AN ABSTRACT OF THE DISSERTATION OF

Frank Stappenbeck for the degree of Doctor of Philosophy in Chemistry presented on November 22, 1994.

Title: Synthetic Studies on Alkaloids. Part I: An Approach toward the Synthesis of (±)-Koumine, Part II: An Approach toward the Synthesis of (±)-Morphine.

Abstract approved: Redacted for Privacy

James D. White

Part I. Two approaches to a tricyclic ketone **61**, the carbocyclic nucleus of the indolenine alkaloid koumine (**1**), are described. The first approach entails a projected intramolecular Michael addition of the butenolide **96**. The second route proceeded in eight steps to the allylic alcohols **113** and **138** respectively from 3,4-furandicarboxylate **106**. With the latter compounds, construction of key structural elements of ketone **61** were studied via cyclizations that involve a furan template. Thus, alcohol **113** was converted to lactam **115** which shares the isoquinoline substructure with **61**. Furan oxidation of **113** or **138** with N-bromosuccinimide in the presence of methanol afforded acetal derivatives **124** and **139**. These substances contain the pyran moiety of ketone **61**. Hydroboration of the allylic alcohols **138** afforded triol **143** which bears the incorrect regiochemistry for conversion to the α-hydroxy ketone fragment contained in **61**. This was independently proven by X-ray analysis of a lactone derivative **147**.

Part II. An approach toward (±)-morphine is presented which envisions key bond formation between the carbon atoms 13 and 15 of the morphine structure. Implementation of this plan entailed the study of phenanthrene derivatives for that particular carbon-carbon bond construction. Thus, diazoketone **73**, containing the phenanthrenone skeleton, was prepared in nine steps from isovanillin (**46**). Rhodium acetate-catalyzed decomposition of **73** in dichloromethane resulted in the formation of cyclobutanone **75** through an intramolecular C-H insertion. This process generated a new bond between carbons 14 and 15 rather than 13 and 15. Exposure of the diol **85** derived from **75** to boron trifluoride resulted in a Wagner-Meerwein rearrangement which connected carbons 13 and 15. The rearranged product **86** was converted to ketone **87** which possesses the complete carbon framewok of morphine. The failure to perform a Beckmann rearrangement by conventional methods on compound **87** is discussed.

Synthetic Studies on Alkaloids:

Part I: An Approach toward the Synthesis of (±)-Koumine,

Part II: An Approach toward the Synthesis of (±)-Morphine.

by
Frank Stappenbeck

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APPROVED:

Redacted for Privacy

Professor of Chemistry in charge of major

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Chairman of the Department of Chemistry

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Dean of Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

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Frank Stappenbeck, Author

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PART I: AN APPROACH TOWARD THE SYNTHESIS OF (±)-KOUMINE

Chapter I. General Introduction

A widely adopted characterization of secondary metabolites, known collectively as natural products, defines them as substances that appear to be nonessential to the plant, insect or microorganism producing them. These natural products are thereby distinguished from those of the primary metabolism such as fatty acids, sugars, amino acids and nucleotides that are indispensable for cell growth and maintenance of the organism.

Natural products, in the form of crude plant extracts, have been used by man since the dawn of time: primitive man found these extracts expedient as medicines for the relief of pain or alleviation of the symptoms of disease, as poisons for use in warfare and hunting, as effective agents for euthanasia and capital punishment, and as narcotics, hallucinogens, or stimulants to alleviate fatigue and hunger.

The term *Alkaloids* comprises a large class of natural products that are biogenetically derived from amino acids and owe their behavior as bases to the presence of nitrogen in their molecular structure. They principally occur in the leaves, seeds, roots and the bark of higher plants, particularly those of the families *Papilonaceae* (lupis), *Papaverceae* (poppies), *Ranunculae* (aconites) and *Solanaceae* (tobacco, potato, tomato).

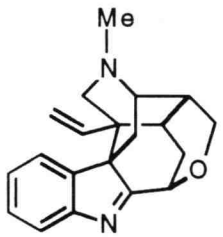
The biological activity of some alkaloids such as strychnine or yohimbine is legendary. In fact, almost all plant alkaloids possess in varying degrees interesting pharmacological activity. Although the number of medicinally useful

alkaloids is restricted due to the toxicity that they frequently display, those alkaloids that are in therapeutic use today constitute a very important group of medicinal agents.

Organic chemists have long been fascinated by the complex structural and synthetic puzzles posed by alkaloid chemistry. Total synthesis of alkaloid natural products, aside from being the ultimate proof of structure, has been central to the development of new methods for synthesis and structure elucidation in organic chemistry. While some alkaloids are still obtained from plant sources for economic reasons even after their total synthesis has been achieved (for example, reserpine, ergotamine, morphine), synthesis has largely replaced the plant source in the supply of a number of other alkaloids important to medicine (for example, ephedrine or quinine).

Chapter II: An Approach toward the Synthesis of (±)-Koumine.

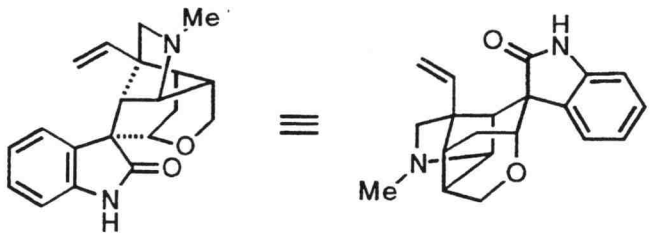
History and Background



1

(-)-Koumine (**1**) is the principle constituent of *Gelsemium elegans Bentham*, a plant used in traditional folk medicine in China.[1] Reportedly, the toxic plant (known locally as "Kou-Wen") also has a notorious reputation in Chinese forensic medicine for its implication in homicides.

The first report available in the West of the isolation and purification of koumine appeared in 1931.[2] While the Chinese plant *Gelsemium elegans* over the centuries has found use for treatment of severe pain, the pharmacological properties of (-)-koumine have not been systematically studied outside of China. Crude preparations from *Gelsemium elegans* in combination with aspirin are commonly used in China for the palliation of various acute cancer pains, particularly hepatic cancer. Recent clinical evaluation of (-)-koumine in the treatment of malignant tumors has given good results.[3]



2

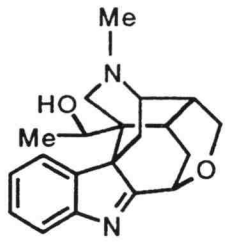
(-)-Koumine bears some structural resemblance to (+)-gelsemine (**2**), the principal alkaloid isolated from various *Gelsemium* species such as *Gelsemium sempervirens* (Carolina jasmine). The latter plant is commonly found throughout the southeastern United States and northern Mexico. Roots of that plant are an ingredient in some Mexican liquors and extracts of its flowers have been used by the perfume industry.[4] (+)-Gelsemine, a compound with a long western medicinal history,[5] was first isolated in 1870. It is a strong central nervous system stimulant as well as an analgetic and antihypertensive agent, and its pharmacological properties have been quite thoroughly explored.

Toxicity studies in rodents have shown that the acute toxicity of (-)-koumine is comparable to that of (+)-gelsemine which has a medium lethal dose (MLD) of 180 mg/Kg, while other alkaloids of *Gelsemium elegans* are much more toxic.[6] For example, humantenidine has a MLD of 185 μg/Kg. Toxicity presents a serious limitation for the clinical application of these alkaloids. The clinical symptoms of gelsemium poisoning in humans and rodents have been described as closely resembling those of strychnine poisoning . Intoxication produces powerful excitation of all parts of the central nervous system, which does not result from direct synaptic excitation but rather from selective blockage of inhibitory neurons. Strychnine is known to antagonize the inhibitory neurotransmitter glycine which has its highest

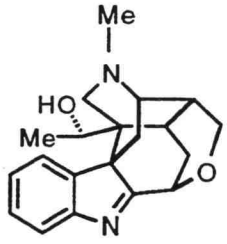
receptor density in the spinal cord, brain stem and thalamus. In the spinal cord, the alkaloid suspends the reciprocal inhibition that exists between antagonistic muscles. Minor sensory stimulation then induces violent convulsions that follow a characteristic motor pattern. The pattern of the convulsion is determined by the most powerful muscles acting at a given joint. During these convulsions all skeletal muscles including those of the face are in full contraction and the body is arched in hyperextension so that the crown of the head and the heels may be touching the ground. If untreated, death usually occurs after the second to fifth full convulsion.

