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PART I. PREPARATION OF STEREOISOMERS OF GEPHYROTOXIN-223AB.
PART II. STUDY OF ALPHA-ACYLAMINO RADICAL CYCLIZATIONS

The Ohio State University

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PART I. PREPARATION OF STEREOISOMERS OF GEPHYROTOXIN-223AB.

PART II. STUDY OF α-ACYLAMINO RADICAL CYCLIZATIONS.

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Yeun-Min Tsai, B.S.

* * * * *

The Ohio State University
1983

Reading Committee:

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Adviser
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ACKNOWLEDGEMENTS

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PUBLICATIONS


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PART I - INTRODUCTION

OBJECTIVES The primary goal of this research was to establish the structure of gephyrotoxin-223AB (GTX-223AB), a Dendrobatid alkaloid isolated in minute quantities from skin extracts of the Columbian frog Dendrobates histrionicus, by way of synthesis. An equally important objective was to demonstrate the use of the concept of A-1,3 strain as a powerful tool for solving stereochemical problems in the area of alkaloid synthesis.

BACKGROUND AND SYNTHETIC STRATEGY The skin secretion of certain brightly colored frogs found in the rain forest of western Columbia have been used by the native indians to poison blow darts. The groups of Daly and Witkop at NIH have examined extracts from the skins of these frogs and have detected the presence of over ninety alkaloids, many of which possess diverse pharmacological properties. One of the major alkaloids isolated from extracts of the frog Dendrobates histrionicus was shown, by X-ray crystallographic analysis of a derivative, to have structure and was named gephyrotoxin. No further alkaloids possessing the tricyclic structure of gephyrotoxin have
been identified in extracts from dendrobatid frogs. However, three simpler bicyclic indolizidine alkaloids have been isolated and included in the gephyrotoxin class. Due to a lack of sufficient quantities for crystallization, optical rotation or nuclear magnetic resonance spectra, these alkaloids have only been analyzed by gas chromatography–mass spectrometry (GC-MS). Based on the limited information available, the Daly group proposed structure 2 for the simplest member of this group, GTX-223AB. The proposed structure was tentative and was based on a number of considerations. The mass spectrum of GTX-223AB suggested that it was saturated bicyclic alkaloid with the molecular formula $C_{15}H_{29}N$. It did not form N-acetyl derivatives and two fragments corresponding to loss of $C_3H_7$ and $C_4H_9$ dominated the mass spectrum. This mass spectral behavior was in accord with fragmentation patterns reported for other $2,9$-dialkylindolizidines. Finally, the proposal of structure 2 for GTX-223AB seemed
reasonable on biosynthetic grounds. At the time the structure of GTX-223AB was proposed, the structures of all of the non-steroidal dendrobatid alkaloids, such as the tricyclic gephyrotoxins, were consistent with a biosynthetic origin from 2,6-disubstituted piperidines with side chains having either lengths of three, five, seven or nine carbons (Scheme I). Therefore, it was thought that the bicyclic gephyrotoxin might have arisen from a 2,6-disubstituted piperidine with a three carbon side chain and a seven carbon side chain. With the uncertainty of the structural assignment coupled with the unanswered question of stereochemistry, it was felt that development of a stereoselective approach to 2 (GTX-223AB) was warranted.

Scheme I
There are four possible diastereomers having structure 2. Prior to the onset of our work, one of these diastereomers was synthesized by Macdonald at the University of Vanderbilt. \(^{1a}\) The Vanderbilt approach proceeded via N1-C2 vincinal *annulation* of a 1,4-dibromoalkane onto a pyrroline system (Scheme II). Pyrroline 3 was alkylated exclusively at the primary carbon site with 1,4-dibromoheptane to give a 1:1 mixture of diastereomeric bromides 4. N-Decarbomethoxylation of 4 and cyclization gave a 1:1 mixture of isomeric dehydroindolizidines 5. Catalytic hydrogenation afforded a single stereoisomer
(2a) of the gross structure proposed for GTX-223AB. The synthetic 2a and natural gephyrotoxin were reported to be chromatographically different, although identical in their mass spectral fragmentation patterns by GC/MS. Therefore, we set as our initial goal the synthesis of diastereomers 2b and 2c. The approach that was adopted revolves around the chemistry of N-acyliminium ions. Thus, pertinent information available prior to these studies will be presented here.

Scheme II

(a) 1,4-Dibromoheptane, LDA, THF (b) MeOH, Na₂CO₃
- (c) H₂, PtO₂, AcOH
Primarily through the work of Speckamp,\textsuperscript{12} intramolecular N-acyliminium ion initiated olefin cyclizations have been shown to be a potent tool in the construction of alkaloids. The cyclizations can be performed with unactivated double bonds and proceed in a high yield. A relevant example is shown in Scheme III.\textsuperscript{13} These cyclizations are thought to take place through a chair-like transition state in a synchronous manner resulting in a highly stereoselective reaction. The reaction is also very sensitive to conformational effects. For example,
the presence of a single methyl group is sufficient to direct the cyclization of 6 to produce 7 as the major product (Scheme IV). This result was rationalized in terms of a favored pseudo-equatorial position for the C(7)-methyl group in the chair-like transition state. The avoidance of a single 1,3-diaxial interaction (C(7)-Me/C(5)-H) is assumed to be the main driving force for the observed stereoselectivity.

The presence of a secondary carbon atom next to the imide nitrogen also introduces a novel element into the stereochemical course of N-acyliminium ion cyclizations. As discovered by Hart, treatment of 8 and 9 with formic acid gave quinolizidinones 10 and 11 in 63% and 71% yields, respectively (Scheme V). Only small amounts (2-5%) of substances stereoisomeric to 10 and 11 were formed in these cyclizations. It was suggested that the N-acyliminium ions derived from 8 and 9 cyclize via chair conformations in which the incipient C(4) substituent

Scheme V

\[
\begin{align*}
8 & \quad R=\text{Ph} \\
9 & \quad R=\text{CH}_2\text{CH}=\text{CH}_2 \\
10 & \quad R=\text{Ph} \\
11 & \quad R=\text{CH}_2\text{CH}=\text{CH}_2
\end{align*}
\]
occupies an axial site (Scheme VI), in contrast to the equatorial orientation of substituents usually observed in olefin cyclizations and other reactions whose transition-state geometries resemble chair cyclohexane. This unusual observation was attributed to the unfavorable development of A-1,3 strain in the transition states leading to C(4) isomers of 10 and 11. The results presented by Hart indicate that A-1,3 strain is an important consideration in predicting the stereochemical course of certain N-acyliminium ion cyclizations. Applications of this concept within the context of the total synthesis of depentylperhydrogephyrotoxin, vertaline, gephyrotoxin and dihydrogephyrotoxin have been successfully demonstrated.

From the aforementioned stereochemistry displayed in the N-acyliminium ion cyclizations, it was felt that
formic acid induced cyclization of 12 would lead to the formation of 13 with high stereoselectivity (Scheme VII). Removal of the oxygen functionality at C(4) with further manipulation at C(9) would then result in the preparation of 2b and 2c. The realization of the approach outlined in Scheme VII and several observations made along the way will now be discussed.
Our synthesis began with the preparation and cyclization of carbinolamide 12. As outlined in Scheme VIII, treatment of n-butyaldehyde with alkylmagnesium bromide gave homoallylic alcohol 14 (85%), which was converted to imide 15 (67%) via the method of Mitsunobu. Imide 15 was reduced with diisobutylaluminum hydride and the resulting crude carbinolamide 12 (96%) was treated with formic acid to give formate 13 (65%) along with trace amounts of other bicyclic lactams. In a separate experiment, careful separation of the crude cyclization products from 12 by column chromatography gave in addition to 80% of formate 13 a single compound 16 (4%) epimeric with 13 at C(4).

The stereochemical assignments for 13 and 16 were based on spectral and chemical data. The infrared spectrum of 13 exhibited a normal lactam carbonyl at 1695 cm\(^{-1}\). Similarly, 16 revealed a strong absorption at 1675 cm\(^{-1}\). Based on the fact that indolizidinones of type 13 cannot adopt a conformation in which the C(6)-C(7) bond is axially disposed on a chair piperidine without destroying amide resonance, the infrared data require that H(6)
occupy an axial site on the rigid indolizidinone framework. In the proton NMR spectrum, H(4) of 13 appears as a triplet of triplets (J=10, 4 Hz), establishing that it is axially disposed. On the contrary, H(4) of 16 appears as a quintet (J=3 Hz), indicating an equatorial

**Scheme VIII**

![Scheme VIII](image)

(a) Ph₃P, EtO₂CN=NCO₂Et, succinimide (b) iBu₂AlH, toluene (c) HCOOH (d) NaOH, H₂O-CH₃OH (e) NaH, CS₂, CH₃I (f) nBu₂SnH
orientation. The axial disposition of the C(2) propyl group in 13 was established by the transformations shown in Scheme IX. Mitsunobu coupling16 of diallyl carbinol,

**Scheme IX**

![Scheme IX](image)

(prepared from allylmagnesium bromide and ethyl formate, with succinimide gave imide 20 (74%) which was reduced with diisobutylaluminum hydride to afford carbinollactam 21 (64%). Treatment of 21 with formic acid as before resulted in the isolation of formate 22. The stereochemical identity of this compound at C(2), C(4) and C(6)
with that of formate 13 was proven by the conversion of 22 to 13 (100%) via catalytic hydrogenation. Hydrolysis of formate 22 was accomplished with sodium hydroxide in aqueous methanol, and the resulting crude carbinol was transformed into xanthate 23 by the method of Barton (82%). It was reasoned at this stage that if the C(2) substituent occupied an axial position as proposed, generation of a radical at C(4) would lead predominantly to trapping of this radical by the properly oriented side chain olefin (Scheme X). On the other hand, confined

Scheme X

\[
\begin{align*}
\text{Scheme X} & \\
\xrightarrow{\text{Cyclization}}
\end{align*}
\]
by a rigid chair form six-membered ring, it would be impossible for an equatorially disposed C(2) substituent to attain the required orbital overlap necessary for cyclization. As expected, when xanthate 23 was treated with tri-n-butyltin hydride,21 a 2:1 mixture of tricyclic lactams 24 and 25 was obtained (74%) along with minor amount of uncyclized reduction product. The spectroscopic data were in full agreement with our structural assignments, although no attempt was made to determine whether 24 or 25 was the major stereoisomer. This result clearly established the axial disposition of the C(2) side chain in 22 and 15. It should be noted that this represents an obviously simple but heretofore unused entry to the 5-hexenyl radical manifold. That formate 16 is only epimeric with 13 at C(4) was fully confirmed by chemical correlation (vide infra).

With the relative stereochemistry at C(2) and C(6) of 13 established, the undesired oxygen functionality at C(4) was removed by use of the Barton procedure19 to afford an 80% yield of lactam 19. The syntheses of 2b and 2c were completed as outlined in Scheme XI. Lactam 19 was treated with phosphorous pentasulfide to afford thiolactam 26 (82%). Sequential treatment of 26 with 1-bromo-2-butanone,22 triethylamine, and triphenylphosphine gave vinyloous amide 27 (92%).23 Reduction of 27 with either sodiumcyanoborohydride24 or Pt-H2-AcOH25 was complicated by
overreduction which led to the formation of some alcohols. This problem was overcome by an oxidative workup (Jones reagent) to give a mixture of isomeric amino ketones 28 and 29 (70-75%). Difficulties were encountered during attempts to separate 28 and 29 due to the ease with which they interconverted upon chromatography over silica gel or alumina, presumably via a retro-Michael-Michael process. Only the major and least polar isomer 28 could be obtained
in pure form by column chromatography. Thus, we assumed that the major product was the thermodynamically most stable indolizidine and assigned it structure 28. This assignment was based on reports that indolizidines show a large preference for conformations in which the nitrogen lone pair and angular hydrogen atom adopt an antiperiplanar relationship. Examination of the two conformers which fulfill the above requirement (28 and 29b, Scheme XII) show that a severe 1,3-diaxial alkyl-alkyl interaction in 29b raises its energy substantially. The other two possible conformers of 29 (29a and 29c) also have more 1,3-diaxial alkyl-hydrogen interactions than 28. Supporting evidence for this assignment will be presented later (vide infra).
When a mixture of crude 28 and 29 was treated with propan-1,3-dithiol and hydrochloric acid in chloroform, thioketals 30 and 31 (60% and 23% respectively, from 27) were obtained and separated by column chromatography (Scheme XI). Our first attempt to reduce 30 with Raney nickel led to the formation of 2b in a low yield (24%). However, when the reduction was carried out with lithium in ethylamine28 the yield of 2b improved to 60%. The minor isomer 31 was successfully reduced by the latter method to give 2c, albeit in low yield (26%). This completed the synthesis of the target molecules 2b and 2c. However, several other experiments were performed to ensure that the C(9) stereochemical assignments were correct.

Scheme XIII

(a) LAH, THF (b) NaH, CS₂, CH₃I (c) nBu₂SnH
correct.

The mode of synthesis of 30 did not necessarily insure that it was stereochemically related to 28 at C(9). That 28 and 30 were stereochemically related was established by the conversion of 28 to 2b as outlined in Scheme XIII. Reduction of amino ketone 28 with lithium aluminum hydride gave a mixture of isomeric amino alcohols 32 and 33 (40 and 48% respectively), separable by column chromatography over silica gel. The stereochemical assignments for 32 and 33 at the newly constructed chiral center were uncertain and based only on spectroscopic data. Analysis of the structure of 32 (Scheme XIV) indicates that in order to maintain intramolecular hydrogen bonding arranged in a chair like six-membered ring, the C(2) hydrogen of 32 would occupy an axial position. The proton NMR spectrum of this hydrogen revealed its axial orientation with a large coupling of 9 Hz and a small coupling of 3 Hz in addition to a small methylene coupling of 6 Hz.
On the contrary, the C(2) hydrogen of 33 appeared as a quintet with a coupling constant of 6 Hz in the proton NMR, in agreement with that expected for an equatorially disposed hydrogen. To complete the correlation, alcohols 32 and 33 were converted to the corresponding xanthates 34 and 35 (87% and 70% respectively). Reduction of 34 and 35 with tri-n-butyltin hydride gave the same pyrrolizidine 2b (65% and 82% respectively) identical in all respects with that prepared from the thiketal 30.

Finally, in an attempt to obtain better evidence for the stereochemical assignments of amino ketones 28 and 29 made on thermodynamic grounds above, we performed the experiments shown in Scheme XV. Thus, treatment of thiolactam 26 with ethyl bromoacetate followed by triethylamine and triphenylphosphine gave vinylogous urethane 36 (99%). The same transformation was accomplished by treating 26 sequentially with methyl iodide and the dibasic magnesium salt of ethyl hydrogen malonate (82%). The latter procedure provides an alternative to the excellent procedure of Eschenmoser with the operational advantage that phosphines need not be employed. Treatment of 36 with sodium cyanoborohydride gave a mixture of amino esters 37 (50%) and 38 (27%). Unlike amino ketones 28 and 29, esters 37 and 38 were configurationally stable and easily separated by column chromatography. The stereochemical assignments of 37 and 38 were based in part
Scheme XV

26 X=S

EtMgBr

NaBH₃CN

37 R=CO₂Et
39 R=CH₂OH

MsCl, Et₃N

41

38 R=CO₂Et
40 R=CH₂OH

MsCl, Et₃N

42
on a comparison of their $^1$H NMR spectra with those of intermediates prepared during the course of the synthesis of gephyrotoxin performed in our group. For example, the chemical shifts of H(2), H(6) and H(9), and the multiplicities of H(6) and H(9) in 37 and 38 compare favorably with those recorded for 43a, b and 44a, b, respectively (see Table 1). In addition, it was demonstrated during

Table 1. Chemical Shifts of Selected α-Amino Esters

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<td>3.14</td>
<td>3.42</td>
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All spectra were taken in C<sub>6</sub>D<sub>6</sub>. Data are reported in parts per million downfield from internal tetramethylsilane. $^b$H<sub>α</sub> refers to the diastereotopic hydrogens of the CH<sub>2</sub>CO<sub>2</sub>Et group.
the total synthesis of gephyrotoxin that similar reduction of vinylogous urethane 45 by sodium cyanoborohydride gave a mixture of amino esters 43b and 44b with 43b as the major product (Scheme XVI). The stereochemical assignment of 43b was confirmed by the conversion of this compound to gephyrotoxin. Therefore, on the basis of the stereochemical course of the sodium cyanoborohydride reduction described above, it is reasonable that amino ester 37 be the major reduction product in our case.

We initially tried to correlate the structures of 37 and 38 with those of 2b and 2c as outlined in Scheme XV. Reduction of 37 and 38 with lithium aluminum hydride gave amino alcohols 39 (97%) and 40 (96%). Once again, the $^1$H NMR spectra of these alcohols were similar to related intermediates in the gephyrotoxin series. We intended to convert 39 and 40 to derivatives suitable for coupling with lithium diethyl cuprate. Treatment of 39 and 40 with either tosyl chloride or mesyl chloride at $0^\circ$C, however, afforded quaternary ammonium salts 41 (61%) and 42 (86%).

Scheme XVI
isolated as their tetrafluoroborate salts. Although cyclizations of γ-amino alcohol derivatives to azetidines and azetidinium ions are known, the ease with which 39 and 40 can be converted to salts 41 and 42 is noteworthy.

The correlation of 37 and 38 with 2b and 2c was finally accomplished in the following manner. Independent treatment of 37 and 38 with ethylmagnesium bromide (5.0 equiv, 7 h, 25 °C) followed by addition of the reaction mixture to water gave 28 (65%) and 29 (69%), respectively, establishing the stereochemical relationship between the two C(9) side-chain series. This ester to ketone conversion is also noteworthy. We initially felt that amino esters 37 and 38 might react with Grignard reagents to give nitrogen chelated tetrahedral intermediates that would break down slowly, thus facilitating the desired ester to ketone transformation. The observation that a large excess of ethylmagnesium bromide and long reaction times were necessary, however, led us to consider a mechanistic pathway other than direct carbonyl addition. Specifically, we thought that sequential enolization of 37 (38), fragmentation to afford a ketene, trapping of the ketene with the Grignard reagent, and protonation upon aqueous workup might afford a less conventional pathway for the conversion of 37 (38) to 28 (29). Attempts to demonstrate the intermediacy of the ester enolate, however, met with failure. Thus, whatever the
mechanism by which 37 (38) is converted to 28 (29), enolization of the starting ε-amino ester does not appear to be involved. 35

At the same time we finished our synthesis of 2b and 2c, Spande and Daly at NIH accomplished a stereorandom preparation of 2a-2d from the reduction (H₂/Rh-Al₂O₃, (5%) AcOH-EtOH (1:4)) of the pyrrole 46 in 12%, 37%, 10% and 42% yields, respectively. 36 Our synthetic 2b and 2c were identical with two of the above isomeric mixture by spectral and GC/MS comparisons carried out at NIH. 37-39 The structure of GTX-223AB was identified as 2a by GC/MS analysis of Macdonald's 1a and Spande's samples with the authentic natural product. The EI spectra for the reduction

\[
\begin{align*}
R_1 = & \text{nPr, } R_2 = \text{nBu} \\
R_1 = & \text{nBu, } R_2 = \text{nPr}
\end{align*}
\]

products obtained from 47 differ significantly enough from 2a and the natural material, 36 and thus, exclude the 2-butyl-9-propylindolizidine structure for GTX-223AB.

Before leaving this topic, it should be noted that the critical N-acyliminium ion cyclization (12→13) used in the syntheses of 2b and 2c is more complicated from a mechanistic standpoint than as depicted in Scheme III. Some experiments which reveal the complexity of this reaction will be presented here. Thus, treatment of
carbinolamide 12 with trifluoroacetic acid-dichloromethane (25°C, 5 min) gave a 49% yield of lactam 48, 13% of lactam 49, and 12% of a mixture of lactam 50 (Scheme XVII). Similarly, treatment of 12 with formic acid-dichloromethane (25°C, 10 h) gave a 60% yield of formate 13 and

Scheme XVII

12

RCOOH-CH2Cl2

\[ 48 \quad R=\text{CF}_3 \]
\[ 13 \quad R=\text{H} \]
\[ 49 \quad R=\text{CF}_3 \]
\[ 16 \quad R=\text{H} \]

50

RCOOH-CH2Cl2-Et2SiH

52

53 \quad R=\text{CH}_2\text{CH}=\text{CH}_2

54 \quad R=\text{OEt}
trace amounts of lactam 16 and 50. The structure of 50 was confirmed by catalytic hydrogenation (H₂, Pd/C) of the mixture to lactam 19 (86%) which had been prepared previously (see Scheme VII). The stereochemical relationship between 13, 16, 48 and 49 was established as shown in Scheme XVIII. Formate 13 was hydrolyzed (NaOH-MeOH-H₂O, 100%) and oxidized (Jones, 53%)²⁶ to give ketolactam 51. Ketolactam 51 was reduced (NaBH₄, EtOH) and the resulting mixture of alcohols was esterified ((CF₃CO)₂O, Et₃N) to give a separable mixture of 48 (13%) and 49 (35%). This result demonstrated that trifluoroacetates 48 and 49 were isomeric and differed from 13 only by virtue of the substituent on C(4). Furthermore, when formate 16 was hydrolyzed (NaOH-MeOH-H₂O) followed by esterification ((CF₃CO)₂O, Et₃N), a single trifluoroacetate 49 was obtained. Clearly, formates 13 and 16 are epimeric at

Scheme XVIII

\[
\begin{align*}
16 \text{ or } 13 & \xrightarrow{a,b} 51 \\
& \downarrow \text{a, d} \\
49 + 48 & \xrightarrow{c, d} \\
\text{(a) NaOH, MeOH-H}_2\text{O (b) Jones oxidation (c) NaBH}_4, \text{EtOH (d) (CF}_3\text{CO})_2\text{O, Et}_3\text{N}}
\end{align*}
\]
C(4). That formate 16 and trifluoroacetate 49 have equatorially disposed hydrogens at C(4) was indicated by their appearance as quintets in the $^1$H NMR spectra ($J=3$ Hz for 16 and 2 Hz for 49). This assignment is also in agreement with the product distribution observed in the sodium borohydride reduction of ketolactam 51. Suffering from the steric effects imposed by the axially oriented C(2) propyl group, hydride attack at the C(4) carbonyl took place from the sterically more accessible equatorial face giving 49 as the major product after esterification.

In an attempt to trap the intermediate N-acyliminium ion with a hydride nucleophile under cyclization conditions, carbinolamide 12 was treated with a mixture of trifluoroacetic acid-dichloromethane-triethylsilane (25°C, 25 min).40 No cyclized products were obtained. Instead, to our surprise, a separable 3:5 mixture of lactams 52 and 53 was obtained in a 73% yield. The structure of 52 and 53 were confirmed by independent synthesis. Thus, reduction of 12 with sodium cyanoborohydride$^{41}$ at pH 4 in methanol gave exclusively 52 (84%).$^{42}$ The skelatally rearranged lactam 53 was prepared from N-butylsuccinimide by reduction with sodium borohydride in ethanol (85%)$^{13}$ followed by treatment of the resulting $\omega$-alkoxylactam 54 with allyltrimethylsilane in the presence of titanium tetrachloride ($CH_2Cl_2$, 25°C, 7 h, 78%).$^{43, 44}$ When 12 was treated with formic acid-dichloromethane-triethylsilane
(25°C, 10 h)\(^{40}\) cyclized formate 13 (29%) was obtained in addition to a 3:5 mixture of lactams 52 and 53, respectively (42%). When 13, 16, 48 and 49 were individually subjected to the reaction conditions, no interconversion or reduction was detected.

The aforementioned experiments reveal two important features of the \(\omega\)-acyliminium ion cyclization used in the preparation of GTX-223AB stereoisomers 2b and 2c. First, the cyclization is irreversible and product stereochemistry is kinetically controlled. Second, a fast molecular rearrangement underlies the cyclization reaction. The observation of 53 in the presence of triethylsilane suggests that treatment of carbinolamide 12 with acid gives N-acyliminium ion 55 which rearranges to ion 56, presumably via a 2-aza-Cope process (Scheme XIX). In the presence of triethylsilane, 55 and 56 are reduced to lactams 52 and 53, respectively.\(^{46, 47}\) In the absence of an

Scheme XIX

\[
\begin{align*}
13, 16, 48, 49 & \quad \text{no Et}_2\text{SiH} \\
55 & \quad \text{Et}_2\text{SiH} \\
52 + 53 & \quad 56
\end{align*}
\]
ion trap\textsuperscript{48} cyclized products, typical of those observed upon generation of ions of type 55 in nucleophilic media,\textsuperscript{13} are formed.

Since the ratio of lactams \textsuperscript{52} and \textsuperscript{53} does not vary with reduction media it is tempting to suggest that an equilibrium mixture of 55 and 56 is rapidly established, followed by slower secondary processes such as reduction and cyclization. In trifluoroacetic acid, reduction is faster than cyclization. In the more nucleophilic formic acid media, cyclization and reduction take place at comparable rates. We have not, however, generated ion 56 independently and thus the exact meaning of the observed 52:53 ratio remains uncertain.\textsuperscript{49, 50}

Hetero-Cope rearrangements have previously been reported for substituted 2-aza-1,5-hexadienes 57 and their iminium ion counterparts 58 (Scheme XX).\textsuperscript{51-54} Although

\textbf{Scheme XX}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{\textsuperscript{57}}};
  \node (b) at (1,1) {\text{\textsuperscript{58} R=H, alkyl}};
  \node (c) at (1,-1) {\text{\textsuperscript{59} R=acyl}};
  \draw [->] (a) -- (b);
  \draw [->] (b) -- (c);
\end{tikzpicture}
\end{center}
related \( \text{N-acyliminium ions of type 59} \) have been investigated extensively throughout the past decade,\(^{13}\) hetero-
Cope rearrangements of these systems have remained unknown. These observations document the first example of a fast 2-aza-Cope rearrangement underlying reactions which are typical of ions of type 59.

In summary, indolizidines 2b and 2c were prepared and shown to be stereoisomers of the Dendrobatid alkaloid gephyrotoxin-223AB. A potentially useful entry to the 5-hexenyl radical manifold and an unusual ester to ketone transformation have been described. In addition, a 2-aza-Cope rearrangement underlying the more typical reactions of \( \text{N-acyl-2-aza-1,5-hexadienes} \) has been detected using triethylsilane as an acyliminium ion trap.
GENERAL All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are boiling points. $^1$H nuclear magnetic resonance spectra were recorded on Varian Associates EM-390, Varian Associates EM-360, or Bruker WP-200 spectrometers and are reported in parts per million from internal tetramethylsilane. Data are reported as follows: chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, se=septet, m=multiplet), coupling constants in hertz, integration, interpretation), $^{13}$C nuclear magnetic resonance spectra were recorded on a Bruker WP-80 spectrometer and are reported in parts per million from internal tetramethylsilane. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on an AEI-MS9 instrument at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at $m/e$ greater than those of the parent. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl
ether (distilled from Na metal); toluene (distilled from calcium hydride); methanol (distilled from magnesium methoxide); chloroform (passed through activity I alumina). All reaction temperatures refer to those of the reaction mixture. Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Formic acid (97%) was used in all cyclizations. Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM laboratories silica gel (70-230 mesh) and Woelm neutral alumina. Medium Pressure Liquid Chromatography (MPLC) was performed using EM laboratories Lobar prepacked silica gel columns and a FMI RPSY lab pump. GLC analysis was done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector.

Hept-1-en-4-ol (14). To 50 g (2.0 mol) of magnesium under 650 mL of dry ether, was added 2-3 crystals of iodine. The solution was stirred at room temperature for 1 h until the color of the iodine had disappeared. A solution of 60.5 g (43.2 mL, 0.50 mol) of allyl bromide in 60 mL of dry ether, was added over a period of three hours while the
reaction mixture warmed itself under reflux. The result-
ing Grignard solution was stirred at room temperature for
16 h, transfered under argon to a new reaction vessel, and
28.8 g (0.40 mol) of fresh distilled butyraldehyde in 50
mL of dry ether was added over a period of 1.0 h. The
resulting solution was stirred for an additional 30 min,
poured into 300 mL of aqueous hydrochloric acid. The
organic phase was separated and the aqueous phase was ex-
tracted with 150 mL of dichloromethane. The combined
organic phases were dried (Na$_2$SO$_4$) and concentrated in
vacuo without heating to give the crude product. This
material was distilled to give 38.6 g (84%) of 14 as a
colorless liquid: bp 150-152°C (lit.$^5$ bp 152°C); NMR
( CC1$_4$) $\delta$ 0.7-1.15 (br t, J=6 Hz, 3H, CH$_3$), 1.15-1.80 (m,
4H, CH$_2$ manifold), 1.92-2.40 (br t, at 2.13, J=6 Hz, over-
laped with a br s, 3H, allyl-H, OH), 3.50 (br s, 1H, OCH),
4.80-5.25 (m, 2H, =CH$_2$), 5.80 (tdd, J=18, 10, 6 Hz, 1H,
=CH-).

$\text{N-(Hept-1-en-4-yl)succinimide}$

(15). To a solution of 34.2
g (Cg (0.3 mol) of hept-1-en-4-ol
(14)), 78.6 g (0.3 mol) of tri-
phenylphosphine, and 36.0 g
(0.36 mol) of succinimide in
450 mL of tetrahydrofuran was
added 52.2 g (0.3 mol) of
diethyl azodicarboxylate over a 45-min period with cooling in an ice-water bath. The mixture was stirred at room temperature for 16 h. The tetrahydrofuran was removed in vacuo and 600mL of ethyl acetate-hexane (1:3) was added to the residue. The resulting precipitate was collected and the filtrate was concentrated in vacuo. The residual oil was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexane, 1:2). Fractions containing imide 15 were concentrated and distilled to give 39.5 g (67%) of imide 15: bp 85-90°C (0.15 mm); IR (CCl₄) 1710 cm⁻¹; NMR (CCl₄) δ 0.70-2.93 (m with s at δ 2.50, 13H, (O)CH₂CH₂- C(0) and alkyl), 4.05 (m, 1H, CHN), 4.90 (m, 2H, =CH₂), 5.57 (m, 1H, =CH-); exact mass calcd for C₁₄H₁₇NO₂ 195.1259, found 195.1263.

1-(1-Hepten-4-yl)-5-hydroxy-2-pyrrolidinone (12). To a solution of 28.3 g (0.145 mol) of imide 15 in 360 mL of toluene at -60°C was added 360 mL of diisobutylaluminum hydride (25 wt%) in toluene at a rate that kept the temperature between -60 and -65°C. The progress of the reaction was monitored by TLC analysis of aliquots taken directly from the reaction mixture (silica gel; ethyl acetate-hexane, 3:1). The cold mixture was stirred for an additional 30
min and poured into 500 mL of cold 5% aqueous sulfuric acid. The resulting mixture was extracted with two 500-mL portions of dichloromethane. The extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo to give 27.4 g (96%) of crude hydroxy lactam 12 as a pale-yellow liquid, which was used directly in the preparation of formate 13. A portion of this crude product (507 mg) was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexane, 3:1) to give 300 mg of pure 12 as a pale-yellow oil: IR (CHCl\textsubscript{3}) 3590 (weak), 3490 (br), 1680 cm\textsuperscript{-1}; NMR (CDCl\textsubscript{3}) \delta 0.55-3.18 (m, 13H), 3.55-4.35 (m, 1H, OH), 4.35-6.35 (m, 5H, NCH, OCH, vinylic H); mass spectrum, m/e (relative intensity) 179(9), 156(100), 154(21), 138(91), 136(7), 110(46), 108 (10), 100(23), 84(21), 83(19).

\[
\begin{array}{c}
\text{rel-(2R, 4R, 6R)-9-oxo-2-propyl-1-azabicyclo[4.3.0]nonane-4-yl Formate (13) and} \\
\text{rel-(2R, 4S, 6R)-9-oxo-2-propyl-1-azabicyclo[4.3.0]nonane-4-yl Formate (16). To a} \\
\text{stirred solution of 250 mL of formic acid cooled in an ice} \\
\text{bath was added dropwise 27.4 g (0.13 mol) of carbinolamide 12 via pipet. The resulting straw-colored solution} \\
\text{was stirred at room temperature for 45 min, and the} \\
\text{formic acid was removed in vacuo with slight warming.}
\end{array}
\]
The residual oil was stirred with 320 mL of saturated sodium bicarbonate solution for 15 min and extracted with two 400-mL portions of dichloromethane. The extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give 27.4 g of a brown oil. This oil was chromatographed over 500 g of silica gel (eluted with ethyl acetate-hexane, 3:4, followed by ethyl acetate) to afford 20.3 g (65%) of formate 13 as a pale-yellow oil which solidified slowly on standing: mp 36-37°C; IR (CCl$_4$) 1730, 1695 cm$^{-1}$; NMR (CDCl$_3$) $0.77-2.60$ (m, 15H), $3.43-4.00$ (m, 1H NCH), $4.10-4.57$ (m, 1H, NCH), $5.1$ (tt, $J=10$, 4 Hz, 1H, COOCH), $7.97$ (s, 1H, HCOO); mass spectrum, m/e (relative intensity) 225(M$^+$, 8), 182(11), 136(100), 110(3), 108(10), 84(9); exact mass calcd for C$_{12}$H$_{19}$NO$_3$ m/e 225.1365, found m/e 225.1369.

The minor isomer was not isolated in this case. In a separate experiment starting with 982 mg (4.98 mmol) of pure 12, chromatography of the crude product over 50 g of silica gel (eluted with ethyl acetate-hexane, 7:3) gave 895 mg (80%) of the less polar isomer 13 as a white solid. Continued elution gave 47.7 mg (4%) of 16 as a pale-yellow oil: IR (CHCl$_3$) 1720, 1670 cm$^{-1}$; NMR (CDCl$_3$) $0.80-2.65$ (m with br t at 0.90, $J=7$ Hz, 15H, CH$_3$ and CH$_2$ manifold), 3.70-4.07 (m, 1H, NCH), 4.08-4.40 (m, 1H, NCH), 5.30 (qu, $J=3$ Hz, 1H, COOCH), 8.08 (s, 1H, HCOO); mass spectrum, m/e (relative intensity) 225(M$^+$, 5), 182(6), 136(100), 110(4),
108(10), 84(7); exact mass calcd for C_{12}H_{19}NO_{3} m/e 225.1365, found m/e 225.1358.

**rel-(2R, 4R, 6R)-4-Hydroxy-2-propyl-1-azabicyclo[4.3.0]nonan-9-one (17).** To a solution of 20.3 g (90.0 mmol) of formate 13 in 120 mL of methanol was added a solution of 4.9 g (122 mmol) of sodium hydroxide in 23 mL of water.

The resulting solution was stirred at room temperature for 50 min and partitioned between 500 mL of dichloromethane and 200 mL of water. The aqueous phase was extracted with two 200-mL portions of dichloromethane and the combined organic phases were dried (Na_{2}SO_{4}) and concentrated in vacuo to give 17.2 g (97.3%) of crude carbinol lactam 17 as a pale-yellow oil. This material was used directly for the preparation of xanthate 18. A portion of the crude lactam was chromatographed over silica gel (eluted with ethyl acetate-hexane, 19:1) to afford a sample of pure 17:

IR (neat) 3380 (br), 1660 cm^{-1}; NMR (CDCl_{3}) δ 0.70-2.57 (m, 15H), 2.57-3.27 (br s, 1H, OH), 3.37-4.47 (m, 3H, NCH, OCH); exact mass calcd for C_{11}H_{19}NO_{2} m/e 197.1415, found m/e 197.1415.

**rel-(2R, 4R, 6R)-9-Oxo-2-propyl-1-azabicyclo[4.3.0]nonan-4-yl S-Methyl Dithiocarbonate (18).** A mixture of
3.69 g (0.154 mol) of sodium hydride, 17.2 g (0.087 mol) of carbinol lactam 17, 0.154 g of imidazole, and 380 mL of dry tetrahydrofuran was heated to reflux under nitrogen for 2.5 h followed by the addition of 23.0 mL (0.370 mol) of carbon disulfide. The solution was warmed under reflux for 30 min and 23.0 mL (0.37 mol) of methyl iodide was added. The mixture was warmed for another 60 min and the reaction mixture was partitioned between 700 mL of dichloromethane and 700 mL of water. The aqueous phase was extracted with 200 mL of dichloromethane, and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 27.5 g of a dark-brown oil. The oil was chromatographed over 500 g of silica gel (eluted with ethyl acetate) to give 22.4 (89.3%) of xanthate 18 as a viscous yellow oil: IR (CHCl₃) 1670, 1060 cm⁻¹; NMR (CCl₄) δ 0.75-2.42 (m, 15H), 2.52 (s, 3H, SCH₃), 3.38-4.02 (br s, 1H, NCH), 4.02-4.55 (m, 1H, NCH), 5.75 (tt, J=11, 4 Hz, 1H, OCH); mass spectrum, m/e (relative intensity) 287(1), 254(4), 240(4), 180(100), 179(6), 136(48), 179(16), 117(16), 108(8), (4), 84(76); exact mass calcd for C₁₅H₂₁NO₂S₂ m/e 287.1014, found m/e 287.1018.
Anal. Calcd for C\textsubscript{13}H\textsubscript{21}NO\textsubscript{2}S\textsubscript{2}: C, 54.32; H, 7.37.

Found: C, 55.10; H, 7.44.

rel-(2R, 6S)-2-Propyl-1-aza-bicyclo 4.3.0 nonan-9-one (19). To a solution of 27.2 g (93.4 mmol) of tri-n-butyl-tin hydride in 540 mL of dry toluene under reflux was added 18.0 g (62.7 mmol) of xanthate in 540 mL of dry toluene over a period of 2 h. The resulting solution was warmed under reflux for an additional 22 h, allowed to stand overnight at room temperature, and concentrated in vacuo. The residue was chromatographed over 500 g of silica gel (eluted with ethyl acetate) to afford 9.12 g (80%) of lactam 19 as a pale-yellow oil: IR (neat) 1690 cm\textsuperscript{-1}; NMR (CCl\textsubscript{4}) 0.63-2.50 (m, 17H), 3.17-3.77 (br s, 1H, NCH), 3.83-4.33 (m, 1H, NCH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) 13.64(q), 18.60(t), 19.27(t), 25.00(t), 27.19 (t), 31.99(t), 33.55(t), 47.59(d), 52.92(d), 173.37(s); mass spectrum, m/e (relative intensity) 181(3.6), 138 (100), 110(1.4), 84(2.6); exact mass calcd for C\textsubscript{11}H\textsubscript{19}NO m/e 181.1466, found m/e 181.1470.

N-(Hepta-1,6-dien-4-yl)succinimide (20). To a mixture of 3.18 g (32.1 mmol) of succinimide, 7.03 g (26.8 mmol) of triphenylphosphine and 3.00 g (26.8 mmol) of
1,6-heptadien-4-ol\textsuperscript{56} in 40 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise over 1 h a solution of 4.66 g (26.8 mmol) of diethyl azodicarboxylate in 10 mL of dry tetrahydrofuran. The solution was stirred at 0 °C for an additional hour. The solvent was removed in vacuo, and the resulting solid residue was triturated with 75 mL of ethyl acetate-hexane (15:85) and filtered. The white solid was collected and triturated again with 25 mL of the same solvent pair. The combined extracts were concentrated in vacuo. The resulting residue was stirred with 50 mL of the extracting solvent pair for 15 min, filtered and concentrated in vacuo to give a pale-yellow oil (6.20 g). The oil was chromatographed over 75 g of silica gel (eluted with dichloromethane) to afford 3.92 g (74%) of 20 as a colourless liquid which solidified slowly to give a white solid: mp 40-41 °C; IR (neat) 1770, 1700, 1640 cm\textsuperscript{-1}; NMR (CDCl\textsubscript{3}) \(\delta 2.20-3.00\) (m with s at 2.90, 6H, allyl and CH\textsubscript{2} manifold), 4.17 (tt, \(J=9, 6\) Hz, 1H, NCH), 4.87-5.13 (m, 4H, =CH\textsubscript{2}), 5.43-5.93 (m, 2H, =CH-); mass spectrum, m/e (relative intensity) 193(6), 152(100), 100(24), 94(35); exact mass calcd for C\textsubscript{11}H\textsubscript{15}NO\textsubscript{2} m/e 193.1103, found m/e 193.1096.
5-Hydroxy-N-(hepta-1,6-dien-4-yl)pyrrolidone (21). To a solution of 797 mg (4.13 mmol) of imide 20 in 10 mL of dry toluene cooled in a dry ice-acetone bath under argon was added dropwise 5 mL of a 25% diisobutylaluminum hydride solution in toluene at a rate as to keep the reaction temperature below -65°C. The reaction was monitored by TLC (ethyl acetate). When the starting material disappeared, the cold reaction mixture was poured into 20 mL of 5% aqueous sulfuric acid. The aqueous phase was extracted with 50 mL of toluene and the combined organic phases were dried (MgSO₄), filtered through Celite and concentrated in vacuo to give 573 mg of 21 as a pale-yellow oil. This oil was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane, 9:1) to afford 515 mg (64%) of 21 as a pale-yellow oil: IR (CH₂Cl₂) 3570, 3360(br), 1690 cm⁻¹; NMR (CDCl₃) δ 1.67-2.90 (m, 8H, CH₂ manifold), 3.9 (qu, J=6 Hz, 1H, NCH), 4.77-6.10 (m, 7H, \(-CH=CH₂\) and \(NCHO\)); mass spectrum, m/e (relative intensity) 195(4), 177(3), 169(3), 154(100), 136(25), 127(2), 117(10), 108(12); exact mass calcd for C₁₁H₁₇NO₂ m/e 195.1259, found m/e 195.1266.

