted the olefin to the 
nitroso chloride. In situ reduction of the chloride using 229 mg 
(3.72 mmol) of sodium cyanoborohydride in acetonitrile in the presence 
of 0.20 ml of methanol saturated with HCl yielded the desired oxime 72. 
The reaction mixture was partitioned between ether and dilute HCl and 
the ether layer was washed with a saturated solution of sodium 
bicarbonate, dried over anhydrous magnesium sulfate, filtered and 
evaporated. When the crude product was dissolved in absolute ethanol, 
white crystals of the desired oxime precipitated, giving 639 mg (61.9%) 
of product with mp 220°C (dec.).
IR (CH$_2$Cl$_2$):  3558, 3385, 1755, 1699, 1668

NMR (CDCl$_3$):  0.73 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.42 (1H, d of d, J = 11 Hz, J = 7 Hz), 2.52 (1H, d, J = 11 Hz), 2.90 (1H, s), 3.00 (1H, d, J = 7 Hz), 3.67 (3H, s), 3.74 (3H, s), 3.79 (3H, s), 4.40 (1H, d, J = 10 Hz), 4.98 (1H, AB, J = 12 Hz), 5.12 (1H, AB, J = 12 Hz), 5.42 (1H, d, J = 5 Hz), 5.93 (1H, d, J = 1 Hz), 6.06 (1H, br s), 7.25 − 7.48 (5H, m), 7.86 (1H, br s), 8.32 (1H, br s)

MS:  555 (<1, M+), 539 (<1), 522 (<1), 91 (100)

Exact Mass:  Calcd. for C$_{24}$H$_{33}$N$_3$O$_9$  555.2216  
            Found  555.2210
Amine lactam (73)

The oxime (317 mg, 0.571 mmol) was reduced to the desired amine isomer with 1100 psi of hydrogen at 120°C for 30 minutes, requiring an excess of Raney Nickel catalyst and 0.10 ml of triethylamine in 15 ml of absolute ethanol. After filtering off the catalyst through a celite column, the crude reaction product was separated on a preparative silica gel tlc using 10% methanol in ether, yielding 185 mg (71.9%) of the pure amine.

IR (CH₂Cl₂): 3395, 1744, 1700, 1660

NMR (CDCl₃): 1.22 (3H, m), 2.21 (3H, s), 2.53 (1H, m), 2.70 (1H, d, J = 10 Hz), 2.82 - 3.24 (1H, m), 3.71 (3H, s), 3.77 (6H, s), 3.86 - 4.29 (3H, m), 4.29 - 4.58 (1H, m), 4.96 (1H, s), 6.85 (1H, s), 7.28 (1H, br s)

MS: 451 ([M⁺], 434 (1), 250 (39), 196 (100)

Exact Mass: Calcd. for C₁₁H₁₃N₂O₃ 451.1954
Found 451.1963
**Isoquinoline methyl ester (74)**

Cyclization of the amine **73** (79 mg, 0.175 mmol) required heating at 90°C with 0.014 ml of formaldehyde (37% aqueous solution) in 4 ml of methanol. Upon completion of the reaction, the solvent was evaporated and purification of the product on a preparative tlc, eluting with 10% methanol in ether, yielded 52 mg (65%) of isoquinoline **74**.

**IR (CH$_2$Cl$_2$):** 3527, 3398, 3217, 1743, 1700, 1654, 1115, 1056

**NMR (CDCl$_3$):** 1.25 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.54 (1H, m), 2.74 (1H, d, J = 7 Hz), 2.98 (1H, m), 3.75 (6H, s), 3.80 (3H, s), 3.86 - 4.08 (1H, m), 4.16 (1H, s), 4.28 (2H, q, J = 7 Hz), 4.52 (1H, d, J = 4 Hz), 5.76 (2H, br s)

**MS:** 463 (10, M+), 431 (3), 220 (100)

**Exact Mass:** Calcd. for C$_{22}$H$_{29}$N$_3$O$_8$ 463.1954

**Found** 463.1946
Isoquinolinol lactam (75)

Isoquinoline 74 (36.9 mg, 0.80 mmol) was heated at 110°C for 90 minutes in 4 ml of acetonitrile with 0.04 ml of butyraldehyde present. Evaporation followed by purification on a preparative silica gel tlc, eluting with 10% methanol in methylene chloride, yielded 34.0 mg (98.9%) of the pentacyclic lactam 75.