Both (-)-koumine and (+)-gelsemine resisted structure elucidation by chemical degradation and spectroscopic analysis for many years. Eventually, both structures were solved through crystallographic studies.[7,8] The absolute stereochemistry of (-)-koumine was established through partial synthesis from vobasin.[9]

A variety of structurally diverse alkaloids have been isolated from *Gelsemium sempervirens* and *Gelsemium rankinii* found in the southeastern United States as well as from the less explored Chinese species *Gelsemium elegans* .[6] Recently, an alkaloid extract of the latter plant has afforded two new koumine-related substances, (19*R*)-hydroxydihydrokoumine (**3a**) and (19*S*)-hydroxydihydrokoumine (**3b**), whose structures and stereochemistry were confirmed by X-ray diffraction analysis.[10] Along with (-)-koumine-N-oxide (**4**) and (+)-21-oxo-gelsemine (**5**) *Gelsemium elegans* has yielded (-)-taberpsychine (**6**), a compound believed to be a key biogenetic precursor for both (-)-koumine and (+)-gelsemine.[6]



3 a



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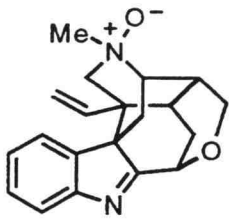

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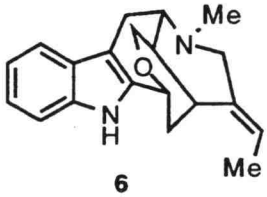

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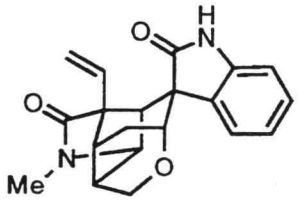
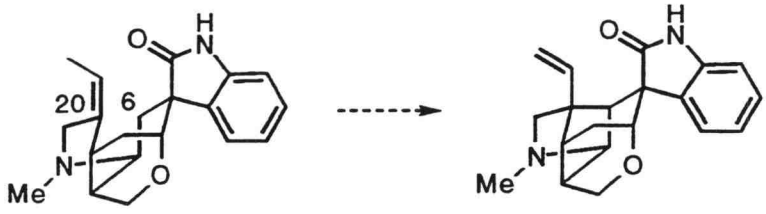


5

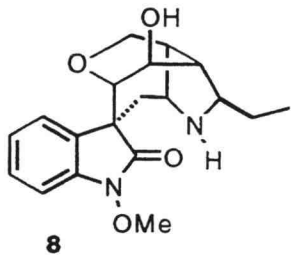
Several alkaloids of the humantenine family have also been isolated. Their oxindole skeleton is similar to that of gelsemine but is lacking a bond between C-6 and C-20. It has been speculated that humantenine (**7**) may be the immediate biogenetic precursor of gelsemine (scheme 1).[1]



7 2

scheme 1

In addition, gelsedine (**8**), koumindine (**9**), and sempervirine (**10**) represent examples of structurally interesting alkaloids obtained from *Gelsemium* species.[1]



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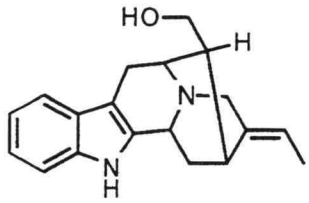

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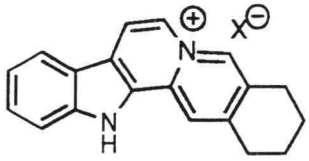
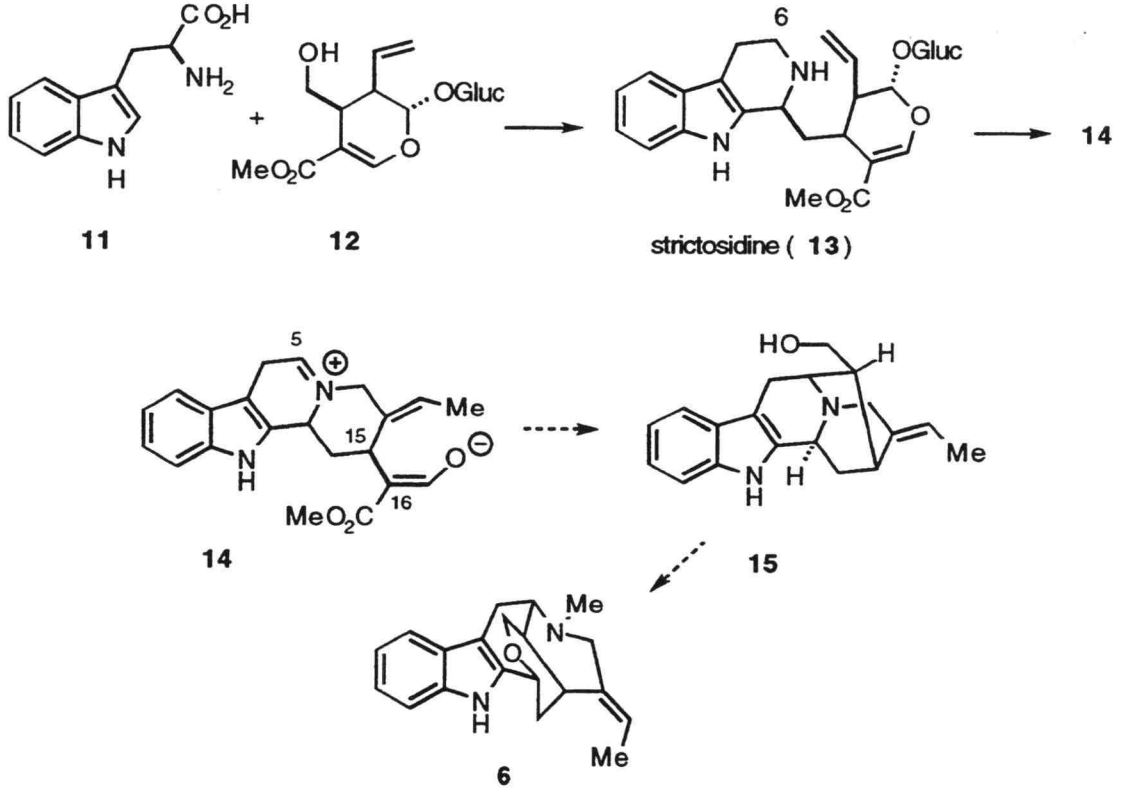


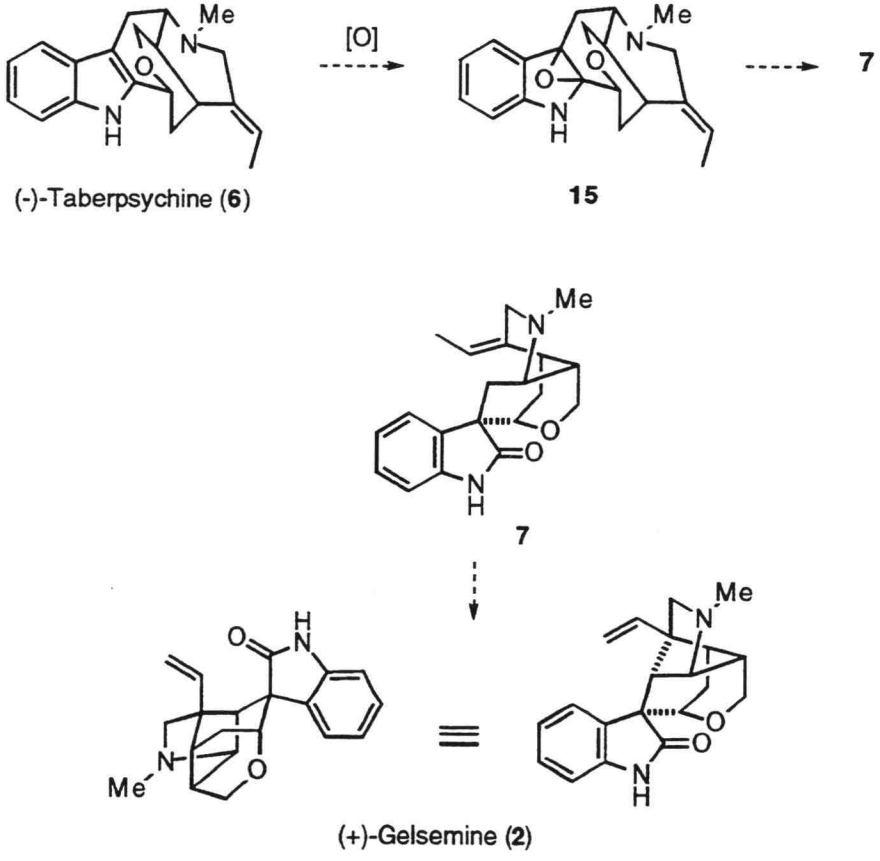
10

Zenk et al. proposed that the *Gelsemium* alkaloids are biosynthesized by a route analogous to that leading to monoterpenoid alkaloids and which follows the biological transformations of strictosidine (**13**) (scheme 2).[11] This was confirmed through incorporation of [6-^{14}C]-strictosidine into gelsemine (0.47%). However, the detailed biogenetic relationship between the different alkaloids in the series remains to be elucidated.



scheme 2

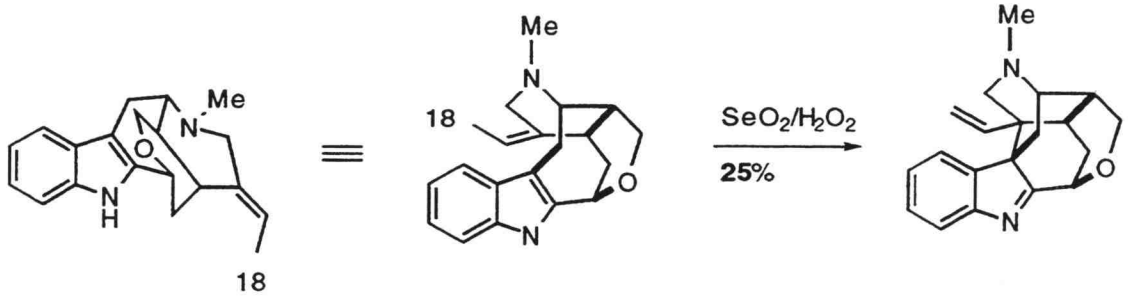
Nevertheless, a "map of biogenetic speculation" has been proposed for the origin of the *Gelsemium* alkaloids (scheme 2).[12] According to this scheme strictosidine, after being transformed to a coryantheine-type base **14**, forms the koumidine skeleton **15** by closure between C-5 and C-16. After N-methylation, **15** is converted to (-)-taberpsychine (**6**). (-)-Taberpsychine (**6**) has been proposed as the biogenetic precursor of the humantenine-type alkaloids which in turn are transformed to the gelsemine skeleton (scheme 3).