\(\text{rel}-(2R, 4R, 6R)-9\text{-oxo-2-}-(\text{prop-1-en-3-yl})\text{-1-azabi-cyclo}[4.3.0]\text{nonan-4-yl Formate (22).} \) To 350 mg (1.80
mmol) of carbinollactam 21 was added 4 mL of formic acid in a single portion. The resulting solution was stirred at room temperature for 10 min, and the formic acid was removed in vacuo with slight warming. The red brown residue was dissolved in 30 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate aqueous solution. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give an orange oil (373 mg). The oil was chromatographed over 16 g of silica gel (eluted with ethyl acetate-hexane, 7:3) to give 276 mg (69%) of 22 as a pale-yellow oil: IR (CH₂Cl₂) 1720, 1680 cm⁻¹; NMR (CDCl₃) δ 1.00-2.45 (m, 10H, CH₂ manifold), 3.47-3.90 (m, 1H, NCH), 4.33 (q, J=7 Hz, 1H, NCH), 4.85-5.35 (m, 3H, =CH₂ and OCH), 5.40-6.05 (m, 1H, -CH=), 7.97 (s, 1H, HCOO); mass spectrum, m/e (relative intensity) 223(1), 182(8), 136(100), 109(18); exact mass calcd for C₁₂H₁₇NO₃ m/e 223.1208, found m/e 223.1214.

Catalytic Hydrogenation of Formate 22. A mixture of 10 mg of 5% palladium on charcoal, 61 mg (0.27 mmol) of formate 22, and 2 mL of absolute ethanol was hydrogenated under an initial hydrogen pressure of 58.5 psi for 2 h.
The resulting mixture was diluted with dichloromethane, dried with magnesium sulfate, and filtered through Celite. The filtrate was concentrated in vacuo to give 61 mg of a colorless oil, which was chromatographed over 5 g of silica gel (eluted with ethyl acetate) to give 61 mg (100%) of a colorless oil that had identical NMR, IR, and TLC (ethyl acetate) characteristics as formate 13.

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\text{rel-(2R, 4R, 6R)-4-Hydroxy-2-(prop-1-en-3-yl)-1-azabicyclo-[4.3.0]nonan-9-one (60).}
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To 202 mg (0.907 mmol) of formate 22 was added 2.3 mL of a 0.85 N sodium hydroxide solution in aqueous methanol (H\textsubscript{2}O-MeOH, 1:5). The resulting mixture was stirred at room temperature for 35 min and partitioned between 20 mL of dichloromethane and 15 mL of water. The aqueous phase was extracted with nine 20-mL portions of dichloromethane. The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated in vacuo to give a pale-yellow oil (162 mg). The oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate followed by ethyl acetate-methanol, 5:1) to yield 160 mg (90%) of 60 as a pale-yellow oil: IR (CH\textsubscript{2}Cl\textsubscript{2}) 3600, 3400(br), 1680 cm\textsuperscript{-1}; NMR (CDCl\textsubscript{3}) \(\delta\) 0.90-2.90 (m, 11H, CH\textsubscript{2} manifold and OH), 3.50-4.60 (m with \(\text{tt}\) at 4.00, \(J=11\), 4 Hz, and q at 4.45,}
J=7 Hz, 3H, NCH and OCH), 4.90-5.25 (m, 2H, =CH₂), 5.55-6.05 (m, 1H, -CH=); mass spectrum, m/e (relative intensity) 195(0.6), 154(100), 136(8), 110(96), 86(15), 84(26); exact mass calcd for C₁₁H₁₇NO₂ m/e 195.1259, found 195.1265.

rel-(2R, 4R, 6R)-9-Oxo-2-(prop-1-en-3-yl)-1-azabicyclo[4.3.0]nonan-4-yl S-Methyl Dithiocarbonate (23). To 81.8 mg (3.40 mmol) of sodium hydride and 2.1 mg (0.031 mmol) of imidazole under argon was added a solution of 160 mg (0.319 mmol) of carbinollactam 60 in 3.4 mL of dry tetrahydrofuran. The resulting mixture was heated at 60°C for 30 min followed by the addition of 0.31 mL (5.2 mmol) of carbon disulfide. The resulting mixture was heated for another 5 min and 0.31 mL of (5.0 mmol) of methyl iodide was added in a single portion. After stirring for another 5 min at the same temperature, the reaction mixture was diluted with 30 mL of dichloromethane and washed with two 10-mL portions of water. The combined aqueous layers were extracted with 10 mL of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to give an orange oil (216 mg). The oil was chromatographed over 5 g of silica gel (eluted with ethyl
acetate-hexane, 7:3) to give 192 mg (82%) of 23 as a light yellow oil: IR (CH$_2$Cl$_2$) 1680 cm$^{-1}$; NMR (CCl$_4$) $\delta$
1.00-2.60 (m with s at 2.60, 13H, CH$_3$ and CH$_2$ manifold),
3.50-3.90 (m, 1H, NCH), 4.39 (q, J=7 Hz, 1H, NCH), 4.90-5.25 (m, 2H, =CH$_2$), 5.50-6.10 (m, 2H, -CH= and OCH); mass spectrum, m/e (relative intensity) 285(1), 244(19), 178 (10), 136(100), 103(11); exact mass calcd for C$_{13}$H$_{19}$NO$_2$S$_2$
m/e 235.0357, found m/e 235.0849.

rel-(1R, 6R, 8R, 9R)-9-Methyl-3-Oxo-2-azatricyclo[6.2.1.0$^2$]undecane (24) and rel-(1R, 6R, 9R, 9S)-9-Methyl-3-oxo-2-azatricyclo[6.2.1.0$^2$]undecane (25). To a solution of 304 mg (1.04 mmol) of tri-n-butyltin hydride in 6 mL of dry toluene

heated to reflux under argon was added dropwise a solution of 192 mg (0.67 mmol) of xanthate 23 in 6 mL of dry toluene via a dropping funnel over a period of 50 min. The resulting solution was heated under reflux for another 17 h and the solvent was removed in vacuo to give 450 mg of a pale-yellow oil. This material was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexane, 3:7) to give 24.1 mg of a less polar material, which was distilled bulb-to-bulb to give 19 mg (16%) of a colorless oil identified as the reduction product: bp 60-70°C (0.14
mmHg); IR (CH₂Cl₂) 1670 cm⁻¹; NMR (CCl₄) δ 0.90-2.38 (m, 12H), 3.29-3.68 (m, 1H, NCH), 4.08-4.40 (m, 1H, NCH), 4.87-5.20 (m, 2H, =CH₂), 5.54-6.05 (m, 1H, CH=); continued elution gave 99 mg (74%) of a mixture of 24 and 25 as a colorless oil after bulb-to-bulb distillation (60-70°C (0.14 mmHg)) separable by gas-liquid chromatography (2m x 1/8 in. column packed with 10% OV-101 on Chrom W, Hp 80/100; column temperature, 185°C; flow rate, 24 mL/min) in a ratio of 2:1. 24: t_R=7.4 min; IR (CH₂Cl₂) 1675 cm⁻¹; NMR (CDCl₃) δ 1.02 (d, J=7 Hz, 3H, CH₃), 1.28 (ddd, J=14, 11, 6 Hz, 1H), 1.34-1.44 (m, 2H), 1.52 (dtd, J=13, 11, 8 Hz, 1H), 1.68 (dddd, J=13, 6, 3, 2 Hz, 1H), 1.79 (dtd, J=13, 6, 2 Hz, 1H), 1.91 (ddd, J=14, 8, 3 Hz, 1H), 2.00-2.21 (m, 3H), 2.30-2.44 (m, 2H), 3.66 (dddd, J=14, 9, 8, 6 Hz, 1H, NCH), 4.54 (br t, J=4.5 Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 179(20), 136(100); exact mass calcd for C₁₁H₁₇NO m/e 179.1310, found m/e 179.1315. 25: t_R=8.7 min; IR (CH₂Cl₂) 1670 cm⁻¹; NMR (CDCl₃) δ 1.12 (d, J=7 Hz, 3H, CH₃), 1.27 (ddd, J=15, 11, 4 Hz, 1H), 1.44-1.67 (m, 4H), 1.94 (br d, J=15 Hz, 1H), 2.13-2.25 (m, 4H), 2.30-2.40 (m, 2H), 3.62-3.76 (m, 1H, NCH), 4.47-4.55 (br s, 1H, NCH); mass spectrum, m/e (relative intensity) 179 (20), 136(100); exact mass calcd for C₁₁H₁₇NO m/e 179.1310, found m/e 179.1314.

rel-(2R,6S)-2-Propyl-1-azabicyclo[4.3.0]nonane-9-thione (26). A mixture of 3.71 g (16.6 mmol) of
phosphorous pentasulfide, 100 mL of dry toluene, and 6.00 g (33.2 mmol) of lactam 19 was warmed to reflux under nitrogen for 30 min. The resulting solution phase was decanted, and the residual solid was crushed with a spatula followed by stirring with dichloromethane for 1 h. The resulting mixture was filtered, and the combined organic solutions were filtered again through Celite. The filtrate was concentrated in vacuo to give 6.00 g of an orange liquid which was bulb-to-bulb distilled to afford 4.80 g (73%) of thiolactam 26 as a light-yellow oil that solidified on standing: bp 110°C (0.1 mmHg); mp 37-39°C. The residue after the first filtration was stirred with 50 mL of water and 50 mL of dichloromethane and the aqueous phase was extracted with 50 mL of dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$), concentrated in vacuo, and bulb-to-bulb distilled to give an additional 0.61 g (9%) of thiolactam 26 as a yellow solid: mp 36.5-38.5°C; IR (neat) 1475, 1160, 1130 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.63-2.63 (m, 14H), 2.63-3.20 (m, 2H, C(S)CH$_2$), 3.53-4.16 (m, 1H, NCH), 4.67-5.20 (br s, 1H, NCH); mass spectrum, m/e (relative intensity) 197(57), 196 (7), 168(33), 164(81), 155(100), 154(43), 122(43); exact
mass calcd for C_{11}H_{19}NS m/e 197.1238, found m/e 197.1242.

Anal. Calcd for C_{11}H_{19}NS: C, 66.95; H, 9.70. Found: C, 66.99; H, 9.34.

1-(rel-(2R,4S)-2-Propyl-1-aza-bicyclo[4.3.0]nonan-9-ylidene)butan-2-one (27). To a solution of 2.61 g (13.2 mmol) of thiolactam 26 in 25 mL of dry ether was added 2.67 (17.7 mmol) of 1-bromo-2-butanone in 20 mL of dry ether, and the resulting solution was stirred under nitrogen at room temperature for 47 h. The ether layer was removed with a pipet and concentrated in vacuo to give a yellow oil (60.3 mg), which was dissolved in 65 mL of chloroform and returned to the original reaction vessel. The resulting solution was cooled in an ice bath followed by sequential addition of 3.46 g (13.2 mmol) of triphenylphosphine and 2.66 g (26.4 mmol) of triethylamine. The solution was stirred under nitrogen at room temperature for 2 h and concentrated in vacuo. The resulting solid residue was triturated with two 50-mL portions of ethyl acetate-hexane (1:9), and the combined extracts were concentrated in vacuo. The resulting yellow oil was treated with 30 mL of ethyl acetate-hexane (1:9) and filtered through Celite. The filtrate was concentrated in vacuo, and excess bromo
ketone was removed under a pressure of 0.1 mm at room temperature to afford 3.69 g of a yellow oil. The oil was chromatographed over 150 g of silica gel (eluted with ethyl acetate-hexane, 3:7, followed by ethyl acetate-hexane, 1:1) to give 3.09 g (100%) of vinylogous amide 27 as a yellow oil. Part of this oil (2.74 g) was bulb-to-bulb distilled to give 2.54 g (92%) of 27 as a pale-yellow oil: IR (CHCl₃) 1625, 1530 cm⁻¹; NMR (CDCl₃) δ 0.82-2.48 (m with t, J=5 Hz, at 1.10 and q, J=5 Hz, at 2.31, 2OH, COCH₂CH₃, CH₃, CH₂), 2.93 (se, J=6 Hz, 1H, NCH), 3.27-3.93 (m, 3H, allyl), 5.07 (s, 1H, vinyl); mass spectrum, m/e (relative intensity) 235(28), 206(100), 192 (28), 188(14), 178(28), 164(16), 136(71); exact mass calcd for C₁₅H₂₅NO m/e 235.1936, found m/e 235.1943.

1-(rel-(2R,6S,9S)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl)-butan-2-one (28). Method A.

To a mixture of 399 mg of platinum oxide in a 500 mL Parr bottle were added 1.75 g (7.45 mmol) of vinylogous amide 27 and 50 mL of glacial acetic acid. The resulting mixture was hydrogenated under an initial hydrogen pressure of 60 psi for 160 min. Some magnesium sulfate was added, and the resulting mixture was filtered through Celite. The filtrate was
concentrated in vacuo, and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 40 mL of saturated sodium bicarbonate solution and the aqueous phase was extracted with two 40-mL portions of dichloromethane. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to give 1.64 g of a pale-yellow oil.

Part of this oil (1.55 g) was dissolved in 25 mL of acetone. To this solution cooled in an ice bath was added 1.42 mL of Jones reagent over a period of 10 min. The resulting green mixture was stirred with cooling for an additional 20 min followed by the addition of isopropyl alcohol. The mixture was stirred at 0°C for another 5 min and solvent was removed in vacuo. The greenish residue was mixed with 50 mL of water and 5 g of sodium bicarbonate was added in small portions with stirring. The resulting mixture was extracted with 150 mL of dichloromethane. The organic layer was washed with two 50-mL portions of water, dried (Na₂SO₄), and concentrated in vacuo to give 1.45 g of a dark-orange oil. The oil was chromatographed over 260 g of silica gel (eluted with methanol (12% ammonium hydroxide)-chloroform, 1.5:98.5) to give 747 mg (46%) of amino ketone 28 as a yellow oil: IR(CHCl₃) 1710 cm⁻¹; NMR (CDCl₃) δ 0.73-2.13 (m with t, J=7 Hz, at 1.03, 2OH, CH₃, CH₂), 2.17-2.7 (m, 4.5H), 2.73-3.33 (m, 2.5H); NMR (C₆D₆) δ 0.70-1.57 (m with t, J=7 Hz at 0.97,
20H), 1.87-2.67 (m, 5H, C(0)CH2, NCH), 2.67-2.97 (m, 1H, NCH), 2.97-3.33 (m, 1H, NCH); 13C NMR (CDCl3) δ 7.77(q), 14.38(q), 19.19(t), 20.89(t), 23.49(t), 27.85(t), 29.76 (t), 29.90(t), 32.41(t), 37.08(t), 46.67(t), 53.04(d), 54.44(d), 56.01(d), 210.14(s); mass spectrum, m/e (relative intensity) 237(5), 194(100), 166(46), 122(70); exact mass calcd for C15H27NO m/e 237.2092, found m/e 237.2096; and 238 mg (22%) of a mixture of 28 and 29 by NMR analysis and thin-layer chromatography (silica gel eluted with methanol (2% ammonium hydroxide)-chloroform, 12:88); Rf 0.52 for 28 and Rf 0.35 for 29.

Method B. To 33.8 mg (0.540 mmol) of sodium cyanoborohydride in 0.5 mL of dry methanol under nitrogen was added 122 mg (0.520 mmol) of vinylogous amide 27 in 0.5 mL of dry methanol followed by a trace of bromocresol green. To the resulting blue green solution was added dropwise a solution of 1.64N hydrochloric acid in methanol until the solution maintain a yellow color. The resulting solution was stirred at room temperature for 30 min and poured into 3 mL of 1.5 N sodium hydroxide solution. The mixture was extracted with two 15-mL portions of dichloromethane, and the combined organic layers were dried (Na2SO4) and
concentrated in vacuo to give 114 mg of a pale-green oil.

To the oil in 3 mL of acetone cooled in an ice bath was added 0.13 mL of Jones reagent over a period of 3 min. The reaction mixture was stirred at 0 °C for an additional 10 min and 10 drops of isopropyl alcohol was added. After the mixture was stirred at 0 °C for 5 min, the solvent was removed in vacuo and the greenish residue was mixed with 20 mL of water. Sodium bicarbonate was added in small portions with stirring until the solution was basic. The resulting mixture was extracted with 30 mL of dichloromethane. The extract was washed with two 10-mL portions of water, dried (Na₂SO₄), and concentrated in vacuo to give 102.3 mg of a brown oil. The oil was chromatographed over 11 g of silica gel (eluted with methanol (12% ammonium hydroxide)-chloroform, 1.5:98.5) to give 59.6 mg (48%) of amino ketone 28 as a yellow oil and 33.1 mg (27%) of a mixture of 28 and 29.

Following method B of the preparation of amino ketone 28, vinylogous amide 27 (659
mg, 2.8 mmol) was reduced with 191 mg (3.03 mmol) of sodium cyanoborohydride and oxidized with 1.03 mL of Jones reagent to give 637 mg of a brown oil. To this oil in 9 mL of dry chloroform was added 1.02 g (9.43 mmol) of 1,3-propanedithiol in one portion. Hydrogen chloride was bubbled through the resulting solution for 10 min. The resulting turbid solution was allowed to stand at room temperature for 3 h and partitioned between 30 mL of saturated sodium bicarbonate solution and 70 mL of dichloromethane. The aqueous phase was extracted with two 15-mL portions of dichloromethane, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give 0.902 g of a yellow oil. This oil was chromatographed over 95 g of silica gel (eluted with methanol (12% ammonium hydroxide)-chloroform, 1:99) to give 553 mg (60%) of thioketal 30 as a pale-orange oil (IR (CHCl$_3$) 2940, 2870 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.73-2.35 (m, 20H), 2.35-3.27 (m, 7H, NCH, SCH$_2$); $^{13}$C NMR (C$_6$D$_6$) $\delta$ 9.66(q), 14.90(q), 19.86(t), 21.21 (t), 24.08(t), 25.49(t), 26.17(t), 26.26(t), 28.26(t), 31.36(t), 32.43(t), 33.15(t), 45.10(t), 52.97(d), 53.89 (s), 54.86(d), 55.64(d); mass spectrum, $m/e$ (relative intensity) 327(2), 284(29), 166(100), 122(26); exact mass
calcd for C_{19}H_{33}NS_{2} m/e 327.2054, found m/e 327.2049; and 235 mg (26%) of thioketal 31 as a pale-yellow oil (IR (CHCl_{3}) 2940, 2870 cm^{-1}; NMR (CDCl_{3}) \delta 0.70-2.47 (m, 26H), 2.47-3.40 (m, 7H, NCH, SCH_{2}); \textsuperscript{13}C NMR (C_{6}D_{6}) \delta 9.76(q), 14.56(q), 19.95(t), 20.73(t), 23.64(t), 25.44(t), 26.07(t), 26.22(t), 27.19(t), 30.10(t), 32.48(t), 35.44(t), 47.58(t), 51.95(d), 53.99(s and d), 55.00(d); mass spectrum, m/e (relative intensity) 327(2), 284(33), 166(100), 122(12); exact mass calcd for C_{19}H_{33}NS_{2} m/e 327.2054, found m/e 327.2062).

\[ \text{rel-} (2R,6S,9R)-9-\text{Butyl-2-propyl-1-azabicyclo[4.3.0]-nonane} \] (2b). A solution of 132 mg (0.405 mmol) of thioketal 30 in 5 mL of ethylamine in a test tube was cooled in a dry ice-carbon tetrachloride bath with the test tube stoppered with a rubber stopper. Lithium (60.0 mg) was cut into the test tube in small pieces. The test tube was stoppered and cooled with constant shaking, and the pressure was released periodically. When the reaction mixture remained blue, it was poured carefully into 10 mL of water. The aqueous solution was extracted twice with dichloromethane (50 mL total). The combined organic layers were dried (Na_{2}SO_{4}), concentrated in vacuo, and
chromatographed over 11 g of silica gel (eluted with methanol (12% ammonium hydroxide)-chloroform, 2:98) to give 54.2 mg (60%) of \( \text{2b} \) as a pale-yellow oil: IR \((\text{CHCl}_3)\) \(2970, 2940, 2890 \text{ cm}^{-1}\); NMR \((\text{CDCl}_3)\) \(\delta 0.67-2.00 \text{ (m, 26H)}, 2.20-2.77 \text{ (br s, 2H, NCH)}, 2.77-3.17 \text{ (br s, 1H, NCH)}\); \(^{13}\text{C} \) NMR \((\text{C}_6\text{D}_6)\) \(\delta 14.37, 14.66, 20.05, 21.31, 23.64, 28.45, 28.79, 30.44, 33.21, 33.45, 52.72, 56.41, 58.40\); mass spectrum, \(m/e\) (relative intensity) 223(5), 180(100), 166(93), 122(5); exact mass calcd for \(\text{C}_{15}\text{H}_{29}\text{N}\) \(m/e\) 223.2300, found \(m/e\) 223.2304.

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\text{rel-(2R,6S,9S)-9-Butyl-2-propyl-1-azabicyclo[4.3.0]-nonane (2c). A solution of 220 mg of thiketal 31 in 8.0 mL of ethylamine in a 50-mL pear-shaped flask was cooled in a dry ice-carbon tetrachloride bath with the flask stoppered with a rubber stopper. Lithium (100 mg) was cut into the flask in small pieces. The flask was stoppered and cooled with constant shaking and the pressure was released periodically. When the reaction mixture stayed blue, it was poured carefully into 20 mL of water. The resulting mixture was extracted with dichloromethane (80 mL total). The combined organic phases were dried (\(\text{Na}_2\text{SO}_4\)) and concentrated in vacuo to give 146 mg of a}
pale-yellow oil. This oil was chromatographed over 10 g of silica gel (eluted with methanol (12% ammonium hydroxide)-chloroform, 1:99) to give 34 mg (23%) of indolizidine 2c as a yellow oil, homogeneous by GLC (2 m x 1/8 in. OV-101, 190 C): IR (CHCl₃) 2960, 2940, 2870 cm⁻¹; NMR (CDCl₃) δ 0.73-2.47 (m, 26H), 2.53-3.47 (m, 3H); ¹³C NMR (C₆D₆) δ 14.47, 14.56, 20.10, 20.73, 23.64, 27.72, 28.94, 29.76, 35.54, 36.27, 52.89, 54.81, 58.50; mass spectrum, m/e (relative intensity) 223(6), 190(94), 166(100); exact mass calcd for C₁₅H₂₉N m/e 223.2300, found m/e 223.2296.  

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\begin{align*}
\text{rel-2S-(rel-(2R,6S,9S)-2-Propyl-1-azabicyclo[4.3.0]-nonan-9-yl)-butan-2-ol (32) and rel-2R-(rel-(2R,6S,9S)-2-Propyl-1-azabicyclo[4.3.0]-nonan-9-yl)-butan-2-ol (33).}
\end{align*}
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To a mixture of 170 mg (4.47 mmol) of lithium aluminum hydride in 25 mL of dry tetrahydrofuran under nitrogen was added a solution of 690 mg (2.92 mmol) of amino ketone 28 in 25 mL of dry tetrahydrofuran over a 30 min period. The resulting mixture was stirred at room temperature for an additional 15 min followed by the sequential addition of 8 drops of water, 18 drops of 3N sodium hydroxide solution, 36 drops of water, magnesium sulfate and 18 mL of ether. The resulting mixture was filtered through Celite.
and concentrated in vacuo to obtain a pale-yellow oil (688 mg). The oil was chromatographed over 70 g of silica gel (eluted with 12% ammonium hydroxide in methanol-chloroform, 1:99) to afford 282 mg (40%) of the less polar 32 as a yellow oil: IR (CHCl₃) 3160 (br) cm⁻¹; NMR (CDCl₃) δ 0.67-2.23 (m, 24H, CH₂ manifold), 2.23-2.72 (m, 1H, NCH), 2.90-3.40 (br s, 2H, NCH), 3.67-4.00 (dtd, J=9, 6, 3 Hz, OCH), 5.67-6.43 (br s, 1H, OH); ¹³C NMR (C₆D₆) δ 10.24, 14.47, 19.27, 21.17, 23.93, 26.41, 28.16, 31.51, 31.65, 32.58, 35.39, 52.48, 56.56, 80.98; mass spectrum, m/e (relative intensity) 239(3), 210(10), 196(100), 166(77), 124(39), 122(12); exact mass calcd for C₁₅H₂₉NO m/e 239.2249, found m/e 239.2256. Further elution gave 332 mg (48%) of 33 as an orange oil: IR (CHCl₃) 3560 (br), 3190 (br) cm⁻¹; NMR (CDCl₃) δ 0.77-2.30 (m, 24H, CH₂ manifold), 2.30-2.77 (m, 1H, NCH), 2.77-3.23 (m, 2H, NCH), 3.23-4.50 (m, with qu, J=6 Hz, at 3.60, 2H, OCH, OH); ¹³C NMR (C₆D₆) δ 10.15, 14.61, 19.95, 21.22, 24.37, 28.40, 29.71, 30.25, 31.99, 32.77, 41.51, 53.79, 56.17, 56.95, 71.56; mass spectrum, m/e (relative intensity) 239(4), 210(9), 196(100), 166(53), 124(37), 122(15); exact mass calcd for C₁₅H₂₉NO m/e 239.2249, found m/e 239.2243.

rel-2S-(rel-(2R,6S,9S)-2-Propyl-1-azabicyclo[4.3.0]-nonan-9-yl)-butan-2-yl S-Methyl Dithiocarbonate (34).

To a mixture of 83.7 mg (3.49 mmol) of sodium hydride and 1.6 mg (0.024 mmol) of imidazole under nitrogen was added
a solution of 196 mg (0.321 mmol) of 32 in 3.4 mL of dry tetrahydrofuran. The resulting mixture was stirred at 60°C for 30 min followed by the addition of 0.31 mL (5.1 mmol) of carbon disulfide. The reaction mixture was stirred for an additional 5 min followed by the addition of 0.31 mL (5.0 mmol) of methyl iodide. The resulting mixture was heated for another 5 min, diluted with 30 mL of dichloromethane, and washed with two 10-mL portions of water. The combined aqueous layers were extracted with 5 mL of dichloromethane. The organic layers were dried (Na₂SO₄) and concentrated in vacuo to obtain a yellow oil (280 mg). The oil was chromatographed over 30 g of silica gel (eluted with 12% ammonium hydroxide in methanol-chloroform, 1:99) to give 235 mg (87%) of 34 as a pale-yellow oil: IR (CHCl₃) 1235, 1055 cm⁻¹; NMR (CDCl₃) δ 0.80-1.07 (br t, J=6 Hz, 6H, CH₃), 1.07-2.20 (m, 8H, CH₂ manifold), 2.20-2.37 (m with s at 2.52, 5H, NCH and SCH₂), 2.87-3.20 (br s, 1H, NCH), 5.57-5.87 (qu, 1H, J=7 Hz, OCH); mass spectrum, m/e (relative intensity) 329(2), 286(100), 221(7), 178(60), 166(93), 122(27); exact mass calcd for C₁₇H₃₁NOS₂ m/e 329.1847, found m/e 329.1840.
rel-2R-(rel-(2R,6S,9S)-2-Propyl-1-azabicyclo[4.3.0]-nonan-9-yl)butan-2-yl S-Methyl Dithiocarbonate (35).

To a mixture of 102 mg (4.25 mmol) of sodium hydride and 1.6 mg (0.024 mmol) of imidazole under nitrogen was added a solution of 248 mg (1.04 mmol) of 33 in 4.3 mL of dry tetrahydrofuran. The resulting mixture was heated at 60 °C for 30 min, followed by the addition of 0.39 mL (6.4 mmol) of carbon disulfide. The resulting mixture was heated for another 5 min, and 0.39 mL (6.4 mmol) of methyl iodide was added in a single portion. After heating for another 5 min, the mixture was diluted with 20 mL of dichloromethane and washed with two 10-mL portions of water. The combined aqueous phases were extracted with 10 mL of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 341 mg of a brownish residue. This crude product was chromatographed over 35 g of silica gel (eluted with 20% ammonium hydroxide in methanol-chloroform, 0.5:99.5) to afford 23.3 mg (70%) of 35 as a pale-yellow oil: IR (CHCl₃) 1235, 1055 cm⁻¹; NMR (CDCl₃) δ 0.80-1.05 (br t, J=6 Hz, 6H, CH₃), 1.05-2.37 (m with s at 2.58, 23H, SCH₂ and CH₂ manifold), 2.37-3.23 (br s, 1H), 5.57-5.99 (dtd, J=9, 6, 3 Hz,
Formation of Amine 2b via Tri-n-butyltin Hydride Reduction of Xanthate 34. To a solution of 286 mg (0.981 mmol) of tri-n-butyltin hydride in 6 mL of dry toluene heated under nitrogen at an oil bath temperature between 125-130°C was added dropwise a solution of 215 mg (0.653 mmol) of 34 in 6 mL of dry toluene over a 20 min period. The resulting solution was heated for an additional 18 h. The solvent was removed in vacuo to afford a pale-yellow oil (456 mg) which was chromatographed over 45 g of silica gel (eluted with 12% ammonium hydroxide in methanol-chloroform, 2:98, followed by 6% ammonium hydroxide in methanol-chloroform, 4:96) to give 124 mg (85%) of 2b as a pale-yellow oil, identical in all respects with that prepared via the dithiane reduction.

Formation of Amine 2b via Tri-n-butyltin Hydride Reduction of Xanthate 35. To a solution of 299 mg (1.03 mmol) of tri-n-butyltin hydride in 6 mL of dry toluene heated under nitrogen at an oil bath temperature between 125-130°C was added dropwise over a 10 min period a solution of 220 mg (0.668 mmol) of xanthate 35 in 6 mL of
dry toluene. The resulting solution was heated for another 30 h and the solvent was removed in vacuo to give 481 mg of a pale-yellow oil. The oil was chromatographed over 45 g of silica gel (eluted with 12% ammonium hydroxide in methanol-chloroform, 2:98, followed by 6% ammonium hydroxide in methanol-chloroform, 4:96) and then over 15 g of activity II alumina oxide (eluted with ethyl acetate-hexane, 0.5:99.5) to give 105 mg (82%) of 2b as a pale-yellow oil identical in all respects with that obtained via the dithiane reduction route.

**Ethyl**(rel-(2R,6S)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yldene)acetate (36). Method A.

To a solution of 5.23 g (26.5 mmol) of thiolactam 26 in 90 mL of dry ether was added 5.57 g (33.4 mmol) of ethyl bromoacetate in one portion and the resulting solution was stirred under nitrogen at room temperature for 37 h. The ether layer was removed with a pipet and concentrated in vacuo to give a pale-yellow oil. The oil was dissolved in 130 mL of dry chloroform and the mixture returned to the original reaction vessel. The reaction mixture was cooled in an ice bath followed by sequential addition of 8.94 g (26.5 mmol) of triphenylphosphine and 7.4 mL (53.2 mmol) of triethylamine. The
resulting solution was stirred at room temperature under nitrogen for 30 min and concentrated in vacuo. The residual solid was triturated sequentially with 100- and 500-mL portions of ethyl acetate-hexane (1:9). The combined extracts were concentrated in vacuo. The residual oil was stirred with 50 mL of ethyl acetate-hexane (1:9) and filtered through Celite. The filtrate was concentrated in vacuo, and excess ethyl bromoacetate was removed under a pressure of 0.1 mm at room temperature to afford 7.47 g of an orange oil that contained about 0.62 g of triphenylphosphine sulfide and 6.85 g (100%) of vinyllogous urethane 36 by NMR analysis. This crude product was used directly in the next reaction. A portion of the crude 36 was chromatographed over silica gel (eluted with ethyl acetate-hexane, 1:9) to give pure 36 as a pale-yellow oil: IR (CHCl₃) 1675, 1590 cm⁻¹; NMR (CDCl₃) δ 0.70-3.83 (m with t, J=7 Hz, at 1.23, 22H, CH₃, CH₂), 4.07 (q, J=7 Hz, 2H, OCH₂), 4.50 (s, 1H, =CH-); mass spectrum, m/e (relative intensity) 251(19), 236(8), 222(10), 209(67), 208(31), 206(36), 178(19), 164(33), 162(17), 136 (100); exact mass calcd for C₁₅H₂₅NO₂ m/e 251.1895, found m/e 251.1892.

**Method B.** To a stirred solution of 1.20 g (6.10 mmol) of thiolactam 26 in 18 mL of dry ether was added 2.84 g (20.0 mmol) of methyl iodide in one portion. The mixture was stirred under argon for 16 h at room
temperature. The resulting mixture was filtered and the collected crystals were rinsed with 15 mL of dry ether. The hygroscopic crystals were dried in high vacuume at room temperature for 2.5 h to give 2.11 g (100%) of a pale-yellow solid; mp 106-110°C. To 339 mg (1.00 mmol) of the salt prepared above was added 400 mg (2.00 mmol) of magnesium monoethyl malonate and 3 mL of dry DMF. The resulting yellow mixture was heated at 65°C for 23 h under nitrogen, diluted with 20 mL of dichloromethane and washed with two 20-mL portions of water. The aqueous layer was extracted with 10 mL of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a yellow oil (642 mg). The oil was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexane, 8:2) to give 205 mg (32%) of 36 as a yellow oil.

Ethyl (rel-(2R,6S,9S)-2-propyl-1-azabicyclo(4.3.0)-nonan-9-yl)acetate (37) and Ethyl (rel-(2R,6S,9R)-2-propyl-1-azabicyclo(4.3.0)-nonan-9-yl)acetate (38). To a solution of 7.47 g (26.5 mmol) of crude vinylogous urethane 36 in 55 mL of dry methanol was added a trace of bromocresol green followed by 1.68 g (26.6 mmol) of sodium
cyanoborohydride. A 1.14 N methanolic hydrochloric acid solution (40 mL total) was added dropwise until the reaction mixture maintained a yellow color. The resulting solution was poured into 140 mL of 0.2 N aqueous sodium hydroxide and extracted with two 200-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 8.23 g of a colorless liquid with an immiscible blue oil at bottom. This mixture was chromatographed over 500 g of silica gel (eluted with methanol (5% ammonium hydroxide)-chloroform, 1.5:98.5, followed by methanol (2% ammonium hydroxide)-chloroform, 8:92) to give 3.39 g (50%) of amino ester 37 as a colorless liquid: IR (CHCl₃) 1715 cm⁻¹; NMR (CDCl₃) δ 0.76-2.00 (m with t, J=7 Hz, at 1.27, 20H, CH₂, CH₂ manifold), 2.00-2.76 (m, 3H, COCH₂, NCH), 2.76-3.33 (m, 2H, NCH), 4.12 (q, J=7 Hz, 2H, OCH₂); ¹³C NMR (CDCl₃) δ 14.32 (q), 14.47(q), 19.27(t), 20.88(t), 23.50(t), 27.96(t), 29.86(t), 32.58(t), 39.32(t), 52.82(d), 54.96(d), 56.02 (d), 60.15(t), 172.64(s); mass spectrum, m/e (relative intensity) 253(3), 210(100), 166(30), 122(52); exact mass caled for C₁₅H₂₇NO₂ m/e 253.2042, found m/e 253.2050.
Anal. Calcd for C_{15}H_{27}NO_2: C, 71.10; H, 10.74.

Found: C, 71.04; H, 10.49.

Continued elution gave 1.81 g (27%) of amino ester 38 as a colorless liquid: IR (CHCl_3) 1715 cm^{-1}; NMR (CDCl_3) 6 0.67-2.33 (m with t, J=7 Hz, at 1.23, 23H, CH_3, CH_2), 2.83-3.67 (m, 2H, NCH), 4.08 (q, J=7 Hz, 2H, OCH); \(^{13}\)C NMR (CDCl_3) 6 14.27(q), 19.37(t), 20.34(t), 23.40(t), 27.49(t), 28.94(t), 29.18(t), 25.25(t), 41.85(t), 52.63 (d), 54.67(d), 55.68(d), 60.06(t), 172.83(s); mass spectrum, m/e (relative intensity) 253(5), 210(100), 166(40), 122(45); exact mass calcd for C_{15}H_{27}NO_2 m/e 253.2042, found m/e 253.2050.

\[ \theta-(R)\{2R,6S,9S\}-2-\text{Propyl}-1\text{-azabicyclo}[4.3.0]nonan-9-yl\text{ethanol} (39). \] To a mixture of 274 mg (7.22 mmol) of lithium aluminum hydride in 35 mL of dry tetrahydrofuran was added dropwise 1.20 g (4.75 mmol) of amino ester 37 in 35 mL of dry tetrahydrofuran over a period of 25 min. The mixture was stirred under nitrogen for an additional 15 min at room temperature followed by sequential addition of 1.4 mL of water, 1.4 mL of 3 N sodium hydroxide solution, 2.8 mL of water, a portion of magnesium sulfate, and 28 mL of ether. The resulting mixture was
filtered through Celite and concentrated in vacuo to give
0.971 g (97%) of crude amino alcohol 39 as a pale-yellow
oil, homogeneous by thin-layer chromatography (alumina;
ethyl acetate-hexane, 7:3): IR (CHCl₃) 3200 (br) cm⁻¹;
NMR (CDCl₃) δ 0.60-2.77 (m, 20H), 2.77-3.43 (br s, 2H,
NCH), 3.62 (td, J=11, 4 Hz, 1H, OCH), 4.02 (dt, J=11, 3
Hz, 1H, OCH); mass spectrum, m/e (relative intensity) 211
(3), 168(100), 166(34), 124(8), 122(6); exact mass calcd
for C₁₃H₂₅NO m/e 211.1936, found m/e 211.1941.

\[
\text{ft-(gel-(2R,6S,9R)-2-Propyl-1-azabicyclo[4.3.0]nonan-9-yl)ethanol (40). To a mix-
}
\]

40 \(R = \text{CH}_2\text{OH}\)

4 ml of dry tetrahydrofuran over a period of 5 min. The
mixture was stirred at room temperature for 15 min follow-
ed by sequential addition of 3 drops of water, 3 drops of
3 N aqueous sodium hydroxide, 6 drops of water, magnesium
sulfate, and 3 mL of ether. The resulting mixture was
filtered through Celite and concentrated in vacuo to
afford 104 mg (96%) of crude amino alcohol 40 as a pale-
yellow oil, homogeneous by thin-layer chromatography (alu-
mina; ethyl acetate-hexane, 7:3): IR (CHCl₃) 3190 cm⁻¹;
NMR (CDCl$_3$) $\delta$ 0.70-2.90 (m, 2OH, CH$_2$, CH$_3$, NCH), 2.90-4.13 (m, 4H, NCH, OCH$_2$), 5.60-6.60 (br s, 1H, OH); mass spectrum, m/e (relative intensity) 211(5), 210(2), 168(100), 166(46), 124(6), 122(6); exact mass calcd for C$_{13}$H$_{25}$NO m/e 211.1936, found m/e 211.1929.

![Diagram](image)

rel-[(1R,4S,7S,11R)-11-Propyl-1-azatricyclo[5.4.0.$^{1,4}$]undecane Tetrafluoroborate (41). To a solution of 81 mg (0.43 mmol) of amino alcohol 39 in 0.5 mL of dry dichloromethane cooled in an ice bath under argon was added 0.15 mL of triethylamine in a single portion followed by the addition of a solution of 55 mg (0.48 mmol) of methanesulfonyl chloride in 0.5 mL of dichloromethane. The resulting solution was stirred at 0°C for 7 min, diluted with 15 mL of dichloromethane, and poured into 5 mL of a mixture of equal parts of 10% potassium hydroxide aqueous solution and saturated sodium chloride aqueous solution. The aqueous phase was extracted with 5 mL of dichloromethane, and the combined organic layers were dried (MgSO$_4$) and concentrated in vacuo to give 110 mg of a white solid. This solid was dissolved in 0.5 mL of methanol and stirred with an aqueous solution of 1.4 g of sodium tetrafluoroborate (12.7 mmol) in 6 mL of water for 1 h. The
resulting solution was extracted with chloroform (2 x 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 102 mg of a white solid. This material was recrystallized from ether-di-chloromethane (3:2) to give 74 mg (61%) of the tetrafluoroborate salt 41 as white crystals: mp 162-163°C; IR (CHCl₃) 3040, 2960, 2850, 1460 cm⁻¹; NMR (CDCl₃) δ 0.85-2.50 (m, 15H), 2.50-3.60 (m with qu, J=11 Hz, at 2.97, 2H, NCH, methylene CH), 3.60-4.60 (m, with qu, J=10 Hz, at 4.27, 3H, NCH), 4.60-5.00 (m, 1H, NCH); ¹³C NMR (CDCl₃) 13.79(q), 17.53(t), 19.42(t), 20.10(t), 21.26(t), 22.33(t), 27.04(t), 27.58(t), 30.15(t), 35.00(t), 64.13(d), 65.83(d), 71.66(d).

Anal. Calcd for C₁₃H₂₄NBF₄: C, 55.50; H, 8.60. Found: C, 54.61; H, 8.83.

rel-(1S,4R,7S,11R)-11-Propyl-1-azatricyclo[5.4.0₁⁴]undecane Tetrafluoroborate (42).

To a solution of 73 mg (0.37 mmol) of amino alcohol 40 in 0.43 mL of dry dichloromethane cooled in an ice bath under argon was added 0.13 mL (0.93 mmol) of triethylamine in one portion followed by the addition of a solution of 47 mg (0.41 mmol) of methane-sulfonyl chloride in 0.43 mL of dichloromethane. The
resulting solution was stirred at 0°C for 7 min, diluted with 20 mL of dichloromethane, and poured into 4 mL of a mixture of equal parts of 10% potassium hydroxide aqueous solution and saturated sodium chloride aqueous solution. The aqueous phase was extracted with 5 mL of dichloromethane and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 92 mg of a yellow solid. This material was dissolved in 0.4 mL of methanol and stirred with a solution of 1.2 g (10.9 mmol) of sodium tetrafluoroborate in 4 mL of water for 1 h. The resulting solution was extracted with two 15- mL portions of dichloromethane, and the combined organic layers were dried (MgSO₄) and concentrated to give 90 mg (36%) of the tetrafluoroborate salt 42 as a yellow oil: IR (CHCl₃) 3040, 2960, 2880, 1470 cm⁻¹; NMR (CDCl₃) δ 0.30-3.40 (m, 19H), 3.40-4.40 (m, 5H), 4.70-5.07 (m, 1H, NCH); ¹³C NMR (CDCl₃) δ 13.74(q), 15.44(t), 19.57(t), 20.34(t), 22.53(t), 25.78(t), 29.94(t), 30.44(t), 56.66(t), 63.11(d), 66.66(d), 74.57(d).