IR (CH₃Cl₂): 3523, 3390, 1700, 1670, 1112

NMR (CDCl₃): 1.28 (3H, t, J = 7 Hz), 2.24 (3H, s), 2.71 (1H, t of d, J = 12 Hz, J = 7 Hz), 3.19 (1H, m), 3.76 (3H, s), 3.78 (3H, s), 3.93 (1H, s), 4.18 (2H, q, J = 7 Hz), 4.62 (1H, d, J = 7 Hz), 4.72 (1H, d, J = 2 Hz), 4.88 (1H, d of d, J = 7 Hz, J = 4 Hz), 5.13 (1H, AB, J = 20 Hz), 5.72 (1H, s), 5.92 (1H, br s)

MS: 431 (22), 360 (22), 220 (100)

Exact Mass: Calcd. for C₂₁H₂₂N₃O₂, 431.1692
Found 431.1690
**Amino methyl ester lactam (76a)**

Amine 73 (84.3 mg, 0.19 mmol) was heated in a sealed tube at 120°C for 1 hour with 0.93 mmol of hydrated methyl glyoxylate and 4 ml of methanol as solvent. After completing cyclization, the reaction mixture was evaporated and directly separated on a preparative silica gel TLC plate, eluting with 5% methanol in ethyl acetate to give 77.1 mg (73.3%) of the tetracyclic amine 76a.

**IR (CH₂Cl₂):** 3522, 3395, 3200, 1742, 1700, 1661

**NMR (CDCl₃):** 1.24 (3H, t, J = 7 Hz), 2.24 (3H, s), 2.56 (1H, m), 2.74 (1H, d, J = 7 Hz), 3.30 (1H, br s), 3.68 (3H, s), 3.77 (6H, s), 3.79 (3H, s), 4.17 (2H, q, J = 7 Hz), 4.64 (1H, br s), 4.91 (1H, d, J = 6 Hz), 5.61 (1H, br s), 6.16 (1H, br d, J = 13 Hz)

**MS:** 521 (<1, M⁺), 490 (<1), 476 (1), 462 (75), 68 (100)

**Exact Mass:** Calcd. for C₁₄H₁₁N₂O₁₀ 521.2009

**Found** 521.2004
Amino methyl ester lactam (77a)

Aclylation of phenol 76a (20.8 mg, 0.037 mmol) proceeded at room temperature in 0.50 ml of acetic anhydride with 0.10 ml of pyridine. After evaporation under reduced pressure, the crude product was separated by tlc, eluting with 5% methanol in methylene chloride to yield 16.9 mg (75.6%) of the desired amine 77a.

IR (CH$_2$Cl$_2$): 3395, 3300, 1740, 1700, 1661, 1190

NMR (CDCl$_3$): 1.23 (3H, t, J = 7 Hz), 2.25 (6H, s), 2.38 (1H, m), 2.74 (1H, d, J = 7 Hz), 3.06 (1H, t, J = 11 Hz), 3.41 (1H, t, J = 6 Hz), 3.67 (3H, s), 3.75 (3H, s), 3.78 (3H, s), 3.81 (3H, s), 4.18 (2H, q, J = 7 Hz), 4.45 (1H, t, J = 8 Hz), 4.64 (1H, s), 4.74 (1H, d, J = 6 Hz), 5.62 (1H, br s)

MS: 563 (<1, M+), 532 (1), 505 (68), 462 (66), 220 (86)

Exact Mass: Calcd. for C$_{26}$H$_{33}$N$_3$O$_{11}$ 563.2114
Found 563.2121
REFERENCES


13. (a) For a review, see L. G. Donaruma and W. Z. Heldt, Org. React., 11, 1 (1960); (b) G. R. Krow, Tetrahedron, 37, 1283 (1981).


18. (a) The benzyl carbamate was cleaved to the amine using palladium on carbon under a hydrogen atmosphere in ethanol; (b) M. Bergmann and L. Zervas, *Ber.*, 65, 1192 (1932).


28. The aromatic bromide was obtained by adding one equivalent of bromine to 2,6-dimethoxytoluene in methylene chloride with two equivalents of pyridine present.


31. (a) Anhydrous magnesium bromide was generated by adding one equivalent of 1,2-dibromoethane to magnesium turnings in anhydrous tetrahydrofuran under argon with heating; (b) D. E. Pearson, D. Cowan, and J. D. Beckler, J. Org. Chem., 24, 504 (1959).


37. The Michael acceptor was formed by refluxing ethyl pyruvate with urethane in the presence of camphorsulfonic acid and quinoline, using toluene as the solvent.


46. (a) M. Betti, Org. Syn., Coll. Vol., 1, 381; (b) E. L. Eliel and M. T. Fisk, Org. Syn., Coll. Vol., 2, 626; (c) See also reference 26.


50. See reference 48.