scheme 3

Research directed at a biomimetic synthesis of (-)-koumine has confirmed its relationship to (-)-taberpsychine (**6**) (scheme 4). Thus, taberpsychine was converted to koumine by oxidation with selenium dioxide

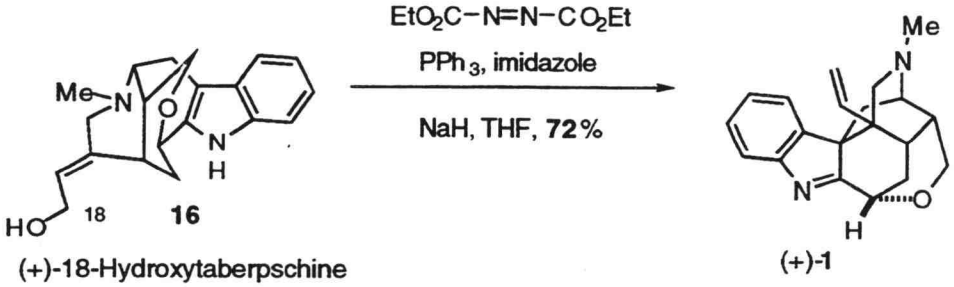
in the presence of hydrogen peroxide in a sequence believed to mimic the final steps in the biosynthesis of (-)-koumine.[13] This precedent had direct bearing on the synthetic planning and execution of the first total synthesis of (+)-koumine (**1**) (the unnatural enantiomer) by Magnus.[14]



(-)-Taberpsychine (**6**) **1**

scheme 4

It was recognized that if the taberpsychine structure possessed a leaving group at C-18, a facile intramolecular S_{N2}' process could lead to the ring system of koumine.



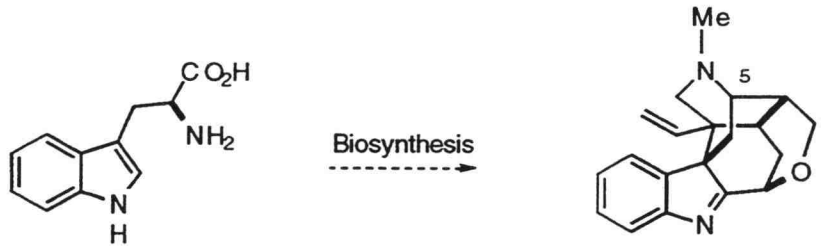
(+)-18-Hydroxytaberpschine (+)-**1**

scheme 5

In fact, while the cyclization of natural (-)-taberpsychine (**6**) via allylic oxidation with selenium dioxide provides (-)-koumine only in modest yield,

treatment of (+)-18-hydroxytaberpsychine (**16**) under Mitsunobu conditions was found to give (+)-koumine (**1**) smoothly in 72% yield (scheme 5).

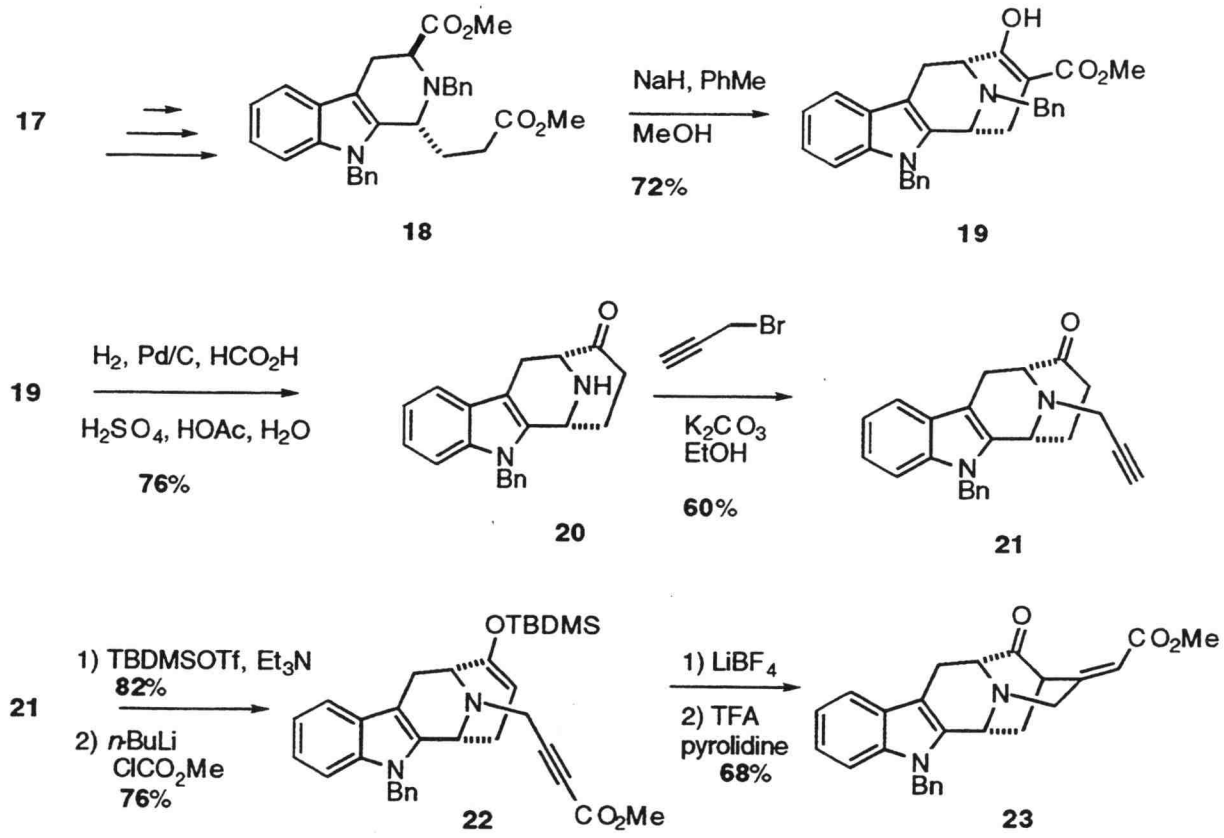
The Magnus synthesis begins with the natural amino acid (*S*)-(-)-tryptophane (**17**) which bears the same absolute configuration at C-5 as that found in natural (-)-koumine (scheme 6).



(S)-(-)-Tryptophan (**17**) (-)-Koumine (**1**)

scheme 6

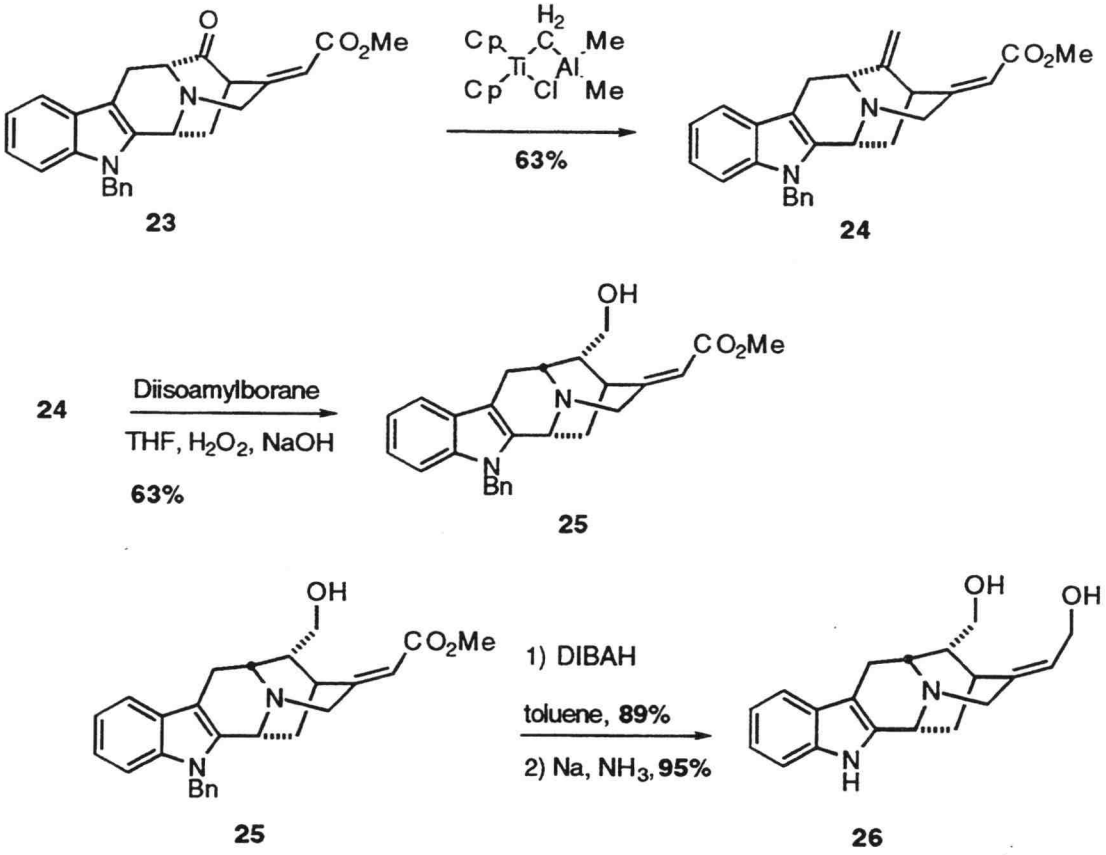
However, in the course of a Dieckmann condensation performed on the intermediate **18** the C-5 stereocenter is inverted, resulting in the synthesis of (+)-koumine, the unnatural enantiomer. Recently, Bailey[15] reported that it is possible to avoid this epimerization. Thus, a route to natural (-)-koumine is formally available which does not require (*R*)-(+)-tryptophane as starting material.