**Formation of Amino Ketone 28 via Grignard Addition to Amino Ester 37.** To a solution of 97 mg (0.33 mmol) of amino ester 37 in 0.4 mL of dry ether under argon was added dropwise 1.5 mL of a solution of 1.29 M (5 equiv) ethylmagnesium bromide in ether. The resulting solution was stirred at room temperature for 6 h and transferred via syringe into a vigorously stirred mixture of 15 mL of
dichloromethane, 10 mL of water, and approximately 5 g of ice. The resulting mixture was diluted with 30 mL of dichloromethane and separated. The aqueous phase was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were dried and concentrated in vacuo to give 77 mg of a pale-yellow oil. This material was chromatographed over 8 g of silica gel (eluted with methanol (2% ammonium hydroxide)-chloroform, 8:92) to give 59 mg (65%) of a pale-yellow oil, which was identical by NMR and TLC (silica gel, methanol (2% ammonium hydroxide)-chloroform, 12:88) with amino ketone 28 prepared as described above.

**Formation of Amino Ketone 29 via Grignard Addition to Amino Ester 38.** To a solution of 104 mg (0.41 mmol) of amino ester 38 in 0.4 mL of dry ether under argon was added dropwise 1.5 mL of 1.278 M ethylmagnesium bromide in ether (4.7 equiv). The resulting solution was stirred at room temperature for 8 h and transferred via syringe into a vigorously stirred mixture of 10 mL of dichloromethane, 10 mL of water, and about 5 g of ice. The resulting mixture was diluted with 30 mL of dichloromethane and separated. The aqueous phase was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 32 mg of a pale-yellow oil, which was a mixture of amino ketone 29 and unreacted amino ester 38 by NMR, IR,
and TLC (silica gel, methanol (2% ammonium hydroxide)-chloroform, 12:88; alumina, ethyl acetate-hexane, 1:9). Attempts to purify this crude material by chromatography over 10 g of neutral activity III alumina (eluted with ethyl acetate-hexane, 2:98) resulted in isomerization of amino ketone 29 to a mixture of 29 and 28. Signals due to 29 were visible at \( \delta 0.70-2.30 \) and \( \delta 3.00-3.80 \) (m, 3H, NCH) in NMR spectrum (CDCl\(_3\)) of the crude product mixture.

Cyclization of Carbinol Lactam 12 in Trifluoroacetic Acid and Dichloromethane. To 1.03 g (5.25 mmol) of carbinol lactam 12 cooled in an ice-water bath was added in a single portion 11 mL of a mixture of trifluoroacetic acid and dichloromethane (1:1 by volume). The resulting solution was stirred cold for 5 min and at room temperature for 15 min. The reaction mixture was partitioned between 30 mL of water and 30 mL of dichloromethane. The aqueous phase was extracted with 20 mL of dichloromethane. The combined organic phases were washed with 15 mL of saturated sodium bicarbonate solution. The base wash was extracted with 15 mL of dichloromethane, and the combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give a pale-yellow oil (1.44 g).
This oil was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to afford 867 mg of a mixture of 48 and 50 in a ratio of 4:1 by NMR analysis; characteristic signals for 48:

NMR (CDCl₃) δ 3.50-3.90 (m, 1H, NCH), 4.17-4.50 (m, 1H, NCH), 5.23 (tt, J=9, 3 Hz, 1H, OCH). Continued elution gave 200 mg (13%) of 49 as a pale-yellow oil: IR (CHCl₃) 1780, 1675 cm⁻¹; NMR (CDCl₃) δ 0.77-2.50 (m, 15H, CH₃ and CH₂ manifold), 3.67-4.07 (m, 1H, NCH), 4.07-4.40 (m, 1H, NCH), 5.31(q, J=2 Hz, 1H, OCH); mass spectrum, m/e (relative intensity) 293(11), 251(9), 250(15), 180(7), 154(21), 136(100), 110(18), 108(15), 69 (67); exact mass calcd for C₁₃H₁₉NO₃F₃ m/e 293.1238, found m/e 293.1231.

The mixture of 48 and 50 was stirred with 4 mL of a 0.85 N sodium hydroxide solution in methanol at room temperature for 50 min. The resulting solution was poured into a mixture of 5 mL of water, and 5 mL of saturated sodium chloride solution, and extracted with two 20-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexane, 1:1, followed by ethyl
acetate and finally with ethyl acetate-methanol, 5:1) to yield 97.8 mg (10%) of an isomeric mixture of 50 as a pale yellow oil: IR (CHCl₃) 1670 cm⁻¹; NMR (CCl₄) δ 0.80-2.50 (m, 13H, CH₃ and CH₂ manifold), 3.37-3.77 (m, 1H, NCH), 3.77-4.40 (m, 1H, NCH), 5.53-5.80 (m, 2H, =CH-); GC-MS (2m x 1/8in column packed with 10% OV-101 on Chrom W; mesh 80/100; column temperature, 190°C; flow rate, 21 mL/min) for minor isomer, t_R=4.8 min, mass spectrum, m/z (relative intensity) 179(M⁺, 10), 136(100), 108(5); for major isomer, t_R=5.2 min, mass spectrum, m/z (relative intensity) 179(M⁺, 3), 136(100), 108(35), 80(10). Continued elution gave 465 mg (45%) of alcohol 17 as a pale-yellow oil.

Catalytic Hydrogenation of Alkenes 50. To 10.2 mg of 5% palladium on charcoal was added a solution of 46.3 mg of the mixture 50 in 2 mL of absolute ethanol. The resulting mixture was hydrogenated under an initial hydrogen pressure of 60 psi for 2 h, diluted with dichloromethane followed by the addition of magnesium sulfate. The resulting mixture was filtered through Celite and the filtrate was concentrated in vacuo to give 43.3 mg of a pale-yellow oil. The oil was chromatographed over 4 g of silica gel (eluted with ethyl acetate) to give 40.3 mg (86%) of a pale-yellow oil which was identical in all respects with 19 prepared from xanthate 18.

Cyclization of Carbinol Lactam 12 in Formic Acid and Dichloromethane. To 113 mg (0.60 mmol) of carbinol lactam
12 was added in a single portion a mixture of 0.65 mL of formic acid and 1.9 mL of dichloromethane. The resulting solution was stirred at room temperature for 10 h and partitioned between 50 mL of dichloromethane and 50 mL of saturated sodium bicarbonate aqueous solution. The aqueous phase was extracted with 50 mL of dichloromethane, and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 121 mg of a yellow oil. The oil was chromatographed over 7 g of silica gel (eluted with ethyl acetate-hexane, 35:65) to yield 30 mg (60%) of formate 13 as a pale-yellow oil. Trace amounts of formate 16 and alkenes 50 were detected by TLC in the crude reaction mixture (silica gel; ethyl acetate) but not isolated by column chromatography.

Trapping of Acyliminium Ions with Triethylsilane in Formic Acid and Dichloromethane. To 143 mg (0.749 mmol) of carbinol lactam 12 was added in a single portion a solution of 0.8 mL of formic acid and 0.5 mL of triethylsilane in 1.9 mL of dichloromethane. The resulting solution was stirred at room temperature for 12 h, diluted with 50 mL of dichloromethane and washed with 50 mL of saturated sodium bicarbonate solution. The aqueous phase was extracted with 50 mL of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give a yellow oil (173 mg). The oil was chromatographed over 10 g of silica gel (eluted with ethyl
acetate-hexane, 35:65, followed by ethyl acetate-hexane, 7:3) to yield 57.4 mg (42%) of a mixture of 52 and 53 (3:5, respectively) as a pale-yellow liquid identified by comparison with authentic samples of each. Further elution gave 50.0 mg (30%) of formate 13 as a pale-yellow oil.

**Trapping of Acyliminium Ions with Triethylsilane in Trifluoroacetic Acid and Dichloromethane.** To 343 mg (1.74 mmol) of carbinolamide 12 in 0.5 mL of dichloromethane was added a mixture of trifluoroacetic acid-triethylsilane-dichloromethane, 1 mL:1 mL:0.5 mL, in a single portion. An exothermic reaction took place. The reaction mixture was allowed to stand at room temperature for 15 min, diluted with 20 mL of dichloromethane, and washed with two 30-mL portions of water. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to give a yellow liquid which was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to yield 230 mg (73%) of a mixture of 52 and 53 in a ratio of 3:5 by ¹H NMR integration.

**N-(1-Hepten-4-yl)pyrrolidin-2-one (52).** To a solution of 495 mg (2.51 mmol) of carbinolamide 12 in 2.0 mL of methanol was added 198 mg (5.21 mmol) of sodium.
cyanoborohydride and a few crystals of bromocresol green. To the resulting blue solution was added via syringe a 0.68 N solution of hydrogen chloride in methanol. The addition was controlled such that the pH of the solution was at the endpoint of bromocresol green. When the reaction maintained a yellow color, the addition of HCl/MeOH was stopped and the mixture was stirred at room temperature for 60 min. A total of 3.5 mL of the hydrogen chloride solution was added. During the period of stirring, an occasional drop of HCl/MeOH had to be added to maintain the yellow color. The mixture was diluted with 20 mL of dichloromethane, washed with 10 mL of water, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to give 363 mg (84%) of 52 as a colorless oil: IR (CCl₄) 1685 cm⁻¹; NMR (CDCl₃) δ 0.77-1.10 (br t, J=6 Hz, 3H, CH₃), 1.10-2.60 (m, 10H, CH₂ manifold), 3.23 (t, J=7 Hz, 2H, NCH₂), 4.20 (qu, J=7 Hz, 1H, NCH), 4.90-5.15 (m, 2H, =CH₂), 5.72(tdd, J=17, 9, 7 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 181 (1.5), 140(63), 121(10), 119(13), 98(20), 98(37), 96(100), 84(90); exact mass calcd for C₁₁H₁₉NO m/e 181.1466, found m/e 181.1462.

1-Butyl-5-allyl-2-pyrrolidinone (53). To a solution of 203 mg (1.10 mmol) of lactam ether 54 in 1.5 mL of dry dichloromethane under argon was added 0.133mL (1.21
(0.040 mL, 0.36 mmol) was added. The resulting mixture was stirred for another 7 h followed by the addition of 0.5 mL of a 3 N hydrogen chloride aqueous solution. The reaction mixture was stirred for 20 min and partitioned between 5 mL of water and 15 mL of dichloromethane. The aqueous phase was extracted with 10 mL of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford 169 mg of a yellow oil. The oil was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to yield 156 mg (75%) of 53 as a yellow oil: IR (CHCl₃) 1665 cm⁻¹; NMR (CDCl₃) δ 0.77-1.10 (br t, J=6 Hz, 3H, CH₃), 1.10-2.60 (m, 10H, CH₂ manifold), 2.90 (br td, J=12, 6 Hz, 1H, NCH), 3.45-3.83 (m, 2H, NCH₂), 4.98-5.30 (m, 2H, =CH₂), 5.72 (tdd, J=17, 9, 7 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 181(M⁺, 0.6), 169(4),
rel-(2R,6R)-2-Propyl-1-azabicyclononan-4,9-dione (51).

To a solution of 530 mg (2.42 mmol) of formate 13 in 2 mL of methanol at room temperature was added 3 N sodium hydroxide aqueous solution until TLC analysis (ethyl acetate, silica gel) indicated that no formate remained.

The mixture was diluted with 15 mL of dichloromethane and washed with 15 mL of water. The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. To this crude hydroxylactam in 10 mL of acetone cooled in an ice bath was added 1.2 mL (3.19 mmol) of the Jones reagent over a 2-3 min period. The resulting mixture was stirred at room temperature for 10 min, diluted with 30 mL of dichloromethane and washed with two 30-mL portions of water. The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residual yellow oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate) to give 251 mg (53%) of 51 as a colorless oil: IR (CHCl$_3$) 1710, 1675 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.80-1.10 (br t, J=6 Hz, 3H, CH$_3$), 1.10-3.00 (m, 12H, CH$_2$ manifold), 3.77-4.17 (m, 1H, NCH), 4.63 (dq, J=7, 2 Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 195(23), 152(69), 110(100); exact mass
calcd for C_{11}H_{17}NO_{2} m/e 195.1259, found m/e 195.1253.

Conversion of Ketolactam 51 to Trifluoroacetate 48 and 49. To a solution of 230 mg (1.19 mmol) of 51 in 5 mL of ethanol was added 40 mg (1.05 mmol) of sodium borohydride in a single portion at room temperature with stirring. TLC analysis (ethyl acetate, silica gel) after 5 min indicated that reduction was complete. A solution of 2.15 N hydrogen chloride solution in ethanol was added until the mixture was acidic to pH paper. The solution was diluted with dichloromethane and washed with water. The organic phase was dried (Na_{2}SO_{4}) and concentrated in vacuo to give 210 mg of a pale-yellow oil. This material was dissolved in 3 mL of dichloromethane and to it was added sequentially 10 drops of triethylamine and 10 drops of trifluoroacetic anhydride. An exothermic reaction took place. The mixture was diluted with dichloromethane after stirring at room temperature for 5 min, washed with water, dried (Na_{2}SO_{4}) and concentrated in vacuo. The crude product was chromatographed over 15 g of silica gel (eluted with ethyl acetate-hexane with increasing increment of ethyl acetate) to give 47 mg (13%) of the less polar 48 as a colorless oil. Further elution gave 122 mg (35%) of 49 as a colorless oil.

Conversion of Formate 16 to Trifluoroacetate 49. To 45.2 mg (0.201 mmol) of formate 16 was added in a single portion 0.5 mL of a 0.95 N solution of sodium hydroxide
in aqueous methanol (H₂O-MeOH, 1:5). The resulting mixture was stirred at room temperature for 50 min and partitioned between 20 mL of dichloromethane and 15 mL of water. The aqueous phase was extracted with two 15-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford 38.5 mg of a yellow oil. The oil was dissolved in 1 mL of dry dichloromethane and cooled in an ice-water bath under argon, to it was added sequentially 4 drops of triethylamine and 4 drops of trifluoroacetic anhydride. The resulting solution was stirred cold for 5 min and at room temperature for 20 min. The reaction mixture was then partitioned between 10 mL of water and 20 mL of dichloromethane. The aqueous phase was extracted with 10 mL of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 55.9 mg of a yellow oil. The oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexane, 9:2) to yield 34.2 mg (58%) of trifluoroacetate 49 as a pale-yellow oil.
PART I - REFERENCES


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9. For the first total synthesis of gephyrotoxin, see: 31.

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15. See: ref 5 and references cited therein.


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38. For a detailed description of these comparisons, see: ref 36.


40. The relative concentrations of 12 and acid (TFA or HCOOH) and the molar concentration of 12 were held constant for all experiments.

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42. To our knowledge this represents a new and general method for reducing carbinolamides to amides and lactams.

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44. After the disclosure of our results in this respect (ref 45) several accounts employing this method have been reported: (a) Kraus, G. A.; Neuenschwander, K. J. Chem. Soc. Chem. Commun. 1982, 134; (b) Aratani, M.; Sawada, K.; Hashimoto, M. Tetrahedron Lett. 1982, 3925. For an intramolecular version, see: (c) Hiemstra, H.; Speckamp, W. N. Tetrahedron Lett. 1983,

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49. We do not know the relative rates of reduction of 55 and 56.

50. Previous work (ref 5) suggests that ion 56 should be born as the E geometrical isomer. Isomerization of E-56 to Z-56 via an addition-elimination process should be possible under current reaction conditions. These factors make it difficult to enter the 55 + 56 manifold from the side of 56 in a meaningful way.

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58. The author wishes to thank Professor David J. Hart for supplying this compound.
PART II - INTRODUCTION

OBJECTIVES The purpose of this research was to develop a better understanding of how free radical carbon-carbon bond forming reactions can be used to construct highly functionalized molecules, specifically, in the area of alkaloid synthesis. Our efforts concentrated on the issues of:

(i) site selective entries to α-acylamino radicals

\[ \overset{\circ}{C}-N-C-X \rightarrow \overset{\circ}{C}-N-C \cdot \]

(ii) the feasibility of constructing pyrrolizidines via intramolecular cyclizations of these radicals and

(iii) the effect of substituents on the regiochemical and stereochemical course of these cyclizations.

BACKGROUND AND STRATEGY Carbon-carbon bond forming reactions can be classified as either polar or non-polar coupling processes. In polar processes, nucleophiles and electrophiles combine to make a carbon-carbon bond. The most widely used carbon-carbon bond forming reactions fall into this category.\(^1\) Non-polar processes can be divided into two major categories. These are pericyclic reactions (electrocyclizations, sigmatropic
rearrangements, certain cycloadditions)\textsuperscript{2} and radical reactions.\textsuperscript{3-5} Pericyclic reactions have been well developed\textsuperscript{2} and are now appreciated as potent tools for the construction of highly functionalized organic compounds. Although carbon-carbon bond forming free radical chain addition reactions are well known,\textsuperscript{3-5} such reactions have long remained in the domain of physical organic chemistry,\textsuperscript{5,6} and polymer science.\textsuperscript{7}

Despite the efforts led by Julia's group,\textsuperscript{8} synthetic organic chemists have made only limited use of these reactions in the synthesis of complex molecules\textsuperscript{9} compared with the attention received by the polar coupling processes, pericyclic reactions, and photochemical reactions. Several factors appear to be responsible for this apparent neglect:\textsuperscript{10}

(i) It is frequently difficult to carry out stoichiometric bimolecular radical addition reactions. The rate of telomerization of the unsaturated component of the reaction is often greater than the rate of chain transfer.

(ii) Rates of radical disproportionation and other hydrogen atom abstraction reactions are frequently competitive with rates of addition.

(iii) Little is known about the stereochemical course of addition reactions, particularly in a complex setting.\textsuperscript{11}
In spite of the problems outlined above, carbon-carbon bond forming radical reactions permit the construction of certain bonds which cannot be made easily via polar coupling reactions. Several such reactions are outlined below (Eq. 1-4). These reactions illustrate several important points. In equations 1 and 2, bonds are formed between carbon radicals and carbon fragments which are

\[ \begin{align*}
\text{OMe} & \quad \text{HgCl} & \quad \text{NaBH}_4 & \quad \text{OMe} \\
& & & \quad \text{Me}^+ \quad \text{CO}_2\text{Me} \\
\end{align*} \]

\[ \text{OMe} \quad \text{CO}_2\text{Me} \]

\[ \text{Ph}_2\text{CO}, \text{h} \quad \overset{\text{O}}{\text{O}} \quad \overset{\text{CH}_3}{\text{O}} \]

\[ \text{Cl} \quad \text{SiMe}_3 \quad \overset{n\text{Bu}_2\text{SnH}}{\text{SiMe}_3} \quad \text{Me}_3\text{Si} \]

\[ \text{Br} \quad \overset{n\text{Bu}_2\text{SnH}}{\text{CH}_3} \quad \text{C}_7\text{H}_{16} \]

\[ (1)^{12} \quad (2)^{13} \quad (3)^{9b} \quad (4)^{14,15} \]
regarded as classical electrophiles. Construction of these same bonds via polar coupling reactions would not be likely to succeed because the required nucleophilic components would autodestruct via $\alpha$- or $\beta$-elimination processes. Thus, radical addition reactions can simulate polar coupling processes between typical electrophiles and inaccessible nucleophiles. In equations 3 and 4 bonds are formed between carbon radicals and carbon fragment which have ambident (Eq. 3) or nucleophilic (Eq. 4) electronic properties. Thus, radicals can form bonds to electron rich or electron deficient carbon atoms, a property which classical nucleophiles lack. In addition, equations 3 and 4 illustrate that intramolecularity effectively combats several of the rate problems noted earlier. Finally, equation 3 illustrates that radical addition reactions frequently allow the construction of hindered carbon-carbon bonds. Clearly, radical reactions can be used to form certain carbon-carbon bonds in a unique manner. Stimulated by these encouraging aspects, it was felt that efforts to systematically explore synthetic aspects of radical chemistry would be worthwhile.

This research focused on using radicals in the area of alkaloid synthesis and relevant work of others in this area will now be discussed.

Construction of carbon-carbon bonds adjacent to nitrogen plays a central role in alkaloid chemistry
Both biosynthetic and laboratory pathways to these natural products rely heavily on variants of the Mannich reaction (path A) for construction of these bonds. Recently, methods which couple $\alpha$-aminocarbanion equivalents with electrophiles have been developed to accomplish the same task (path B). The use of $\alpha$-amino and $\alpha$-acylamino radicals for assembling these bonds, however, has been largely ignored (path C).

\begin{center}
\textbf{Scheme I}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {$\text{Path A}$};
  \node (B) at (2,0) {$\text{Path B}$};
  \node (C) at (1,-2) {$\text{Path C}$};
  \draw[->] (A) -- (B);
  \draw[->] (B) -- (C);
  \draw[->] (C) -- (A);
\end{tikzpicture}
\end{center}

$\alpha$-Amino radicals have been generated by treating amines with $t$-butoxyl radicals, $t$-butylperoxyl radicals, and triplet benzophenone, and intermolecular addition reactions of several of these radicals have been examined (Eq. 5). These reactions were plagued by the kinetic difficulties noted previously and did not generally give high yields of 1:1 adducts. There has been one discouraging report of an attempt to effect an
intramolecular α-amino radical addition reaction (Eq. 6). It appears that in addition to kinetic difficulties, a lack of site selective radical generation may be resposible for the failure of these reactions. α-Acyl-

\[
\begin{align*}
\text{N} & \quad \text{CH}_3 \\
\text{H} & \quad (\text{tBuO})_2
\end{align*}
\]

(5)\textsuperscript{18a}

\[
\begin{align*}
\text{N} & \quad \text{R} \\
\text{H} & \quad \text{R}
\end{align*}
\]

(6)\textsuperscript{18b,c}

amino radicals have also been generated by treating amides with t-butoxyl radicals\textsuperscript{22} and triplet carbonyl compounds.\textsuperscript{23} Once again addition reactions of these radicals suffer from a preparative standpoint due to kinetic and regiochemical problems. We felt that developing site selective methods of generating α-amino or α-acylamino radicals would solve some of the problems encountered in the formentioned reactions. Experiments which address this issue and the development of α-acylamino radicals as intermediates in alkaloid synthesis will now be discussed.\textsuperscript{24,25}
Our initial success with site specific generation of \( \alpha \)-acylamino radicals is outlined in Scheme II. Thus, imide \( \text{1}^{27} \) was reduced with sodium borohydride followed by an acidic work up\( \text{28} \) to give alkoxy lactam \( \text{3} \). The crude lactam was treated with an excess of thiophenol containing 0.04 equivalent of \( \text{p} \)-toluenesulfonic acid monohydrate.

**Scheme II**

\[
\begin{align*}
\text{1} \xrightarrow{1) \text{NaBH}_4} & \text{2} \quad & \text{3} \quad & \text{4} \quad & \text{5} \\
\text{X=OH} \quad & \text{X=OEt} \quad & \text{X=SPh} \\
\text{1)} & \text{11} \\
\text{9} \quad & \text{10} \\
\end{align*}
\]
(25 °C, 10 min) to afford thiophenoxylactam 4 in an 54% yield from 1. Eventually, it was found to be most convenient to follow the reduction with a basic work-up to isolate crude hydroxylactam 2 followed by treatment with thiophenol. It should be noted that when excess thiophenol was used, long reaction times led to the addition of thiophenol to the olefin, possibly via a free radical pathway. This complication became serious when the olefin was more highly substituted, and could be avoided by using only one equivalent of thiophenol. Not only did the latter procedure avoid the problem of thiophenol addition to double bonds, but it also eliminated the nuisance of separating the product from large quantities of unreacted thiophenol.

Slow addition of a solution of tri-n-butyltin hydride (1.4 equiv.) and AIBN (0.04 equiv.) in benzene to a benzene solution of 4 heated at reflux gave an 94% yield of lactams 6, 7, 8 and 9 in a 12:45:4:23 ratio, presumably via the intermediacy of α-acylamino radical 5. The possibility that indolizidinone 2 came from an ionic cyclization followed by tri-n-butyltin hydride reduction of an intermediate sulfide was tested. Heating thiophenoxylactam 4 with one equivalent of tetra-n-butyltin in benzene at reflux for 7 h resulted in 88% recovery of starting lactam. In addition, 4 was also stable to sodium cyanoborohydride (pH 4, MeOH, 4 h) and was reduced
to 6 only slowly by TFA-triethylsilane ($t_{1/2} = 35$ min). Thus, ionization of 4 under the cyclization conditions employed here is unlikely.

The structure of 6, separable from 7, 8, and 9 by column chromatography, was proven by an alternative synthesis via reduction of 3 with either TFA-triethylsilane$^{33}$ or sodium cyanoborohydride (pH 4).$^{34}$ To aid our analysis of the unseparable mixture of 7, 8 and 9, we prepared pure 9 via a different route (Scheme III).

Treatment of alkoxy lactam 3 with formic acid followed by hydrolysis of the resulting crude mixture of formates 13 and 14 (85:15 by $^1$H NMR integration) gave a 73% yield of a mixture of carbinollactams 15 and 16. Preparation of a

\[
\text{Scheme III}
\]

\[
\begin{array}{ccc}
3 & \xrightarrow{a-c} & 9 \\
\end{array}
\]

13 $R_1 = H$, $R_2 = OCHO$
14 $R_1 = OCHO$, $R_2 = H$
15 $R_1 = H$, $R_2 = OH$
16 $R_1 = OH$, $R_2 = H$
17 $R_1 = H$, $R_2 = OCSCH$_3$
18 $R_1 = OCSCH$_3$, $R_2 = H$

(a) $\text{HCOOH}$ (b) $\text{NaOH, MeOH-H}_2\text{O}$ (c) $\text{NaH, CS}_2$, $\text{CH}_3\text{I}$, THF (d) $\text{nBu}_3\text{SnH}$, toluene
mixture of xanthates 17 and 18 (90%) and subsequent reduction according to the method of Barton gave pure 9 (78%). The presence of 9 in the cyclization mixture was established by comparison of their high field 1H NMR spectrum. In order to identify the structure of 7, we first prepared an authentic sample of (†)-heliotridane (11)·picrate via a known procedure. To our surprise, borane reduction of the cyclization mixture (7-9) only led to the isolation of pure (±)-6-coniceine (10). This material and its picrate were identical to samples prepared by borane reduction of pure 9. This unexpected reduction result led to the assumption that 11 was more basic than 10 and formed a strong tetracoordinate complex with boron species. The desired reduction of 7-9 to 10-12 could be accomplished by using lithium aluminum hydride. Indeed, when the resulting amine mixture (10, 11 and 12) was treated with one equivalent of picric acid with respect to 11, pure (±)-11·picrate, identical with an authentic sample, was obtained. Furthermore, when the mother liquor was treated with one equivalent of picric acid with respect to 10, (±)-10·picrate was isolated. Although (±)-pseudoheliotridane (12) was not isolated, the presence of small amounts of 8 in the cyclization mixture was apparent from NMR analysis of mixtures 7-9 and partially purified samples of 8 obtained by preparative gas chromatography.
It should be noted that reduction of the mixture of xanthates 17 and 18 with tri-n-butyltin hydride\(^{40}\) gave 9 as the only product (78%). This indicates that radical 19 does not revert back to ɑ-acylamino radical 5. In order to obtain more evidence about the nature of this cyclization\(^ {8d} \) (5 → 7-9) we prepared xanthate 22 from acetate 20 (vide infra). Hydrolysis of 20 with sodium hydroxide in aqueous methanol gave alcohol 21 (65%) which was converted to xanthate 22 (79%) by Barton's procedure.\(^ {35} \) Tri-n-butyltin hydride reduction of 22 under the conditions employed for cyclization of 4 gave only 7 in a 61% yield. Apparently radical 23 does not fragment to give radical 5. Therefore we conclude that the ratio of 7-9 obtained in the cyclization reflects the kinetic partitioning of radical 5.

Several aspects of the results presented in Scheme II are noteworthy. The combined yield of monomeric products obtained from ɑ-acylamino radical 5 is very high. We
attributed this in part to the site-selective method of radical generation employed herein. In addition, radical 5 gives a 2:1 ratio of exo and endo cyclization products, respectively, contrary to the considerably larger exo:endoratios (50:1) usually observed in simple hexenyl radical systems.\textsuperscript{41,42} It is possible that geometric constraints imposed by the $sp^2$ character at nitrogen are responsible for the similar rates of endo and exo cyclization. Finally, cyclization of 5 to pyrrolizidinones 7 and 8 proceeds with high diastereoselectivity which parallels results obtained in related carbocyclic systems.\textsuperscript{43}

To examine the possibility of generating $\alpha$-acylamino radicals from substrates similar to that of type 4, we prepared lactams 24–27 as follows. Sodium borohydride reduction of imide 1 with a basic work-up\textsuperscript{29} gave crude hydroxylactam 2. Treatment of 2 with excess thiolacetic acid afforded thiolacetoxy lactam 24 in a 90\% yield. Hydrolysis of 24 (NaOH, MeOH–H$_2$O) gave the unstable crude lactam thiol 25 (91\%). Attempted purification of 25 by

\[
\begin{align*}
24 & \quad X=SC\text{CH}_3 \\
25 & \quad X=\text{SH} \\
26 & \quad X=\text{SCH}_3 \\
27 & \quad X=S\text{NO}_2
\end{align*}
\]
column chromatography led to decomposition and this crude material was used directly in our cyclization study. Hydrolysis of 24 followed by the addition of 2,4-dinitrofluorobenzene gave 2,4-dinitrothiophenoxylactam 26 (47%). When methyl iodide was used instead of 2,4-dinitrofluorobenzene, thiomethoxylactam 27 was isolated in a 90% yield.

Under the same conditions used for the cyclization of 4, no cyclization products could be detected from 24, 25 and 26 except for decomposition of the starting lactams. Thiomethoxylactam 27 reacted only slowly (27 h compared with 8 h for cyclization of 4) with tri-n-butyltin hydride to give a mixture of 6-9 (61%) in addition to 28% of unreacted 27. The apparent discrepancy between the reactivity of 4 towards tri-n-butyltin hydride and that of 24-27 is not fully understood.

In an attempt to delineate the effect of olefin substitution on the regiochemical course of this radical cyclization, thiophenoxylactam 28a-d were prepared from the appropriate imides by using the reaction sequence outlined in Scheme II in 83%, 88%, 89% and 93% yields, respectively. The results of these cyclization studies are shown in Table 1. Entry 1 shows that internal olefin substitution leads to preferential endo cyclization with modest stereoselectivity. Entry 2 shows that terminal E-alkyl substitution gives the same endo:exo cyclization ratio as observed for the parent radical 5. On the other
Table 1. Treatment of α-Thiophenoxylactams with Tri-n-butylin Hydride.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>thiophenoxylactam</th>
<th>reaction time (h)</th>
<th>products (% yield; ratio)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28a</td>
<td>5.3</td>
<td>29a (12), 34+35+36 (70; 7:73:20)\textsuperscript{c,d,e}</td>
</tr>
<tr>
<td>2</td>
<td>28b</td>
<td>5.5</td>
<td>29b (13), 30+31+37 (69; 7:61:32)\textsuperscript{f}</td>
</tr>
<tr>
<td>3</td>
<td>28c</td>
<td>6.7</td>
<td>29c (25), 30+31+37 (56; 12:90:8)\textsuperscript{f}</td>
</tr>
<tr>
<td>4</td>
<td>28d</td>
<td>6.7</td>
<td>29d (12), 32+33 (75; 20:80)\textsuperscript{g}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} R\textsubscript{1}=R\textsubscript{2}=H, R\textsubscript{3}=Me  
\textsuperscript{b} R\textsubscript{1}=Me, R\textsubscript{2}=R\textsubscript{3}=H  
\textsuperscript{c} R\textsubscript{1}=R\textsubscript{3}=H, R\textsubscript{2}=Me  
\textsuperscript{d} R\textsubscript{1}=R\textsubscript{2}=Me, R\textsubscript{3}=H  
\textsuperscript{e} R\textsubscript{1}=Eth, R\textsubscript{2}=H  
\textsuperscript{f} R\textsubscript{1}=H, R\textsubscript{2}=Et  
\textsuperscript{g} R\textsubscript{1}=iPr, R\textsubscript{2}=H  
\textsuperscript{h} R\textsubscript{1}=H, R\textsubscript{2}=iPr  
\textsuperscript{i} R\textsubscript{1}=R\textsubscript{2}=Me
| Reduction products were separated from cyclization products by column chromatography. The ratios of cyclization products were based on VPC and 300 MHz $^1$H NMR data collected on purified mixtures of cyclization products.  
| The structure of 34 is tentative and relied only on its 300 MHz $^1$H NMR analysis. A pure sample of 35 was obtained by preparative VPC. The stereochemistry of the major and minor indolizidinones was not determined. The ratio may be the reverse of that shown here. A pure sample of 37 was obtained by VPC and by independent synthesis. Lactams 30 and 31 were analyzed as a pure mixture of stereoisomers. The stereochemical assignments for 30 and 31 are tentative and based in part on analogy with results obtained in the cyclizations of 4 and 53. Similarities between $^1$H NMR spectra of 30 and 31 and those of 9 and 7, respectively, support this assignment. Pure samples of 29d, 32 and 33 were obtained by a combination of column chromatography and preparative VPC. The stereochemical assignments for 32 and 33 were determined as for 30 and 31.  

| Hand, terminal Z-alkyl substitution (entry 3) leads to almost exclusive formation of exo cyclization products. Once again, good stereoselectivity was observed in the exo cyclizations ($^{28b}$, c $\rightarrow$ 30, 31; see Table 1, footnote f). In addition, high stereoselectivity was observed in the endo cyclization process ($^{28b}$, c $\rightarrow$ 37).
A plausible explanation for the observed regioselectivity of the cyclization of 28b and 28c is shown in Scheme IV. Assuming a chair form six-membered ring transition state for endo cyclization, the methyl substituent in 28c would occupy a pseudoaxial position. The resulting unfavorable 1,3-diaxial interactions would decrease the rate of endo cyclization in 28c and lead predominately to exo cyclization. This is revealed in the inability to isolate 38 from the cyclization products of 28c. The origin of 37 in the cyclization of 28c is presumably derived from the contamination of a small amount of 28b in 28c. Therefore the exo-endo selectivity in the cyclization of 28c may be greater than the 92:8 ratio reported in Table 1. This is further supported by the

![Scheme IV](image)
exclusive exo cyclization found in the case of 28d (entry 4). The stereoselectivity in the exo products dropped further compared with that of 28b and c due to the combined effects of two terminal methyl substituents. The reasons for this drop may be a combination of steric factors, decreased secondary orbital interactions or less favored electrostatic interactions in a dipolar transition state.\(^4,5^2\) Furthermore, compared with the corresponding formic acid cyclization of carbinollactam 42 (Scheme V), prepared from imide 41 via sodium borohydride reduction,\(^2^8\) similar exo products 43 and 44 were obtained exclusively\(^5^3,5^4\) after hydrolysis in 34% and 48% yield respectively (based on imide 41). Apparently the \(\alpha\)-acyl-amino radical cyclization is more stereoselective. Whether 43 and 44 are kinetic or thermodynamic products is not completely clear. Therefore, the exact meaning of this difference is not certain.

**Scheme V**

![Scheme V](image_url)
We next examined briefly the effect of chain length on the α-acylamino radical cyclizations. Thus, thio-
phenoxy lactams 45 and 46 were prepared as before in 87% and 85% yield respectively, from the corresponding imides. Treatment of 45 with tri-n-butyltin hydride under the same conditions used with 4 gave only reduction product 47. This result is in accord with the reported behavior of 4-pentenyl radicals.41 When 46 was treated with tri-n-butyltin hydride, the reduction product 48 was obtained in 8% yield along with a mixture of 37, 38 and 49 (75%; 32:40:28, respectively). The stereochemical assignments for 37 and 38 were based on spectral data. The infrared spectra of 37 and 38 exhibited a normal lactam carbonyl at 1690 cm⁻¹. Based on the fact that indolizidinones of this type can not adopt a conformation in which the C(6)-C(7) bond is axially disposed on a chair piperidine without destroying amide resonance, the infrared data require that H(6) occupy an axial site on the rigid indolizidinone framework. Appropriate 300 MHz ¹H
NMR decoupling experiments revealed a large coupling \( (J=9.6\, \text{Hz}) \) between \( H(5) \) and \( H(6) \) in \( 37 \), and a small coupling \( (J=3.7\, \text{Hz}) \) between \( H(5) \) and \( H(6) \) in \( 38 \). These data indicate a trans diaxial relationship of \( H(5) \) and \( H(6) \) in \( 37 \), and a cis equatorial-axial relationship between \( H(5) \) and \( H(6) \) in \( 38 \). Of course, lactam \( 37 \) was identical to the material obtained from the cyclizations of \( 28b \) and \( 28c \). Here again a drop of exo/endo ratio (2.5:1) was observed compared with the 6:1 ratio of reported for the 6-heptenyl radical.\(^{41} \)

The aforementioned studies gave us considerable insight into what to expect from various \( \alpha \)-acylamino radical cyclization. With this background, we began to investigate cyclizations which had more direct bearing on projected alkaloid synthesis. Two of our earliest efforts are presented in Scheme VI. Thus treatment of thiophenoxy-lactam \( 50^{56} \) with tri-\( \text{n} \)-butyltin hydride gave exo cyclization product \( 51 \) (51\%)\(^{58} \) and endo cyclization product \( 52 \) (31\%), an intermediate in a synthesis of the Dendrobatid alkaloid gephyrotoxin.\(^{59} \) It is noteworthy that no reduction product was obtained and that both cyclizations proceed with high stereoselectivity at the radical center. We attribute these observations to pronounced conformational preferences expected for the intermediate radical.\(^{59,60} \)
Cyclization of lactam 53, prepared from tartaric acid, gave a separable mixture of lactams 54 (24%), 55 (25.5%), 56 (31%) and 57 (2.5%). The structure of 55 was proven by an independent synthesis as outlined in Scheme VII. Treatment of imide 58 with sodium borohydride with a basic work up gave carbinol-lactam 60 in a 76% yield. Cyclization of 60 in formic acid (RT, 18 h) followed by hydrolysis of the resulting product gave a separable mixture of lactams 54, 55, 56 and 57.

Scheme VI
diastereomeric formate mixture 61 (78%) gave carbinollactam 62 in 88% yield. Conversion of 62 to xanthate 63 (50%) was accomplished by the method of Barton. Reduction of 63 with tri-n-butyltin hydride afforded 55 (35%), identical in all respect with the material isolated from the free radical cyclization. The stereochemical assignment for 56 was based on NOE experiments performed at 300 MHz $^1$H NMR. Irradiation of the C(1) methyl group showed a 15% NOE at H(7) indicating a cis relationship. In addition, a 15% NOE at H(1) resulted from irradiation of H(8), indicating their cis relationship. Pyrrolizidine 56 contains C(1), C(7) and C(8) substitution, which is similar to that of the more complex pyrrolizidine alkaloids. Although this experiment (53 → 54-57) was promising in some respects, it was clear that more

**Scheme VII**

![Chemical Structure](attachment:image.png)

(a) NaBH$_4$, H$_2$O  (b) HCOOH  (c) NaOH, MeOH-H$_2$O  
(d) NaH, CS$_2$, CH$_2$I, THF  (e) nBu$_3$SnH, toluene
developmental studies were required before this free radical technology could be successfully applied to complex pyrrolizidine alkaloid synthesis. The rest of this chapter will be devoted to a discussion of experiments directed toward this end.

Before proceeding further with chemistry, a brief introduction to the pyrrolizidine alkaloids is in order. The pyrrolizidine alkaloids constitute a large group of compounds which are found in different

![Representative Pyrrolizidine Alkaloids](image)

**Figure 1.** Representative Pyrrolizidine Alkaloids
species of plants within a genus (Senecio, astors and ragworts), and related members of which are found in different genera (Heliotropium, Trachelanthes and Trichodesma) within different botanic families (Compositae, Boraginaceae, and Leguminosae). They are usually composed of two moieties: the pyrrolizidine alcohol and a carboxylic (usually hydroxy) acid, which are combined by an ester linkage. The pyrrolizidine moieties may appear as monohydric, dihydric, or trihydric alcohols. Some representative examples are shown in Figure 1.65

The uses of pyrrolizidine derivatives are many and varied. A wide range of pyrrolizidine-containing pharmaceuticals, including antiinflammatory drugs, have been prepared.65 Some quaternary pyrrolizidine salts are powerful parasiticides.65 A number of the naturally occurring alkaloids are heptotoxic and carcinogenic, but some derivatives have potentially useful physiological properties, including antiviral activities.65

The ultimate goal of our free radical entry to these alkaloids is the development of enantioselective routes to the dihydroxypyrrolizidine bases shown in Figure 1. The remainder of this chapter, however, will discuss the development of suitable technology within the context of syntheses of isoretronecanol (64) and supinidine (66).

We began by studying the cyclization of thiophenoxylactam 74. The preparation of 74 is outlined in Scheme
Thus, treatment of alkyne 75 with n-butyllithium followed by acetaldehyde gave alcohol 76 (78%). Reduction of 76 with lithium aluminum hydride in the presence of sodium methoxide resulted in the formation of trans allylic alcohol 77 (96%) which was a single compound by GLC. Subsequent protection of the alcohol with acetic anhydride (100%) and removal of the tetrahydropyranyl group afforded alcohol 79 in a 77% yield. Mitsunobu condensation of 79 with succinimide gave imide 80 (97%) which was reduced with sodium borohydride. The resulting crude alcohol was directly treated with thiophenol in the presence.

Scheme VIII

(a) nBuLi, CH₂CHO (b) LAH, NaOMe (c) Ac₂O, Py, 4-DMAP
(d) AcOH, THF, H₂O (e) Ph₃P, EtO₂CN=NCO₂Et, succinimide
(f) NaBH₄, H⁺ (g) PhSH, TSOH·H₂O
of catalytic amount of p-toluenesulfonic acid monohydrate to give thiophenoxy lactam 74 in an 87% yield.

To confirm that the olefin geometry was strictly trans we carried out a stereorandom synthesis of 77 as shown in Scheme IX. Thus, treatment of acetylene 75 with tri-n-butyltin hydride in the presence of catalytic amount of AIBN (1 mol%)\textsuperscript{51,70} gave the vinyltin compound 81 (75%). Generation of the corresponding vinyl lithium by treatment of 81 with n-butyl lithium followed by treatment with acetaldehyde gave 77 in an 89% yield. VPC analysis of this material revealed two peaks in a 1:3 ratio, presumably the cis and trans isomers,\textsuperscript{71,72} respectively. The major isomer had the same GC retention time as that of the compound prepared via the LAH reduction route.

Cyclization of 74 with tri-n-butyltin hydride (AIBN, PhH, reflux, 23 h, reverse addition) gave 95% of a mixture of 82, 83, 84 and 85 in a ratio of 5.5:4:9.5:81\textsuperscript{73,74} (Eq. 7). Noteworthy is the high exo:endo ratio obtained in this cyclization. Based on entry 2 in Table 1, we had
anticipated only modest regioselectivity. Whether the observed selectivity is due to simple steric effects or arises from stabilization of the cyclized radical by the adjacent α-acetoxy group is not known.

A synthesis of (±)-isoretronecanol (64) from 85 was completed as outlined in Scheme X. Thus, hydrolysis of acetate 85 gave alcohol 86 in an 83% yield. Swern

**Scheme X**

\[
\begin{align*}
85 & \xrightleftharpoons{\text{1) NaOH, MeOH-H}_2\text{O}}^{\text{2) DMSO, (COCl)}_2, \text{Et}_3\text{N}} 86 & \quad \text{X=H, OH} \\
87 & \quad \text{X=O} \\
80 & \xrightleftharpoons{\text{1) CF}_3\text{CO}_2\text{H}}^{\text{2) LiAlH}_4, \text{Et}_2\text{O}} \quad \text{64} & \quad \text{R=Ac, X=O} \\
64 & \quad \text{R=H, X=H, H}
\end{align*}
\]
oxidation\textsuperscript{76} of 86 gave ketone 87 (94%) which was treated with trifluoroperacetic acid\textsuperscript{77,78} to afford acetate 20 in a 56% yield. Final conversion of this material to (±)-isoretronecanol (64) was accomplished by lithium aluminum hydride reduction (86\%).\textsuperscript{79,80} Our synthetic 64 was identical to material prepared by Danishefsky\textsuperscript{79} by comparison.

\begin{align*}
\text{Scheme XI}
\end{align*}

\begin{align*}
\text{88} + \text{Ph}_3\text{PCHX} &\rightarrow \text{90} \\
\text{89} &\rightarrow \text{91} + \text{92} \\
\text{91} + \text{92} &\rightarrow \text{93} + \text{95} + \text{96} \\
\text{93} &\rightarrow \text{94} \\
\text{93} &\rightarrow \text{95} + \text{96}
\end{align*}

(a) NaBH\textsubscript{4}, H\textsuperscript{+} (b) PhSH, TsOH·H\textsubscript{2}O(cat) (c) nBu\textsubscript{3}SnH, AIBN(cat), PhH, reflux
with their 250 MHz $^1$H NMR spectrum. This synthesis of 64 demonstrated the viability of the $\alpha$-acylamino radical cyclization approach to pyrrolizidine alkaloids, and, most importantly, established our stereochemical assignment for 85.

We continued by studying cyclizations with $\alpha,\beta$-unsaturated esters and nitriles as terminating groups (Scheme XI). The required imides 90 (cis and trans mixtures) were prepared by Wittig condensation of aldehyde 88 with appropriate ylids (89a, 89b, 89c and 89d). All of the ylids were prepared by literature procedures with the exception of the unknown chiral ylid 89d which was prepared as follows. Treatment of alcohol 97, obtained from (+)-pulegone via a published procedure, with bromoacetic acid (DCC, 4-DMAP, Et$_2$O) gave bromoacetate 98 (98%) (Eq. 8) which was converted to 89d (Ph$_2$P, PhH; NaOH) in a 98% yield.

\[
\begin{align*}
\text{Ph} & \quad \text{DCC} \quad \text{4-DMAP} \\
\text{OH} & \quad \text{BrCH}_2\text{COOH} \\
97 & \quad \text{Et}_2\text{O} \quad \rightarrow \\
\text{Ph} & \quad \text{O} \quad \text{Br} \\
98 & 
\end{align*}
\]

Sodium borohydride reduction of 90a (t/c=7/3) followed by exchange reaction as described in Scheme II gave an 87% yield of a mixture of 91a and 92a. Thiophenoxy lactam
92a was not separable from 91a and presumably resulted from unexpected conjugate reduction of 90a. Cyclization of the above mixture (nBu$_3$SnH, AIBN, PhH, reverse addition) gave a 57% yield of 93a and 94a in a ratio of 1:8 in addition to 20% of 95a, resulting from reduction of 92a. It should be noted that no reduction product corresponding to 96 was isolated, and the cyclization gave exclusively exo products. The disturbing feature of this sequence was the aforementioned observation of conjugate reduction (90a → 92a). Two solutions to this problem were developed. A report that unsaturated ketones underwent exclusive 1,2-reduction upon treatment with NaBH$_4$-CeCl$_3$-MeOH prompted us to try these conditions with 90a. We found that these conditions rapidly effected the conversion of 90a to 91a without producing 92a. Ultimately it was found that the CeCl$_3$ was, in fact, unnecessary. Thus, reduction of 90a (NaBH$_4$, MeOH, 0°C) followed by exchange reaction (PhSH, TsOH·H$_2$O) gave 91a in an 81% yield. A second solution surfaced when we found that tert-butyl ester 90b could be reduced under Speckamp's conditions (EtOH-HCl) to give lactam 91b (91%) contaminated with only small amounts of 92b. The difference in behavior of 90a and 90b is presumably due to a steric effect of some sort. Cyclization of pure 91a gave the same 1:8 mixture of 93a and 94a (87%).
To prove our stereochemical assignment of 94a and establish another route to (±)-isoretronecanol (64) using radical cyclizations, we performed the transformations shown in Scheme XII. Hydrolysis of the mixture of 93a and 94a (NaOH, EtOH) followed by recrystallization of the crude acid resulted in the isolation of the major isomer 99 (70%). Treatment of acid 99 with thiophenol in the presence of DCC and catalytic amount of 4-DMAP gave thioester 100 in an 89% yield. Treatment of 100 with lithium dimethyl cuprate gave methyl ketone 87 in an 84% yield. This material was identical in all respects to that prepared from 85. Since 87 had been converted to (±)-isoretronecanol (64), our relay was formally complete.

Ester 91b was also converted to acid 99. Cyclization of 91b (mixture with 92b) under modified conditions (nBu₃SnH, AIBN, PhH, reflux, direct mixing), gave 86% of a mixture of 93b, 94b and 95b in a ratio of 9.5:85.5:6.

Scheme XII

\[
\begin{align*}
\text{EtO}₂\text{C-} & \xrightarrow{a,b} \text{X-} & \xrightarrow{c} \text{O}\text{C-} & \\
\text{94a} & \text{99 X-OH} & \text{87} & \\
\text{100 X-SPh} & \\
\text{(a) NaOH, EtOH} & \text{(b) DCC, 4-DMAP, PhSH, CH₂Cl₂} & \text{(c) Me₂CuLi, THF, -20 C}
\end{align*}
\]
Treatment of this mixture with trifluoroacetic acid followed by recrystallization gave pure lactam acid 99 in a 65% yield.

To test the possibility of asymmetric induction using this methodology, imide 90d was reduced,28 exchanged (87%) and cyclized to give 95% of a mixture of 93d, 94d and 95d in a ratio of 7.5:68: 9.5.95 Conversion of 94d to 99 was accomplished by hydrolysis of the above mixture (KOH, EtOH) followed by direct esterification (EtOH, PhH, H2SO4, 3Å molecular seives). The resulting ethyl ester 94a (52%) was hydrolyzed (NaOH, EtOH-H2O) and recrystallized to give 99 in a 52% yield. To our dismay, this acid exhibited no optical rotation. This lack of asymmetric induction is probably due to the remote nature of the chiral inducing group. Further experiments directed toward this goal were not pursued.

Intrigued by the fast radical cyclization rate of these unsaturated esters, we examined the effect of concentration on the product ratio using 91b as a model. The results are shown in Table 2. Entry 1 shows our original conditions which gave no reduction product 96b. It should be noted that even in the extreme case (entry 4) only 13% of 96b was present. The most practical procedure is shown in entry 5 where a combination of high concentration and reverse addition gave 99% of cyclization relative to 1% of reduction.
Similar to the above three examples, imide 90c was reduced with sodium borohydride under the Speckamp conditions \((\text{EtOH-HCl})^{28}\) to afford thiophenoxylactams 91c (45\%) and 92c (21\%) separable by column chromatography. As expected, cyclization of 82c \((\text{nBu}_3\text{SnH, AIBN, PhH, reflux, direct mixing})\) gave 85\% of a mixture of 93c and 94c in a 1:9 ratio.

We also studied the radical cyclization of highly functionalized thiophenoxylactam 106. The preparation of 106 is outlined in Scheme XIII. Thus, condensation of

Table 2. **Effect of Concentration on the Radical Cyclization of Thiophenoxylactam 91b**

<table>
<thead>
<tr>
<th>entry</th>
<th>final conc. of 91b (M)</th>
<th>yield(%)</th>
<th>product ratio ((93b+94b/96b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.048</td>
<td>81</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>0.46</td>
<td>79</td>
<td>97 : 3</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>85</td>
<td>96 : 4</td>
</tr>
<tr>
<td>4</td>
<td>neat</td>
<td>72</td>
<td>87 : 13</td>
</tr>
<tr>
<td>5</td>
<td>0.84^e</td>
<td>76</td>
<td>99 : 1</td>
</tr>
</tbody>
</table>

^A 97\% pure 91b contaminated by 3\% of 92b was used in this study. \(\text{nBu}_3\text{SnH (1.5 equiv.)}, \text{AIBN (4-12 mol\%) and 91b was mixed in benzene and heated at 80\°C for 30 min.}^\)\Purified by column chromatography. ^Determined by VPC. ^A solution of \(\text{nBu}_3\text{SnH (1.5 equiv.) and AIBN (6 mol\%)}\) in benzene was added over 50 min into a solution of 91b in benzene heated at 80\°C.
Seebach's reagent 101 with aldehyde 102 gave α-trimethylsilylvinylsulfide 103 in a 54% yield along with 42% of recovered 101 resulting from enolization of 102. Deprotection of 103 (MeOH, TsOH·H₂O) gave alcohol 104 in a 92% yield. Mitsunobu condensation of 104 with succinimide gave imide 105 (93%) which was reduced (NaBH₄, MeOH, 0°C) followed by the exchange reaction (PhSH, TsOH·H₂O) to afford 106 in an 89% yield as a 1:1 mixture of E and Z isomers.

Scheme XIII

PhSCH(SiMe₃)₂ + PhSCH(SiMe₃)(SPh)

101 102 103 X=THP

104 X=H

105 X=0

106 X=H, SPh

107 X=H₂

(a) nBuLi, THF (b) MeOH, TsOH·H₂O (c) Succinimide, Ph₃P, EtO₂CN=NCO₂Et (d) NaBH₄, MeOH (e) PhSH, TsOH·H₂O (f) nBu₂SnH, AIBN, PhH
Cyclization of 106 (nBu₂SnH, AIBN, PhH, reflux, direct mixing) gave 87% of a mixture of 108, 109, 110 and 107 in a ratio of 17:68:11.5:3.5. Lactams 108, 110 and 107 were analyzed as greater than 90% pure samples obtained by a combination of column chromatography and recrystallization. Lactam 109 was obtained as a separable diastereomeric mixture (1:1) and each isomer was analyzed in its pure form after recrystallization. The stereochemical assignment of lactam 110 is uncertain. We presume that 110 is merely an overreduction product derived from 108 (109). Similar to the cyclization of 28d, an endo/exo ratio (109:108) of 4:1 was obtained. It should be noted that the reaction rate of 106 with nBu₂SnH is very slow. This was reflected in the long reaction time (24.5 h) and the isolation of 8% of unreacted 106. Despite the long reaction time necessary for cyclization, only a small amount of reduction product 107 was isolated. This result suggests that in this case the rate of radical generation is diminished for some unknown reason and cyclization is much faster than reduction due to stabilization of the cyclized radical intermediate by the two α substituents.

Although various attempts to convert 109 to (i)-iso-retronecanol (64) were disappointing, the cyclization of 106 demonstrates the ability of this reaction sequence to accommodate the presence of vinyl silanes and vinyl
The aforementioned radical cyclizations all involve the addition of a free radical onto an $sp^2$-hybridized carbon. The possibility of approaching pyrrolizidines by way of radical addition to an $sp$-hybridized carbon was also examined.

We began our studies in this direction by examining the cyclization of thiophenoxylactam 111. This material was prepared from the corresponding imide via the route described in Scheme II in an overall yield of 87%. Under our standard cyclization conditions, reduction product 112 and endo cyclization product 113 were obtained in 66% and 20% yields, respectively (Scheme XIV).

Scheme XIV
The structure of 113 was established by its conversion to a separable mixture of indolizidinones 37 and 38, obtained previously from cyclization of 46. It is noteworthy that no products derived from exo cyclization were detected. Although only a few examples of 5-hexynyl radicals have been reported, in all cases only exo cyclization products were obtained.4,5,103

We next turned our attention to thiophenoxy lactam 115b which was prepared from imide 114b according to the methods described in Scheme II. The required imide 114b (90%) was prepared from succinimide and 3,4-pentadien-1-ol104 by the method of Mitsunobu.69,105 It should be noted that a small amount of 118b resulting from thiophenol addition to the allene moiety was detected during the thiol exchange reaction. Attempted cyclization of 115b gave
products arising predominately from tri-n-butyltin radical addition to the allenyl group. With the hope that the rate of reduction of a phenylselenyl group by tri-n-butyltin hydride\textsuperscript{32} might compete favorably with the serious side reaction mentioned above, we prepared 116b from 114b in a 90\% yield via methods described in Scheme II replacing thiophenol with selenophenol.\textsuperscript{106} Indeed, when 116b was treated with tri-n-butyltin hydride (AIBN, PhH, reverse addition, 8.5 h) cyclization product 113 was obtained in a 60\% yield along with 26\% of reduction product 117b. Under similar cyclization conditions (14 h) selenophenoxylactam 116a, prepared in 82\% yield from 114a,\textsuperscript{107} gave only cyclization products 121 and 122 in 50\% and 14\% yields, respectively. In addition, 5\% of 120a was isolated. This material was derived from 119a which was a side product in the selenol exchange reaction as mentioned above.

In the above two examples, the $\alpha$-N-acylamino radicals added specifically to the central carbon of the allene in accord with the limited literature data available.\textsuperscript{4,109} In the case of 116a, previous results on the attempted cyclization of 45 suggest that radical 123 gives 125 instead of 124 (Scheme XV). It is interesting to note that the initial adduct 125 would require the partially filled $\pi$-orbital to be orthogonal to the $\pi$-bond. Hydrogen atom abstraction from this intermediate would give 121. Simple bond rotation in 125 would lead to allylic radical
Hydrogen atom abstraction from this intermediate would give 121 and 122. Thus, the exact meaning of the ratio of 121:122 is not certain.

In summary, methods for site specific generation of α-acylamino radicals have been developed. Extensive studies on substituent effects indicate that by controlling olefinic substitution patterns, it is possible to guide the regiochemical course of α-acylamino radical cyclization toward indolizidinone or pyrrolizidinone formation. In several cases, conversions of the cyclized products to pyrrolizidine alkaloids were accomplished. This work marks our initial effort in this area. Although further experiments will be necessary to pinpoint the mechanistic details of the reactions involved, we feel that the stage is set to apply α-acylamino radical cyclizations to the synthesis of certain alkaloids.

Scheme XV
PART II - EXPERIMENTAL

**GENERAL** All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are boiling points. $^1$H nuclear magnetic resonance spectra were recorded on Varian Associates EM-390, Varian Associates EM-360, Bruker WP-200, or Bruker WM-300 spectrometers and are reported in parts per million from internal tetramethysilane on the $^\delta$ scale. Data are reported as follows: chemical shift multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, m=multiplet), coupling constants in hertz, integration, interpretation, $^{13}$C nuclear magnetic resonance spectra were recorded on a Bruker WP-90 spectrometer and are reported in parts per million from internal tetramethylsilane. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on AEI-MS9 or DS-55 spectrometers at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at m/e greater than those of the parent. Combustion analyses were performed by Micro-analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl
ether (distilled from Na metal); benzene, dimethyl sulfoxide, pyridine, toluene (distilled from calcium hydride); methanol (distilled from magnesium methoxide); chloroform, dichloromethane (passed through activity I alumina). All reaction temperatures refer to those of the reaction mixture. Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Formic acid (97%) was used in all ionic cyclizations. Tri-n-butyltin hydride was prepared according to a known procedure. Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70-230 mesh). Medium Pressure Liquid Chromatography (MPLC) was performed using EM Laboratories Lobar prepacked silica gel columns and a FMI RPSY lab pump. GLC analysis was done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector. Bulb-to-bulb distillations were accomplished in a Büchi KR3 Kugelrohr apparatus.

In most cases, the product ratios were determined by \textsuperscript{1}H NMR integrations. Ratios determined by GLC were reported without calibrations. In the mass spectra of thioenoxyxylactams and related compounds, parent peaks were in general too small to monitor for exact mass measurements; however, the fragmentation patterns were in accord with our structural assignments.
1-(3-Butenyl)-2,5-pyrrolidinedione (1). To a mixture of 1.00 g (13.6 mmol) of 3-buten-1-ol, 1.48 g (14.9 mmol) of succinimide and 3.92 g (15.0 mmol) of triphenylphosphine in 20 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 2.60 g (14.9 mmol) of diethyl azodicarboxylate in 6 mL of dry tetrahydrofuran over a period of 30 min. The solvent was removed in vacuo. The resulting residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo to give 3.61 g of a pale-yellow oil. The oil was chromatographed over 45 g of silica gel (eluted with dichloromethane) to yield 2.01 g (96%) of imide 1 as a colorless oil: NMR (CCl₄) δ 2.33 (br q, J=7 Hz, 2H, allyl), 2.63 (s, 4H, NC0CH₂), 3.50 (t, J=7 Hz, 2H, NCH₂), 4.90-5.20 (m, 2H, =CH₂), 5.73 (tdd, J=16, 10, 7 Hz, 1H, -CH=).

1-(3-Butenyl)-5-phenylthio-2-pyrrolidinone (4). To a solution of 1.50 g (9.80 mmol) of imide 1 in 60 mL of absolute ethanol cooled in an ice-water bath under argon was added
1.10 g (29.1 mmol) of sodium borohydride. A 1.94 N solution of hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 5 min over a period of 2 h and 15 min. The reaction mixture was then acidified with 1.94 N hydrogen chloride in absolute ethanol (about 14 mL) to approximately pH 3. The resulting mixture was stirred at 0°C for 15 min and basicified with 1% potassium hydroxide in absolute ethanol (about 30 mL) to approximately pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The reaction mixture was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 1.75 g of crude ethoxylactam as a colorless liquid. This material was dissolved in 10 mL of thiophenol followed by the addition of 71.5 mg (0.376 mmol) of p-toluenesulfonic acid monohydrate. The resulting solution was stirred at room temperature for 10 min and partitioned between 110 mL of 1 N sodium hydroxide solution and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford 2.30 g of a white turbid liquid. This material was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexane, 2:8, followed by ethyl acetate-hexane, 4:6) to
yield 2.14 g (88%) of thiophenoxylactam 4 as a colorless liquid: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.43-2.70 (m, 6H, methylene manifold), 3.20 (td, J=13, 6 Hz, 1H, NCH₂), 3.78 (td, J=13, 6 Hz, 1H, NCH₂), 4.75-5.20 (m with dd, J=7, 3 Hz, at 4.80, 3H, =CH₂ and SCH), 5.47-6.00 (m, 1H, =CH-), 7.33 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 218(16), 138(M⁺-SPh, 100), 110(31), 109(19), 96(25), 84(12).

Cyclization of Thiophenoxylactam 4: 1-(3-Butenyl)-2-pyrrolidinone (6), trans-(±)-Hexahydro-7-methyl-3H-pyrrolizin-3-one (7), cis-(±)-Hexahydro-7-methyl-3H-pyrrolizin-3-one (8) and Hexahydro-3(2H)-indolizinone (9).^a To a solution of 1.00 g (4.05 mmol) of thiophenoxylactam 4 in 50 mL of dry benzene heated to reflux under argon was added a solution of 1.50 mL (5.68 mmol) of tri-n-butyltin hydride and 40.1 mg (0.244 mmol) of AIBN in 40 mL of dry benzene over a period of 5 h. The resulting solution was heated at the same temperature for another 2h and the solvent was removed in vacuo to give a white turbid oil (2.74 g). This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) and again over a Lobar size B column
(eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) to yield 68.6 mg (12%) of the less polar lactam \(6\) as a colorless oil: IR (CCl\(_4\)) 1690 cm\(^{-1}\); NMR (CCl\(_4\)) \(\delta\) 1.80-2.40 (m, 6H, \(-\text{CH}_2-\) manifold), 3.30 (overlapping t's, \(J=7\) Hz, 4H, \(\text{CH}_2\text{NCH}_2\)), 4.90-5.20 (m, 2H, \(=\text{CH}_2\)), 5.50-6.00 (m, 1H, \(=\text{CH}-\)); mass spectrum, m/e (relative intensity) 139(15), 98(100); exact mass calcd for C\(_9\)H\(_{13}\)NO m/e 139.0997, found m/e 139.1002. Further elution gave 405 mg (72%) of a mixture of lactams 7, 9 and 2 (58:7:35 respectively by NMR) as a pale-yellow oil: characteristic signals of 7, NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.84 (d, \(J=7.4\) Hz, 3H, methyl), 2.40 (ddt, \(J=16.6, 9.4, 2.8\) Hz, 1H), 2.70 (td, \(J=17, 9\) Hz, 1H), 3.05 (br t, \(J=10.7\) Hz, 1H), 3.49 (td, \(J=11.3, 7.6\) Hz, 1H), 4.00 (dt, \(J=7.7, 5.5\) Hz, 1H); 8, NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.04 (d, \(J=5.9\) Hz, 3H, methyl), 3.16 (br t, \(J=11.1\) Hz, 1H); 9, NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.12 (br d, \(J=13.6\) Hz, 1H, equatorial-\text{NCH}_2).
trans- and cis-(±)-Hexahydro-7-hydroxy-3(2H)-indolizinone (15 and 16). To 131 mg (0.714 mmol) of 1-(3-butenyl)-5-ethoxy-2-pyrrolidinone (3) was added 1.6 mL of formic acid in a single portion. The resulting solution was stirred at room temperature for 15 min. The excess formic acid was removed in vacuo. The residue was diluted with 30 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate solution. The aqueous wash was extracted with two 10-mL portions of dichloromethane and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a pink oil (126 mg). To this material was added 1.7 mL of a 0.85 N solution of sodium hydroxide in aqueous methanol (H₂O-MeOH, 1:5). The resulting solution was stirred at room temperature for 30 min, diluted with 25 mL of dichloromethane and washed with 5 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford a pale-yellow oil (52.0 mg). The aqueous phase was saturated with sodium chloride and extracted again with three 30-mL portions of dichloromethane. The organic layers were dried (MgSO₄) and concentrated in vacuo to give a pale-yellow oil (40.9 mg). The
combined crude material was chromatographed over 4 g of silica gel (eluted with ethyl acetate followed by ethyl acetate-methanol, 5:1) to obtain 84.7 mg (76%) of isomeric alcohols 15 and 16 as a pale-yellow oil (trans:cis=85:15 by NMR): IR (CH₂Cl₂) 3590, 3380(br), 1670 cm⁻¹; NMR (CDCl₃) δ 0.85-3.25 (m with a big dt at 2.63 and a small dt at 3.06, J=12, 3 Hz, 9H, axial-NCH and -CH₃), 3.25-4.55 (m with tt, J=12, 4.5 Hz, at 3.68, 4H, HOCH, angular-NCH and equatorial-NCH); mass spectrum, m/e (relative intensity) 155(26), 154(11), 137(M⁺-H₂O, 100), 136(57), 135(26); exact mass calcd for C₅H₁₃NO₂ m/e 155.0946, found m/e 155.0951.

Carbonodithioic Acid S-Methyl O-trans- and cis-(+)-Octahydro-3-oxo-7-indolizinyl Ester (17 and 18). To a mixture of 2.1 mg (0.031 mmol) of imidazole and 52.8 mg (2.20 mmol) of mineral oil free sodium hydride under argon was added a solution of 80.7 mg (0.521 mmol) of alcohols 15 and 16 in 2.3 mL of dry tetrahydrofuran. The resulting mixture was heated at 60°C for 30 min followed by the addition of 0.21 mL of carbon disulfide. After stirring at 60°C for 5 min, methyl iodide (0.21 mL) was added and heated under reflux for another 5 min. The mixture was diluted with 30 mL of
dichloromethane and washed with 10 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane and the combined organic layers were dried ($\text{Na}_2\text{SO}_4$) and concentrated in vacuo to give an orange oil (134 mg). This oil was chromatographed over 4 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) to yield 115 mg (90%) of isomeric xanthates 17 and 18 as a yellow oil: IR($\text{CCl}_4$) 1695, 1220, 1060 cm$^{-1}$; NMR ($\text{CCl}_4$) δ 1.17-2.00 (m, 3H), 2.00-3.27 (m with s at 2.59 and dt, J=12, 3 Hz, at 2.71, 9H, -CH$_3$, axial-NCH and -CH$_2$- manifold), 3.27-3.83 (br s, 1H, angular-NCH), 3.83-4.33 (m with the major isomer's signal clearly shown as br ddd, J=12, 6, 3 Hz, 1H, equatorial-NCH), 5.40-5.85 (m with the major isomer's signal clearly shown as tt, J=12, 4.5 Hz, 1H, OCH); mass spectrum, m/e (relative intensity) 245(4), 212(2), 198(8), 138($\text{M}^+\text{-OCSSCH}_3$, 100), 137(21), 136(5), 113(4), 111(4), 104(2); exact mass calcd for C$_{10}$H$_{15}$NO$_2$S$_2$ m/e 245.0544, found m/e 245.0537.

**Hexahydro-3(2H)-indolizinone (9).** A solution of 114 mg (0.464 mmol) of xanthates 17 and 18, 166 mg (0.569 mmol) of tri-n-butyltin hydride and 6.0 mg (0.036 mmol) of AIBN in 9 mL of dry benzene was heated under argon at reflux temperature for 11.5 h. Another
portion of tri-n-butyltin hydride was added (0.05 mL, 0.189 mmol) followed by the addition of a few crystals of AIBN. After heating for another 2.5 h, the solvent was removed in vacuo to give a pale yellow liquid (370 mg). This material was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexane, 98:2) and again over a Lobar size A column (eluted with ethyl acetate) to yield 50.0 mg (79%) of 9 as a colorless liquid: NMR (CCl₄) δ 0.80-2.75 (m, 11H, -CH₂- manifold), 3.10-3.55 (m, 1H, NCH), 3.82-4.20 (m, 1H, NCH) 3.82-4.20 (m, 1H, NCH); NMR (CDCl₃, 300 MHz) δ 1.08-1.75(m, 5H), 1.81-1.95 (m, 2H), 2.15-2.27 (m, 1H), 2.33-2.41 (m, 2H), 2.62 (dt, J=12.7, 3.3 Hz, 1H, axial-NCH₂), 3.40 (ddt, J=10.8, 7.2, 3.4 Hz, 1H, angular-NCH), 4.12 (br d, J=13.6 Hz, 1H, equatorial-NCH₂).

Lithium Aluminum Hydride Reduction of the Cyclization Products of Thiophenoxylactam 4. To a mixture of 101 mg (2.66 mmol) of lithium aluminum hydride in 20 mL of dry ether under argon was added dropwise a solution of 98.6 mg (0.710 mmol) of the cyclized products (7-9) obtained from thiophenoxylactam 4 in 2 mL of dry ether over a period of 10 min. The resulting mixture was heated to reflux for 6 h and cooled to room temperature. Water (0.3 mL) was added slowly followed by
the addition of magnesium sulfate. After stirring for 20 min, the reaction mixture was filtered through magnesium sulfate. The solvent was removed by distillation first at atmospheric pressure and then at 160 mmHg to give 44.8 mg of a pale-yellow oil. This material was bulb-to-bulb distilled (oven temperature at 100°C at 30 mmHg) to afford 26.2 mg (32%) of a mixture of (±)-δ-coniceine (10) and (±)-heliotridane (11) as a colorless liquid. This material was dissolved in 1.5 mL of absolute ethanol and treated with 18.5 mg (0.0810 mmol) of picric acid. The resulting mixture was heated to give a clear solution and cooled slowly to room temperature. The resulting yellow crystals (12.5 mg) were collected; mp 235-242°C (dec.). This solid (11.5 mg) was further recrystallized from 1 mL of absolute ethanol to yield 6 mg of pure picrate of amine 11 as yellow crystals; mp 240-243°C, dec. (lit.36 248-250°C, lit.110 243-244°C). This material was identical to an authentic sample by virtue of its 1H NMR, IR and mixed melting point: IR (CH₂Cl₂) 3100-2200(br), 1610, 1320 cm⁻¹; NMR (CDCl₃, 300 MHz) δ 1.15 (d, J=6.7 Hz, 3H, CH₃), 1.60-1.81 (m, 2H), 2.01-2.29 (m, 4H), 2.64 (octet, J=6.7 Hz, 1H), 2.72-2.88 (m, 1H), 3.12 (dd, J=11.6, 7.3 Hz, 1H), 3.70 (sextet, J=6.2 Hz, 1H), 3.90-4.08
The mother liquor of the first recrystallization was concentrated in vacuo, dissolved in 1.5 mL of absolute ethanol and treated with 34.4 mg of picric acid. The resulting mixture was heated to give a clear solution and cooled slowly to room temperature to yield 3 mg of the picrate of amine 10 as a yellow solid; mp 224-229°C, dec. (lit. 227-231°C, lit. 224-228°C). This material was identical to an authentic sample by virtue of its 1H NMR, IR and mixed melting point: IR (CH2Cl2) 3100-2200(br), 1615, 1320 cm⁻¹; NMR (CDCl3, 300 MHz) δ 1.40-2.35 (m, 10H); signals due to the major isomer: 2.59-2.84 (m, 3H), 3.80-3.94 (m, 2H), 8.89 (s, 2H, Ar-H), 10.28 (br s, 1H); signals due to the minor isomer: 3.10-3.30 (m, 2H), 3.39-3.50 (m, 1H), 3.59-3.70 (m, 1H), 8.89 (s, 2H, Ar-H), 10.95 (br s, 1H).

trans-(±)-Hexahydro-7-hydroxy-methyl-3H-pyrrolizin-3-one (21). To 204 mg (1.04 mmol) of lactam acetate 20 (vide infra) was added 2.5 mL of a 1.15 N solution of sodium hydroxide in methanol. The resulting solution was allowed to stand at room temperature for 20 min, diluted with 200 mL of dichloromethane,
stirred with magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give 130 mg of a pale-yellow oil. The oil was chromatographed over 6 g of silica gel (eluted with ethyl acetate-methanol, 9:1) to afford 108 mg (65%) of 21 as a pale-yellow oil: bp 148-152 °C/0.2 mmHg; IR (CH₂Cl₂) 3600, 3380(br), 1680 cm⁻¹; NMR (CDCl₃) δ 1.70-2.75 (m, 7H, -CH₂- manifold), 2.75-3.27 (m, 1H, NCH), 3.27-3.88 (m, 4H, OCH₂, OH and NCH), 4.07 (q, J=7 Hz, 1H, angular-NCH); NMR (CDCl₃, 200 MHz) δ 1.90-2.52 (m, 7H), 2.69 (td, J=16, 9 Hz, 1H), 3.02 (dddd, J=12, 8.5, 5, 1 Hz, 1H, NCH), 3.50-3.73 (m with two dd at 3.56, J=10, 6 Hz, and 3.69, J=10, 6.5 Hz, 3H, OCH₂, NCH), 4.00 (q, J=6.5 Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 155(33), 138(9), 97(100), 69(43); exact mass calcd for C₈H₁₃NO₂ m/e 155.0946, found m/e 155.0952.

Carbonodithioic Acid S-Methyl 
O-(trans-(±)-Hexahydro-3-oxo-7-pyrrolizinyl)methyl Ester

(22). To a mixture of 1.9 mg (0.027 mmol) of imidazole and 30.0 mg (1.25 mmol) of mineral oil free sodium hydride under argon was added a solution of 78.8 mg (0.510 mmol) of lactam alcohol 21 in 1.8 mL of dry tetrahydrofuran. The resulting mixture was stirred at 64 °C for 30 min followed by the careful addition of 0.16 mL (2.66 mmol) of carbon
disulfide. The resulting yellow mixture was stirred at 64 °C for 5 min followed by the addition of 0.16 mL (2.57 mmol) of methyl iodide. After stirring at 64 °C for another 5 min, the reaction mixture was partitioned between 30 mL of dichloromethane and 10 mL of water. The aqueous phase was extracted with three 30-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 121 mg of a brown oil. The oil was chromatographed over 6 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) to give 99.1 mg (79%) of 22 as a yellow oil: IR (CH₂Cl₂) 1690 cm⁻¹; NMR (CDCl₃) δ 1.70-3.13 (m with s at 2.56, 11H, -CH₂- manifold and CH₃), 3.63 (td, J=12, 7 Hz, 1H, NCH), 4.05 (q, J=7 Hz, 1H, angular-NCH), 4.55 (d, J=8 Hz, 2H, OCH₂); mass spectrum, m/e (relative intensity) 245(M⁺, 2), 212(24), 198(32), 170(24), 138(M⁺-OCSSCH₃, 100), 137(36), 136(24).

**Tri-n-butyltin Hydride Reduction of Xanthate 22.** To a solution of 87.1 mg (0.37 mmol) of xanthate 22 in 4.7 mL of dry benzene heated at 80 °C under argon was added a solution of 0.15 mL (0.569 mmol) of tri-n-butyltin hydride and 3.8 mg (0.023 mmol) of AIBN in 3.3 mL of dry benzene over 2 h and 20 min. The
resulting solution was stirred at 90°C for another 70 min. The solvent was removed in vacuo, and the residue (235.2 mg) was chromatographed first over 6 g of silica gel (eluted with ethyl acetate) and then over a Lobar size A column (eluted with ethyl acetate) to give 31.8 mg (61%) of 7 as a colorless liquid. The 200 MHz $^1$H NMR spectrum of this material compared favorably with that synthesized from the cyclization route yet free from the presence of 8: IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CDCl$_3$, 300 MHz) $\delta$ 0.84 (d, J=7 Hz, 3H, CH$_3$), 1.65-2.32 (m, 5H, -CH$_2$- manifold), 2.40 (ddd, J=17, 9 Hz, 1H, COCH), 2.70 (td, J=17, 9 Hz, 1H, COCH), 3.05 (br t, J=11 Hz, 1H, NCH), 3.49 (td, J=11, 8 Hz, 1H, NCH), 4.00 (dt, J=7.7, 5.5 Hz, 1H, angular-NCH); mass spectrum, m/e (relative intensity) 139(92), 138(42), 98(17), 97(100); exact mass calcd for C$_8$H$_{13}$NO m/e 139.0997, found m/e 139.1002.

1-(3-Butenyl)-5-thioacetoxy-2-pyrrolidinone (24). To a solution of 1.00 g (6.54 mmol) of imide 1 in 40 mL of absolute ethanol cooled in an ice-water bath under argon was added 726 mg (19.1 mmol) of sodium borohydride in one portion. A 1.49 N solution of hydrogen chloride in ethanol was added in a rate of 3 drops every 5 min over a period of 110 min. The resulting
mixture was partitioned between 35 mL of water, 35 mL of saturated sodium chloride solution and 70 mL of dichloromethane. The aqueous phase was extracted with three 70-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 979 mg of a pale-yellow oil. Part of this oil (952 mg) was stirred with 3.5 mL of thiolacetic acid at room temperature for 20 min. The resulting solution was partitioned between 100 mL of dichloromethane and 70 mL of saturated sodium bicarbonate solution. The aqueous phase was extracted with two 100-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a yellow oil (1.30 g). The oil was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane, 2:8, followed by ethyl acetate-hexane, 4:6) to yield 1.22 g (100%) of 24 as a yellow oil: IR (neat) 1710 cm⁻¹; NMR (CDCl₃) δ 1.90-3.08 (m with s at 2.31, 10H, CH₃, NCH₂ and -CH₂-manifold), 3.61 (td, J=12, 7 Hz, 1H, NCH), 4.81-5.25 (m, 2H, =CH₂), 5.25-6.05 (m, 2H, NCH₃ and =CH-); mass spectrum, m/z (relative intensity) 213(M⁺, 0.6), 172(10), 138(M⁺-SCOCH₃, 100), 127(9), 130 (11), 101(14), 96(24), 84(29).

1-(3-Butenyl)-5-mercaptop-2-pyrrolidinone (25). To 149 mg (0.70 mmol) of lactam thioacetate 24 under argon was added 1.6 mL of a 0.96 N solution of sodium hydroxide in aqueous methanol (H₂O-MeOH, 1:5). The resulting
solution was stirred at room temperature for 10 min and acidified with 1 N hydrogen chloride solution to pH 1. The resulting mixture was partitioned between 5 mL of water and 20 mL of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to yield 109 mg (91%) of 25 as a pale-yellow oil: NMR (CCl$_4$) δ 1.80-2.73 (m, 7H, SH and -CH$_2$- manifold), 3.00 (td, J=14, 7 Hz, 1H, NCH), 3.67 (td, J=14, 7 Hz, 1H, NCH), 4.50-5.20 (m, 3H, -CH$_2$ and NCHS), 5.70 (tdd, J=16, 10, 6 Hz, 1H, =CH-). Since further purification via column chromatography led to decomposition, this material was used directly in the next reaction.

![Image of molecule 25](image)

$1$-(3-Butenyl)-5-(2,4-dinitrothiophenoxy)-2-pyrrolidinone (26). To 199 mg (0.934 mmol) of lactam thioacetate 24 under argon was added 0.65 mL of a 1.50 N sodium hydroxide solution in aqueous methanol (H$_2$O-MeOH, 1:5). The resulting brownish solution was stirred at room temperature for 5 min followed by the addition of 177 mg (0.950 mmol) of 2,4-dinitrofluorobenzene in a single portion. The resulting mixture was stirred for 5 min
to give a mixture of a solution with a yellow solid suspension. This mixture was partitioned between 5 mL of water and 20 mL of dichloromethane. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford a yellow solid. This material was chromatographed over 13 g of silica gel (eluted with ethyl acetate-hexane, 1:1, followed by ethyl acetate-hexane, 7:3) to yield a yellow solid which was recrystallized from ethyl acetate (3 mL) and hexane (5 mL) to give 149 mg (47%) of 26 as a yellow crystalline solid: mp 134-135 °C; IR (KBr) 1695, 1590, 1510, 1345 cm⁻¹; NMR (CDCl₃) δ 2.10-2.87 (m, 6H, -CH₂- manifold), 3.13 (td, J=14, 7 Hz, 1H, NCH₂), 3.83 (td, J=14, 7 Hz, 1H, NCH₂), 4.87-6.00 (m, 4H, -CH=CH₂ and NCHS), 7.47 (d, J=9 Hz, 1H, Ar-H(5)), 8.32 (dd, J=9, 3 Hz, 1H, Ar-H(6)), 9.00 (d, J=3 Hz, 1H, Ar-H(3)).

Anal. Calcd. for C₁₄H₁₅N₃O₅S: C, 49.84; H, 4.49. Found: C, 50.12; H, 4.70.

1-(3-Butenyl)-5-methylthio-2-pyrrolidinone (27). To 232 mg (1.09 mmol) of lactam thioacetate 24 under argon was added in a single portion 2.9 mL of a 0.85 N solution of sodium hydroxide in aqueous
methanol (H₂O-MeOH, 1:5). The resulting solution was stirred at room temperature for 15 min followed by the addition of 0.39 mL (6.3 mmol) of methyl iodide. The reaction mixture was stirred for another hour and partitioned between 20 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford 190 mg of a pale-pink liquid. This material was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexane, 45:55) to yield 181 mg (90%) of 27 as a colorless liquid: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.97 (s, 3H, CH₃), 2.00-2.70 (m, 6H, -CH₂- manifold), 3.10 (td, J=14, 7 Hz, 1H, NCH), 3.70 (td, J=14, 7 Hz, 1H, NCH), 4.60 (dd, J=7, 5 Hz, 1H, NCHS), 4.90-5.20 (m, 2H, =CH₂), 5.80(tdd, J=16, 10, 6 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 139(M⁺-SCH₃, 100), 96(15), 84(27).

1-(3-Methyl-3-butenyl)-2,5-pyrrolidinedione (127). To a mixture of 1.03 g (11.6 mmol) of 3-methyl-3-buten-1-ol, 1.15 g (11.6 mmol) of succinimide and 3.04 g (11.6 mmol) of triphenylphosphine in 17 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 2.02 g
(11.6 mmol) of diethyl azodicarboxylate in 5 mL of dry tetrahydrofuran over a period of 40 min. The resulting solution was stirred at room temperature for 4 h, and the solvent was removed in vacuo. The residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filter cake was triturated again with 20 mL of the same solvent pair, and the combined extracts were concentrated in vacuo. The residue was suspended in 30 mL of ethyl acetate-hexane (3:7), filtered and concentrated in vacuo to give 3.09 g of a pale yellow oil. The oil was chromatographed over 35 g of silica gel (eluted with dichloromethane followed by dichloromethane-methanol, 100:0.5) to yield 1.68 g (87%) of imide 127 as a colorless oil: NMR (CDCl₃) δ 1.80 (br s, 3H, CH₋), 2.27 (br t, J=7 Hz, 2H, allyl), 2.70 (s, 4H, NC0CH₂), 3.61 (br t, J=7 Hz, 2H, NCH₂), 4.55-4.90 (m, 2H, =CH₂).