scheme 7

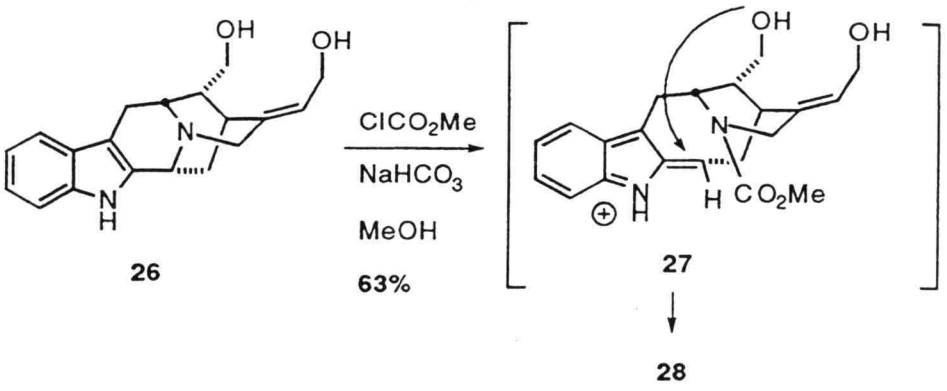
Dieckmann condensation of **18** afforded the tetracyclic compound **19** which, after selective debenzylation and decarboxylation, was converted to the amino ketone **20** (scheme 7). N-alkylation of **20** with propargyl bromide gave the alkyne **21**. Treatment of **21** with *tert*-butyldimethylsilyl triflate followed by acylation of the alkyne with methyl chloroformate produced the α,β-unsaturated acetylenic ester **22**. Cleavage of the silyl enol ether, followed by treatment of the resulting ketone with pyrrolidine and trifluoroacetic acid, promoted an intramolecular Michael addition yielding **23**. The quinuclidinic ketone **23** was subjected to Tebbe's reagent resulting in homologation of the carbonyl group to give **24** (scheme 8). Hydroboration with diisoamylborane introduced the hydroxymethyl group in a stereoselective fashion leading to

25. Reduction of **25** with diisobutylaluminum hydride followed by removal of the remaining benzyl group with sodium in ammonia, afforded the allylic diol **26** (scheme 8).



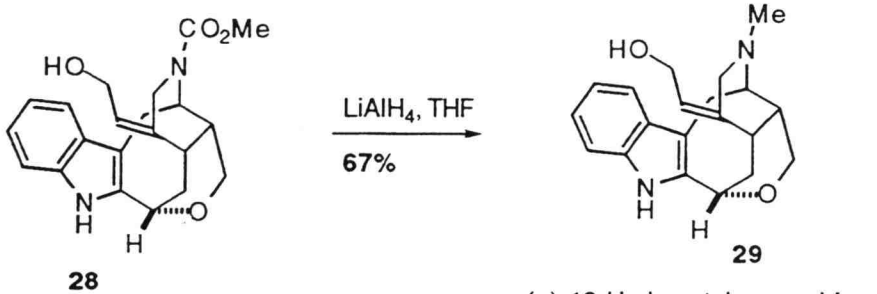
scheme 8

Fragmentation of **26** in the presence of methyl chloroformate is presumed to occur via the extended iminium ion **27** to afford **28** which, after reduction of the methyl carbamate, yielded (+)-18-hydroxytaberpsychine (**28**). Finally, $S_{N2'}$ cyclization of (+)-18-hydroxytaberpsychine (**29**) in the presence of diethyl azodicarboxylate and triphenylphosphine afforded (+)-koumine (**1**) in 72% yield (scheme 9).



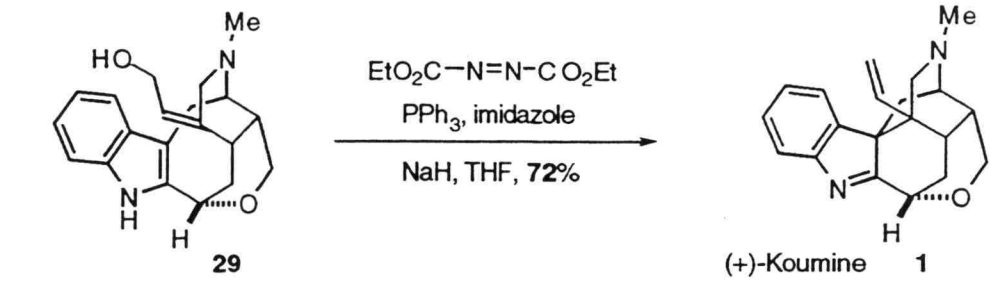
26 **27**

28



28 **29**

(+)-18-Hydroxytaberpsychine

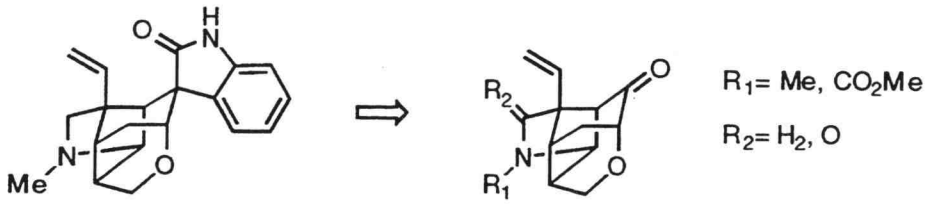


29 (+)-Koumine **1**

(+)-18-Hydroxytaberpsychine

scheme 9

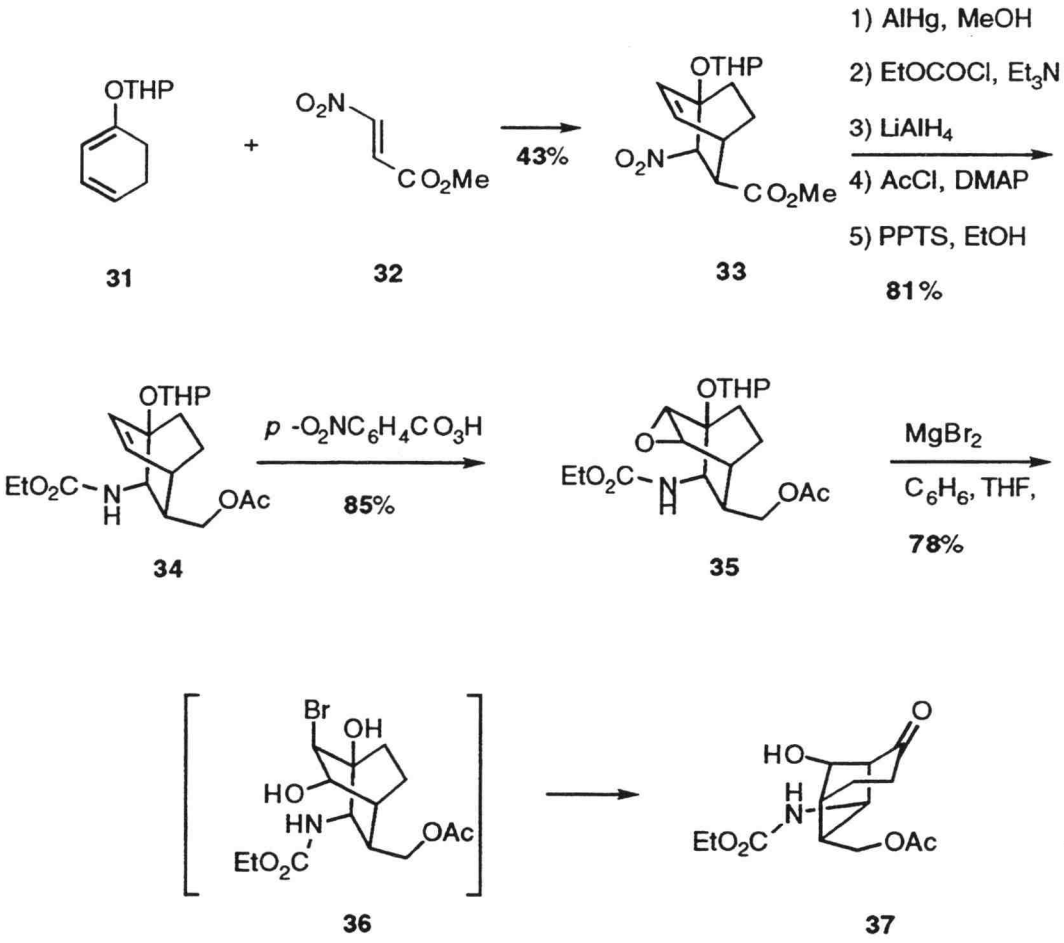
Frequent reports of synthetic approaches toward gelsemine have appeared ever since the structure elucidation of that alkaloid was first announced. However, only very recently have three separate accounts claiming total syntheses of racemic gelsemine been published.[16] In terms of their synthetic plan, virtually all the approaches share the common feature that the oxindole portion is elaborated from the tetracyclic ketone **30** (scheme 10).



2 **30**

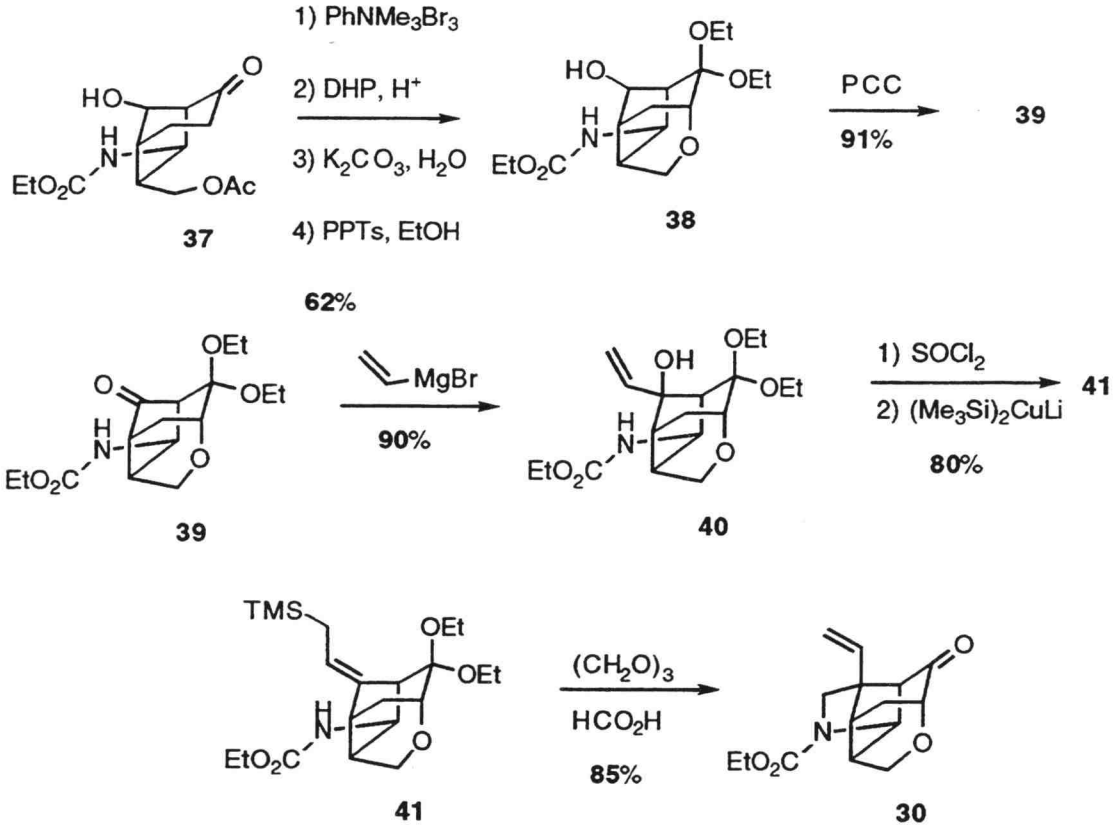
scheme 10

Many different strategies have been employed for the assembly of **30** and the difficult problem of its oxindolization. The first synthesis of **30** was achieved by Fleming et al. in 1986 (scheme 11). However these researchers were unable to complete the synthesis of gelsemine from **30**.[17]



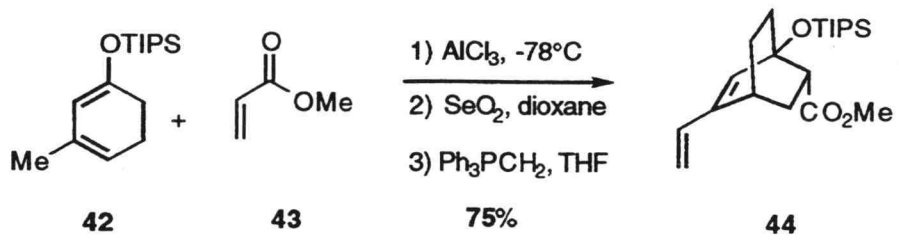
scheme 11

The central feature of the Fleming synthesis is the rearrangement of the bicyclo[2.2.2]octene system **33** to the bicyclo[3.2.1.]octane skeleton embedded in the target ketone **30**. A Diels-Alder reaction provided a convenient entry to the bicyclo[2.2.2]octene **33** (scheme 12) which was transformed to the rearrangement precursor **35** in six steps. After rearrangement of **35** to **37**, the pyran ring of **38** was installed and the latter was taken on to the allyl silane **41**. A Mannich reaction of **41**, in which advantage was taken of the carbon nucleophilicity of the allyl silane, yielded **30** (scheme 12).



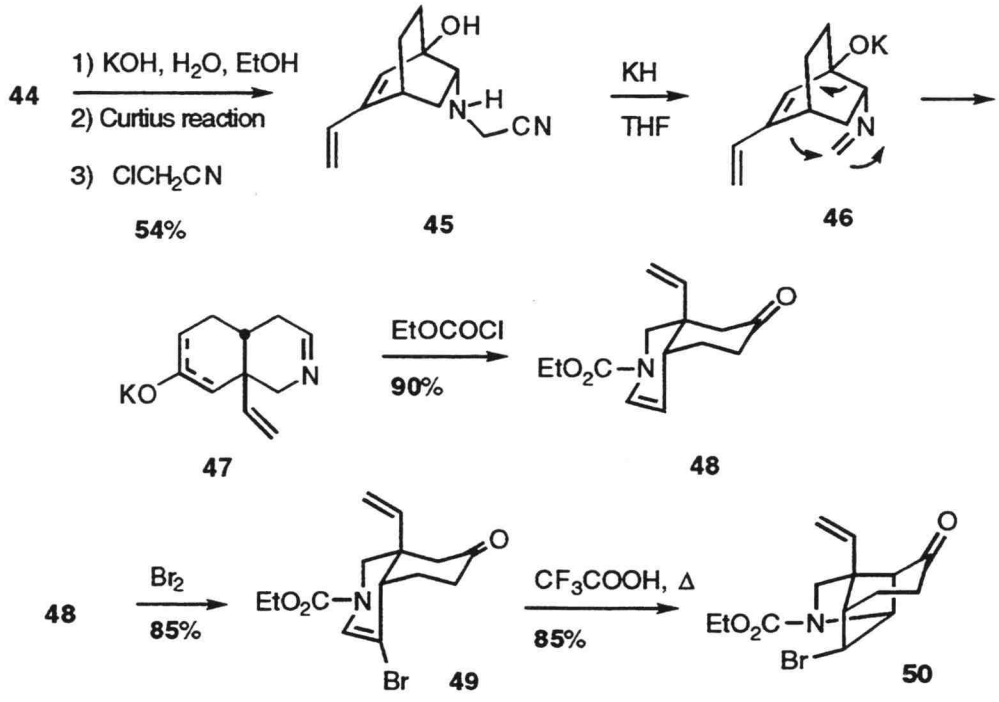
scheme 12

Other successful routes to the tetracyclic ring system of **30** have been reported by the Hart, Johnson and Speckamp groups.[16] Progress toward a very efficient entry to this ring system has also been announced by Overman.[18] This latter approach features the construction of the azatricyclo[4.4.0.0.^{2,8}]decane substructure of gelsemine from a readily available bicyclo[2.2.2]octenylamine precursor.



scheme 13

Thus, the Diels-Alder adduct was homologated to the diene **44** (scheme 13) by oxidation with selenium dioxide followed by Wittig methylenation. Curtius rearrangement and reaction of the resultant amine with chloroacetonitrile afforded **45** which was subjected to a base-catalyzed aza-Cope rearrangement with excess potassium hydride in tetrahydrofuran. Quenching of the resulting imine enolate **47** with ethyl chloroformate provided **48** (scheme 14).



scheme 14

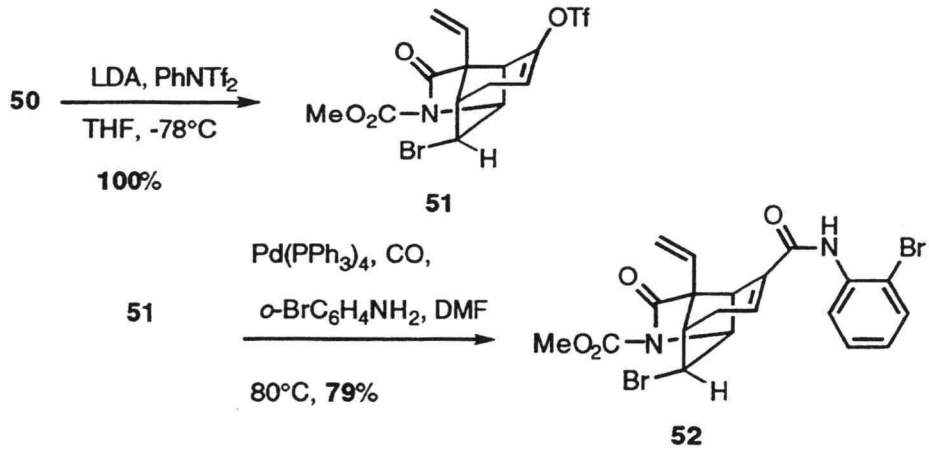
Bromination of **48** introduced functionality that could allow the eventual elaboration of the hydropyran ring of gelsemine. In this connection, the β-bromo enamide **49** was found to readily undergo acid-catalyzed Mannich cyclization to give **50** (scheme 14) in 85% yield. In contrast, imine enolate **47** did not undergo Mannich cyclization, perhaps due to fast retro-Mannich fragmentation of the tricyclic product (scheme 15).