1-(trans-3-Pentenyl)-2,5-pyrrolidinedione (128). To a mixture of 1.00 g (11.7 mmol) of trans-3-penten-1-ol, 1.16 g (11.7 mmol) of succinimide and 3.06 g (11.7 mmol) of triphenylphosphine in 17 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 2.04 g (11.7 mmol) of diethyl azodicarboxylate in 5 mL of dry
tetrahydrofuran over a period of 25 min. The resulting solution was stirred at room temperature for 2 h, and the solvent was removed in vacuo. The residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filter cake was triturated again with 20 mL of the same solvent pair and filtered. The combined extracts were concentrated in vacuo. The resulting residue was mixed with 30 mL of ethyl acetate-hexane (3:7), filtered, and the filtrate was concentrated in vacuo to give 3.00 g of a pale-yellow oil. The oil was chromatographed over 35 g of silica gel (eluted with dichloromethane) to afford 1.67 g (85%) of imide 128 as a colorless oil: NMR (CCl₄) δ 1.65 (br d, J=4 Hz, 3H, CH₃), 2.21 (br q, J=7 Hz, 2H, allyl), 2.63 (s, 4H, NC0CH₂), 3.43 (br t, J=7 Hz, 2H, NCH₂), 5.00-5.65 (m, 2H, -CH=).

1-(cis-3-Pentenyl)-2,5-pyrrolidinedione (129). A mixture of 1.32 g (9.00 mmol) of 1-(3-pentynyl)-2,5-pyrrolidinedione (134) and 308 mg of 5% palladium on barium sulfate in 15 mL of dry pyridine was stirred under one atmosphere of hydrogen. The hydrogen uptake was monitored, and the reaction was stopped when 204 mL of hydrogen had been consumed. A small portion of magnesium sulfate was added to catalyze
the desorption of hydrogen on the catalyst. The mixture was filtered through Celite and partitioned between 75 mL of 3 N aqueous hydrogen chloride and 100 mL of ether. The aqueous phase was extracted with two 100-mL portions of ether. The combined organic layers were washed with 50 mL of saturated brine, dried (MgSO₄) and concentrated in vacuo to afford 1.27 g of a pale-yellow oil. The oil was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexane, 47:53) to yield 1.22 g (92%) of imide 129 as a pale-yellow oil: IR (CCl₄) 1775#, 1705 cm⁻¹; NMR (CDCl₃) δ 1.60 (br d, J=6 Hz, 3H, CH₃), 2.30 (br q, J=7 Hz, 2H, allyl), 2.60 (s, 4H, NCOCH₂), 3.43 (br t, J=7 Hz, 2H, NCH₂), 5.00-5.70 (m, 2H, vinyl); mass spectrum, m/e (relative intensity) 167(14), 112(7), 100(100), 94(21); exact mass calcd for C₉H₁₃NO₂ m/e 167.0946, found m/e 167.0950. 1-(4-Methyl-3-pentenyl)-2,5-pyrrolinedione (41). To a mixture of 1.38 g (13.8 mmol) of 4-methyl-3-penten-1-ol,¹¹² 1.37 g (13.8 mmol) of succinimide and 3.62 g (13.8 mmol) of triphenylphosphine in 20 mL of dry tetrahydrofuran under argon was added a solution of 2.40 g (13.8 mmol) of diethyl azodicarboxylate in 5.8 mL of dry tetrahydrofuran over a period of 1 h. The resulting solution was stirred at room temperature for 3 h, and
the solvent was removed in vacuo. The resulting residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filter cake was triturated again with 20 mL of the same solvent pair. The combined extracts were concentrated in vacuo. The residue was mixed with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo to give 4.50 g of a pale-yellow oil. The oil was chromatographed over 50 g of silica gel (eluted with dichloromethane) to afford 2.14 g (86%) of imide 41 as a colorless liquid which solidified slowly to give a white solid: mp 42.5-43.5 C; IR (KBr) 1705 cm$^{-1}$; NMR (CDCl$_3$) 1.60 (br s, 3H, CH$_3$), 1.69 (br s, 3H, CH$_3$), 2.22 (br q, J=7 Hz, 2H, allyl), 2.60 (s, 4H, COCH$_2$), 3.39 (br t, J=7 Hz, 2H, NCH$_2$), 5.03 (br t, J=7 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 181(17), 113(4), 112(2), 100(36), 92(100), 69(25), 67(51); exact mass calcd for C$_{10}$H$_{15}$NO$_2$ m/e 181.1103, found m/e 181.1107.

Anal. Calcd. for C$_{10}$H$_{15}$NO$_2$: C, 66.27; H, 8.34.

Found: C, 66.46; H, 8.20.

1-(3-Methyl-3-butenyl)-5-phenylthio-2-pyrrolidone (28a). To a solution of 1.48 g (8.87 mmol) of imide 127 in 55 mL of absolute ethanol cooled in an ice-water bath under argon was added 990 mg
(26.0 mmol) of sodium borohydride. A 1.6 N solution of hydrochloric acid in absolute ethanol was added in a rate of 3 drops every five minutes over a 2.5 h period. The reaction mixture was then acidified to pH 3 (about 20 mL of 1.6 N HCl/EtOH), stirred at 0°C for 1 h and basicified with 1% potassium hydroxide in absolute ethanol (about 30 mL) to approximately pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The resulting mixture was partitioned between 100 mL of dichloromethane and 100 mL of water. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to give 1.68 g of crude lactam ether as a colorless oil. The solution of the crude lactam ether and 65.5 mg (0.345 mmol) of p-toluenesulfonic acid monohydrate in 8 mL of thiophenol was stirred under argon at room temperature for 30 min and partitioned between 100 mL of dichloromethane and 110 mL of 1 N aqueous sodium hydroxide solution. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to afford 2.20 g of a white turbid liquid. This material was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexane, 2:8) to yield 1.92 g (83%) of thiophenoxy lactam 26a as a colorless oil which solidified when stored in refrigerator: mp 55.5-56.5°C;
IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) 1.30-2.50 (m with br s at 1.75, 9H, -CH₂ and -CH₃- manifold), 3.25 (td, J=13, 7 Hz, 1H, NCH), 3.90 (td, J=13, 7 Hz, 1H, NCH), 4.59-4.95 (m, 3H, =CH₂ and SCHN), 7.32 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 206(1), 152(M⁺-SPh,100), 151 (4), 136(2), 123(2), 110(13), 109(5), 108(1), 96(9), 84 (26).


Found: C, 68.75; H, 7.35.

trans-1-(3-Pentenyl)-5-phenyl-thio-2-pyrrolidone (28b). To a solution of 1.50 g (8.99 mmol) of imide 128 in 55 mL of absolute ethanol cooled in an ice-water bath under argon was added 1.00 g (26.3 mmol) of sodium borohydride. A solution of 1.94 N hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 5 min over a 2 h and 15 min period. The reaction mixture was acidified to pH 3 (about 11 mL of 1.94 N HCl-EtOH), stirred at 0°C for 30 min and basicified with 1% potassium hydroxide in absolute ethanol to pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The resulting mixture was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of
dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give 1.67 g of crude lactam ether as a colorless liquid. A solution of this crude material and 64.4 mg (0.339 mmol) of p-toluenesulfonic acid monohydrate in 9 mL of thiophenol was stirred under argon at room temperature for 15 min and partitioned between 100 mL of 1 N sodium hydroxide solution and 100 mL of dichloromethane. The aqueous phase was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford 2.24 g of a white turbid liquid. This material was chromatographed over 45 g of silica gel (eluted with ethyl acetate-hexane, 2:8, followed by ethyl acetate-hexane, 4:6) to yield 2.05 g (88%) of thiophenoxy lactam 28b as a colorless oil: IR (CCl$_4$) 1700, 970 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.42-2.65 (m, 9H, -CH$_3$ and -CH$_2$- manifold), 3.15 (td, J=13, 7 Hz, 1H, NCH), 3.71 (td, J=13, 7 Hz, 1H, NCH), 4.80 (dd, J=7, 3 Hz, 1H, SChN), 5.26-5.50 (m, 2H, =CH-), 7.32 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 206(M$^+$-CH$_2$CH=CHCH$_3$, 1.5), 153(10), 152(M$^+$-SPh, 100), 110(15), 109(6), 96(13), 84(32).

To a solution of 1.17 g (7.00 mmol) of imide 129 in 45 mL of absolute ethanol cooled in an
ice-water bath under argon was added 770 mg (20.3 mmol) of sodium borohydride. A 1.94 N solution of hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 5 min over a 2 h period. The reaction mixture was then acidified to pH 3 (about 11 mL of 1.94 N HCl-EtOH). The resulting mixture was stirred at 0 °C for 1 h and basified with 1% potassium hydroxide in absolute ethanol (about 30 mL) to pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The resulting mixture was partitioned between 100 mL of dichloromethane and 75 mL of water. The aqueous phase was extracted with four 100-ml portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 1.33 g of crude ethoxylactam as a colorless liquid. A solution of this crude material and 52.6 mg (0.277 mmol) of p-toluenesulfonic acid monohydrate in 7 mL of thiophenol was stirred under argon at room temperature for 15 min and partitioned between 80 mL of 1 N sodium hydroxide solution of 100 mL of dichloromethane. The aqueous phase was extracted with two 100-ml portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford 1.78 g of a white turbid liquid. This material was chromatographed over 38 g of silica gel (eluted with ethyl acetate-hexane, 2:8, followed by ethyl acetate-hexane, 4:6) to yield 1.63 g (89%) of thiophenoxy lactam 28c as a colorless oil:
IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.40–2.60 (m with d, J=7 Hz, at 1.60, 9H, -CH₃ and -CH₂- manifold), 3.18 (td, J=13, 7 Hz, 1H, NCH), 3.72 (td, J=13, 7 Hz, NCH), 4.81 (dd, J=7, 3 Hz, 1H, SCHN), 5.10–5.70 (m, 2H, –CH–), 7.33 (br s, 5H, Ar-H); mass spectrum, m/z (relative intensity) 206(M⁺-CH₂CH=CHCH₃, 1.5), 152(M⁺-SPh, 100), 151(9), 110(27), 109 (9), 96(25), 84(37).

1-(4-Methyl-3-pentenyl)-5-phenylthio-2-pyrrolidinone (28d). To a solution of 1.06 g (5.88 mmol) of imide 4 in 38 mL of absolute ethanol cooled in an ice-water bath under argon was added 648 mg (17.0 mmol) of sodium borohydride. A 1.49 M solution of hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 5 min over a 2.5 h period. The resulting mixture was partitioned between 50 mL of water, 20 mL of saturated sodium chloride solution and 70 mL of dichloromethane. The aqueous phase was extracted with three 70-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 1.08 g of crude lactam carbinol as a white solid: mp 49–52°C. Part of this crude product (0.800 g, 4.37 mmol) was stirred with 0.450 mL (4.39 mmol) of thiophenol and 41.0 mg (0.216 mmol) of p-toluenesulfonic acid monohydrate
under argon at room temperature for 2 h and 10 min. The reaction mixture was partitioned between 50 mL of dichloromethane and 30 mL of 1 N aqueous sodium hydroxide solution. The aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried (MgSO\textsubscript{4}) and concentrated in vacuo to afford 1.18 g of a white turbid oil. The oil was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexane, 3:7, followed by ethyl acetate-hexane, 4:6) to yield 1.12 g (93\%) of thiophenoxy lactam \textit{28d} as a colorless liquid:

\text{IR (CCl\textsubscript{4})} 1700 cm\textsuperscript{-1}; \text{NMR (CCl\textsubscript{4})} \delta 1.62 (br s, 3H, -CH\textsubscript{3}), 1.67 (br s, 3H, -CH\textsubscript{3}), 1.40-2.55 (m, 6H, -CH\textsubscript{2}- manifold), 3.11 (dt, J=13, 7 Hz, 1H, NCH), 3.65 (dt, J=13, 7 Hz, 1H, NCH), 3.79 (dd, J=7, 3 Hz, 1H, NCH\textsubscript{S}), 5.02 (br d, J=7 Hz, 1H, =CH\textsubscript{-}), 7.31 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 166(M\textsuperscript{+}-SPh, 100), 110(59), 96(47), 84(41), 83(59), 92(29).

Cyclization of Thiophenoxy lactam \textit{28a}: 1-(3-Methyl-3-butenyl)-2-pyrrolidinone (\textit{29a}), Hexahydropyrrolizin-3-one (\textit{34}).

\begin{center}
\includegraphics[width=0.5\textwidth]{c9a.png}
\end{center}

\text{trans-(+)-Hexahydro-7-methyl-3(2H)-indolizinone (\textit{35}) and \textit{cis-(+)-Hexahydro-7-methyl-3(2H)-indolizinone (\textit{36})}. To a solution of 1.03 g (3.95 mmol) of thiophenoxy lactam \textit{28a} in
in 50 mL of dry benzene heated to reflux under argon was added a solution of 1.4 mL (5.3 mmol) of tri-n-butyltin hydride and 35.5 mg (0.235 mmol) of AIBN in 35 mL of dry benzene over a period of 3 h and 20 min. After heating for another 2 h, the solvent was removed in vacuo to give 2.65 g of a white turbid liquid. This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) and again over a Lobar size C column (eluted with ethyl acetate-hexane, 6:4) to yield 70.9 mg (12%) of the less polar lactam 29a as a colorless liquid:

IR (CCl₄) 1690 cm⁻¹; NMR (CCl₄): 1.60-2.50 (m with br s at 1.80, 9H, -CH₃ and -CH₂- manifold), 3.38 (t, J=6 Hz, 4H, NCH₂), 4.70 (br s, 2H, =CH₂); mass spectrum, m/e (relative intensity) 153(M⁺, 24), 138(1), 98(100), 97(1), 86(3), 84(1); exact mass calcd for C₉H₁₅NO m/e 153.1154, found m/e 153.1158. Continued elution gave 425 mg (70%) of a colorless liquid. This material consists of three components separable by GLC (2m x 1/8 in column packed with 10% OV-101 on Chrom W, Hp 80/100; column temperature=
165°C, flow rate = 28 mL/min). The minor compound, presumably lactam 34, $t_R = 6.20$ min (7%), was not identified by all means. However, a distinct broad peak, $J = 9$ Hz, at $\delta 3.15$ can be seen in the $^1$H NMR (CDCl$_3$, 300 MHz) spectrum of the mixture. The other two major components were shown to be lactams 35, $t_R = 7.85$ min (14%), and 36, $t_R = 6.70$ min (51%), by preparative GLC and high field $^1$H NMR; IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CDCl$_3$, 300 MHz) δ signals due to major isomer: 0.97 (d, $J = 6.6$ Hz, 3H, -CH$_3$), 2.63 (dt, $J = 13$, 3.5 Hz, 1H, NCH), 3.44 (m, 1H, NCH), 4.11 (ddd, $J = 13.1$, 4.9, 1.6 Hz, 1H, NCH); signals due to minor isomer: 1.09 (d, $J = 7.4$ Hz, 3H, -CH$_3$), 2.87 (dt, $J = 14$, 3.7 Hz, 1H, NCH), 3.65 (m, 1H, NCH), 3.84 (ddd, $J = 13.4$, 5.3, 1.8 Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 153(99), 152(100), 138(24), 111(12), 110(20), 99(24), 97(28), 84(56), 93(60), 82(36); exact mass calcd for C$_9$H$_{15}$NO m/e 153.1154, found m/e 153.1158.

Cyclization of Thiophenoxy-lactam 28b: 1-((trans-3-Pentenyl)-2-pyrrolidinone (29b), cis-(±)-Hexahydro-7-ethyl-3H-pyrrolizin-3-one (30), trans-(±)-Hexahydro-7-ethyl-3H-pyrrolizin-3-one (31) and cis-(±)-Hexahydro-8-methyl-3(2H)-indolizinone (37). To a solution of 1.00 g (3.84 mmol) of thiophenoxy lactam 28b
in 50 mL of dry benzene heated to reflux under argon was added a solution of 1.41 mL (5.34 mmol) of tri-n-butyltin hydride and 37.0 mg (0.226 mmol) of AIBN in 35 mL of dry benzene over a period of 3.5 h. The resulting solution was heated for another 2 h and the solvent was removed in vacuo to give a white turbid liquid (2.69 g). This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) and again over a Lobar size B column (eluted with ethyl acetate-hexane, 6:4, followed by ethyl acetate-hexane, 8:2) to yield 77.8 mg (13%) of a less polar pale-yellow oil. The major constituent of this material was identified as lactam 29b: IR (CCl₄) 1690, 970 cm⁻¹; NMR (CCl₄) δ 1.68 (d, J=5 Hz, 3H, -CH₃), 1.73-2.40 (m, 6H, -CH₂- manifold), 3.22 (t, J=7 Hz, 2H, NCH₂), 3.32 (t, J=7 Hz, 2H, NCH₂), 5.10-5.70 (m, 2H, =CH-); NMR (CDCl₃, 300 MHz) δ 1.65 (d, J=6 Hz, 3H, -CH₃), 2.00 (qu, J=7 Hz, 2H, NCOCH₂CH₂), 2.20 (q, J=7 Hz, 2H, allyl-CH₂), 2.37 (t, J=7 Hz, 2H, NCOCH₂), 3.30 (t, J=7 Hz, 2H, NCH₂), 3.38 (t, J=7 Hz, 2H, NCH₂), 5.37 (qtd, J=16, 7, 1.5 Hz,
collapses to td, \( J=7 \), 1.5 Hz, upon irradiation at 1.65, 
1H, \( =\text{CHCH}_2\)-), 5.51 (br qd, \( J=16 \), 6.5 Hz, collapses to d, 
\( J=16 \) Hz, upon irradiation at 1.65, 1H, \( =\text{CH}-\text{CH}_3\); mass 
spectrum, \( m/e \) (relative intensity) 153 (\( M^+ \), 14), 98(100); 
extact mass calcd for \( C_9H_{15}NO \) \( m/e \) 153.1154, found \( m/e \) 
153.1158. A GLC coinjection study with authentic samples 
(5 ft x 1/8 in column packed with 10% FFAP on Chrom W, 
80/100 mesh; column temperature= 160°C, flow rate= 30 
ml/min) showed that the minor components were 40, \( t_R=10.7 
\) min and 29c, \( t_R=14 \) min with 29b having \( t_R=12.8 \) min 
(2:8:90 respectively).

Continued elution gave 408 mg (69%) of a pale-yellow 
liquid. This material was identified as a mixture of 
lactams 37, 30 and 31 in a ratio of 32:7:61 by high field 
NMR. Analytical samples of the two major isomers were ob­ 
tained by preparative GLC (2m x 1/8 in column packed with 
10% OV-101 on Chrom W, Hp 80/100; column temperature= 
170°C, flow rate= 28 ml/min): 37, \( t_R=5.90 \) min, identical 
with authentic sample (vide infra); 31, \( t_R=6.85 \) min; IR 
\( (CCL_4) \) 1690 cm\(^{-1}\); NMR \( (CCL_4, 90 \) MHz) \( \delta \) 0.80-3.20 (m, 13H), 
3.20-3.75 (m, 1H, NCH), 3.75-4.20 (m, 1H, NCH); NMR 
\( (CDCl_3, 300 \) MHz) \( \delta \) 0.90-1.16 (m with t, \( J=7 \) Hz, at 0.94, 
5H, ethyl), 1.38-2.13 (m, 5H), 2.36 (ddd, \( J=16.5, 9, 2.5 
\) Hz, 1H), 2.62 (td, \( J=17, 9 \) Hz, 1H), 2.97 (dt, \( J=11.5, 5 
\) Hz, 1H, NCH), 3.56 (dt, \( J=11.8, 6.6 \) Hz, 1H, NCH), 4.02 
(dt, \( J=7, 7 \) Hz, 1H, NCH); mass spectrum, \( m/e \) (relative
intensity) 153(39), 152(7), 138(7), 136(11), 134(4), 128 (7), 106(25), 105(14), 97(100), 91(36); exact mass calcd for C₉H₁₃NΟ m/e 153.1154, found m/e 153.1150. In the NMR spectrum of 31, the presence of the minor isomer 30 can be detected by the signal at δ 3.15 (br t, J=11.1 Hz, 1H, NCH).

Cyclization of Thiophenoxylactam 28c. To a solution of 0.999 g (3.93 mmol) of thiophenoxylactam 28c in 50 mL of dry benzene heated to reflux under argon was added a solution of 1.41 mL (5.34 mmol) of tri-n-butyltin hydride and 37.4 mg (0.228 mmol) of AIBN in 35 mL of dry benzene over a period of 4 h and 40 min. After heating for another 2 h, the solvent was removed in vacuo to give a white turbid liquid (2.66 g). This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate) and then over a Lobar size B column to yield 145 mg (25%) of a less polar colorless oil. The major constituent of this material was identified as 1-(cis-3-pentenyl)-2-pyrrolidinone (29c): IR (CCl₄) 1690 cm⁻¹; NMR (CCl₄, 90 MHz) δ 1.66 (d, J=6 Hz, 3H, -CH₃), 1.80-2.50 (m, 6H, -CH₂- manifold), 3.22 (t, J=7 Hz, 2H, NCH₂), 3.32 (t, J= 7 Hz, 2H, NCH₂), 5.10-5.70 (m, 2H, -CH=); NMR (CDCl₃, 300 MHz) δ 1.62 (d, J=7 Hz, 3H, -CH₃), 2.00 (qu, J=7 Hz, 2H,
NCOCH₂CH₂), 2.29 (q, J=7 Hz, 2H, allyl-CH₂), 2.38 (t, J=7 Hz, 2H, NCOCH₂), 3.32 (t, J=7 Hz, 2H, NCH₂), 3.40 (t, J=7 Hz, 2H, NCH₂), 5.35 (qtd, J=11, 7, 2 Hz, collapses into td, J=11, 7 Hz, upon irradiation at 1.62, 1H, =CHCH₂⁻), 5.54 (tqd, J=11, 7, 1.5 Hz, collapses into td, J=11, 1.5 Hz, upon irradiation at 1.62, 1H, =CHCH₃), with the allylic methylene protons of trans isomer 29b distinctly shown at 2.20 as q, J=7 Hz; mass spectrum, m/e (relative intensity) 153(17), 106(6), 105(3), 99(9), 98(100), 91 (10), 86(3); exact mass calcd for C₉H₁₅NO m/e 153.1154, found 153.1158. A GLC coinjection study with authentic samples (5 ft x 1/8 in column packed with 10% FFAP on Chrom W, 80/100 mesh; column temperature= 160°C, flow rate= 30 mL/min) showed that the minor components were 40 (vide infra), tᵣ=10.4 min, and 29b, tᵣ= 12.5 min, with 29c having tᵣ=13.7 min (5:14:81 respectively).

Continued elution gave 326 mg (56%) of a pale-yellow liquid. This material was identified as a mixture of 37 (vide infra), 30 (vide supra) and 31 (vide supra) in a ratio of 7:12:81 respectively.

1-Pentyl-2-pyrrolidinone (40). A mixture of 55.3 mg (0.392 mmol) of lactam 29c and 13.4 mg of 5% palladium on activated carbon in 2.7 mL of absolute ethanol was stirred
under a balloon full of hydrogen at room temperature for 2.5 h. The resulting mixture was stirred with a small amount of magnesium sulfate for a few minutes and filtered through Celite. The filtrate was concentrated in vacuo to give a colorless oil (53.6 mg). The oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate) to yield 48.3 mg (79%) of 40 as a colorless oil: NMR (CCl₄): 1.01 (br t, J=6 Hz, 3H, -CH₃), 1.10–1.80 (m, 7H, -CH₂-manifold), 1.80–2.40 (m, 4H, NCOCH₂CH₂), 3.05–3.45 (overlaped t, J=7 Hz, at 3.18 and 3.32, 4H, NCH₂).

Cyclization of Thiophenoxy-lactam 28d: 1-(4-Methyl-3-pentenyl)-2-pyrrolidinone (29d), cis-(±)-Hexahydro-7-isopropyl-3H-pyrrolizin-3-one (32) and trans-(±)-Hexahydro-7-isopropyl-3H-pyrrolizin-3-one (33). To a solution of 1.00 g (3.64 mmol) of thiophenoxy-lactam 28d in 47 mL of dry benzene under argon was added a solution of 1.35 mL (5.11 mmol) of tri-n-butyltin hydride and 37.5 mg (0.229 mmol) of AIBN in 33 mL of dry benzene over a period of 6 h and 40 min. The resulting mixture was concentrated in vacuo to give 2.64 g of a colorless
liquid. This material was chromatographed first over 35 g of silica gel (eluted with ethyl acetate) then over a Lobar size B column (eluted with ethyl acetate-hexane, 85:15) to yield 440 mg (72%) of a colorless liquid as a mixture of lactams 29d and 33 in a ratio of 13:87, respectively: IR (CCl₄) 1700 cm⁻¹; characteristic signals for 29d, NMR (CDCl₃, 200 MHz) δ 1.61 (br s, 3H, -CH₃), 1.69 (br s, 3H, -CH₃), 3.28 (t, J=6.5 Hz, 2H, NCH₂), 3.39 (t, J=6.5 Hz, 2H, NCH₂), 5.08 (br t, J=7.5 Hz, 1H, =CH-); for 33, NMR (CDCl₃, 200 MHz) δ 0.91 (d, J=6.5 Hz, 3H, -CH₃), 0.96 (d, J=6.5 Hz, 3H, -CH₃), 2.81 (ddt, J=12, 5, 1 Hz, 1H, NCH), 3.83 (ddd, J=12, 7.5, 1 Hz, 1H, NCH), 4.04 (ddd, J=10, 9, 6.5 Hz, 1H, angular NCH).

Continued elution gave 92.4 mg (15%) of lactam 32 as a colorless liquid: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄, 90 MHz) δ 0.87-1.06 (two overlapped d, J=6.5 Hz, 6H, -CH₃), 1.21-2.80 (m, 8H, -CH₂- manifold), 3.00 (br t, J=9 Hz, 1H, NCH), 3.23-3.68 (t, J=9 Hz, at 3.37 overlaped with q, J=7.5 Hz, at 3.55, 2H, NCH and angular NCH); NMR (CDCl₃, 200 MHz) δ 0.93 (d, J=6.5 Hz, 3H, -CH₃), 0.95 (d, J=6.5 Hz, 3H, -CH₃), 1.30-1.93 (m, 4H), 2.20-2.37 (m, 2H), 2.44 (ddd, J=17, 10, 2 Hz, 1H), 2.74 (td, J=17, 10 Hz, 1H), 3.15 (br t, J=10 Hz, 1H, NCH), 3.47 (br t, J=10 Hz, 1H, NCH), 3.63 (q, J=7 Hz, 1H, angular NCH); mass spectrum, m/e (relative intensity) 167(28), 97(100), 69(14); exact mass calcd for C₁₀H₁₇NO m/e 167.1310, found m/e 167.1314.
cis-(±)-Hexahydro-7-(1-hydroxy-1-methyl)ethyl-3H-pyrrolizin-3-one (43) and trans-(±)-Hexahydro-7-(1-hydroxy-methyl)ethyl-3H-pyrrolizin-3-one (44). To a solution of 1.00 g (5.52 mmol) of imide 41 in 36 mL of absolute ethanol cooled in an ice-water bath under argon was added 609 mg (16.0 mmol) of sodium borohydride. Over a period of 2 h, a solution of hydrogen chloride in absolute ethanol was added at a rate of two drops every 5 min. The resulting mixture was partitioned between 50 mL of water, 20 mL of saturated sodium chloride aqueous solution and 70 mL of dichloromethane. The aqueous phase was extracted with three 70-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give 1.03 g of a white solid, mp 49-52°C. Part of this solid (0.897 g) cooled in an ice-water bath under argon was dissolved in 9.8 mL of formic acid, stirred at 0°C for 5 min and then at room temperature for 45 min. The resulting solution was dissolved in 50 mL of dichloromethane and washed with 30 mL of water. The aqueous phase was extracted with 50 mL of dichloromethane. The combined organic layers were washed with 50 mL of saturated sodium bicarbonate solution. The base wash was extracted with 50 mL of
dichloromethane. The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to afford 1.04 g of a pale-yellow oil. The oil was mixed with a 0.89 N solution of sodium hydroxide in aqueous methanol (H₂O-MeOH, 1:5) and stirred at room temperature for 30 min. The resulting mixture was diluted with 200 mL of dichloromethane, dried (MgSO₄) and concentrated in vacuo to give 0.977 g of a pale-yellow oil. The oil was chromatographed over a Lobar size B column (eluted with 5% methanol in ethyl acetate) to yield 418 mg (48%) of the less polar 44 as a white solid: mp 110.5-111.5°C; IR (CH₂Cl₂) 3600, 3400(br), 1680 cm⁻¹; NMR (CDCl₃, 90 MHz) δ 1.30 (s, 3H, -CH₃), 1.38 (s, 3H, -CH₃), 1.62-3.05 (m, 8H, -CH₂- manifold), 3.72-4.20 (m, 3H, NCH and NCH₂); NMR (CDCl₃, 200 MHz) δ 1.28 (s, 3H, -CH₃), 1.34 (s, 3H, -CH₃), 1.70-2.62 (m, 8H, -CH₂- manifold, and OH), 2.96 (dt, J=11, 6 Hz, 1H, NCH), 3.98 (ddd, J=11, 7, 2 Hz, 1H, NCH), 4.08 (dt, J=9, 5.5 Hz, 1H, angular NCH); mass spectrum, m/e (relative intensity) 183 (100), 168(20), 166(7), 165(13), 150(47), 140(53), 124 (33), 112(47), 108(60), 107(80), 106(20); exact mass calcd for C₁₀H₁₇NO₂ m/e 183.1259, found m/e 183.1264.
Anal. Calcd. for C₁₀H₁₇NO₂: C, 65.54; H, 9.35.
Found: C, 65.56; H, 9.49.
Continued elution gave 297 mg (34%) of 43 as a white solid: mp 55-56°C; IR (CCl₄) 3400(br), 1670 cm⁻¹; NMR (CCl₄, 90 MHz) δ 1.18 (s, 3H, -CH₃), 1.20 (s, 3H, -CH₃),
1.52-2.80 (m, 7H, -CH2- manifold), 2.85-3.20 (m, 1H, NCH),
3.28-3.65 (td, J=11, 7.5 Hz, at 3.33 overlapped with br s
at 3.53, 2H, OH, NCH), 3.88 (q, J=6.5 Hz, 1H, angular NCH);
NMR (CDCl3, 200 MHz) δ 1.25 (s, 3H, -CH3), 1.26 (s, 3H,
-CH3), 1.67-1.91 (m, 2H), 1.96 (br s, 1H, OH), 2.01-2.25
(m, 2H), 2.26-2.40 (m, 1H), 2.48 (ddd, J=16, 9, 2Hz, 1H),
2.75 (td, J=16, 9 Hz, 1H), 3.15 (br t, J=11 Hz, 1H, NCH),
3.57 (td, J=11, 8 Hz, 1H, NCH), 3.94 (q, J=6 Hz, 1H,
angular NCH); mass spectrum, m/e (relative intensity) 183
(95), 168(26), 165(12), 150(100), 125(9), 124(9), 114(20),
102(29), 97(97), 84(29), 82(20); exact mass calcd for
C10H17NO2 m/e 183.1259, found m/e 183.1264.

Anal. Calcd. for C10H17NO2: C, 65.54; H, 9.35.
Found: C, 65.20; H, 9.51.

1-(2-Propenyl)-2,5-pyrrolidinedione (130). To a
mixture of 0.769 g (13.2 mmol)
of allyl alcohol, 1.44 g (14.6 mmol) of succinimide and 3.90
g (14.5 mmol) of triphenylphosphine in 18 mL of dry
tetrahydrofuran was added dropwise a solution of 2.51 g
(14.4 mmol) of diethyl azodicarboxylate in 5.5 mL of dry
tetrahydrofuran over a period of 30 min. The resulting
solution was stirred at room temperature for 40 min and
the solvent was removed in vacuo. The residue was
triturated with 30 mL of ethyl acetate (35:65) and filtered. The filtrate was concentrated in vacuo to give 4.03 g of a yellow oil. The oil was chromatographed over 50 g of silica gel (eluted with dichloromethane) to afford 1.57 g (85%) of imide 130 as a colorless liquid: NMR (CDCl₃) δ 2.60 (s, 4H, NCOCH₂), 3.93 (br d, J=6 Hz, 2H, allyl), 4.36-5.30 (m, 2H, =CH₂), 5.30-6.05 (m, 1H, -CH=).

1-(4-Pentenyl)-2,5-pyrroli- dinedione (131). To a mixture of 1.39 g (14.0 mmol) of succinimide, 3.05 g (11.6 mmol) of triphenylphosphine and 1.00 g (11.6 mmol) of 5-penten-1-ol in 17 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 2.03 g (11.6 mmol) of diethyl azodicarboxylate in 5 mL of dry tetrahydrofuran over a period of 30 min. The resulting solution was stirred at room temperature for 9 h and concentrated in vacuo. The residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filter cake was triturated again with 20 mL of ethyl acetate-hexane (3:7) and filtered. The combined filtrates were concentrated in vacuo. The residual oil was mixed with 30 mL of ethyl acetate-hexane (3:7), filtered and the filtrate was concentrated in vacuo to give 3.12 g of a pale-yellow oil. The oil was
chromatographed over 35 g of silica gel (eluted with dichloromethane) to yield 1.64 g (84%) of \(131\) as a colorless oil: IR (CCl\(_4\)) 1705 cm\(^{-1}\); NMR (CCl\(_4\)) \(\delta\) 1.65 (br qu, J=7 Hz, 2H), 2.03 (br q, J=7 Hz, 2H, allyl), 2.65 (s, 4H, NCOCH\(_2\)), 3.43 (t, J=7 Hz, 2H, NCH\(_2\)), 4.85-5.20 (m, 2H, =CH\(_2\)), 5.55-6.05 (tdd, J=17, 11, 7 Hz, 1H, -CH=); mass spectrum, m/e (relative intensity) 167(3), 125(6), 113 (16), 112(6), 100(100), 83(14); exact mass calcd for \(\text{C}_9\text{H}_{13}\text{NO}_2\) m/e 167.0946, found m/e 167.0948.

1-(2-Propenyl)-5-phenylthio-2-pyrrolidinone (45). To a solution of 394 mg (2.83 mmol) of imide 130 in 16 mL of absolute ethanol cooled in an ice-water bath under argon was added 305 mg (8.02 mmol) of sodium borohydride. To this stirred mixture was added a 1.49 N solution of hydrogen chloride in absolute ethanol in a rate of one drop every 5 min over a period of 1 h and 50 min. The resulting mixture was partitioned between 10mL of water, 10 mL of saturated aqueous sodium chloride and 40 mL of dichloromethane. The aqueous phase was extracted with four 20-mL portions of dichloromethane. The combined organic layers were dried (MgSO\(_4\)) and concentrated in vacuo to give 369 mg of a colorless oil. The oil was stirred with 8.2 mg (0.043 mmol) of p-toluenesulfonic acid
and 0.27 mL (2.63 mmol) of thiophenol at room temperature for 2.5 h and chromatographed directly over 20 g of silica gel (eluted with ethyl acetate-hexane, 2:8, followed by ethyl acetate-hexane, 35:65) to yield 552 mg (85%) of thiophenoxy lactam 45 as a colorless liquid: IR (neat) 1685 cm\(^{-1}\); NMR (CCl\(_4\)) \(\delta 1.50-2.60\) (m, 4H, NCOCH\(_2\)CH\(_2\)), 3.27 (t, J=6 Hz, 2H, NCH\(_2\)), 3.73 (d, J=6 Hz, 2H, allyl), 4.87-5.30 (m, 2H, =CH\(_2\)), 5.73 (tdd, J=18, 9, 6 Hz, 1H, -CH=); mass spectrum, m/e (relative intensity) 218(10), 124(M\(^+\)-SPh, 100), 109(14), 84(11).

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\text{1-(4-Pentenyl)-5-phenylthio-2-pyrrolidone (46). To a solution of 1.54 g (9.20 mmol) of imide 131 in 55 mL of absolute ethanol cooled in an ice water bath under argon was added 964 mg (25.5 mmol) of sodium borohydride. To this mixture was added a 1.6 N solution of hydrogen chloride in absolute ethanol in a rate of 10 drops every 10 min over a period of 3.5 h. The resulting mixture was acidified to pH 3 (about 20 mL of 1.6 N HCl-EtOH), stirred at 0°C for 1 h and basicified with 1% potassium hydroxide in absolute ethanol (about 10 mL) to pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The reaction mixture was partitioned between 100 mL of water and 50 mL of}
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dichloromethane. The aqueous phase was extracted with three 100-mL portions of dichloromethane, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give 1.70 g of crude ethoxylactam as a pale-yellow liquid. Part of this material (1.66 g) was dissolved in 10 mL of thiophenol followed by the addition of 71.0 mg (0.374 mmol) of p-toluenesulfonic acid monohydrate. The resulting solution was stirred under argon at room temperature for 1.5 h, diluted with 100 mL of dichloromethane and washed with 100 mL of 1 N sodium hydroxide solution. The aqueous layer was extracted with two 100-mL portions of dichloromethane, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford 2.30 g of a pale-yellow oil. The oil was chromatographed over 45 g of silica gel (eluted with ethyl acetate-hexane, 4:6) to yield 2.03 g (87%) of thiophenoxy-lactam 46 as a colorless oil: IR (CCl$_4$) 1700 cm$^{-1}$; NMR (CCl$_4$) δ 1.30-2.60 (m, 8H, -CH$_2$- manifold), 3.15 (td, J=14, 7 Hz, 1H, NCH), 3.67 (td, J=14, 7 Hz, 1H, NCH), 4.75-5.20 (m, 3H, NCHS, =CH$_2$), 5.73 (tdd, J=17, 10, 6 Hz, 1H, =CH-), 7.35 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 261(4), 189(3), 152(M$^+$-SPh, 100), 151(7), 110 (58), 109(18), 98(34), 96(38); exact mass calcd for C$_{15}$H$_9$NOS m/e 261.1187, found m/e 261.1193.

1-Allyl-2-pyrrolidinone (47). To a solution of 520 mg (2.23 mmol) of thiophenoxy-lactam 45 in 20 mL of
dry benzene heated at 80°C under argon was added dropwise over a period of 4.5 h a solution of 0.88 mL (3.3 mmol) of tri-n-butyltin hydride and 192 mg (0.111 mmol) of AIBN in 27 mL of dry benzene. The solvent was removed in vacuo, and the residue was dissolved in 30 mL of hexane and extracted with two 15-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo. The residue was bulb-to-bulb distilled to yield 247 mg (89%) of 47 as a colorless liquid: $\text{bp 100-105^\circ C/8 mmHg (lit.}\,^{115}105-107^\circ C/12 \text{ mmHg)}$; NMR (CCl$_4$) $\delta$ 1.50-2.60 (m, 4H, NCOCH$_2$CH$_2$), 3.27 (t, $J=6 \text{ Hz}, 2H, \text{NCH$_2$}$), 3.73 (d, $J=6 \text{ Hz}, 2H, \text{allyl}$), 4.87-5.30 (m, 2H, =CH$_2$), 5.73 (tdd, $J=18, 9, 6 \text{ Hz}, 1\text{H}, -\text{CH=}$).

**Cyclization of Thiophenoxy-lactam 46:** 

cis-(±)-Hexahydro-9-methyl-3(2H)-indolizinone (37), trans-(±)-Hexahydro-9-methyl-3(2H)-indolizinone (38), 1-(4-Pentenyl)-2-pyrrolidinone (48) and (±)-Octahydro-pyrrolo[1,2-a]azepin-3-one (49). To a solution of 1.00 g (4.02 mmol) of thiophenoxy-lactam 46 in 50 mL of dry
benzene heated to reflux under argon was added a solution of 1.29 g (4.43 mmol) of tri-n-butyltin hydride and 38.8 mg (0.236 mmol) of AIBN in 35 mL of dry benzene over a period of 2 h and 45 min. After heating for another 2 h, the solvent was removed in vacuo to give 2.40 g of a white turbid liquid. This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate followed by ethyl acetate-methanol, 98:2) and then over a Lobar size B column (eluted with ethyl acetate) to yield 52 mg (8%) of the least polar lactam 49 as a colorless liquid: IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.10-2.40 (m, SH, -CH$_2$- manifold), 3.20 (t, J=8 Hz, 2H, NCH$_2$), 3.33 (t, J=6 Hz, 2H, NCH$_2$), 4.70-5.13 (m, 2H, =CH$_2$-), 5.73 (tdd, J=17, 11, 6 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 153(18), 111(10), 99(64), 98(100), 86(10); exact mass calcd for C$_9$H$_{15}$NO m/e 153.1154, found m/e 153.1149. Continued elution gave 460 mg (75%) of lactams 37, 38 and 49 (32:40:28, respectively by GLC). Pure samples were obtained by preparative GLC of different column chromatography fractions (2m x 1/8 in
column packed with 10% OV-101 on Chrom W, Hp 80/100; column temperature = 170°C, flow rate = 25 mL/min).  37: $t_R$ = 5.40 min; IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CDCl$_3$, 300 MHz) $\delta$ 0.92 (d, $J$=6.2 Hz, 3H, -CH$_3$, collapses to s upon irradiation at 1.23), 1.04-1.22 (m, 2H, changing shape upon irradiation at 0.92), 1.31-1.49 (m, 1H), 1.52-1.86 (m, 3H), 2.16-2.30 (m, 1H), 2.33-2.42 (m, 2H), 2.56 (dt, $J$=13.5, 4.5 Hz, 1H, axial-NCH$_2$), 2.95 (q, $J$=9 Hz, collapses to t, $J$=9 Hz, upon irradiation at 1.23, 1H, NCH), 4.13 (br d, $J$=13.5 Hz, 1H, equatorial-NCH$_2$); mass spectrum, m/e (relative intensity) 153(60), 152(30), 138(20), 125(4), 124(4), 111(10), 99 (100), 97(7), 96(4), 86(5), 84(9), 83(13), 82(5); exact mass calcd for C$_9$H$_{15}$NO m/e 153.1154, found m/e 153.1158.  38: $t_R$=6.15 min; IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CDCl$_3$, 300 MHz) $\delta$ 0.90 (d, $J$=7 Hz, 3H, -CH$_3$, collapses to s upon irradiation at 1.92), 1.38-1.48 (m, 1H), 1.50-1.95 (m, 4H), 1.92 (m, collapses to q, $J$=3.6 Hz, upon irradiation at 0.90, 1H, CHCH$_3$), 1.99-2.10 (m, 1H), 2.34 (br t, $J$=9.1 Hz, 2H), 2.64 (br t, $J$=12.7 Hz, 1H, axial-NCH$_2$), 3.63 (ddd, $J$=9, 5.4, 3.6, collapses to dd, $J$=6.2, 4 Hz, upon irradiation at 1.92, 1H, NCH), 4.11 (br d, $J$=12.7 Hz, 1H, equatorial-NCH$_2$); mass spectrum, m/e (relative intensity) 153(54), 152(24), 138(18), 125(3), 124(4), 111(9), 110(10), 98(100), 97(7), 96(3), 86(4), 84(9), 83(13), 82(4); exact mass calcd for C$_9$H$_{15}$NO m/e 153.1154, found m/e 153.1156.  49: $t_R$= 6.75 min; IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CDCl$_3$, 300 MHz) $\delta$
1.40-1.70 (m, 8H, -CH₂- manifold), 1.70-1.90 (m, 1H), 2.10 (dt, J=11, 6.5, 4.5 Hz, 1H), 2.33-2.42 (m, 2H), 3.09 (td, J=15.5, 6.5 Hz, 1H, NCH), 3.65-3.82 (m, 2H, NCH); mass spectrum, m/e (relative intensity) 153(100), 152(31), 138 (40), 124(39), 122(9), 111(35), 110(38), 105(11), 98(44), 97(29), 96(10), 84(20), 82(12); exact mass calcd for C₉H₁₅NO m/e 153.1154, found m/e 153.1156.