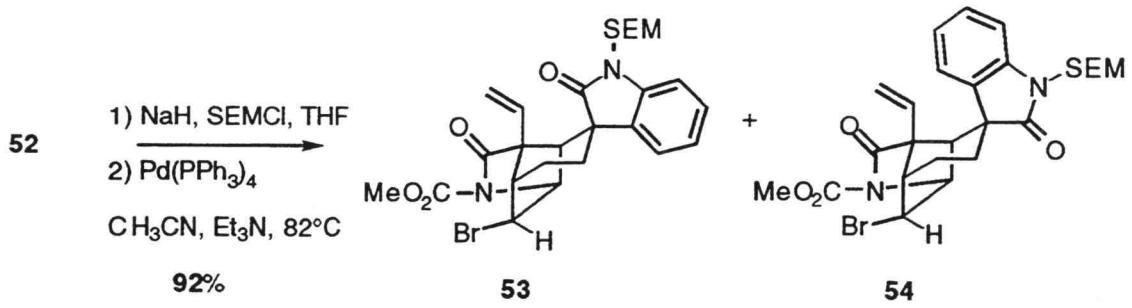
47

scheme 15

Although traditional oxindole syntheses such as the Brunner reaction and its variations proved unsuccessful with **30**, extensive investigations on model systems by Fleming, Johnson and Overman have led to the development of practical methods for this particular oxindolization.[19]

Over the last five years the Overman group has extensively explored the scope of intramolecular palladium-catalyzed alkene arylations (Heck reactions) to create congested quaternary carbon centers.[20] Heck methodology has been successfully applied to this problem by conversion of ketone **50** to its enol triflate **51** which then underwent palladium-catalyzed carbonylation in the presence of *ortho*-bromoaniline to afford the cyclization precursor **52** (scheme 16).

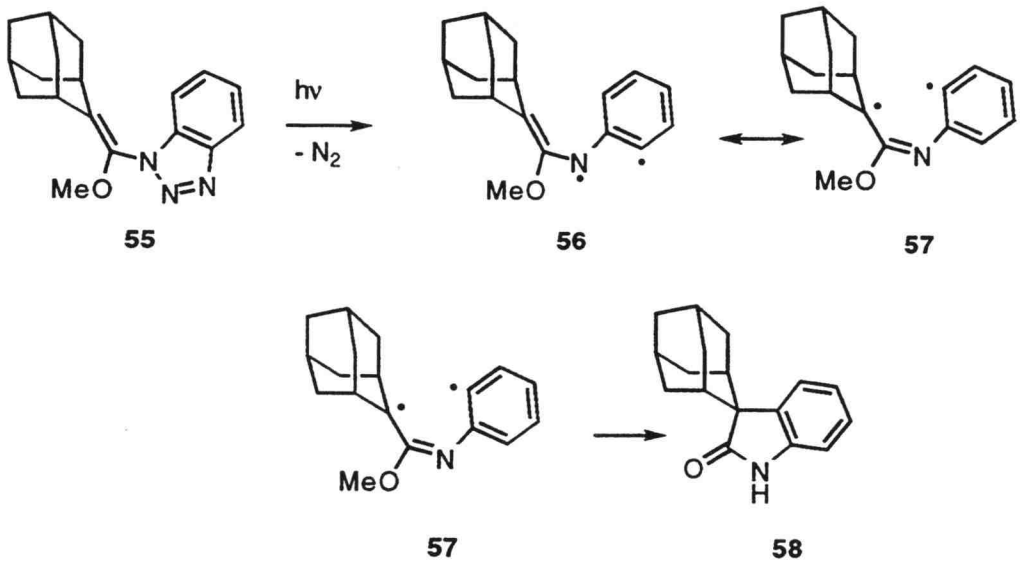




scheme 16

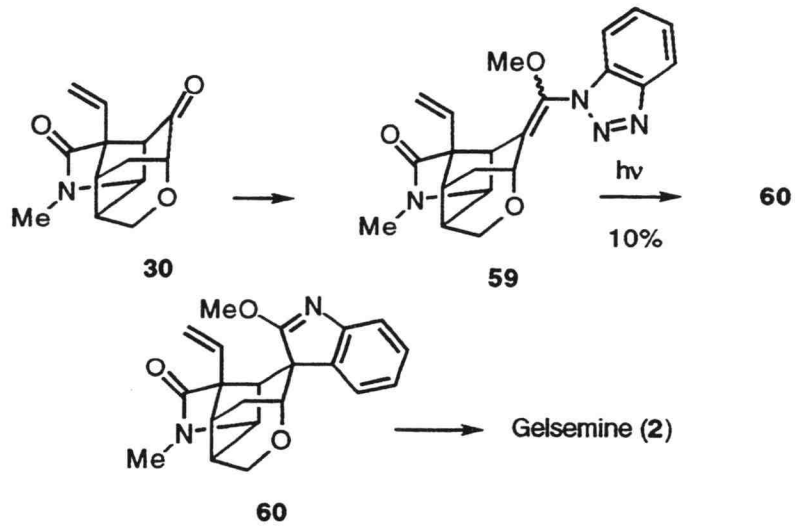
Protection of amide **52** and cyclization under standard Heck conditions gave a stereoisomeric mixture of the pentacyclic oxindoles **53** and **54** with low stereoselection (1.8:1) but in excellent chemical yield. Either of the stereoisomers **53** or **54** could be prepared with high selectivity when the Heck cyclization conditions were varied. Thus, the use of tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_2$) yielded a 9:1 ratio of **53**:**54**, whereas addition of silver phosphate under otherwise identical conditions resulted in almost exclusive formation of the oxindole **54**. The former conditions were used by Speckamp et al. in their total synthesis of gelsemine.[16 a)]

When confronted with this problem, Johnson[21] designed an interesting oxindole annelation based on a variation of an indole synthesis originally developed by Wender.[22] In this case, the final C-C bond formation takes place by coupling of the two carbon radical centers in **57**, a process which is insensitive to steric hindrance due to the low activation barrier associated with radical recombination (scheme 17).



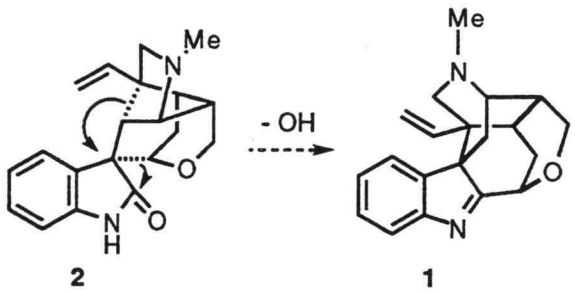
scheme 17

When applied to **30** this method produced 21-oxogelsemine in low yield, but it concluded a formal total synthesis of gelsemine (scheme 18).



scheme 18

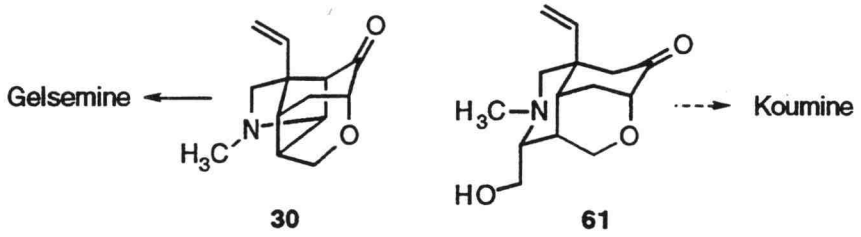
As mentioned previously, koumine bears a structural resemblance to gelsemine. Koumine and gelsemine are in the same overall oxidation state, and the two alkaloids could be interconverted in principle by a pair of two 1,2-alkyl shifts and addition or loss of water (scheme 19).



2 1

scheme 19

Likewise, ketone **30** is structurally related to a potential koumine precursor **61** (scheme 24) that provides a focal point for the synthetic studies described in the following chapter.



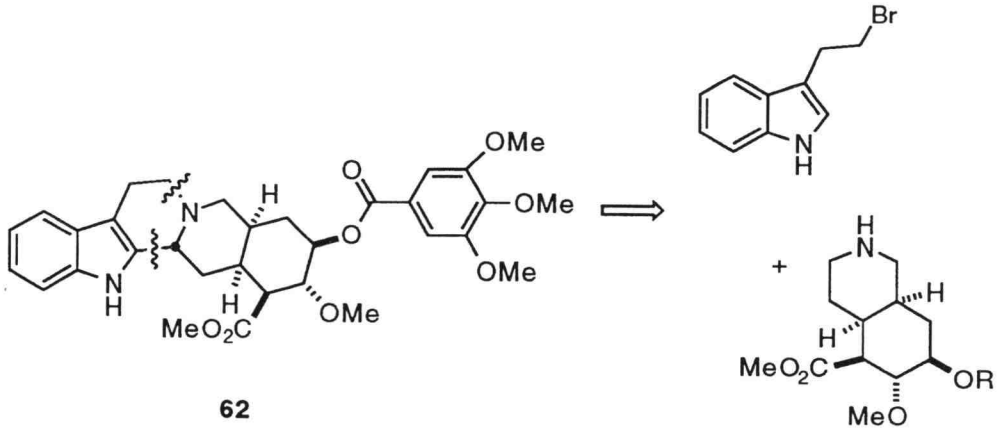
30 61

scheme 20

Results and Discussion

The chemistry of alkaloids has been central to the development of classical methods of synthesis and structure elucidation in organic chemistry. Many well known name reactions such as the Hofmann elimination,[23] the Mannich reaction,[24] and the Fischer indole synthesis[25] were discovered during the era of chemical degradation of alkaloid natural products. The development of these methods paved the way for the first major synthetic achievements in alkaloid chemistry, including the total syntheses of quinine,[26] strychnine,[27] and reserpine.[28] This has subsequently led organic chemists to design and carry out syntheses of increasingly complex members of the large family of alkaloids.