(3R,4R)-1-(3-Butenyl)-3,4-dimethoxy-2,5-pyrrolidinedione

To a mixture of 5.95 mg (8.10 mmol) of 3-buten-1-ol, 1.29 g (8.10 mmol) of (3R,4R)-3,4-dimethoxy-2,5-pyrrolidinedione and 2.12 g (8.10 mmol) of triphenylphosphine in 11 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 1.41 g (8.10 mmol) of diethyl azodicarboxylate in 3 mL of dry tetrahydrofuran over a period of 30 min. The resulting solution was stirred at room temperature for 3 h and 20 min and the solvent was removed in vacuo. The residual solid was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The solid collected was triturated again with 20 mL of the same solvent pair. The combined extracts were concentrated in vacuo and the solid residue was triturated with 30 mL of ethyl acetate-hexane (3:7) and filtered. The
filtrate was concentrated in vacuo to give 2.65 g of a white solid. This material was chromatographed over 55 g of silica gel (eluted with ethyl acetate-hexane, 25:75) to yield 1.54 g (90%) of imide 58 as a colorless oil: NMR (CDCl₃) δ 2.35 (br q, J=7 Hz, 2H, allyl), 3.45-3.80 (t at 3.69, J=7 Hz, overlapped with s at 3.71, SH, NCH₂ and OCH₃), 4.09 (s, 2H, NCOCH), 4.90-5.20 (m, 2H, =CH₂), 5.71 (tdd, J=17, 9, 7 Hz, 1H, -CH=).

1-[((1α,2α,3β)-2,3-Diethenyl-cyclohexyl)-5-phenylthio-2-pyrrolidinone (50). A mixture of 222 mg (5.87 mmol) of sodium borohydride and 490 mg (2.10 mmol) of 1-[(1α,2α,3β)-2,3-diethenylcyclohexyl]-2,5-pyrrolidinedione⁵⁷,⁵⁹ in 13 mL of absolute ethanol was cooled in an ice-water bath under argon. Over a period of 3.5 h, three to four drops of 1.6 N ethanolic hydrogen chloride was added at 5 min intervals. The mixture was adjusted to pH 3 with 1.6 N ethanolic hydrogen chloride and stirred at 0°C for another 30 min. The mixture was then adjusted to pH 9 with a solution of 1% ethanolic potassium hydroxide. The temperature was maintained below 5°C throughout the entire process. The resulting mixture was partitioned between 25 mL of water and 50 mL of dichloromethane and the combined organic phases were dried
(Na$_2$SO$_4$) and concentrated in vacuo. The residual oil (519 mg) was stirred with 2.3 mL of thiophenol and 19.2 mg (0.1 mmol) of p-toluenesulfonic acid monohydrate for 30 min under argon. The mixture was partitioned between 30 mL of dichloromethane and 27 mL of 1 N aqueous sodium hydroxide. The aqueous phase was extracted with two 30-mL portions of dichloromethane and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residual yellow oil (621 mg) was first chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexane, 13:87) and then over a Lobar size B column (eluted with ethyl acetate-hexane, 1:9) to afford 419 mg (61%) of the least polar and major diasteromer of 50 as pale-yellow crystals: mp 92-94°C; IR (CCl$_4$) 1690 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.50-2.90 (m, 12H, -CH$_2$- manifold), 4.15-4.50 (m, 1H, NCH), 4.90-5.48 (m, 5H, =CH$_2$ and SCHN), 5.72-6.50 (m, 2H, =CH-), 7.15-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 218(M$^+$-SPh, 100), 217(5), 135(5), 134(5), 124(5), 110(15), 109(10), 93(15), 91(8), 84(40).

Further elution gave 27 mg (4%) of the minor diasteromer of 50 as a light yellow solid: mp 72.5-74.5°C; IR (CCl$_4$) 1700 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.30-3.00 (m, 12H, -CH$_2$- manifold), 3.70 (td, J=11, 3 Hz, 1H, NCH), 4.70-5.20 (m, 5H, =CH$_2$ and SCHN), 5.60 (m, 2H, =CH-), 7.15-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 218(M$^+$-SPh, 100), 217(7), 134(11), 110(29), 93(14), 84(41).
Continued elution gave 68 mg (12%) of the unreacted starting imide.

\[ (3\text{R},4\text{R})-1-(3\text{-Butenyl})-3,4\text{-dimethoxy-5-hydroxy-2-pyrroli-dinone (60)} \] and \( (2\text{R},3\text{S})-\text{N-}(3\text{-Butenyl})-2,3\text{-dimethoxy-5-hydroxybutyramide (132).} \)

To a solution of 268 mg (1.26 mmol) of imide 58 in 15 mL of absolute ethanol cooled in an ice-water bath under argon was added 150 mg (3.95 mmol) of sodium borohydride. A 1.6 N solution of hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 10 min over a 1.5 h period. The resulting mixture was partitioned between 10 mL of water and 50 mL of dichloromethane. The aqueous phase was extracted with three 25-mL portions of dichloromethane. The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to afford 259 mg of a colorless liquid. This material was chromatographed over 13 g of silica gel (eluted with ethyl acetate-hexane, 55:45, followed by ethyl acetate-methanol, 10:1) to yield 206 mg (76%) of carbinollactam 60 as a colorless liquid: NMR (CDCl\(_3\)) \( \delta \) 2.30 (br q, J=7 Hz, 2H, allyl), 3.00-3.75 (m with
two s at 3.50 and 3.57, 10 H, CH$_2$OCH and NCH$_2$), 4.60-5.20 (m, 4H, HOCHN and =CH$_2$), 5.74 (tdd, J=17, 10, 7 Hz, 1H, =CH-). Continued elution gave 20 mg (7%) of amide alcohol 132 as a colorless liquid: IR (CCl$_4$) 3410(br), 1660, 1525 cm$^{-1}$; NMR (CCl$_4$) 2.30 (br q, J=6 Hz, 2H, allyl), 3.00-3.90 (m with two s at 3.39 and 3.45, 13H, NCH$_2$, CH$_2$, OH, OCH and OCH$_2$), 4.90-5.25 (two overlapped d at 5.05, J=11 Hz, and 5.08, J=16 Hz, 2H, =CH$_2$), 5.80 (tdd, J=16, 11, 6 Hz, 1H, =CH-), 6.90(br s, 1H, NH); mass spectrum, m/e (relative intensity) 217(9), 187(4), 176(14), 156(18), 155(27), 143(73), 129(36), 119(36), 114(32), 102(18), 101(9), 98(14), 89(91), 88(50), 87(52), 86(32), 85(100); exact mass calcd for C$_{10}$H$_{19}$NO$_4$ m/e 217.1314, found m/e 217.1320.

(3R,4R)-1-(3-Butenyl)-3,4-dimethoxy-5-phenylthio-2-pyrrolidinone (53) and (3R,4R)-1-(4-Phenylthiobutyl)-3,4-dimethoxy-5-phenylthio-2-pyrrolidinone (59). A mixture of 55 mg (0.256 mmol) of carbinollactam 60, 3.0 mg (0.016 mmol) of p-toluenesulfonic acid monohydrate and 0.28 mL (2.73 mmol) of thiophenol was stirred under argon at room temperature for 8 h and partitioned between 20 mL of dichloromethane and 5 mL of 1 N sodium hydroxide solution. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The
Combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford 73.8 mg of a white turbid liquid. This material was chromatographed by MPLC over a Lobar size A column to give 34.7 mg (44%) of a diastereoisomeric mixture (1:1) of thiophenoxy-lactams 53 as a colorless oil. This mixture was used directly in the cyclization reaction. However, pure samples of each isomer could be obtained by collecting appropriate fractions; the more polar isomer of 53: IR (CCl$_4$) 1715 cm$^{-1}$; NMR (CCl$_4$) δ 2.21 (q, J=7 Hz, 2H, allyl), 3.02 (td, J=13, 7 Hz, overlaped with a d, J=8 Hz, at 2.95, 2H, NCH and OCH), 3.50-3.90 (two s at 3.45 and 3.46, 6H, OCH$_3$), 3.50-3.90 (m, 2H, NCH and OCH), 4.80-5.12 (m with d at 4.82, J=7 Hz, 3H, =CH$_2$ and SCHN), 5.42-5.88 (m, 1H, =CH-), 7.18-7.53 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 307(M$^+$, 0.5), 199(11), 198(M$^+$-SPh, 100), 170(8), 166(3), 138(2.5), 119(3), 117(3), 110(4), 109(2), 110 (8.5); the less polar isomer of 53: IR (CCl$_4$) 1710 cm$^{-1}$; NMR (CCl$_4$) δ 2.18 (q, J=7 Hz, 2H, allyl), 3.05-4.00 (m with two s at 3.46 and 3.51, 10H, -CH$_3$ and -CH$_2$- manifold), 4.49 (d, J=3 Hz, 1H, SCHN), 4.82-5.10 (m, 2H, =CH$_2$), 5.40-6.00 (m, 1H, =CH-), 7.20-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 307(M$^+$, 0.2), 198
Continued elution gave 21.7 mg (19%) of dithiophenoxy lactam 59 as a colorless oil: IR (CCl₄) 1710 cm⁻¹; NMR (CCl₄) δ 1.40-1.75 (m, 4H, -CH₂- manifold), 2.70-3.20 (m with d, J=8 Hz, at 3.01, 4H, COCHO, NCH and SCH₂), 3.45 (s, 6H, OCH₃), 3.65-3.87 (m with dd, J=12, 6 Hz, at 3.70, 2H, OCH and NCH), 4.83 (d, J=6 Hz, 1H, SCHN), 7.00-7.55 (m, 10H, Ar-H); mass spectrum, m/e (relative intensity) 308(M⁺-SPh, 100), 276(14), 243(7), 212(4), 198(9), 165 (50), 158(4), 128(14), 123(14), 117(9), 110(9), 109(4), 101(23), 99(9), 98(9).

Cyclization of Thiophenoxy lactam 50: (4α,8α,9α,9α₉)-(±)-8-Ethenyldecahydro-9-methyl-3H-pyrrolo [1,2-a]indol-3-one (51) and (3α,5α,6α,9α₉)-(±)-6-Ethenyldecahydro-pyrrolo[1,2-a]quinolin-1(2H)-one (52). To a solution of 398 mg (1.22 mmol) of the major diastereomer of 50 in 16 mL of dry benzene warmed under argon at 80°C was added dropwise a solution of 0.4 mL (0.152 mmol) of tri-n-butyltin hydride and 12 mg (0.07 mmol) of AIBN in 11 mL of benzene over a 100 min period. The
resulting solution was warmed at 80 °C for 2 h, cooled to room temperature, and concentrated in vacuo. The residual yellow oil (866 mg) was chromatographed first over 40 g of silica gel (eluted with ethyl acetate-hexane, 55:45) and then over a Lobar size A column to give 136 mg (51%) of 51 as a pale-yellow oil: IR (CCl₄) 1690 cm⁻¹; NMR (CDCl₃) δ 0.87 (d, J=6 Hz, 3H, -CH₃), 1.09-1.40 (m, 3H), 1.46-2.17 (m, 9H), 2.38 (ddd, J=16, 9, 3 Hz, 1H, COCH), 2.74 (ddd, J=16, 11.7, 8.6 Hz, COCH), 3.92 (q, J=5 Hz, 1H, pyrrolizidinone angular NCH), 4.22 (td, J=9, 6.5 Hz, 1H, NCH), 4.98-5.07 (m, 2H, =CH₂), 5.78 (ddd, J=17, 9, 8 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 219(100), 204(10), 190(6), 176(19), 164(6), 150(13), 138(13), 136 (13), 134(13), 114(32), 93(13), 84(32); exact mass calcd for C₁₄H₂₁NO m/e 219.1623, found m/e 219.1615.

Continued elution afforded 83 mg (31%) of lactam 52, which was identical in all respects to the material prepared via the N-acyliminium ion route: mp 46-50 °C; IR (CHCl₃) 1670 cm⁻¹; NMR (CDCl₃) δ 1.0-2.5 (m, 16H), 3.4 (m, 1H, C(3a)H), 4.09 (m, 1H, C(9a)H), 4.8-5.2 (m, 2H, =CH₂), 6.0 (eight-line m, 1H, =CH-); exact mass calcd for C₁₄H₂₁NO m/e 219.1881, found m/e 219.1885.

Cyclization of Thiophenoxylactam 53: (3R,4S)-1-(3-Butenyl)-3,4-dimethoxy-2-pyrrolidinone (54), (1S,2R)-Hexahydro-1,2-dimethoxy-3(2H)-indolizinone (55), (1S,2R,7S,
To a solution of 392 mg (1.28 mmol) of thio-phenoxylactams \( \text{53} \) in 16.5 mL of dry benzene warmed under argon at 80°C was added a solution of 0.41 mL (1.60 mmol) of tri-\( n \)-butyltin hydride and 12.2 mg (0.0744 mmol) of AIBN in 11.5 mL of dry benzene over a period of 1 h and 40 min. The resulting solution was heated for another 1.5 h, and the solvent was removed in vacuo to give a white turbid liquid (975 mg). This material was chromatographed first over 17 g of silica gel (eluted with ethyl acetate-hexane, 65:35, followed by ethyl acetate) and then over a Lobar size B column (eluted with ethyl acetate-hexane, 55:45) to give 61.6 mg (24%) of the less polar lactam \( \text{54} \) as a colorless oil: IR (CC\( \text{l}_4 \)) 1700 cm\(^{-1} \); NMR (CC\( \text{l}_4 \)) \( \delta \) 2.25 (q, \( J=7 \) Hz, 2H, allyl), 2.88-3.91 (m with two s at 3.36 and 3.59, 12H), 4.83-5.27 (m, 2H, =CH\(_2\)), 5.40-6.18 (m, 1H, =CH\(-\)); mass spectrum, \( m/e \) (relative intensity) 199(50), 169(8), 158(100), 139(16), 131(53), 127(5), 102(82); exact
Continued elution gave 72.2 mg (28%) of a colorless oil. GLC analysis (6 ft x 1/8 in column packed with 10% FFAP on WAW, 90/100 mesh; column temperature= 190°C, flow rate= 17 mL/min) showed the presence of three components with t_R= 17.7 min, t_R=21.0 min and t_R= 23.3 min in a ratio of 9:50:41. Preparative GLC (2m x 1/8 in column packed with10% OV-101 on Chrom W; column temperature= 170°C, flow rate= 28 mL/min) combined with high field ¹H NMR analysis shown that the minor component was lactam 57: characteristic peaks in NMR (CDCl₃, 300 MHz) δ 1.15 (d, J=6.5 Hz, 3 H, -CH₃), 1.60-1.95 (m, 2H), 2.09-2.21 (m, 1H), 3.09-3.19 (m, 2H, NCH₂), 3.40-3.70 (m with two s at 3.48 and 3.67, SH, OCH₃, OCH and angular-NCH), 4.16 (d, J=7 Hz, 1H, NCOCH). The other two components, identical with authentic samples prepared via another route (vide infra), were lactams 55: NMR (CDCl₃, 300 MHz, signals due to major isomer) δ 2.62 (br t, J=12 Hz, 1H, axial-NCH₂), 3.18 (sebtet, 1H, NCH), 3.47 (s, 3H, OCH₃), 3.52 (t, J=5.5 Hz, 1H, CHOMe), 3.68 (s, 3H, OCH₃), 3.88 (d, J=5.5 Hz, 1H, COCHOMe), 4.16 (br d, J=12 Hz, 1H, equatorial-NCH₂), NMR (CDCl₃, 300 MHz, signals due to minor isomer) δ 2.64 (m, 1H, axial-NCH₂), 3.44 (s, 3H,
OCH₃), 3.60 (m, 2H, CHOME and angular-NCH), 3.64 (s, 3H, OCH₃), 3.85 (d, J=4 Hz, 1H, COCH₃), 4.16 (br d, J=13 Hz, 1H, equatorial-NCH₂).

Continued elution gave 78.3 mg (31%) of lactam 56 as a colorless oil: IR (CCl₄) 1710 cm⁻¹; NMR (CCl₄, 300 MHz)

δ 0.94 (d, J=6.5 Hz, 3H, -CH₃), 1.70 (11 line m, 1H, H₂a), 2.17 (11 line m, 1H, H₂b), 2.39 (q with fine coupling, 1H, H₁), 3.08 (t with fine coupling, 1H, H₃a), 3.44 (s, 3H, OCH₃), 3.49 (m, 1H, H₃b), 3.62 (t, 1H, H₇), 3.69 (s, 3H, OCH₃), 3.76 (t, 1H, H₇), 4.18 (d with fine coupling, 1H, H₆); JH₁-CH₃=6.5 Hz; JH₁-H₂a=2.6 Hz; JH₁-H₂b=6.5 Hz; JH₂a-H₂b=12 Hz; JH₂a-H₃a=3 Hz; JH₂b-H₃a=7 Hz, JH₂b-H₂b=9 Hz, JH₂b-H₃b=9 Hz, JH₃a-H₃b=12 Hz, JH₆-H₇=6.5 Hz, JH₇-H₈=6.5 Hz, JH₅-H₁=6.5 Hz; irradiation of CH₃ gives 5% of NOE at H₁; irradiation of H₉ gives 5% NOE at H₁; mass spectrum, m/e (relative intensity) 199(13), 184(10), 169(66), 168(18), 167(3), 154(7), 140(7), 139(4), 138(39), 128(7), 126(15), 88(100), 85(35), 84(44); exact mass calcd for C₁₀H₁₇NO₃ m/e 199.1208, found m/e 199.1212.

(1S,2R)-Hexahydro-1,2-dimethoxy-7-formyloxy-3(2H)-indolizinone (61). A solution of 146 mg (0.677 mmol) of carbinollactam 60 in 1.5 mL of formic acid was stirred at
room temperature for 18 h, and the excess formic acid was removed in vacuo. The residue was dissolved in 20 mL of dichloromethane and washed with 5 mL of saturated sodium bicarbonate aqueous solution.

The aqueous phase was extracted with two 10-mL portions of dichloromethane and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford 156 mg of a pale-yellow oil. Part of this material (130 mg) was chromatographed over Lobar size A column (eluted with ethyl acetate-hexane, 1:1) to yield 107 mg (78%) of isomeric mixture of 61 as a colorless oil: NMR (CCl₄) 1.20-5.40 (m with s at 3.40, 3.59 and 3.63, 16H), 7.90-8.10 (overlaped d, J=1 Hz, at 7.92 and br s at 8.03, 1H, OCHO).

**(1S,2R)-Hexahydro-1,2-dimethoxy-7-hydroxy-3(2H)-indolizinone (62).** A solution of 105 mg (0.432 mmol) of formate 61 in 1.1 mL of a 0.95 N solution of sodium hydroxide in aqueous methanol (H₂O-MeOH, 1:5) was stirred at room temperature for 30 min and partitioned between 20 mL of dichloromethane and 5 mL of saturated aqueous sodium chloride solution. The aqueous phase was extracted
with five 10-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to give a pale-yellow oil (90 mg). The oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate followed by ethyl acetate-methanol, 9:1) to afford 82 mg (88%) of a mixture of isomeric alcohols as a white solid: mp 63-107°C; IR (CCl$_4$) 3580, 3410(br), 1690 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.00-2.85 (m with dt at 2.66, J=12, 3 Hz, 6H), 3.00-4.40 (m with s at 3.45, 3.49, 3.62 and 3.66, 11H, OCH$_3$ and others); mass spectrum, m/e (relative intensity) 215(6), 185(50), 154(100), 136(6), 100(10), 88(94), 95(26); exact mass calcd for C$_{10}$H$_{17}$NO$_4$ m/e 215.1157, found m/e 215.1163.

(1S,2R)-Hexahydro-1,2-dimethoxy-3(2H)-indolizinone (55). To a mixture of 1.3 mg (0.019 mmol) of imidazole and 33 mg (1.4 mmol) of mineral oil free sodium hydride under argon was added a solution of 80 mg (0.37 mmol) of carbinollactam 60 in 1.7 mL of dry tetrahydrofuran. The resulting mixture was heated at 60°C for 30 min followed by the addition of 0.15 mL of carbon disulfide. After stirring at 60°C for 5 min, 0.15 mL of methyl iodide was added in a single portion. The reaction mixture was diluted with 20 mL of dichloromethane and
washed with 7 mL of water. The aqueous phase was extracted with three 10-mL portions of dichloromethane. The combined organic layers were dried (\(\text{Na}_2\text{SO}_4\)) and concentrated in vacuo to give a brown oil (112 mg). This material was chromatographed first over 5 g of silica gel (eluted with ethyl acetate-hexane, 4:6, followed by ethyl acetate-hexane, 6:4) and then over a Lobar size A column to yield 45.2 mg (40%) of the less polar diastereomeric mixture of xanthates 63 as a yellow oil: IR (\(\text{CH}_2\text{Cl}_2\)) 1700, 1220, 1060 cm\(^{-1}\); NMR (\(\text{CCl}_4\)) \(\delta\) 1.20-1.90 (m, 2H, \(-\text{CH}_2\)-), 1.90-3.00 (m with s at 2.59, 6H, \(\text{SCH}_3\) and others), 3.10-3.85 (m with s at 3.43, 3.58 and 3.67, 9H, \(\text{OCH}_3\) and others), 4.21 (br dd, J=13.5 Hz, 1H, equatorial-\(\text{NCH}_2\)), 5.37-5.90 (m, 1H, CSOCH). Continued elution gave 12.0 mg (10%) of another diastereomeric mixture of xanthates 63 as a yellow oil: IR (\(\text{CH}_2\text{Cl}_2\)) 1695, 1210, 1050 cm\(^{-1}\); NMR (\(\text{CCl}_4\)) \(\delta\) 1.20-1.93 (m, 2H, \(-\text{CH}_2\)-), 1.93-2.73 (m with s at 2.59, 5H, \(\text{SCH}_3\) and others), 2.95 (br t, J=13 Hz, 1H, axial-\(\text{NCH}_2\)), 3.20-3.87 (m with s at 3.40, 3.57 and 3.63, 9H, \(\text{OCH}_3\) and others), 4.03 (br dd, J=13, 6 Hz, 1H, equatorial-\(\text{NCH}_2\)), 5.95-6.05 (br s, 1H, CSOCH).
A solution of the major diastereoisomeric mixture of xanthates 63 (45.2 mg, 0.143 mmol), 0.05 mL (0.19 mmol) of tri-n-butyltin hydride and 1.8 mg (0.011 mmol) of AIBN in 2.9 mL of dry toluene was heated under argon at 80°C for 1 h and 45 min. The solvent was removed in vacuo and the residue was chromatographed first over 5 g of silica gel (eluted with ethyl acetate-hexane, 1:1) then over 5 g of silica gel (eluted with ethyl acetate-hexane, 65:35) and finally over 3 g of silica gel (eluted with ethyl acetate-hexane, 65:35) to yield 10.2 mg (35%) of a mixture of isomeric lactams 55 in a ratio of 64:36, respectively, by GLC ($t_R=20.9, 23.2$ min, respectively; 6 ft x 1/8 in column packed with 10% FFAP on WAW, 80/100 mesh; column temperature= 190°C, flow rate= 17 mL/min): IR (CCl₄) 1700 cm⁻¹; NMR (CDCl₃, 300 MHz) δ 1.20-2.14 (m, 6H); signals due to major isomer, 2.62 (br t, $J=12$ Hz, 1H, axial-NCH₂), 3.18 (septet, 1H, NCH), 3.47 (s, 3H, OCH₃), 3.52 (t, $J=5.5$ Hz, 1H, OCHMe), 3.68 (s, 3H, OCH₃), 3.88 (d, $J=5.5$ Hz, 1H, COCHOMe), 4.16 (br d, $J=12$ Hz, 1H, equatorial-NCH₂); for minor isomer, 2.64 (m, 1H, axial-NCH₂), 3.44 (s, 3H, OCH₃), 3.60 (m, 2H, CHOMe and angular-NCH), 3.64 (s, 3H, OCH₃), 3.85 (d, $J=4$ Hz, 1H, COCHOMe), 4.16 (br d, $J=13$ Hz, 1H, equatorial-NCH); mass spectrum, m/e (relative intensity) 199(4), 184(4), 170(5), 169(43), 168(9), 140(14), 139(12), 138(100); exact mass calcd for C₁₀H₁₇NO₃ m/e 199.1208, found m/e 199.1204.
6-(Tetrahydro-2H-pyran-2-yl-oxy)-3-hexyn-2-ol (76). To a solution of 7.99 g (51.9 mmol) of 3-(2-tetrahydro-2H-pyran-2-yl-oxy)butyne in 50 mL of dry tetrahydrofuran cooled in a dry ice-acetone bath under argon was added dropwise 51 mL of a 1.06 N solution of n-butyllithium in hexane over a period of 25 min. The resulting solution was stirred at -78 °C for 30 min and at -20 °C (dry ice-carbon tetrachloride bath) for 10 min followed by the addition of a solution of 5.8 mL (104 mmol) of fresh distilled acetaldehyde in 25 mL of dry tetrahydrofuran over a 20 min period. The reaction mixture was stirred at -20 °C for 20 min and partitioned between 300 mL of ether and 50 mL of water. The aqueous phase was extracted with 100 mL of ether. The combined organic layers were washed with 50 mL of brine, dried (MgSO₄) and concentrated in vacuo to give 11.4 g of a pale yellow oil. The oil was vacuum distilled to yield 8.06 g (78%) of alkynol 76 as a pale-yellow oil: bp 100-101 °C/0.3 mmHg; IR (CCl₄) 3620, 3450(br) cm⁻¹; NMR (CCl₄) δ 1.10-2.15 (m with d, J=7 Hz, at 2.35, 10H, -CH₃, -OH and -CH₂- manifold), 2.41 (dt, J=7, 2 Hz, 2H, -CCH₂), 3.30-3.95 (m, 4H, OCH₂), 4.33 (br s, 1H, -CCH), 4.67 (br s, 1H, OCHO); mass spectrum, m/e (relative intensity) 99(12),
The resulting mixture was stirred at room temperature for 10 min followed by the addition of a solution of 8.53 g (43.1 mmol) of alkynol 76 in 50 mL of dry tetrahydrofuran over a 40 min period. The reaction mixture was heated to reflux for 1 h. The reaction flask was cooled in an ice-water bath and 4.5 mL of water, 4.5 mL of 3 N sodium hydroxide solution and 13.4 mL of water was carefully added in sequence. The resulting mixture was stirred at room temperature for 90 min, filtered and concentrated in vacuo. The residual colorless oil was vacuum distilled to afford 8.31 g (96%) of allylic alcohol 77 as a colorless oil: bp 94°C/0.4 mmHg; IR (CCl₄) 3610, 3430(br) cm⁻¹; NMR (CCl₄) δ 1.20 (d, J=7 Hz, 3H, -CH₃), 1.33-2.00 (m, 7H, -CH₂- manifold and OH), 2.27 (br q, J=6 Hz, 2H, CH₂C=), 3.20-3.95 (m, 4H, OCH₂), 4.15 (br s, 1H, =OCH), 4.53 (br s, 1H, OCHO), 5.50-5.67 (m, 2H, =CH-); mass spectrum, m/e (relative intensity) 98(M⁺-THPOH, 19), 84(100), 83(62).
Stereorandom Synthesis of Alcohol 77. To 5.25 g (34.1 mmol) of 3-(2-tetrahydro-2H-pyran-2-yl-oxy)butyne under argon was added 20.0 mL (22.1 g, 75.8 mmol) of tri-n-butyltin hydride and 65 mg (0.40 mmol) of AIBN. The resulting mixture was stirred at 130°C for 2 h. A small amount of AIBN was added, and the mixture was heated for another 3 h. The excess tin hydride was distilled off at 0.25 mmHg until the temperature of the distillation head reached 140°C. The residue in the distillation flask was chromatographed over 100 g of silica gel (eluted with hexane followed by ethyl acetate-hexane, 25:75) to give 11.3 g of vinyltin 81 as a colorless liquid (R_f = 0.28; silica gel; ethyl acetate-hexane, 15:85): NMR (CCl_4) δ 0.50-2.10 (m, 33H), 2.10-2.55 (m, 2H, allyl), 3.20-4.00 (m, 4H, OCH_2), 4.50 (br s, 1H, OCHO), 5.50-6.40 (m, 2H, =CH-).

To a solution of 11.3 g of the material prepared above in 25 mL of dry tetrahydrofuran cooled in a dry ice-acetone bath under argon was added dropwise 26.4 mL of a 0.995 N solution of n-butyllithium in hexane over a period of 30 min. The resulting light yellow solution was stirred at -78°C for 1.5 h. The cold bath was replaced with a dry ice-carbon tetrachloride bath and the reaction mixture was stirred at -20°C for 30 min. To the resulting mixture was added a solution of 3 mL (53.7 mmol) of fresh distilled acetaldehyde in 25 mL of dry tetrahydrofuran
over a 20 min period. The mixture was stirred at -20°C for another 40 min and then partitioned between 50 mL of water and 50 mL of ether. The aqueous phase was extracted with 50 mL of ether. The combined organic layers were washed with 50 mL of brine, dried (MgSO₄) and concentrated in vacuo to give a pale-yellow liquid (14.5 g). This material was chromatographed over 100 g of silica gel (eluted with hexane followed by ethyl acetate-hexane, 15:85, and finally with ethyl acetate-hexane, 35:65) to give 4.51 g (99%) of **77** as a pale yellow liquid: NMR (CDCl₃) δ 1.20 (d, J=7 Hz, -CH₃), 1.33-2.00 (m, 7H, -CH₃- manifold), 2.10-2.50 (m, 2H, CH₂C=), 3.20-3.95 (m, 4H, OCH₂), 4.15 (br s, 1H, =CCH), 4.53 (br s, 1H, OCHO), 5.30-5.70 (m, 2H, =CH-). GLC analysis (6 ft x 1/8 in column packed with 3% SE-30 on WAW, 80/100 mesh; column temperature= 140°C, flow rate= 25 mL/min) showed that this material consists of three components in a ratio of 4:23:73 (t_R = 8.8 min, 9.4 min and 10.2 min, respectively). The major component was identical with the pure trans isomer of **77** prepared from **76** (homogeneous by GLC under the same conditions, t_R = 10.2 min) by coinjection study. The second major component (t_R = 9.4 min) was assumed to be the cis isomer of **77** and the minor component (t_R = 8.8 min) was not identified by all means.
(E)-6-(Tetrahydro-2H-pyran-2-yloxy)-3-hexen-2-ol Acetate (78). To a solution of 8.02 g (40.1 mmol) of allyl alcohol 77 and 47.4 mg (0.390 mmol) of 4-dimethylaminopyridine in 40 mL of dry pyridine under argon was added 6.7 mL (71.0 mmol) of dry acetic anhydride. The reaction mixture was stirred at room temperature for 1.5 h. The resulting solution was diluted with 300 mL of ether, shaken with 20 mL of water for a few minutes in a separatory funnel and washed with 150 mL of 3 N aqueous hydrochloric acid. The aqueous phase was extracted with 200 mL of ether. The combined organic layers were washed with 100 mL of water, 100 mL of saturated aqueous sodium bicarbonate, 100 mL of saturated aqueous sodium chloride, dried (MgSO₄) and concentrated in vacuo to yield 9.68 g (100%) of allylic acetate 78 as a colorless oil. This material was used directly in subsequent reactions: IR (CCl₄) 1730 cm⁻¹; NMR (CCl₄) δ 1.27 (d, J=6 Hz, 3H, =CCHCH₃), 1.40-1.95 (m, 6H, -CH₂- manifold), 1.96 (s, 3H, COCH₂), 2.29 (br q, J=6 Hz, 2H, =CCH₂), 3.15-3.89 (m, 4H, OCH₂), 4.52 (br s, 1H, OCHO), 5.10-5.95 (m, 3H, =CCHO and =CH-); mass spectrum, m/e (relative intensity) 98(12), 94 (100), 83(55), 80(12), 79(17), 69(22), 68(23), 67(28).
(E)-3-Hexene-1,5-diol 5-Acetate (79). A solution of 3.12 g (12.9 mmol) of allylic acetate 78 in 80 mL of acetic acid, 40 mL of tetrahydrofuran and 25 mL of water was heated at 45°C for 4 h and 40 min.

The resulting solution was diluted with 200 mL of ether and 300 mL of water. Sodium bicarbonate (120 g) was added portionwise with stirring. The resulting mixture was filtered. The filtrate was diluted with 100 mL of ether and the layers were separated. The organic layer was washed with three 50-mL portions of saturated aqueous sodium bicarbonate, three 200-mL portions of water, 100 mL of saturated sodium chloride solution, dried (MgSO₄) and concentrated in vacuo to give 1.18 g of a pale-yellow liquid. The aqueous washes and filter cake were combined and extracted with 500 mL of ether. The ether layer was washed with 100 mL of brine, dried (MgSO₄) and concentrated in vacuo to give 1.09 g of a colorless liquid. The combined aqueous phases were extracted again with 500 mL of dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo to afford 0.494 g of a colorless liquid. The combined crude product was vacuum distilled to give 1.80 g of a colorless liquid: bp 75-77°C/0.75 mmHg. This material was chromatographed over 35 g of
silica gel (eluted with ethyl acetate-hexane, 3:7, followed by ethyl acetate-hexane, 4:6) to yield 1.57 g (77%) of alcohol 79 as a colorless liquid: IR (CCl₄) 3450(br), 1730 cm⁻¹; NMR (CCl₄) δ 1.27 (d, J=6 Hz, 3H, =CCCH₃), 1.96 (s, 3H, COCH₃), 2.09-2.37 (m, 3H, -CH₂C= and OH), 3.53 (br t, J=6 Hz, OCH₂), 5.00-5.85 (m, 3H, OCH and =CH-); mass spectrum, m/e (relative intensity) 115(M⁺-Acyl, 12), 98 (42), 83(38), 81(12), 80(19), 79(31), 77(8), 71(15), 70 (4), 69(23), 68(100), 67(77), 66(8), 65(15).

(E)-1-(5-Acetoxy-3-hexenyl)-2,5-pyrrolidinedione (80). To a mixture of 2.99 g (19.0 mmol) of trans alcohol 79, 1.87 g (19.9 mmol) of succinimide and 4.96 g (19.9 mmol) of triphenylphosphine in 24 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 3.29 g (19.9 mmol) of diethyl azodicarboxylate in 7 mL of dry tetrahydrofuran over a period of 40 min. The resulting solution was stirred at room temperature for 2 min, and the solvent was removed in vacuo. The residue was triturated with 65 mL of ethyl acetate-hexane (3:7) and filtered. The filter cake was triturated again with 30 mL of the same solvent pair. The combined extracts were concentrated in vacuo, suspended in 60 mL of ethyl
acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo to afford 6.75 g of a pale-yellow oil. The oil was chromatographed over 90 g of silica gel (eluted with dichloromethane followed by 0.25% methanol in dichloromethane and finally with 0.5% methanol in dichloromethane) to yield 2.91 g (61%) of imide 80 as a pale-yellow oil. Collection of latter fractions gave 1.81 g of a mixture of yellow oil and white solid. This material was suspended in carbon tetrachloride and filtered twice to remove insoluble solids. The filtrate was concentrated in vacuo to afford a pale-yellow oil. The oil was distilled at 0.5 mmHg at 110°C with a bulb-to-bulb apparatus to trap 209 mg of a colorless liquid identified as the unreacted alcohol with 1.03 g (23%) of imide 80 left in the distillation flask as a pale-yellow oil: IR (CCl₄) 1740, 1705 cm⁻¹; NMR (CCl₄) δ 1.28 (d, J=6 Hz, 3H, OCHCH₃), 1.93 (s, 3H, COCH₃), 2.30 (br q, J=6 Hz, =CHCH₂), 2.57 (s, 4H, NCOCH₂), 3.48 (t, J=6 Hz, 2H, NCH₂), 4.95-5.75 (m, 3H, OCH, =CH-); mass spectrum, m/e (relative intensity) 197(23), 196(M⁺-Acyl, 17), 179(53), 140(10), 136 (10), 127(13), 113(8), 112(8), 100(40), 98(13), 97(20), 85(13), 84(20), 83(12), 82(5), 81(33), 90(100), 79(20).

Anal. Calcd. for C₁₂H₁₇N₀₄: C, 60.24; H, 7.16. Found: C, 60.06; H, 7.22.