Many different strategies have evolved to confront the syntheses of polycyclic indole alkaloids. However it has often been convenient to use a monoterpenoid subunit as a building block for condensation with an indole moiety at a late stage in the synthetic sequence. For example, several approaches toward reserpine (**62**) have followed this strategy (scheme 28).[29]

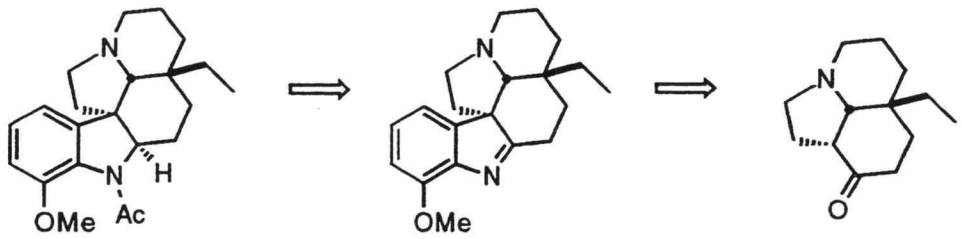


62

scheme 21

Among the known methods of indolization, the Fischer indole synthesis is recognized for its broad scope and general applicability. As a classical method in alkaloid synthesis, this reaction has been used to transform many functionalized aldehydes and ketones to indole alkaloids. Since the indole moiety of these alkaloids is generally the most sensitive part of the structure, its late introduction in a synthetic sequence has great strategic advantage.

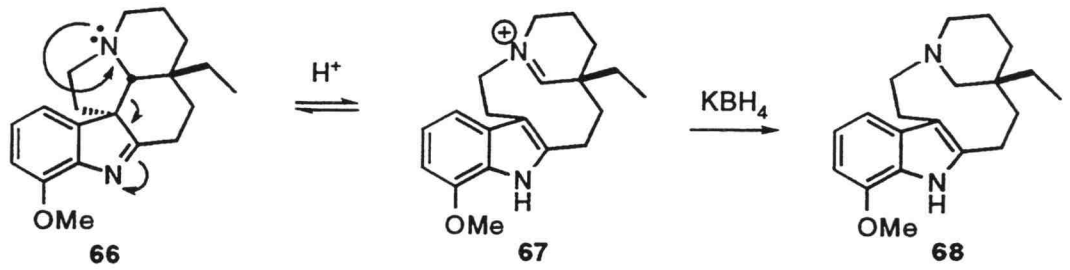
Koumine, being an indolenine alkaloid cannot become directly available through the indolization of a ketone precursor. However, a literature survey reveals that several indolenine alkaloids of the *Aspidosperma* class have been synthesized following a strategy that involves Fischer indolization of a functionalized amino ketone. For example, Stork[30] reported total syntheses of (±)-aspidospermine (**63**) and (±)-quebrachamine (**68**) which were completed through Fischer indolization of the aminoketone **65** (scheme 22).



63 **64** **65**

scheme 22

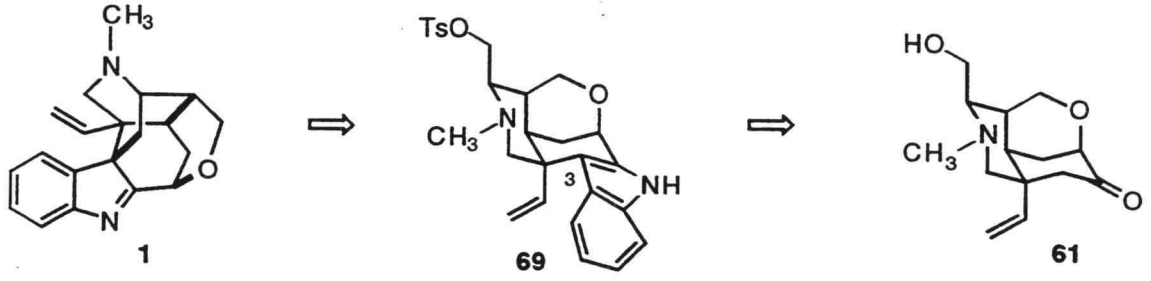
Under the reaction conditions of the indolization, equilibration involving indolenine **66** takes place via a retro-Mannich process. The iminium species **67** can be reduced with potassium borohydride to yield quebrachamine (**68**) (scheme 27). Essentially the same strategy has been extended to the synthesis of other *Vinca* alkaloids by Klioze.[31]



66 67 68

scheme 23

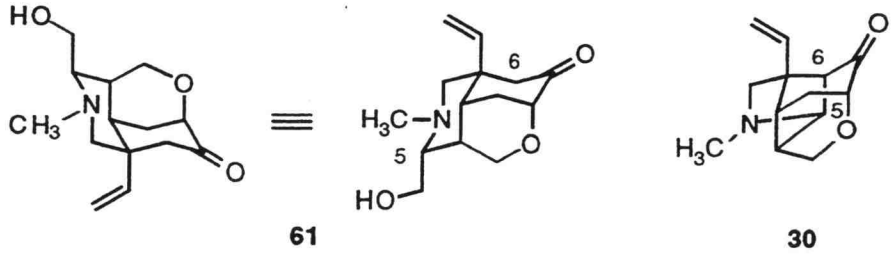
Our approach to (±)-koumine is based on a plan in which the final ring closure to the koumine ring system is accomplished through intramolecular alkylation of the indole nucleus at the 3-position. Therefore, we have focused our attention on synthesis of the tricyclic ketone **61**, which would be subjected to a Fischer indole synthesis in the final stages of the sequence (scheme 24).



1 69 61

scheme 24

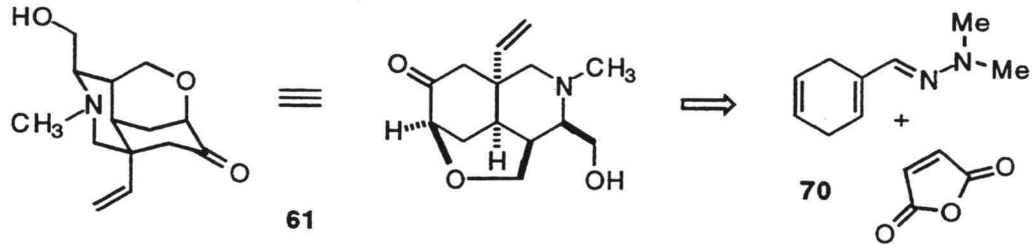
The target ketone **61** bears a close structural resemblance to the gelsemine precursor **30** (scheme 25), differing in the presence of an additional hydroxymethyl group and the absence of a carbon-carbon bond between C-5 and C-6 (gelsemine numbering).



61 30

scheme 25

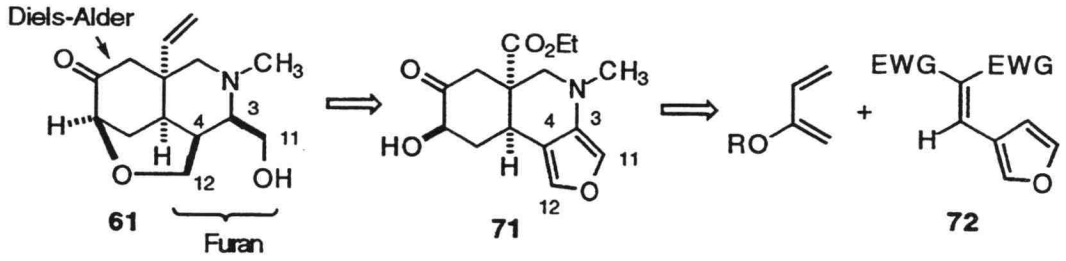
In an earlier approach to this synthetic problem an attempt was made to use a hetero-Diels-Alder reaction of the azadiene **70** as an entry into the hydroisoquinoline system of **61**. However, this approach was abandoned due to a lack of reactivity of the azadiene (scheme 26).[32]



61 70

scheme 26

The strategy outlined in scheme 27 proposes that the carbocyclic ring of **61** can be constructed in a stereocontrolled fashion by a conventional Diels-Alder reaction. A central feature of this plan is the use of a furan synthon as the source of carbons 3, 4, 11 and 12 in **61**.



61 71 72

scheme 27

This logic leads to the tricyclic hydroisoquinoline structure **71** as the precursor of **61**. The hydroisoquinoline nucleus of **71** can be envisioned as the Diels-Alder adduct of the dienophilic furan derivative **72** and an appropriate diene (scheme 27).

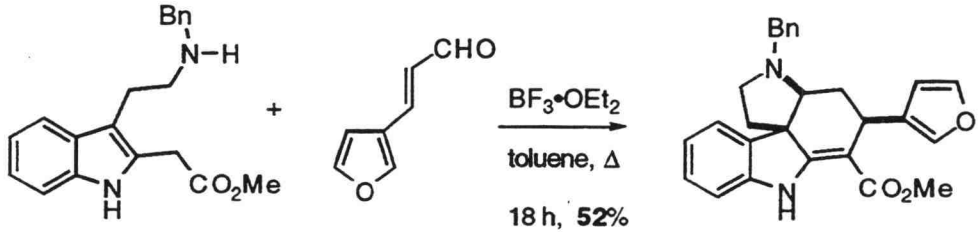
It was reasoned that a functionalized Diels-Alder adduct derived from **72** and a suitable diene would serve as a platform on which the additional architecture needed for **61** could be erected. Specifically, it was hoped that two important objectives could be achieved by this route. First, the stereochemistry of the carbocyclic ring of **61** with respect to the ring fusion and the α-alkoxy ketone could be established, and secondly the two heterocyclic rings (piperidine and hydropyran) in **61** could be conveniently elaborated using cyclization reactions involving the furan template.