1-(5-Acetoxy-3-hexenyl)-5-phenylthio-2-pyrrolidinone (74). To a solution of 3.92 g (16.0 mmol) of imide 80 in
90 mL of absolute ethanol cooled in an ice-water bath under argon was added 1.78 g (47.2 mmol) of sodium borohydride. A 1.49 N solution of hydrogen chloride was added at a rate of 3 drops every 5 min over a period of 2 h and 15 min. The resulting mixture was partitioned between 50 mL of water, 50 mL of saturated sodium chloride solution and 150 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 3.76 g of crude carbinolactam as a colorless oil. The oil was stirred with 60.0 mg (0.320 mmol) of p-toluenesulfonic acid monohydrate and 1.61 mL (15.7 mmol) of thiophenol at room temperature for 2 h and chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 4:6, followed by ethyl acetate-hexane, 1:1) to afford 4.63 g (97%) of thiophenoxylactam 74 as a colorless oil: IR (CCl₄) 1740, 1700 cm⁻¹; NMR (CCl₄)

\[
\begin{align*}
\text{OAc} & \quad \text{SPh} \\
\text{74} & \\
\end{align*}
\]

- 1.27 (d, J=6 Hz, 3H, OCHCH₃),
- 1.42-2.55 (m with s at 1.97, 9H, COCH₃ and -CH₂-
- manifold),
- 3.20 (dt, J=12, 6 Hz, 1H, NCH),
- 3.80 (dt, J=12, 6 Hz, 1H, NCH),
- 4.82 (dd, J=8, 3 Hz, 1H, NCHS),
- 4.95-5.40 (m, 1H, OCH),
- 5.40-5.70 (m, 2H, =CH-),
- 7.31 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 224
Cyclization of Thiophenoxy-lactam 74: 1-(5-Acetoxy-3-hexenyl)-2-pyrrolidinone (82), Hexahydro-8-(1-acetoxy)ethyl-3(2H)-indolizinone (83), cis-(±)-Hexahydro-7-(2-acetoxy)-propyl-3H-pyrrolizin-3-one (84) and trans-(±)-Hexahydro-7-(2-acetoxy)propyl-3H-pyrrolizin-3-one (85). To a solution of 4.61 g (13.8 mmol) of thiophenoxy lactam 74 in 200 mL of dry benzene heated under argon at 80°C was added a solution of 5.10 mL (19.3 mmol) of tri-n-butyltin hydride and 71.8 mg (0.438 mmol) of AIBN in 120 mL of dry benzene over a 23 h period. The solvent was removed in vacuo, and the residue was chromatographed over 120 g of silica gel (eluted with ethyl acetate followed by ethyl acetate-methanol, 9:1) and then over a Lobar size C column (eluted with ethyl acetate-hexane, 95:15, followed by ethyl acetate) to afford in total 2.85 g (95%) of lactams 82, 83, 84 and 85 in a ratio of 5:4:9:82, respectively, by NMR integration. A pure sample of the least polar 82 could not be obtained and it
was characterized only by its $^1$H NMR (CCl$_4$) $\delta$ 1.23 (d, J=6 Hz, 3H, OCHCH$_3$), 1.73-2.36 (m with s at 1.82, 9H, OCOCH$_3$ and -CH$_2$- manifold), 3.10-3.37 (m, 4H, NCH$_2$), 5.00-5.60 (m, 3H, -OCH and -CH=); 83 was not separable from 85 and was characterized only after hydrolysis of the acetate in its alcohol form (vide infra). 85 (2.22 g, 71%): IR (CCl$_4$) 1740, 1700 cm$^{-1}$; NMR (CCl$_4$, 90 MHz) 1.13-1.30 (two overlapped d, J=1.2 Hz, at 1.18 and 1.20, 3H, OCHCH$_3$), 1.37-2.59 (m with s at 1.93, 12H), 2.59-2.98 (m, 1H, NCH), 3.30-3.70 (m, 1H, NCH), 3.99 (br q, J=6 Hz, 1H, angular-NCH), 4.57-5.00 (m, 1H, OCH); NMR (CDCl$_3$, 200 MHz) $\delta$ 1.21-1.28 (two overlapped d, J=6 Hz, at 1.24 and 1.25, 3H, OCHCH$_3$), 1.30-2.80 (m with s at 2.05, 12H, -CH$_2$- manifold), 2.98-3.07 (m, 1H, NCH), 3.47-3.72 (m, 1H, NCH), 4.02 (q, J=6 Hz, 1H, angular-NCH), 4.89-5.03 (m, 1H, OCH); mass spectrum, m/e (relative intensity) 225(9), 182(4), 138(6), 123(12), 97(100), 86(10), 84(10); exact mass calcd for C$_{12}$H$_{19}$NO$_3$ m/e 225.1365, found m/e 225.1371.  The most polar 84: IR (CCl$_4$) 1740, 1700 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.25 (d, J=6 Hz, 3H, OCHCH$_3$), 1.36-2.83 (m with s at 1.89, 12H), 3.05 (br t, J=11 Hz, 1H, NCH), 3.23-3.66 (m, 2H, NCH and angular-NCH), 4.67-5.00 (br s, 1H, OCH); mass spectrum, m/e (relative intensity) 225(16), 182(6), 138(16), 123
trans-(±)-Hexahydro-7-(2-hydroxy)propyl-3H-pyrrolizin-3-one (86) and Hexahydro-8-(2-hydroxy)propyl-3(2H)-indolizinone (133). To 2.15 g (9.54 mmol) of lactam acetate \( \text{85} \) was added 25 mL of a 1.04 N solution of sodium hydroxide in aqueous methanol (\( \text{H}_2\text{O-MeOH, 1:5} \)). The resulting solution was stirred at room temperature for 15 min, diluted with 700 mL of dichloromethane, saturated with sodium chloride, dried (\( \text{MgSO}_4 \)) and concentrated in vacuo to give 1.69 g of a pale-yellow oil. The oil was chromatographed over a Lobar size C column (eluted with ethyl acetate-methanol, 92:8). Overlapping fractions were rechromatographed over a Lobar size B column (eluted with 5% methanol in ethyl acetate), and the overlapping part was chromatographed again over the same column (eluted with 2% methanol in ethyl acetate) to yield in combination 60.3 mg (3%) of the least polar \( \text{133} \) as a colorless oil: IR (\( \text{CCl}_4 \)) 3400 (br), 1670 cm\(^{-1} \); NMR (\( \text{CDCl}_3 \)) 1.00-2.90 (m with two d, J=6 Hz, at 1.09 and 1.21, 13H, ...
-CH₃ and -CH₂- manifold), 2.90-4.25 (m with br d, J=14 Hz, 4H, NCH, NCH₂ and OCH); mass spectrum, m/e (relative intensity) 193(50), 165(11), 150(43), 139(25), 126(11), 115 (12), 114(7), 113(4), 112(7), 111(11), 110(11), 99(100), 97(14), 94(18), 93(18), 82(11), 81(7); exact mass calcd for C₁₀H₁₇NO₂ m/e 183.1259, found m/e 183.1264. Pure 96 was obtained as a pale-yellow oil in a combined yield of 1.46 g (93%): IR (CH₂Cl₂) 3520(br), 1660 cm⁻¹; NMR (CDCl₃) δ 0.90-3.15 (m with d, J=6 Hz, at 1.21, 14H, -CH₃, OH and -CH₂- manifold), 3.40-4.20 (m, 3H, OCH, NCH, NCH₂); mass spectrum, m/e (relative intensity) 183(22), 139(19), 97 (100); exact mass calcd for C₁₀H₁₇NO₂ m/e 183.1259, found m/e 183.1266.

trans-(±)-Hexahydro-7-(2-oxo)-propyl-3H-pyrrolizin-3-one (97). To a solution of 0.79 mL (9.05 mmol) of oxalyl chloride in 20 mL of dry dichloromethane cooled in a dry ice-acetone bath was added dropwise a solution of 1.34 mL (18.9 mmol) of dimethyl-sulfoxide in 4 mL of dichloromethane over a period of 30 min. The resulting solution was stirred at -78°C for 10 min followed by the addition of a solution of 1.40 g (7.67 mmol) of carbinollactam 96 in 8 mL of dry dichloromethane over a 30 min period. The reaction mixture was stirred at
-78°C for 30 min followed by the addition of 5.5 mL (39.5 mmol) of triethylamine over a 7 min period. After stirring at -78°C for 5 min and at room temperature for 1 h, the reaction mixture was quenched by the addition of 10 mL of water. The resulting mixture was stirred until it turned clear, saturated with sodium chloride, and extracted with three 100-mL portions of dichloromethane. The combined extracts were dried (MgSO₄) and concentrated in vacuo to afford a solid residue. This material was triturated with 500 mL of ethyl acetate and filtered. The filtrate was concentrated in vacuo to give 1.94 g of a brown liquid which was chromatographed over 60 g of silica gel (eluted with 2% methanol in ethyl acetate) to yield 1.24 g (89%) of 87 as a pale-yellow oil. Latter fractions contaminated with dimethylsulfoxide were purified by dissolving in 25 mL of 1,2-dichloroethane and washing with 5 mL of water. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to provide an additional 64 mg (5%) of pure 87 as a pale-yellow oil: IR (CCl₄) 1720, 1695 cm⁻¹; NMR (CCl₄) δ 1.35-3.07 (m with s at 2.11-13H, -CH₂, NCH and -CH₂- manifold), 3.49 (td, J=11, 7 Hz, 1H, NCH), 4.01 (q, J=6 Hz, 1H, angular-NCH); mass spectrum, m/e (relative intensity) 184(4), 139(35), 123(100), 110 (4), 97(43), 84(13); exact mass calcd for C₁₀H₁₅NO₂ m/e 131.1103, found 131.1111.
trans-(±)-Hexahydro-7-acetoxy-3H-pyrrolizin-3-one (20). A solution of trifluoroperacetic acid\textsuperscript{77,78} was prepared by dropwise addition of 7 mL of trifluoroacetic anhydride into an ice-water bath cooled mixture of 1 mL of 90% hydrogen peroxide in 5 mL of dichloromethane over a 20 min period. After stirring at 0°C for another 10 min, the resulting solution was ready for use.

Part of the solution prepared above (1.5 mL, 4.25 mmol) was added dropwise into an ice-water bath cooled solution of 97.6 mg (0.539 mmol) of methyl ketone 87 in 2 mL of dry dichloromethane over 5 min. The resulting solution was stirred at room temperature for 3 h and then poured into a mixture of 20 mL of water and 30 mL of dichloromethane. Solid sodium bicarbonate was added with stirring until no gas formation was observed. The mixture was saturated with sodium chloride and extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried (MgSO\textsubscript{4}) and concentrated in vacuo to give 98.7 mg of a pale-yellow oil. The oil was chromatographed over 5 g of silica gel (eluted with 2% methanol in ethyl acetate) to afford 59 mg (56%) of lactam acetate 20 as a pale-yellow oil: IR (CH\textsubscript{2}Cl\textsubscript{2}) 1740, 1685
cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.03-2.17 (m, 7H, -CH\(_2\)- manifold), 2.12-2.77 (m, 2H, NCH), 2.77-3.27 (m, 2H, NCH), 3.27-3.85 (m with d at 3.59, J=7 Hz, 3H, OCH\(_2\) and angular NCH), 4.33 (br s, 1H, OH); mass spectrum, m/e (relative intensity) 141(24), 140(12), 124(18), 93(100); exact mass calcd for C\(_{10}\)H\(_{15}\)NO\(_3\) m/e 197.1057, found m/e 197.1052.

(±)-Isoretronecanol (64).

To a solution of 74.0 mg (0.376 mmol) of lactam acetate \(\text{20}\) in 5.5 mL of dry tetrahydrofuran was added 97.5 mg (2.56 mmol) of lithium aluminium hydride. The reaction mixture was heated to reflux under argon for 30 min, diluted with 30 mL of ether followed by the addition of 69 \(\mu\)L of water, 69 \(\mu\)L of 3 N sodium hydroxide solution. After stirring at room temperature for 1 h, the resulting mixture was filtered. The filtrate was concentrated in vacuo to yield 45.5 mg (86%) of 64 as a pale-yellow oil: picrate mp 188°C (lit.\(^\text{79}\) 189.5-191°C); IR (CCl\(_4\)) 3360(br) cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.03-2.17 (m, 7H, -CH\(_2\)- manifold), 2.12-2.77 (m, 2H, NCH), 2.77-3.27 (m, 2H, NCH), 3.27-3.85 (m with d at 3.59, J=7 Hz, 3H, OCH\(_2\) and angular NCH), 4.33 (br s, 1H, OH); mass spectrum, m/e (relative intensity) 141(24), 140(12), 124(18), 93(100); exact mass calcd
for C₉H₁₅NO m/e 141.1154, found m/e 141.1158.

The high field NMR spectrum compared favorably with that reported in the literature.⁷⁹

cis- and trans-1-(4-Carboethoxy-3-butenyl)-2,5-pyrrolidinedione (90a). To a mixture of 2.01 g (12.2 mmol) of 1-(3-oxopropyl)-2,5-pyrrolidinedione (88)⁸¹ and 4.24 g (12.2 mmol) of carboethoxymethylidenetriphenylphosphine (89a)⁸² was added 13 mL of dry dichloromethane. The resulting solution was stirred under argon at room temperature for 1 h, and the solvent was removed in vacuo. The resulting solid residue was chromatographed over 130 g of silica gel (eluted with 1% methanol in dichloromethane) to give 2.00 g (73%) of imide 90a (cis:trans= 3:7) as a colorless oil: IR (CCl₄) 1720, 1710 cm⁻¹; NMR (CCl₄) δ 1.27 (t, J=7 Hz, 3H, -CH₃), 2.40-3.00 (m with s at 2.60 and 2.63, allyl, cis and trans \text{NCOCH₂}), 3.57 (t, J=7 Hz, 2H, NCH₂), 4.10 (q, J=7 Hz, OCH₂), 5.63-5.90 (two overlaped d, J=12 Hz, at 5.71 and J=15 Hz, at 5.77, 1H, cis and trans \text{COCH=}), 5.90-7.00 (two td, J=12, 7 Hz, at 6.13 and J=15, 7 Hz, at 6.78, 1H, cis and trans \text{-CH=}); mass spectrum, m/e (relative intensity) 225(14), 179(100), 151(73), 112(92), 94(73), 81(73); exact mass calcd for C₁₁H₁₅NO₄ m/e 225.1001, found m/e
cis- and trans-1-(4-Carbo-tert-butoxy-3-butenyl)-2,5-pyrrolidinedione (90b). To a mixture of 395 mg (2.55 mmol) of 1-(3-oxopropyl)-2,5-pyrrolidinedione (88) and 843 mg (2.24 mmol) of carbo-tert-butoxymethylidenetriphenylphosphine (89b) under argon was added 2.3 mL of dry dichloromethane. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with 16 mL of dichloromethane and chromatographed directly over 25 g of silica gel (eluted with ethyl acetate-hexane, 47:53) to afford 519 mg (92%) of imide 90b (cis:trans = 15:85) as a colorless oil: IR (CCl₄) 1715 cm⁻¹; NMR (CCl₄) δ 1.47 (s, 9H, -CH₃), 2.43 (br q, J=7 Hz, 2H, allyl), 2.63 (s, 4H, NCOCH₂), 3.57 (br t, J=7 Hz, NCH₂), 5.55-6.90 (m with trans signal shown as br d, J=16 Hz, at 5.70 and td, J=16, 7 Hz, at 6.67, 2H, =CH-); mass spectrum, m/e (relative intensity) 253(12), 197(39), 180(100), 179(79), 151(36), 112(64), 84(25), 81(96); exact mass calcd for C₁₃H₁₉NO₄ m/e 253.1314, found m/e 253.1320.

cis- and trans-1-(4-Cyano-3-butenyl)-2,5-pyrrolidinedione (90c). A mixture of 356 mg (2.30 mmol) of 1-(3-oxopropyl)-2,5-pyrrolidinedione (88) and 694 mg (2.30 mmol)
of cyanomethylenetriphenylphosphine (89c)$^{34}$ in 2.3 mL of dichloromethane was stirred under argon at room temperature for 2 h and concentrated in vacuo. The resulting pale-yellow solid was chromatographed over 18 g of silica gel (eluted with 1% methanol in dichloromethane) to yield 311 mg (76%) of imide 90c (cis:trans = 4:6) as a pale-yellow oil: IR (CH$_2$Cl$_2$) 2220, 1705 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 2.30-2.85 (m with s at 2.70, 6H, allyl, NCOCH$_2$), 3.50-3.90 (two overlaped t, J=7 Hz, at 3.63 and 3.69, 2H, trans and cis NCH$_2$), 5.20-5.60 (two overlaped d, J=12 Hz, at 5.35 and J=16 Hz, at 5.39, 1H, cis and trans =CHCN), 6.25-6.90 (m with the trans signal clearly displayed as td, J=16, 7 Hz, at 6.63, 1H, -CH=CHCN); mass spectrum, m/e (relative intensity) 178 (18), 112 (100), 84 (73); exact mass calcd for C$_9$H$_{10}$N$_2$O$_2$ m/e 178.0742, found m/e 178.0747.

(1R,2R,5R)-2-(1-Phenyl-1-methyl)ethyl-5-methylcyclohexyl Bromoacetate (98). To a solution of 2.52 g (10.8 mmol) of (1R,2R,5R)-2-(1-phenyl-1-methyl)ethyl-5-methylcyclohexan-1-ol (97)$^{35}$ in 50 mL of dry
ether under argon was added 2.68 g (13.0 mmol) of dicyclohexylcarbodiimide (DCC), 1.91 g (13.0 mmol) of bromoacetic acid and 40.5 mg (0.332 mmol) of 4-dimethylaminopyridine. The resulting mixture was stirred at room temperature for 4 h, diluted with 100 mL of ether and filtered. The filtrate was washed with 20 mL of 3 N aqueous hydrogen chloride, 20 mL of saturated aqueous sodium bicarbonate, 20 mL of saturated aqueous sodium chloride, dried (MgSO₄) and concentrated in vacuo to give 4.13 g of a pale-yellow solid. This material was chromatographed over 120 g of silica gel (eluted with ethyl acetate-hexane, 2:98) to yield 3.75 g (98%) of bromoacetate 98 as a white solid: mp 62-64 °C; IR (CCl₄) 1730 cm⁻¹; NMR (CCl₄) 6 0.78-2.20 (m with d, J=8 Hz, at 0.90 and two br s at 1.20 and 1.30, 17H, CH₂CH- , Ph(CH₃)₂C- and cyclohexyl), 2.90 (s, 2H, BrCH₂), 4.72 (dt, J=11, 4 Hz, 1H, OCH), 6.95-7.25 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 352(0.7), 214(90), 119(100), 118(19); exact mass calcd for C₁₉H₂₅O₂Br m/e 352.1038, found m/e 352.1047.


Carbo-(1R,2R,5R)-2-(1-phenyl-1-methyl)ethyl-5-methylcyclohexyloxymethylidenetriphenylphosphine (99d). A solution of 3.50 g (9.93 mmol) of bromoacetate 98 and 2.60 g (9.92 mmol) of triphenylphosphine in 11 mL of dry benzene was heated to reflux under argon over 6 h. The solvent
was removed in vacuo to give a fluffy yellow solid. The solid was stirred with 200 mL of water and 100 mL of ether. The ether layer was removed. To the aqueous phase was added two drops of 2% phenophthalein in ethanol followed by 3 N aqueous sodium hydroxie until the aqueous phase turned pink. The resulting mixture was extracted with 200 mL of benzene and two 100-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford 5.22 g (98%) of ylid 89d as a fluffy pale-yellow solid: mp 84-86 °C; IR (CCl₄) 1605 cm⁻¹; NMR (CCl₄) 0.53-2.10 (m with d, J=6 Hz, at 0.79 and two br s at 1.30 and 1.40, 17H, CH₂CH-, Ph(CH₃)₂C- and cyclohexyl), 2.55 (br d, J=22 Hz, 1H, COCH=), 4.60 (dt, J=11, 4 Hz, 1H, OCH), 6.90-7.75 (m, 20H, Ar-H). This material was used directly without further purification.

cis- and trans-1-(Carbo-4-((1R,2R,5R)-2-(1-phenyl-1-methyl)ethyl-5-methylcyclohexyl)-3-butenyl]-2,5-pyrroolidinedione (90d). To 5.10 g (9.56 mmol) of ylid 89d was added a solution of 1.78 g (11.5 mmol) of
1-(3-oxopropyl)-2,5-pyrrolidinedione (88) in 18 mL of dry dichloromethane. The resulting yellow solution was stirred at room temperature for 1 h and 20 min. The solution was diluted with 50 mL of dichloromethane and 50 mL of ethyl acetate-hexane (4:6) and directly chromatographed over 140 g of silica gel (eluted with ethyl acetate-hexane, 4:6) to give 3.31 g (84%) of imide 90d (cis:trans = 15:85) as a colorless oil. The pure trans isomer could be crystallized from 3 mL of ethyl acetate and 70 mL of hexane as a white needle: mp 119-120°C; IR (CCl₄) 1715 cm⁻¹; NMR (CCl₄) δ 0.65-2.13 (m with br d, J=6 Hz, at 0.90 and two br s at 1.20 and 1.29, 17H, CH₂CH⁻, Ph(CH₃)₂C⁻ and cyclohexyl), 2.30 (br q, J=7 Hz, 2H, allyl), 2.63 (s, 4H, NCOCH₂), 3.48 (t, J=7 Hz, 2H, NCH₂), 4.70 (dt, J=11, 4 Hz, 1H, OCH), 5.20 (br d, J=16 Hz, 1H, COCH=), 6.27 (td, J=16, 7 Hz, 1H, =CH⁻), 7.15 (br s, 5H, Ar-H).

Anal. Calcd for C₂₅H₃₃NO₆: C, 72.96; H, 8.08. Found: C, 72.66; H, 8.02.

The pure cis isomer could be isolated by MPLC (Lobar size B column, eluted with ethyl acetate-hexane, 3:7) as a colorless oil: IR (CH₂Cl₂) 1710 cm⁻¹; NMR (CCl₄) δ 0.67-2.15 (m with br d, J=6 Hz, at 0.95 and two br s at 1.19 and 1.27, 17H, CH₂CH⁻, Ph(CH₃)₂C⁻ and cyclohexyl), 2.45-2.90 (m with s at 2.59, 6H, allyl and NCOCH₂), 3.50 (t, J=7 Hz, 2H, NCH₂), 4.70 (dt, J=11, 4 Hz, 1H, OCH), 5.10
(br d, J=12 Hz, 1H, COCH=), 5.90 (td, J=12, Hz, 1H, =CH-), 7.13 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 411(2), 242(5), 214(17), 198(7), 182(14), 119(100), 118(48), 106(10), 105(14), 91(28); exact mass calcd for C_{25}H_{33}NO_{4} m/e 411.2409, found m/e 411.2417.

cis- and trans-1-(4-Carboethoxy-3-butenyl)-5-phenylthio-2-pyrrolidinone (91a).

To a solution of 6.37 g (28.3 mmol) of imide ester 90a in 90 mL of anhydrous methanol cooled in an ice-water bath under argon was added 3.17 g (83.4 mmol) of sodium borohydride in one portion. The resulting mixture was stirred at 0°C for 1.5 h and partitioned between 100 mL of dichloromethane, 50 mL of saturated sodium chloride solution and 50 mL of water. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (MgSO_{4}) and concentrated in vacuo to give a colorless oil (6.31 g). The oil was stirred with 55.0 mg (0.305 mmol) of p-toluenesulfonic acid monohydrate and 2.94 mL (29.7 mmol) of thiophenol at room temperature for 14 h and directly chromatographed over 150 g of silica gel (eluted with ethyl acetate-hexane, 1:1) to afford 7.28 g (81%) of thiophenoxylactam 91a as a colorless oil: IR (CCl_{4}) 1715, 1700 cm^{-1}; NMR
(CCl₄) δ 1.15-2.62 (m with t, J=7 Hz, at 1.25, 9H, -CH₃ and -CH₂- manifold), 3.29 (td, J=12, 6 Hz, 1H, NCH), 3.80 (td, J=12, 6 Hz, 1H, NCH), 4.73-5.07 (m, 1H, NCHS), 5.65-5.91 (overlap d, J=12 Hz, at 5.71 and J=15 Hz, at 5.77, 1H, cis and trans COCH=), 5.91-7.00 (two td, J=12, 7 Hz, at 6.15 and J=15, 7 Hz, at 6.78, 1H, cis and trans -CH=), 7.30 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 210(M⁺-SPh, 33), 209(11), 164(25), 163(18), 136(24), 135(11), 134(4), 110(91), 109(24), 96(100).

cis- and trans-1-(4-Carbo-tert-butoxy-3-butenyl)-5-phenylthio-2-pyrrolidinone (051). To a solution of 4.32 g (17.1 mmol) of imide 90b in 100 mL of absolute ethanol cooled in an ice-water bath under argon was added 1.90 g (50.3 mmol) of sodium borohydride. Over a period of 3 h, a 1.94 N solution of hydrogen chloride in absolute ethanol was added in a rate of 2 drops every 5 min. The resulting mixture was poured into a mixture of 50 mL of water, 50 mL of saturated sodium chloride aqueous solution, and 100 mL of dichloromethane. The aqueous phase was extracted with four 100-mL portions of dichloromethane. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to give a colorless oil (4.33 g). The oil was stirred with 130 mg
(0.680 mmol) of \textit{p}-toluenesulfonic acid monohydrate and 1.74 mL (17.0 mmol) of thiophenol under argon at room temperature for 3 h and 20 min. This mixture was diluted with 100 mL of dichloromethane and washed with 50 mL of 1 N sodium hydroxide aqueous solution. The aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a pale-yellow oil (5.90 g) which was chromatographed over 130 g of silica gel (eluted with ethyl acetate-hexane, 45:55) to yield 5.19 g (91%) of \textit{91b} as a colorless oil (cis:trans= 15:85) contaminated with small amount of 1-(4-carbo-tert-butoxybutenyl)-5-phenylthio-2-pyrrolidinone (\textit{92b}). This material was used directly for the cyclization reaction. However, a pure sample could be obtained by MPLC (Lobar size A column, eluted with ethyl acetate-hexane, 3:7). The less polar cis isomer of \textit{91b}: IR (CCl$_4$) 1710 cm$^{-1}$; NMR (CCl$_4$) 1.50 (s, 9H, $-\text{CH}_3$), 1.53-3.45 (m, 7H, NCH and $-\text{CH}_2$- manifold), 3.67-4.07 (m, 1H, NCH), 5.00 (dd, $J$=7, 2 Hz, 1H, NCHS), 5.67 (br d, $J$=12 Hz, 1H, COCH=), 6.08 (ddd, $J$=12, 8, 7 Hz, 1H, $-\text{CH}$-), 7.28 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 274(5), 239(M$^+$-SPh, 26), 218(5), 182(33), 181(21), 164(21), 163(16), 136(15), 110(100), 109 (22), 96(8); trans isomer of \textit{91b}: IR (CCl$_4$) 1710 cm$^{-1}$; NMR (CCl$_4$) 1.50 (s, 9H, $-\text{CH}_3$), 1.53-2.60 (m, 6H, $-\text{CH}_2$- manifold), 3.30 (td, $J$=14, 7 Hz, 1H, NCH), 3.92 (td,
$J=14, 7 \text{ Hz}, 1\text{H, NCH}, 4.83 (\text{dd, } J=9, 3 \text{ Hz}, 1\text{H,NCHS}), 5.75$

(br d, J=16 Hz, 1H, COCH), 6.71 (td, J=16, 7 Hz, =CH-),

7.33 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 274(7), 238(M+-SPh, 15), 182(43), 181(27), 164 (53), 163(27), 136(30), 110(100), 109(23), 96(90).

cis- and trans-1-(4-Cyano-3-butenediy)-5-phenylthio-2-pyrrolidinone (91c).and 1-(4-Cyanobutyl)-5-phenylthio-2-pyrrolidinone (92c). To a solution of 306 mg (1.72 mmol) of imide 90c in 23 mL of absolute ethanol cooled in an ice-water bath under argon was added 190 mg (5.00 mmol) of sodium borohydride. Over a period of 2 h, a 1.94 N solution of hydrogen chloride in absolute ethanol was added in a rate of 1 drop every 5 min. The resulting mixture was partitioned between 20 mL of water, 10 mL of saturated sodium chloride solution and 30 mL of dichloromethane. The aqueous phase was extracted with four 30-mL portions of dichloromethane. The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo to give a pale-yellow oil (296 mg). The oil was stirred with 15 mg (0.079 mmol) of $p$-toluenesulfonic acid monohydrate and 0.168 mL (1.64 mmol) of thiophenol at room temperature for 1 h. The resulting mixture was partitioned between 5 mL of 1 N sodium
hydroxide solution and 25 mL of dichloromethane. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford a pale-yellow oil (391 mg). This material was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexane, 1:1) and then over a Lobar size B column (eluted with ethyl acetate-hexane, 6:4) to yield 210 mg (45%) of the less polar thiophenoxy-lactam 91c as a colorless oil: IR (CH₂Cl₂) 2215, 1700 cm⁻¹; NMR (CDCl₃) δ 1.40-2.70 (m, 6H, -CH₂- manifold), 3.10-3.49 (m, 1H, NCH), 3.59-4.00 (m, 1H, NCH), 4.70-5.05 (two dd, J=8, 3 Hz, at 4.80 and 4.98, 1H, trans and cis NCHS), 5.17-5.43 (two overlaped d, J=12 Hz, at 5.29 and J=16 Hz, at 5.33, 1H, cis and trans NCCH=), 6.29-6.80 (m, 1H, NCC=CH), 7.33 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 163(M⁺-SPh, 100), 109(9), 108(4), 95(6), 83(7), 79(5). Further elution gave 99.6 mg (21%) of lactam thiophenoxy-lactam 92c as a colorless oil: IR (CCl₄) 2240, 1700 cm⁻¹; NMR (CDCl₃) δ 1.40-1.80 (m, 4H, NCCH₂CH₂CH₂-), 1.80-2.60 (m, 6H, -CH₂- manifold), 3.10-3.42 (m, 1H, NCH), 3.49-3.80 (m, 1H, NCH), 4.85 (dd, J=7, 3 Hz), 7.30 (br s, 5H, Ar-H); mass spectrum, m/e
cis- and trans-1-[4-Carbo-
((1R,2S,5R)-2-(1-phenyl-1-
methyl)ethyl-5-methylcyclo-
hexyloxy)-3-butenyl]-5-phenyl-
thio-2-pyrrolidinone (91d).

To a mixture of 2.70 g (6.58 mmol) of imide 90d in 80 mL
of absolute ethanol cooled in an ice-water bath under
argon was added 706 mg (13.7 mmol) of sodium borohydride.
Over a period of 3 h, a 1.94 N solution of hydrogen
chloride in absolute ethanol was added in a rate of 2
drops every 5 min. The resulting mixture was partitioned
between 50 mL of water, 30 mL of saturated sodium chloride
solution and 100 mL of dichloromethane. The aqueous phase
was extracted with four 100-mL portions of dichloro-
methane. The combined organic layers were dried (Na$_2$SO$_4$)
and concentrated in vacuo to give a colorless oil (2.90 g).

The oil was stirred with 50.0 mg (0.260 mmol) of
p-toluenesulfonic acid monohydrate and 0.674 mL (6.57
mmol) of thiophenol under argon at room temperature for
2.5 h. The resulting mixture was partitioned between 30
mL of 1 N sodium hydroxide solution and 100 mL of dichlo-
romethane. The aqueous phase was extracted with two 50-mL
portions of dichloromethane. The combined organic layers
were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a colorless oil. The oil was chromatographed over 70 g of silica gel (eluted with ethyl acetate-hexane, 3:7) to yield 2.90 g (87%) of a colorless oil as a mixture of cis and trans isomers of 91d (15:85, respectively) contaminated with small amount of 1-[4-carbo-((1R,2S,3R)-2-(1-phenyl-1-methyl)ethyl-5-methylcyclohexyloxy)butyl]-5-phenylthio-2-pyrrolidinone (92d). This material was used directly for cyclization reaction; however, pure samples of cis and trans isomers could be separated by MPLC (Lobar size B column, eluted with ethyl acetate-hexane, 3:7). The less polar cis isomer of 91d: IR (CCl$_4$) 1705 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 0.67-3.49 (m, 25H), 3.49-4.07 (m, 1H, NCH), 4.50-5.20 (m, 3H, OCH, COCH= and NCHS), 5.80-6.13 (m, 1H, =CH-), 6.90-7.45 (two overlapped s at 7.13 and 7.30, 10H, Ar-H); mass spectrum, m/e (relative intensity) 250(17), 218(75), 125(75), 110(100), 109(100); trans isomer of 91d: IR (CCl$_4$) 1705 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 1.60-2.50 (m with br d, J=7 Hz, at 0.87 and two br s at 1.20 and 1.27, 23H, CH$_3$CH-, Ph(CH$_3$)$_2$C- and -CH$_2$- manifold), 3.20 (td, J=14, 7 Hz, 1H, NCH), 3.73 (td, J=14, 7 Hz, 1H, NCH), 4.52-4.99 (m with dd, J=7, 3 Hz, at 4.77, 2H, OCH and NCHS), 5.21 (br d, J=16 Hz, 1H, COCH=), 6.30 (td, J=16, 7 Hz, 1H, =CH-), 6.90-7.40 (two overlapped br s at 7.17 and 7.33, 10H, Ar-H); mass spectrum, m/e (relative intensity) 218(5), 121(36), 119(100), 117(91).
Cyclization of Thiophenoxylactam 91a: cis-(\pm)-Hexahydro-7-carboethoxymethyl-3H-pyrrolizin-3-one (93a) and trans-(\pm)-Hexahydro-7-carboethoxymethyl-3H-pyrrolizin-3-one (94a). To a solution of 7.19 g (22.5 mmol) of thiophenoxylactam 91a in 25 mL of dry benzene heated at 80 °C under argon was added dropwise a solution of 11.9 mL (45.1 mmol) of tri-n-butyltin hydride and 80.6 mg (0.490 mmol) of AIBN in 20 mL of dry benzene over a period of 4 h. The resulting solution was stirred at 80 °C for another 25 min. The solvent was removed in vacuo and the residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 6:4, followed by ethyl acetate) to afford 4.14 g (87%) of a mixture of 93a and 94a (93a:94a = 1:8 by 200 MHz $^1$H NMR) as a colorless liquid; 94a: IR (CCl$_4$) 1740, 1695 cm$^{-1}$; NMR (CDCl$_3$, 200 MHz) $^\delta$ 1.26 (t, J=7 Hz, 3H, \text{-CH$_3$}), 1.54-1.92 (m, 2H), 1.93-2.41 (m, 5H), 2.49-2.74 (m, 2H), 3.03 (ddd, J=12, 8.5, 5, 1 Hz, 1H, NCH), 3.58 (td, J=12, 7 Hz, 1H, NCH), 3.99-4.22 (m with q, J=7 Hz, at 4.15, 3H, OCH$_2$, angular-NCH); $^{13}$C NMR (CDCl$_3$) $^\delta$ 14.20(q), 22.29(t), 32.80(t), 33.61(t), 34.69(t), 35.60(d), 40.08(t), 60.70 (t), 63.58(d), 172.23(s), 174.91(s); mass spectrum, m/e (relative intensity) 211(19), 183(11), 166(26), 138(8),
136(3), 123(100), 122(14), 110(17), 97(92); exact mass calcd for C_{11}H_{17}NO_3 m/e 211.1208, found m/e 211.1213.

93a showed the following characteristic signals in the \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta 1.27\) (t, J=7 Hz, 3H, -CH\(_3\)), 3.16 (br t, J=9 Hz, 1H, NCH).

Cyclization of Thiophenoxy-lactam 91b: cis-(\pm)-Hexahydro-7-carbo-tert-butoxymethyl-3H-pyrrolizin-3-one (93b), trans-(\pm)-Hexahydro-7-carbo-tert-butoxymethyl-3H-pyrrolizin-3-one (94b) and 1-(4-Carbo-tert-butoxy)butyl-2-pyrrolidinone (95b). To a solution of 5.19 g (15.5 mmol) of thiophenoxy-lactam 91b in 320 mL of dry benzene under argon was added 5.80 mL (22.0 mmol) of tri-n-butyltin hydride and 127 mg (0.770 mmol) of AIBN. The resulting solution was heated to reflux for 1.5 h and cooled to room temperature. The solvent was removed in vacuo to give 12.5 g of a colorless oil. The oil was chromatographed over 130 g of silica gel (eluted with ethyl acetate) to yield 3.49 g (96%) of a colorless oil composed of 95b, 93b and 94b

\(95b: 93b + 94b = 6:94\) by NMR

Analytical samples were obtained by GLC (2 m x 1/8 in
column packed with 10% OV-101 on Chrom W, Hp 90/100; column temperature = 220°C, flow rate = 25 mL/min). 95b: $t_R=4.8$ min; IR (CCl₄) 1725, 1690 cm⁻¹; NMR (CDCl₃, 200 MHz) $\delta$ 1.44 (s, 9H, -CH₃), 1.50-1.62 (m, 4H, NCCH₂CH₂), 2.02 (br qu, $J=8.5$ Hz, 2H, NCOCH₂CH₂), 2.20-2.29 (m, 2H, NCOCH₂), 2.41 (br t, $J=8.5$ Hz, 2H, COCH₂), 3.23-3.32 (m, 2H, NCH₂), 3.38 (t, $J=7$ Hz, 2H, NCH₂); mass spectrum, m/e (relative intensity) 241(4), 185(64), 182(32), 168(100), 126(27), 124(50), 112(32), 98(77); exact mass calcd for C₁₅H₂₁N₀₃ m/e 241.1678, found m/e 241.1632. 93b And 94b were obtained as an unseparable mixture (93b:94b = 1:9 by NMR): $t_R=6.0$ min; IR (CCl₄) 1730, 1700 cm⁻¹; NMR (CDCl₃, 200 MHz) $\delta$ 1.45 (s, 9H, -CH₃), 1.64-1.95 (m, 2H), 1.95-2.49 (m, 5H), 2.48-2.79 (m, 2H), 3.02 (dddd, $J=13$, 8.5, 5, 1 Hz, 1H, NCH), 3.57 (td, $J=11.5$, 7.5 Hz, 1H, NCH), 4.09 (td, $J=8$, 6.5 Hz, NCH), characteristic signals of 93b could be detected at 3.15 as br t, $J=9.5$ Hz; mass spectrum, m/e (relative intensity) 239(18), 193(100), 167(51), 155(10), 139(8), 125(12), 124(24), 123(12), 98(51); exact mass calcd for C₁₅H₂₁N₀₃ m/e 239.1521, found m/e 239.1529.

For practical purposes, the mixture of cyclization products were used directly in the next reaction.

Cyclization of Thiophenoxylactam 91c: cis-(±)-Hexahydro-7-cyanomethyl-3H-pyrrolizin-3-one (93c) and trans-(±)-Hexahydro-7-cyanomethyl-3H-pyrrolizin-3-one (94c). To a solution of 206 mg (0.756 mmol) of thiophenoxylactam 91c
in 16 mL of dry benzene was added 0.40 mL (1.5 mmol) of tri-\(n\)-butyltin hydride and 8.5 mg (0.052 mmol) of AIBN. The resulting solution was heated at 80°C for 1 h and 30 min. The solvent was removed in vacuo to yield 658 mg of a colorless liquid. This material was chromatographed over 8 g of silica gel (eluted with ethyl acetate followed by 6% methanol in ethyl acetate) and distilled bulb-to-bulb to afford 106 mg (85%) of a mixture of \(93c\) and \(94c\) (1:9, respectively by NMR) as a colorless oil: bp 140-145°C/0.17 mmHg; IR (CH\(_2\)Cl\(_2\)) 2290, 2240, 1690 cm\(^{-1}\); NMR (CDCl\(_3\), 90 MHz) \(\delta\) 1.50-2.95 (m, 9H, -\(\text{CH}_2\)- manifold), 3.13 (ddd, \(J=12, 8.5, 4\) Hz, 1H, NCH), 3.63 (td, \(J=12, 8\) Hz, 1H, NCH), 4.17 (br q, \(J=7\) Hz, 1H, angular-NCH); NMR (CDCl\(_3\), 200 MHz, characteristic signals for \(94c\)) \(\delta\) 1.70-2.94 (m, 9H), 3.11 (ddd, \(J=12, 8.5, 4, 1\) Hz, 1H, NCH), 3.60 (td, \(J=12, 7\) Hz, 1H, NCH), 4.13 (q, \(J=7\) Hz, 1H, angular-NCH); \(93c\) could be detected at \(\delta\) 3.21 (br t, \(J=11\) Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 164(23), 97(100); exact mass calcd for C\(_9\)H\(_{12}\)N\(_2\)O m/e 164.0950, found m/e 164.0954.

**Cyclization of Thiophenoxy lactam 91d:** cis-(\(\pm\))-7-(Carbo-((1\(R\),2\(S\),5\(R\))-2-(1-phenyl-1-methyl)ethyl)-5-methyl-cyclohexyloxy)methyl-hexahydro-3\(H\)-pyrrolizin-3-one (93d),
trans-(±)-7-[[Carbo-((1R,2S,5R)-2-(1-phenyl-1-methyl)ethyl)-5-methylcyclohexyloxy]-methyl-hexahydro-3H-pyrroliizin-3-one (94d) and 1-[4-carbo-((1R,2S,5R)-2-(1-phenyl-1-methyl)ethyl)-5-methylcyclohexyloxy] butyl-2-pyrrolidinone (95d). A solution of 2.89 g (5.73 mmol) of thiophenoxylactam 91d, 2.12 mL (8.04 mmol) of tri-n-butyltin hydride and 37.2 mg (0.227 mmol) of AIBN in 115 mL of dry benzene was heated under argon at reflux temperature for a 1.5 h period. The solvent was removed in vacuo to give 5.68 g of a colorless oil. The oil was chromatographed over 70 g of silica gel (eluted with ethyl acetate-hexane, 45:55, followed by ethyl acetate) to yield 2.443 g (94%) of a mixture of 95d, 93d and 94d (95d:93d + 94d = 9.5:90.5 by NMR) as a colorless oil. Although this mixture was used directly for the next transformation, pure samples could be obtained by MPLC (Lobar size B column, eluted with ethyl acetate-hexane, 7:3). The less polar 95d: IR (CCl₄) 1725, 1695 cm⁻¹; NMR (CCl₄) δ 0.60-2.35 (m with br d, J = 7 Hz, at 0.85 and two br s at 1.20 and 1.30, 27H, CH₃CH-, Ph(CH₃)₂C- and -CH₂-
manifold), 3.07 (br t, J=6 Hz, 2H, NCH₂), 3.27 (br t, J=7 Hz, 2H, NCH₂), 4.69 (dt, J=9, 3 Hz, 1H, OCH), 7.17 (br s, 5H, Ar-H); mass spectrum, m/e (relative intensity) 399 (14), 186(100), 168(57), 119(57); exact mass calcd for C₂₅H₃₇N₀₃ m/e 399.2773, found m/e 399.2781. 93d And 94d were obtained as a mixture (93d:94d = 1:9 by NMR): IR (CCl₄) 1725, 1695 cm⁻¹; NMR (CCl₄) δ 0.60-3.09 (m with d, J=7 Hz, at 0.89 and two br s at 1.19 and 1.29, 27H, CH₃CH-, Ph(CH₂)₂C- and -CH₂- manifold), 3.09-3.61 (m, 1H, NCH), 3.85 (br q, J=7 Hz, 1H, NCH), 4.65 (dt, J=10, 4 Hz, 1H, OCH), 7.09 (br s, 5H, Ar-H); NMR (CDCl₃, 200 MHz) δ 0.80-2.45 (m with d, J=7 Hz, at 0.88 and two br s at 1.19 and 1.29, 25H, CH₃CH-, Ph(CH₂)₂C- and -CH₂- manifold), 2.75 (m, 1H), 2.85-3.03 (m, 1H, NCH₂), 3.43 (tt, J=11, 7 Hz, 1H, NCH), 3.96 (dq, J=8.5, 2 Hz, 1H, angular-NCH), 4.97 (dt, J=10.5, 4 Hz, 1H, OCH), 7.06-7.35 (m, 5H, Ar-H); signals due to 93d could be detected at δ 3.09 as br t, J=12 Hz; mass spectrum, m/e (relative intensity) 397(3), 184(6), 182(5), 119(94), 117(100), 84(14), 82(22); exact mass calcd for C₂₅H₃₅N₀₃ m/e 397.2617, found m/e 397.2626.

trans-(±)-Hexahydro-7-carboxymethyl-3H-pyrrolizin-3-one (99). From Hydrolysis of Ethyl Ester 94a. A solution of 3.59 g (17.0 mmol) of the cyclization products of 91a in 25 mL of a 1 N solution of sodium hydroxide in ethanol was stirred at room temperature for 9 h. The resulting solution was acidified with 2 N hydrogen chloride
in ethanol to pH 5. The resulting mixture was diluted with dichloromethane to a volume of 600 mL, dried with magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resulting solid residue was dissolved in 50 mL of dichloromethane with warming, filtered and concentrated to a total volume of 25 mL. Ether (10 mL) was added while the solution was still warm and the resulting solution was allowed to stand at room temperature to yield 2.21 g (66%) of 99 as white crystals. Further recrystallization of the mother liquor gave 139 mg (4%) of 99 as white crystals: mp 144-145°C; IR (CH2Cl2) 3000(br), 1720, 1680, 1645 cm⁻¹; NMR (CDCl3, 90 MHz) δ 1.60-3.25 (m, 10H), 3.60 (td, J=12, 6 Hz, 1H, NCH), 4.15 (br q, J=7 Hz, 1H, angular-NCH), 10.77 (br s, 1H, COOH); NMR (CDCl3, 200 MHz) δ 1.65-1.91 (m, 2H), 2.00-2.83 (m, 7H), 3.05 (dddd, J=12, 8.5, 5, 1 Hz, 1H, NCH), 3.58 (td, J=12, 7.5 Hz, 1H, NCH), 4.14 (td, J=8.5, 6.5 Hz, 1H, NCH); mass spectrum, m/e (relative intensity) 133(8), 155(12), 123(36), 97(100); exact mass calcd for C9H13NO3 m/e 133.0395, found m/e 133.0910.

Anal. Calcd. for C9H13NO3: C, 59.00; H, 7.15.
Found: C, 59.21; H, 7.24.
From tert-Butyl Ester 94b. A solution of 936 mg (3.90 mmol) of cyclization products of 91b in 2 mL of trifluoroacetic acid was stirred at room temperature under argon for 30 min. The trifluoroacetic acid was removed in vacuo to afford a pale-yellow oil which solidified partially (948 mg). This material was recrystallized from 5 mL of dichloromethane and 10 mL of ether to yield 504 mg (71%) of 99 as a white solid.

trans-(±)-Hexahydro-7-carbo-(phenylthio)methyl-3H-pyrrolozin-3-one (100). To a mixture of 706 mg (3.36 mmol) of acid 99 in 11 mL of dry dichloromethane was added 0.396 mL (3.36 mmol) of thiophenol, 797 mg (3.97 mmol) of dicyclohexylcarbodiimide and 5.5 mg (0.045 mmol) of 4-dimethylaminopyridine. The resulting mixture was stirred at room temperature for 4 h, filtered, and concentrated in vacuo. The residue was suspended in carbon tetrachloride and filtered. The filtrate was concentrated in vacuo to give 1.27 g of a pale-yellow oil which was chromatographed over 60 g of silica gel (eluted with ethyl acetate-hexane, 9:1, followed by ethyl acetate) to afford 943 mg (99%) of 100 as a colorless oil: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.20-3.10 (m, 10H), 3.27-4.15 (m, 2H, NCH), 7.25 (s, 5H, Ar-H); mass spectrum, m/e
Preparation of Methyl Ketone 87 from Thioester 100 via Cuprate Addition. To a mixture of 443 mg (2.33 mmol) of cuprous iodide in 6.2 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added in a single portion 3.5 mL of a 1.33 N solution of methyllithium in ether. The resulting black mixture was stirred at 0°C for 5 min and then cooled in a dry ice-carbon tetrachloride bath for 5 min. A solution of 214 mg (0.777 mmol) of thioester 100 in 3.7 mL of dry tetrahydrofuran was added in one portion and stirred at the same temperature for 5 more min. Methanol (1.25 mL) was added carefully, and the resulting mixture was warmed to room temperature, and partitioned between 25 mL of saturated ammonium chloride solution and 50 mL of dichloromethane. The aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried (MgSO\textsubscript{4}) and concentrated in vacuo to give 145 mg of a yellow oil. The oil was chromatographed over 6 g of silica gel (eluted with 5% methanol in ethyl acetate) to yield 119 mg (94%) of 87 as a
E- and Z-1-Phenylthio-1-trimethylsilyl-4-(tetrahydro-2H-pyran-2-yl)oxy-1-butene (103).

The procedure of Seebach was followed.96 Thus, to a solution of 11.3 g (42.4 mmol) of (phenylthio)bis(trimethylsilyl)methane96 in 30 mL of dry tetrahydrofuran cooled in a dry ice-acetone bath under argon was added dropwise 42 mL of a solution of 1.03 M n-butyllithium in hexane (43.3 mmol) over a 15 min period. The resulting yellow solution was stirred at room temperature for 2 h and cooled again in a dry ice-acetone bath. A solution of 6.83 g (43.2 mmol) of 3-(tetrahydro-2H-pyran-2-yl)oxypionaldehyde (102)97 in 40 mL of dry tetrahydrofuran was added dropwise over an 85 min period. The reaction mixture was stirred at -75°C for 10 min then at room temperature for 1 h. The resulting solution was poured into 200 mL of water and extracted with 400 mL of hexane. The aqueous phase was extracted with two 100-mL portions of hexane. The combined organic layers were washed with three 200-mL portions of water, 100 mL of saturated sodium chloride solution, dried (MgSO₄) and concentrated in vacuo to give 13.9 g of a yellow oil. The oil was chromatographed over 140 g of silica gel (eluted with hexane followed by ethyl
acetate-hexane, 1:9) to yield 4.77 g (42%) of (phenyl-thio)bis(trimethylsilyl)methane. Continued elution gave 7.71 g (54%) of 103 (E:Z = 1:1) as a pale-yellow liquid: IR (CCl₄) 1580, 1480, 1440, 1250 cm⁻¹; NMR (CCl₄) δ 0.00-0.25 (two s at 0.00 and 0.16, 9H, E and Z SiMe₃), 1.17-1.77 (m, 6H, -CH₂- manifold), 2.27-2.77 (two overlapped q, J=7 Hz, at 2.45 and 2.57, 2H, E and Z allyl), 3.07-3.92 (m, 4H, OCH₂), 4.47 (br s, 1H, OCH), 6.09-6.67 (two t, J=7 Hz, at 6.22 and 6.53, 1H, E and Z =CH-), 6.92-7.22 (two overlapped br s at 7.01 and 7.07, 5H, ArH); mass spectrum, m/e (relative intensity) 336(2), 252(5), 236(20), 235(9), 234(12), 221(2), 208(14), 167(10), 159(38), 157(12), 151 (9), 134(7), 85(78), 73(100); exact mass calcd for C₁₅H₂₈O₂SSi m/e 336.1579, found m/e 336.1588.

**E- and Z-4-Phenylthio-4-trimethylsilyl-3-buten-1-ol**

(104). To a solution of 7.71 g (22.9 mmol) of 103 in 120 mL of methanol was added 83.2 mg (0.438 mmol) of p-toluene-sulfonic acid monohydrate. The resulting solution was stirred at room temperature for 6 h, poured into 50 mL of saturated sodium bicarbonate solution and diluted with 400 mL of ether. The resulting mixture was filtered. The filtrate was washed with four 100-mL portions of water, 100 mL of saturated sodium
chloride solution, dried \(\text{MgSO}_4\) and concentrated in vacuo to afford a pale-yellow oil. The oil was chromatographed over 100 g of silica gel (eluted with ethyl acetate-hexane, 15:85) to yield 5.34 g (92%) of alcohol 104 as a colorless oil: IR \((\text{CCL}_4)\) 3630, 3400(br), 1580, 1490, 1440, 1250 cm\(^{-1}\); NMR \((\text{CCL}_4)\) \& 0.00-0.20 (two s at 0.05 and 0.13, 9H, E and Z SiMe\(_3\)), 1.50 (br s, 1H, OH), 2.20-2.73 (overlapped td, J=5, 7 Hz, at 2.39 and q, J=7 Hz, at 2.51, 2H, E and Z allyl), 3.35-3.75 (m, 2H, OCH\(_2\)), 5.99-6.68 (two t, J=8 Hz, at 6.13 and J=7 Hz, at 6.50, 1H, =CH-), 6.95-7.20 (two overlaped br s at 7.01 and 7.10, 5H, Ar-H); mass spectrum, m/e (relative intensity) 252(100), 234(6), 221(6), 221(24), 167(47), 151(35), 147(15); exact mass calcd for \(\text{C}_{13}\text{H}_{20}\text{OSSi}\) m/e 252.1004, found m/e 252.1011.

**E- and Z-1-(4-Phenylthio-4-trimethylsilyl-3-butenyl)-2,5-pyrrolidinedione (105).** To a mixture of 2.00 g (7.59 mmol) of alcohol 104, 0.866 g (9.74 mmol) of succinimide and 2.29 g (8.75 mmol) of triphenylphosphine in 11.5 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 1.52 g (9.76 mmol) of diethyl azodicarboxylate in 4 mL of dry tetrahydrofuran over a period of 35 min. The resulting solution was stirred for 5 min and the solvent
was removed in vacuo. The residue was triturated twice with ethyl acetate-hexane (3:7, 40 mL followed by 20 mL). The combined extracts were concentrated in vacuo, and the residue was triturated again with 30 mL of ethyl acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo and chromatographed over 60 g of silica gel (eluted with dichloromethane) to afford 2.47 g (93%) of imide 105 (E:Z= 1:1 by NMR) as a yellow oil: IR (CCl₄) 1780, 1710 cm⁻¹; NMR (CCl₄) δ 0.00-0.20 (two s at 0.00 and 0.18, 9H, SiMe₃), 2.35-2.30 (m with s at 2.50, 6H, allyl, NCOCH₂), 3.30-3.60 (two overlapped t, J=6 Hz, at 3.43 and 3.53, 2H, NCH₂), 5.80-6.55 (two t, J=8 Hz, at 5.90 and J=7 Hz, at 6.40, 1H, vinyl), 7.00-7.20 (two overlaped br s at 7.03 and 7.15, 5H, Ar-H); mass spectrum, m/e (relative intensity) 333(10), 313(2), 234(9), 203(4), 167(12), 157(15), 1519111), 73(100); exact mass calcd for C₁₇H₂₃NO₂SSi m/e 333.1219, found 333.1227.

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\text{E- and } Z-1-(4-\text{Phenylthio-4-trimethylsilyl-3-butenyl)-5-phenylthio-2-pyrrolidinone (106). To a solution of 2.48 g (7.43 mmol) of imide 105 in 15 mL of methanol cooled in an ice-water bath under argon was added four portions of sodium borohydride at 10 min intervals (205 mg, 175 mg, 195 mg and 191 mg in sequence).}
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The resulting mixture was stirred at 0°C for another 45 min followed by the addition of 201 mg of sodium borohydride. After 45 min the reaction mixture was partitioned between 15 mL of water, 15 mL of saturated sodium chloride solution and 50 mL of dichloromethane. The aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give a colorless oil. To this oil was added 27.5 mg (0.145 mmol) of p-toluenesulfonic acid monohydrate and 0.762 mL (7.43 mmol) of thiophenol. The resulting mixture was stirred at room temperature for 3 h and chromatographed over 70 g of silica gel (eluted with ethyl acetate-hexane, 25:75) to yield 2.82 g (89%) of thiophenoxy lactam 106 as a colorless oil: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 0.00-0.25 (two s at 0.00 and 0.20, 9H, SiMe₃), 1.10-4.20 (m, 8H, -CH₂- manifold), 4.60-4.95 (m, 1H, NCHS), 5.75-6.60 (two t, J=8 Hz, at 5.90 and J=7 Hz, at 6.47, 1H, =CH-), 6.90-7.30 (three br s at 7.00, 7.11 and 7.20, 10H, Ar-H); mass spectrum, m/e (relative intensity) 412(3), 318(M⁺-SPh, 95), 302(3), 278(1), 235 (36), 209(9), 162(19), 149(13), 110(100), 96(22), 84(27), 73(92).

Cyclization of Thiophenoxy lactam 106: 1-(4-Phenylthio-4-trimethylsilyl-3-butenyl)-2-pyrrolidinone (107), cis-(-)-Hexahydro-7-((phenylthio)(trimethylsilyl)methyl)-3H-pyrroloizin-3-one (108),
trans-(±)-Hexahydro-7-((phenylthio)(trimethylsilyl)methyl)-3H-pyrrolizin-3-one (109) and Hexahydro-7-trimethylsilylmethyl-3H-pyrrolizin-3-one (110). A solution of 2.81 g (6.57 mmol) of thiophenoxylactam 106, 2.60 mL (9.36 mmol) of tri-n-butyltin hydride and 23.3 mg (0.142 mmol) of AIBN in 130 mL of dry benzene was heated at reflux temperature for 16.5 h with the addition of a few crystals of AIBN at the end of the first 8 h. The solvent was removed in vacuo, and the residue was dissolved in 100 mL of hexane. This hexane solution was extracted with three 50-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo to afford 2.68 g of a pale-yellow oil. The oil was chromatographed first over 50 g of silica gel (eluted first with ethyl acetate-hexane, 25:75, followed by ethyl acetate-hexane, 1:1, and finally with ethyl acetate) and then over a Lobar size C column (eluted with ethyl acetate-hexane, 25:75, followed by ethyl acetate) to yield 241 mg (8%) of the less polar unreacted starting material 106 as a pale-yellow oil. Continued elution gave
a fraction which was recrystallized from 4 mL of hexane to yield 564 mg (27%) of one diastereoisomer of 109 as the first crop and 63.2 mg (3%) as a second crop as a white solid: mp 93.5-94.5°C; IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄, 60 MHz) δ 0.10 (s, 9H, SiMe₃), 0.90-3.00 (m, 9H), 3.68-4.30 (m, 2H, NCH), 7.13 (br s, 5H, Ar-H); NMR (CDCl₃, 200 MHz) δ 0.13 (s, 9H, SiMe₃), 1.24-2.71 (m, 9H), 2.92 (dt, J=11, 5 Hz, 1H, NCH), 3.95 (dd, J=11, 5 Hz, 1H, NCH), 4.25 (ddd, J=11, 7, 5 Hz, 1H, angular-NCH), 7.10-7.40 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 319(4), 304(2), 286(3), 269(3), 242(4), 234(5), 210(47), 196(19), 182(6), 162(14), 149 (16), 136(7), 110(5), 99(11), 91(5), 95(6), 73(100); exact mass calcd for C₁₇H₃₅NOSSi m/e 319.1426, found m/e 319.1447.

Anal. Calcd. for C₁₇H₂₅NOSSi: C, 63.90; H, 7.89. Found: C, 64.00; H, 8.07.

The mother liquor was concentrated in vacuo to give 86.6 mg (4%) of a colorless oil composed of 109 and 107 (35:65, respectively, by NMR). Characteristic signals of 107:
NMR (CDCl₃) δ 3.30-3.45 (two overlapped t, J=7 Hz, at 3.35 and 3.40, 4H, NCH₂), 6.55 (t, J=7 Hz, 1H, =CH-). Further elution gave 445 mg (25%) of a mixture of 108 and 110
(3:2, respectively, by NMR). A small amount of pure 108 could be obtained by further chromatography over a Lobar column as a colorless oil: IR (CCl₄) 1695 cm⁻¹; NMR (CDCl₃)  δ 0.19 (s, 9H, SiMe₃), 1.37-2.75 (m, 9H), 3.15 (br t, J=12 Hz, 1H, NCH), 3.54 (dt, J=12, 8 Hz, 1H, NCH), 3.90 (td, J=9, 7 Hz, 1H, angular-NCH), 7.13-7.40 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 319(4), 286(3), 269(23), 210(61), 196(20), 177(7), 149(33), 136 (13), 121(4), 110(6), 97(14), 73(100); exact mass calcd for C₁₇H₂₅NOSSi m/e 319.1426, found m/e 319.1474. Only an enriched sample of 110 could be obtained: NMR (CDCl₃, 200 MHz) δ 3.00 (ddd, J=11, 8, 5 Hz, 1H, NCH), 3.56 (td, J=11, 8 Hz, 1H, NCH), 3.96 (q, J=6 Hz, 1H, angular-NCH).

Final elution gave 596 mg (28%) of the most polar diastereoisomer of 109 as a white solid: mp 87-88.5°C; IR (CCl₄) 1695 cm⁻¹; NMR (CCl₄, 60 MHz)  δ 0.17 (s, 9H, SiMe₃), 1.00-3.00 (m, 9H, -CH₂- manifold), 3.44-4.05 (m, 2H, NCH), 7.13 (br s, 5H, Ar-H); NMR (CDCl₃, 200 MHz) δ 0.18 (s, 9H, SiMe₃), 1.42-2.05 (m, 4H), 2.13-2.71 (m, 4H), 2.93 (td, J=12, 7 Hz, 1H, NCH), 3.78 (ddd, J=12, 8, 5 Hz, 1H, NCH), 4.01 (td, J=9, 7 Hz, 1H, angular-NCH), 7.11-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 319(5), 286(4), 269(1.5), 242(5), 210(70), 196(21), 182(7), 167(6), 149(7), 136(11), 110(5), 109(5), 97(4.5), 91(5), 73(100); exact mass calcd for C₁₇H₂₅NOSSi m/e 319.1426, found m/e 319.1452.
Anal. Calcd. for C_{17}H_{25}NOSSi: C, 63.90; H, 7.89.
Found: C, 63.96; H, 7.69.

1-(3-Pentynyl)-2,5-pyrroldinedione (134). To a mixture of 1.00 g (11.9 mmol) of 3-pentyn-1-ol, 1.43 g (14.4 mmol) of succinimide and 3.12 g (11.9 mmol) of triphenylphosphine in 17 mL of dry tetrahydrofuran cooled in an ice-water bath under argon was added dropwise a solution of 2.08 g (11.9 mmol) of diethyl azodicarboxylate in 5 mL of dry tetrahydrofuran over a period of 10 min. The resulting solution was stirred at room temperature for 5.5 h, and the solvent was removed in vacuo. The residue was triturated with 30 mL of ethyl acetate-hexane (3:7), filtered, and the filter cake was triturated again with 20 mL of ethyl acetate-hexane (3:7). After filtration, the combined filtrates were concentrated in vacuo, and the residue was mixed with 30 mL of the same solvent pair and filtered. The filtrate was concentrated to give 3.22 g of a pale-yellow oil. The oil was chromatographed over 35 g of silica gel (eluted with dichloromethane) to yield 1.67 g (85%) of imide 134 as a colorless oil: NMR (CDCl$_3$) δ 1.73 (t, J=2 Hz, 3H, -CH$_3$), 2.20-2.50 (m, 2H, =CCH$_2$-), 2.65 (s, 4H, NCOCH$_2$), 3.53 (t, J=7 Hz, NCH$_2$).
1-(3-Pentynyl)-5-phenylthio-2-pyrrolidinone (111). To a solution of 1.53 g (9.25 mmol) of imide 134 in 55 mL of absolute ethanol cooled in an ice-water bath under argon was added 974 mg (25.8 mmol) of sodium borohydride. A 1.6 N solution of hydrogen chloride in absolute ethanol was added in a rate of 5 drops every 5 min over a period of 2.5 h. The resulting mixture was acidified to pH 3 (about 20 mL of 1.6 N HCl-EtOH), stirred at 0°C for 1.5 h and basicified with 1% potassium hydroxide in absolute ethanol (about 15 mL) to pH 9. Throughout the whole process, the reaction temperature was kept below 5°C. The reaction mixture was then partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous phase was extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford 1.74 g of crude ethoxylactam as a pale-yellow oil. The oil was dissolved in 10 mL of thiophenol followed by the addition of 72.2 mg (0.380 mmol) of p-toluenesulfonic acid monohydrate. The resulting solution was stirred at room temperature for 2 h, diluted with 100 mL of dichloromethane and washed with 110 mL of 1 N sodium hydroxide solution. The aqueous phase was extracted...
with two 100-mL portions of dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$) and concentrated in vacuo to give 2.30 g of a pale-yellow oil. The oil was chromatographed over 45 g of silica gel (eluted with ethyl acetate-hexane, 4:6) to yield 2.08 g (97%) of thiophenoxylactam 111 as a colorless oil: IR (CCl$_4$) 1700 cm$^{-1}$; NMR (CCl$_4$) & 1.40-2.67 (m with t, J=2 Hz, at 1.77, 9H), 3.30 (td, J=13, 6 Hz, NCH), 3.80 (td, J=13, 6 Hz, 1H, NCH), 5.03 (dd, J=8, 2 Hz, 1H, NCH$_2$), 7.15-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 150(M$^+$-SPh, 15), 149(35), 110(100), 109(20), 96(86).

**Cyclization of Thiophenoxylactam 111:** 1-(3-Pentynyl)-2-pyrrolidinone (112) and (Z)-1,5,6,8a-Tetrahydro-8-methyl-3(2H)-indolizinone (113). To a solution of 1.00 g (3.86 mmol) of thiophenoxylactam 111 in 50 mL of dry benzene was added a solution of 1.22 mL (4.62 mmol) of tri-n-butylin hydride and 38.0 mg (0.232 mmol) of AIBN in 35 mL of dry benzene over a period of 2.5 h. The resulting solution was heated for another 2 h followed by the addition of 0.20 mL (0.76 mmol) of
tri-n-butyltin hydride and 9.0 mg (0.055 mmol) of AIBN. After heating for another 1 h, the reaction mixture was cooled to room temperature and the solvent was removed in vacuo to give 2.70 g of a white turbid liquid. This material was chromatographed over 35 g of silica gel (eluted with ethyl acetate) to afford 544 mg (93%) of a pale-yellow liquid as a mixture of lactams 112 and 113 (77:23, respectively, by NMR). Pure samples could be obtained by further chromatographed over a Lobar size B column (eluted with ethyl acetate) and collecting those pure fractions of each isomer. The less polar 113: IR (CCl₄) 1695 cm⁻¹; NMR (CCl₄, 90 MHz) δ 1.30-1.50 (m with br s at 1.70, 4H, -CH₃ and COCH₂CH₂), 1.80-2.88 (m, 6H), 3.70-4.23 (m, 2H, equatorial-NCH₂ and angular-NCH), 5.43 (br s, 1H, =CH-); NMR (CDCl₃, 200 MHz) δ 1.45-1.75 (m, 4H, -CH₃, COCH₂CH₂), 1.90-2.50 (m, 5H), 2.75 (dt, J=12, 5 Hz, axial-NCH₂), 3.99 (br t, J=9 Hz, angular-NCH), 4.20 (ddd, J=12, 6.5, 0.5 Hz, equatorial-NCH₂), 5.49 (br d, J=4 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 151(39), 136(61), 97(39), 94(28), 93(78), 69(100); exact mass calcd for C₉H₁₃NO m/e 151.0997, found m/e 151.1001. 112: IR (CCl₄) 1690 cm⁻¹; NMR (CCl₄) δ 1.50-2.50 (m with t, J=2 Hz, at 1.90, 9H, -CH₃ and -CH₂- manifold), 3.20-3.55 (two overlapped t, J=7 Hz, at 3.33, and J=6 Hz, at 3.47, 4H, NCH₂); mass spectrum, m/e (relative intensity) 151(45), 150(2.5), 136(7), 98(100); exact mass calcd for
1-(2,3-Butadienyl)-2,5-pyrrolidinedione (114a). To an ice-water bath cooled mixture of 0.989 g (14.1 mmol) of 2,3-buta dien-1-ol, 1.54 g (15.5 mmol) of succinimide and 4.08 g (15.6 mmol) of tri-phenylphosphine in 19 mL of dry tetrahydrofuran was added drop-wise under argon a solution of 2.71 g (15.6 mmol) of diethyl azodicarboxylate in 6 mL of dry tetrahydrofuran over a period of 50 min. The resulting solution was stirred at room temperature for 1.5 h. The solvent was removed in vacuo, and the residue was triturated with 40 mL of ethyl acetate-hexane (3:7) and filtered. The filtrate was concentrated in vacuo to afford 5.41 g of a yellow oil which was chromatographed over 55 g of silica gel (eluted with dichloromethane) to give 2.013 g (99%) of imide 114a as a yellow oil: IR (CCl₄) 1960, 1780, 1710 cm⁻¹; NMR (CCl₄) δ 2.60 (s, 4H, COCH₂), 3.93 (td, J=6, 3 Hz, 2H, NCH₂), 4.60-4.87 (m, 2H, =CH₂), 5.07 (qu, J=6 Hz, 1H, =CH-); mass spectrum, m/e (relative intensity) 151(63), 112(21), 100(18), 94(50), 82(19), 80(14), 72(12), 70(33), 69(29), 68(50), 67(68), 57(18), 56(100), 55(79), 53(53), 52(56); exact mass calcd for C₉H₁₃NO₂ m/e 151.0633, found m/e 151.0633.
1-(3,4-Pentadienyl)-2,5-pyrrolidinedione (114b). To an ice-cooled mixture of 1 g (11.9 mmol) of 3,4-pentadien-1-ol, 1.13 g (11.9 mmol) of succinimide and 3.12 g (11.9 mmol) of triphenylphosphine in 17.5 mL of dry tetrahydrofuran was added dropwise under argon a solution of 2.07 g (11.9 mmol) of diethyl azodicarboxylate in 5 mL of dry tetrahydrofuran over a period of 1 h. The resulting solution was stirred at room temperature for 6 h, and the solvent was removed in vacuo. The residue was triturated twice with ethyl acetate-hexane (3:7, 30 mL followed by 20 mL). The combined extracts were concentrated in vacuo and the resulting residue was triturated again with 30 mL of ethyl acetate-hexane (3:7). The extract was concentrated in vacuo to give 3.19 g of a pale yellow oil which was chromatographed over 35 g of silica gel (eluted with dichloromethane) to give 1.76 g (90%) of imide 114b as a colorless liquid which solidified on standing: mp 34-36 °C; NMR (CDCl₃) 2.07-2.43 (m, 2H, allyl-H), 2.63 (s, 4H, COCH₂), 3.50 (t, J=7 Hz, 2H, NCH₂), 4.64 (td, J=6, 3 Hz, 2H, =CH₂), 5.01 (qu, J=6 Hz, 1H, =CH₂).

1-(2,3-Butadienyl)-5-phenylseleno-2-pyrrolidinone (116a). To a solution of 9.73 g (64.4 mmol) of imide 114a
in 150 mL of absolute ethanol cooled in an ice-water bath under argon was added 6.45 g (170 mmol) of sodium borohydride. A 1.49 N solution of hydrogen chloride in absolute ethanol was added at a rate of 5 drops every 5 min over 2 h. The resulting mixture was stirred at 0 °C for another 20 min and partitioned between 75 mL of water, 75 mL of saturated sodium chloride solution and 200 mL of dichloromethane. The aqueous layer was extracted with three 150-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 9.47 g of crude carbinolactam as a pale-yellow oil. The oil was stirred with 152 mg (0.900 mmol) of p-toluenesulfonic acid monohydrate and 6.55 mL (62.0 mmol) of selenophenol under argon at room temperature for 3 h and chromatographed directly over 250 g of silica gel (eluted with ethyl acetate-hexane, 2:9, followed by ethyl acetate-hexane, 4:6) to yield 15.5 g (92%) of selenophenoxy lactam 116a as a yellow oil: IR (CCl₄) 1950, 1700 cm⁻¹; NMR (CCl₄) δ 1.20-2.90 (m, 4H, COCH₂CH₂), 3.30-3.32 (m, 1H, NCH), 4.10-5.20 (m, 5H, ==CH-, NCH and SeCHN), 7.05-7.50 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 170(9), 158(20), 152(25), 136(M⁺-SePh, 96), 126(19), 114(19), 96(51), 84
To an ice-cooled solution of 350 mg (2.12 mmol) of imide 114b in 4 mL of methanol was added 94 mg of sodium borohydride. The resulting mixture was stirred for 20 min at 0°C followed by the addition of 92 mg of sodium borohydride and 64 mg of sodium borohydride after another 40 min. The reaction mixture was stirred at 0°C for another 40 min then partitioned between 7 mL of water, 7 mL of saturated sodium chloride solution and 30 mL of dichloromethane. The aqueous phase was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to give 323 mg of a colorless oil. The oil was stirred with 8.2 mg (0.043 mmol) of 2-toluene-sulfonic acid monohydrate and 0.225 mL (2.13 mmol) of selenolphenol at room temperature under argon for 3 h and then chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexane, 25:75, followed by ethyl acetate-hexane, 35:65) to afford 534 mg (92%) of 116b as a yellow oil: IR (CCl₄) 1950, 1700 cm⁻¹; NMR (CDCl₃) δ 1.20-2.70 (m, 6H), 3.10 (td, J=14, 7 Hz, 1H, NCH), 3.78 (td, J=14, 6 Hz, 1H, NCH), 4.50-4.90 (m, 2H, =CH₂), 4.92-5.18
(m, 2H, SeCHN and =CH-), 7.15-7.65 (m, 5H, Ar-H); mass spectrum, m/e (relative intensity) 166(13), 159(35), 150 (M⁺-SePh, 65), 140(13), 96(30), 83(39), 78(100).

E-1,2,5,7a-Tetrahydro-7-methyl-3H-pyrrolizin-3-one (121) and Hexahydro-7-methyl-ene-3H-pyrrolizin-3-one (122). To a solution of 15.5 g (53.1 mmol) of selenophenoxy-lactam 116a in 800 mL of dry benzene heated to reflux under argon was added a solution of 21.0 mL (79.6 mmol) of tri-n-butyltin hydride and 307 mg (1.37 mmol) of AIBN in 200 mL of dry benzene over a period of 15 h. The solvent was removed in vacuo, and the residue was dissolved in 200 mL of hexane and extracted with four 50-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo and distilled to yield 5.04 g of 121 and 122 as a pale yellow liquid (bp 87°C at 1.65 mmHg). The distillate was first chromatographed over 60 g of silica gel (eluted with ethyl acetate-hexane, 7:3, followed by ethyl acetate) and then over a Lobar size C column (eluted with ethyl acetate-hexane, 9:1) and the overlapping portions were chromatographed again over Lobar size C column (eluted with ethyl acetate-hexane, 65:35, followed by ethyl acetate-hexane, 7:3) to yield in combination 3.67 g (52%) of
the less polar 121 as a colorless liquid: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.60-1.93 (m, 3H, -CH₃), 1.93-2.90 (m, 4H, COCH₂CH₂), 3.20-3.30 (m, 1H, NCH), 3.95-4.55 (m, 2H, NCH), 5.29 (br s, 1H, =CH-)

mass spectrum, m/e (relative intensity) 137(76), 136(21), 122(38), 98(57), 82(52), 81(52), 69(72), 55(100); exact mass calcd for C₉H₁₄NO m/e 137.0341, found m/e 137.0307, 1.04 g (14%) of 122 as a colorless liquid: IR (CCl₄) 1700 cm⁻¹; NMR (CCl₄) δ 1.30-3.50 (m, 7H, -CH₂- manifold), 3.75 (td, J=10, 5 Hz, 1H, NCH), 4.17 (br t, J=6 Hz, 1H, NCH), 4.72-4.98 (a six line AB multiplet, 2H, =CH₂); mass spectrum, m/e (relative intensity) 137(100), 136(79), 92(38), 81(24), 80(23), 59(18), 55(46); exact mass calcd for C₉H₁₄NO m/e 137.0341, found m/e 137.0844.

N-(3,4-Pentadien-1-yl)-2-pyrrolidinone (117b) and Z-1,5,6, Sa-Tetrahydro-9-methyl-3(2H)-indolizinone (113). To a solution of 507 mg (1.66 mmol) of selenophenoxylactam 116b in 15 mL of dry benzene heated to reflux under argon was added dropwise over a period of 2 h and 40 min a solution of 0.656 mL (2.49 mmol) of
tri-n-butyltin hydride, and 6.6 mg (0.04 mmol) of AIBN in 20 mL of dry benzene. The resulting solution was stirred at the same temperature for another 3 h. The solvent was removed in vacuo and the residue was dissolved in 30 mL of hexane. This hexane solution was extracted with three 15-mL portions of acetonitrile. The combined acetonitrile layers were concentrated in vacuo to give 396 mg of a pale-yellow oil. The oil was chromatographed over 15 g of silica gel (eluted with ethyl acetate) to give 216 mg (86%) of a mixture of 113 and 117b (7:3, respectively, by NMR) as a pale-yellow oil separable by GLC (6 ft x 1/8 in column packed with 3% SE-30 on WAW, DMCS 80-100; column temperature= 160°C, flow rate= 25 mL/min). 117b: t_R = 3.5 min; IR (CCl_4) 1690 cm^{-1}; NMR (CDCl_3, 200 MHz) δ 2.02 (qu, J=7 Hz, 2H, COCH_2CH_2), 2.24 (tq, J=7, 3.5 Hz, 2H, allyl), 2.39 (~t, J=7 Hz, 2H, COCH_2), 3.35 (~t, J=7 Hz, 2H, NCH_2), 3.40 (~t, J=7 Hz, 2H, NCH_2), 4.69 (td, J=7 3.5 Hz, 2H, =CH_2), 5.03 (qu, J=7 Hz, 1H, =CH). 113: t_R = 4.2 min; identical in all respects with the material synthesized from 112.
PART II - REFERENCES

1. For a discussion illustrating the emphasis currently placed on polar coupling processes, see: Seebach, D. Ang. Chem. Int. Ed. 1979, 18, 239.


7. For pertinent references see the books listed in ref 3.

8. The research group of Julia in France has investigated certain intramolecular C-C bond forming reactions in depth. Although the group has shown that a number of carbocyclic ring systems common to terpenoids can be constructed via radical processes, this
chemistry has been largely ignored by natural product chemists. For an overview of the contributions of the Julia group, see: (a) Julia, M. Rec. Chem. Prog. 1964, 25, 3; (b) Julia, M. Pure Appl. Chem. 1967, 15, 167; (c) Julia, M. Acct. Chem. Res. 1971, 4, 386; (d) Julia, M. Pure Appl. Chem. 1974, 40, 553.

9. The following applications of radical C-C bond forming reactions to the synthesis of natural products have been reported: (a) Sativene and Copacampene: Bakuzis, P.; Campos, O. O. S.; Baduzis, M. L. F. J. Org. Chem. 1976, 41, 3261; (b) α-Agarofurane and Dihydroagarofurane: Büchi, G.; Wuest, H. ibid. 1979, 44, 546; (c) For a reaction which may proceed via a radical anion cyclization that has seen use in the synthesis of gibberellins, see: Stork, G.; Malhotra, S. K.; Thompson, H.; Uchibayashi, M. J. Am. Chem. Soc. 1965, 87, 1148.

10. See ref 3 for discussions of competing rate problems associated with radical addition reactions.


15. For discussion about substituted hexenyl radical cyclizations, see: ref 11.


24. After the completion of our initial work, the method of α-acylamino radical generation independently developed herein was reported by others: Bachi, M. D.; Hovrnaert, C. Tetrahedron Lett. 1981, 2693.


27. See ref 13 in Part I.


33. See ref 46 in Part I.
34. See ref 41 and 42 in Part I.
35. See ref 19 in Part I.
40. See ref 21 in Part I.
42. For a recent example of a 5-hexen-1-yl type radical that undergoes an unusually large amount of endo cyclization, see: Wilt, J. W. J. Am. Chem. Soc. 1981, 103, 5251.
43. Agosta, W. C.; Wolff, S. J. Chem. Res. (C) 1981, 78. For possible reasons of this selectivity, see: ref 4, 5 and 11.
Reduction of thiols with tri-n-butyltin hydride have been reported: Vedejs, E.; Powell, D. W. J. Am. Chem. Soc. 1982, 104, 2046.

Complication arised from reduction of nitro group with tri-n-butyltin hydride has been reported: Kohler, J.J.; Speckamp, W. N. Tetrahedron Lett. 1977, 635.

Imides corresponding to 28a, b and d were prepared by condensation of the appropriate alcohols with succinimide (ref 27) via the method of Mitsunobu (ref 16 in Part I).

Imide corresponding to 28c was prepared by catalytic hydrogenation (H₂, Pd/BaSO₄; 92%) of the corresponding alkyn which in turn was prepared according to the strategy described in ref 46.

A pure sample of 38 was prepared by independent synthesis (vide infra).

VPC Studies shown that the stereochemical integrity of the starting imide corresponding to 28c was at least 97%, contaminated with 3% of a material presumed to be the fully saturated imide 39. It was found that isomerization occurred in neat 28c, presumably due to the presence of trace amount of thio-phenoxy radical derived from a homolytic process. The possibility of tri-n-butyltin radical catalyzed isomerization also can not be excluded (ref 51).
50. VPC analysis of 29b, obtained from the cyclization study of 28b, shown that it was 90% pure contaminated with 7% of its cis isomer, and 3% of lactam 40. Analysis of 29c shown that it was 81% pure contaminated with 14% of its trans isomer and 5% of lactam 40. The origin of 40 is not clear. To help our analysis, a pure sample of 40 was obtained from 29c by catalytic hydrogenation (H₂, Pd/C) in a 79% yield. The above observations also indicate the fact that isomerization indeed occurred.


52. Although 32 and 33 were assumed as kinetic cyclization product by analogy with the cyclization of 4, our experiments can not rule out the possibility of the interplay of a reversible process.

53. For related acyliminium ion cyclizations leading to the formation of pyrrolizidines, see: Hart, D. J.; Yang, T. K. Tetrahedron Lett. 1982, 2761.

54. The structure of 43 and 44 were based on the similarities between ¹H NMR spectrum of 43 and 44 and those of 9 and 7, respectively.

55. Pure samples of 37, 38 and 49 were obtained by preparative VPC and analyzed with their 300 MHz ¹H NMR spectrum.

56. prepared from the corresponding imide (ref 57) by using the reaction sequence outlined in Scheme II.

57. The author wishes to thank Professor David J. Hart for the availability of this imide.
58. The stereochemical assignment for 51 is tentative and based on analogy with results obtained in the cyclizations of 4 and 53.

59. See ref 6c in Part I.

60. See ref 5 and 6a in Part I.


62. An inductive effect of the α-methoxy substituent slows down the exchange rate drastically. A complication of thiophenol addition to the olefin resulted in the isolation of 19% of 59 in addition to 53 (44% from imide). For a possible method of solving this problem, see: dissertation of J.-K. Choi, Ohio State University, Columbus, Ohio.

\[
\begin{align*}
\text{PhS} &- \text{SPhOMe} \\
&\text{OMe}
\end{align*}
\]

59

63. Obtained as a 5:4 mixture of diastereoisomers.

64. The structure of this compound is tentative and based on the similarity of its 300 MHz \(^1\)H NMR spectrum with that of 8.


69. See ref 16 in Part I.


71. Although tin hydride addition to acetylene of the similar type have been reported to give exclusively trans product (ref 51 and 70), this ratio is the smallest that could be achieved in our hands.

72. We attribute the major isomer as trans 77 by analogy of the literature results (ref 51 and 70).

73. This ratio was calculated from $^1$H NMR integration. Pure 82 and 84 were obtained by column chromatography.

74. A reasonably pure sample of 85 (71% yield based on this material) was obtained by column chromatography contaminated by small amount of 83, and was used for the subsequent reaction sequence. The presence of 83 was identified by the isolation of the corresponding alcohol after hydrolysis. The structure of this alcohol was based on the similarity of its $^1$H NMR with that of 37.


87. Lactams 93a and 94a were analyzed as a mixture. Lactam 95a was analyzed as a pure sample obtained by column chromatography. Yields were based on $^1$H NMR integration.
88. The stereochemical assignments of 93 and 94 were based partially on their 200 MHz $^1H$ NMR spectra. In the case of 94a, 94b and 94d, correlations to (+)-isoretronecanol (64) were made (vide infra).

89. For possible reason of this facile exo addition, see: Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; John Wiley and Sons: New York, 1976; Chap. 5.


91. 200 MHz $^1H$ NMR Spectrum of 99 indicates that it is isomerically pure.


94. To our knowledge this is the first example of cuprate addition with thioester to give a ketone.

95. This ratio was obtained from 200 MHz $^1H$ NMR integration.


99. Radical cyclizations of the corresponding vinyl sulfoxides were also studied. Only products arose from unexpected Pummerer rearrangement were isolated (ref 100).

100. Hart, D. J.; Tsai, Y.-M. "Sila-Pummerer Rearrangement at $sp^2$-Hybridized Carbon", submitted for publication.
The author wishes to thank Mr. Joong-Kwon Choi for carrying out this correlation.

Further studies addressing the issue of substituent effects on cyclizations of this type and their applications to the synthesis of more complicated alkaloids were carried out in depth by Hart and Choi; for the preliminary account of their results, see: Choi, J. K.; Hart, D. J.; Tsai, Y.-M. Tetrahedron Lett. 1982, 4765.


Prepared in a 99% yield from 2,3-butadiene-1-ol (ref 108) and succinimide by the method of Mitsunobu (ref 16 in Part I).


APPENDIX A

SELECTED $^1$H NMR SPECTRA OF NEW COMPOUNDS PREPARED

PART I
15 (CCl₄, 60 MHz)
OH

$\text{ppm}$

$260$

$12 \ (\text{CDCl}_3, \ 60 \ \text{MHz})$

$\text{ppm}$
$^{13}$ (CDCl$_3$, 90 MHz)
$^{1}H$-NMR spectrum of compound 17 (CDCl$_3$, 90 MHz).
18 (CCl₄, 60 MHz)
$^{19}$ (CCl$_4$, 60 MHz)
26 (CDCl₃, 60 MHz)
27 (CDCl₃, 90 MHz)
$^{28}$ (CDCl$_3$, 90 MHz)
$\text{H} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{H} \quad \text{H}$

30 (CDCl$_3$, 90 MHz)
$^{31}$ (CDCl$_3$, 90 MHz)
$2b$ (CDCl$_3$, 90 MHz)
$2c \text{ (CDCl}_3, 90 \text{ MHz)}$
36 (CDCl₃, 60 MHz)
37 (CCl₄, 90 MHz)
Figure 38 (CDCl$_3$, 60 MHz)
$^{1}$ (CCl$_4$, 90 MHz)
$^{1}H$ spectrum of compound 4 (CCl$_4$, 90 MHz)
$7$ (CDCl$_3$, 200 MHz)
$\delta$ (CDCl$_3$, 300 MHz)
76 (CCl₄, 90 MHz)
THPO

77 (CCl₄, 90 MHz)
$\text{THPO}$

78 (CCl$_4$, 90 MHz)
$^{1}H$ NMR (CDCl$_3$, 90 MHz)

$^{13}$C NMR (CDCl$_3$, 235 MHz)
$^{1}H$ NMR (CDCl$_3$, 90 MHz)
$^{1}H$ NMR spectrum of compound 74 (CCl$_4$, 90 MHz)
$^{2}H \text{NMR (CDCl}_3, 90 \text{ MHz)}$
$^{35}$ (CCl$_4$, 90 MHz)
36 (CDCl₃, 90 MHz)
$^{13}C_4 (CCl_4, 90 MHz)$
$\text{AcO}$

20 (CCl$_4$, 90 MHz)

ppm
64 (CDCl₃, 90 MHz)
90b (CCl₄, 90 MHz)
trans 91b (CCl₄, 90 MHz)
cis 91b (CCl₄, 90 MHz)
$^{94b}$ (CCl$_4$, 90 MHz)
$^{1}H$ (CDCl$_3$, 90 MHz)
$^{13}C$ (CCl$_4$, 90 MHz)
$^{11}C$ (CCl$_4$, 90 MHz)
$^{114a}$ (CCl$_4$, 60 MHz)
116a (CCl₄, 60 MHz)
$^{121}$ (CCl₄, 60 MHz)