A large number of simple furan derivatives are commercially available at low cost and have served as starting materials for these synthetic studies. It is known that the aromatic nature of the furan nucleus enhances the reactivity of furoic aldehydes toward Knoevenagel type condensation reactions.[33] This provides easy and flexible access to compounds of the general formula **72**, which we have used as dienophiles in this approach.

Furan derivatives are susceptible to a number of hydrolytic and oxidative ring-opening reactions. Depending on the reagents, reaction conditions and the substitution pattern of the furan, 1,4-diketones or the corresponding five-membered lactones, lactols, butenolides or anhydrides can be obtained.[34]

Most of the methodological studies on furan oxidation have been carried out on simple furan substrates which are devoid of multiple functionality. Hence, the synthetic potential of furan derivatives as masked 1,4-diol equivalents is not well developed in the context of natural product synthesis.

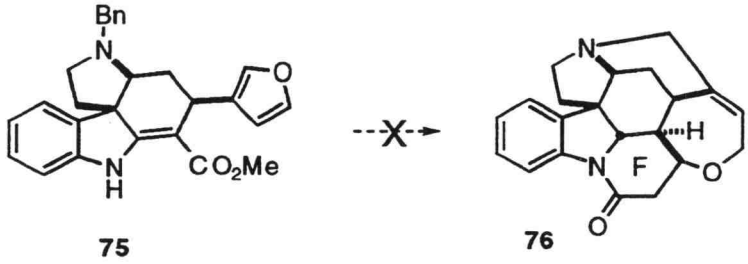
Kuehne, during his work directed toward synthesis of *Strychnos* alkaloids has described an interesting reaction of the furoic aldehyde **74** and the tryptamine derivative **73** which afforded **75** as a single diastereomer (scheme 28).[35]



73 **74** **75**

scheme 28

However, conversion of furan **75** to the structurally complex alkaloid strychnine (**76**), remained elusive (scheme 29). As noted by Kuehne: "while this product contains all but two, acetate derived ring F carbon atoms of strychnine, its further elaboration required considerable exploration and discovery of new methodology...".

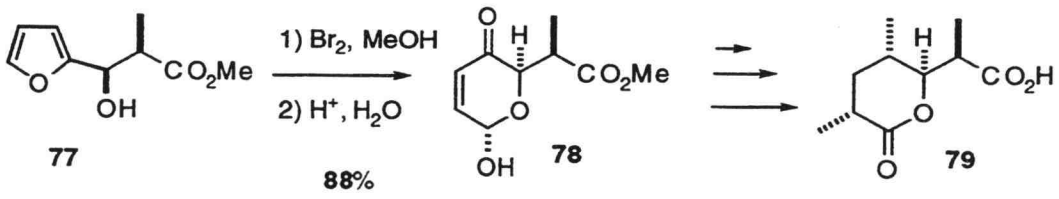


75 **76**

scheme 29

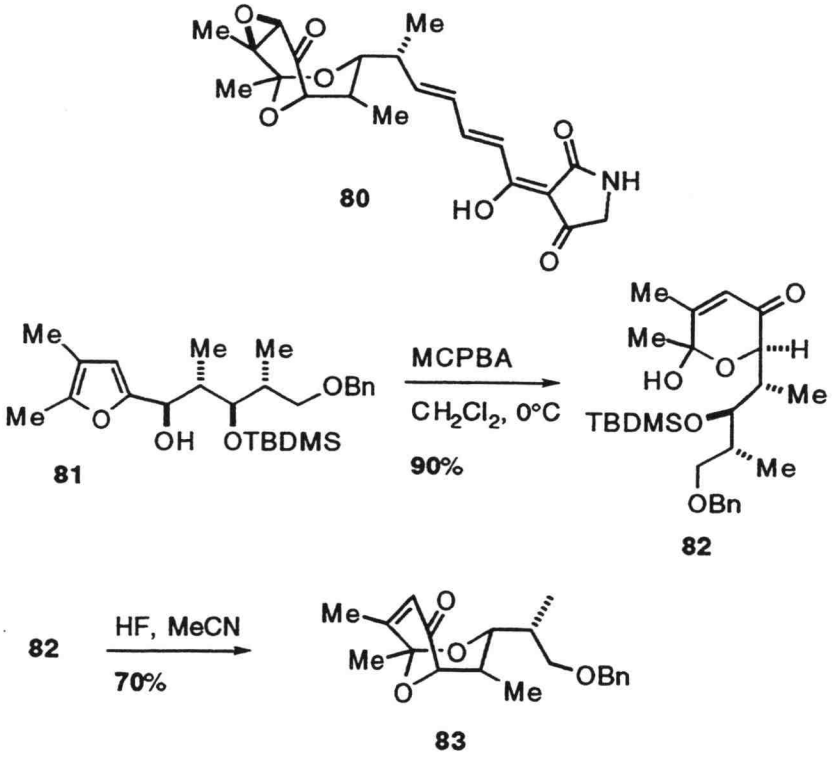
The bromination of furan derivatives in an alcohol solvent is a well studied reaction that is known to involve cationic intermediates. This reaction has been used primarily for the formation of new carbon-oxygen bonds at the

furan nucleus. Thus, in their total synthesis of the Prelog-Djerassi lactone **79**, Martin *et al.*[36] utilized the furan **77** to create the pyranone skeleton **78** (scheme 30).



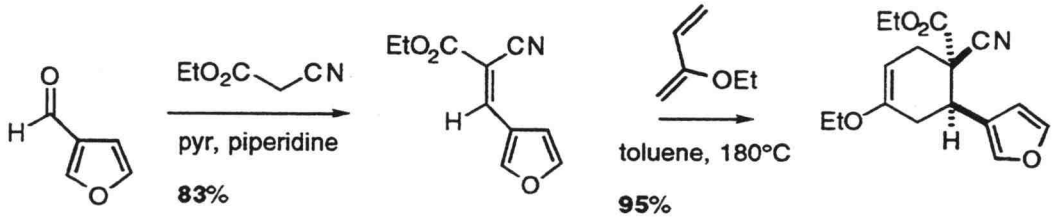
scheme 30

A similar strategy has been employed by DeShong[37] *et al.* in their total synthesis of (±)-tirandamycin A (**80**) (scheme 31). The spiroketal portion **83** of tirandamycin A was synthesized through epoxidation of the hydroxy furan precursor **81** which yielded the pyranone structure **82**.



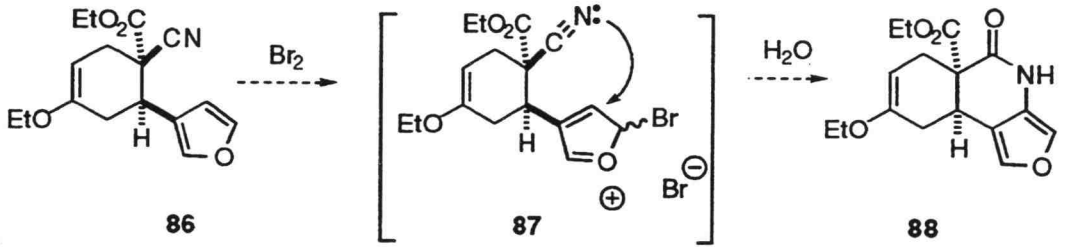
scheme 31

Initial studies indicated that a Diels-Alder reaction of the furan derivative **85** with 2-ethoxy-1,3-butadiene proceeded in high yield to give adduct **86** as a single diastereomer (scheme 32). The dienophile **85** employed in this cycloaddition was prepared by Knoevenagel condensation of **84** with ethyl α-cyanoacetate. A single olefin isomer was obtained from this condensation which based on subsequent results (*vide infra*) can be assumed to have the *E*-configuration shown.



scheme 32

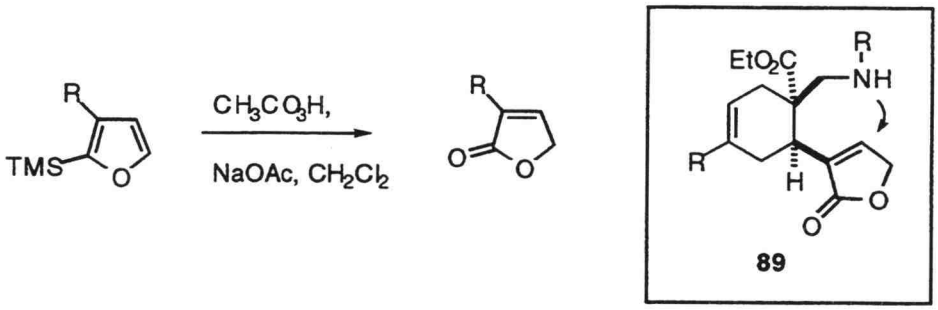
With **86** in hand, the reactivity of the furan towards electrophiles was probed. The hope was that a cationic intermediate such as **87** generated by bromination would result in cyclization with carbon-nitrogen bond formation between the nitrile and furan (scheme 33). This process leading to lactam **88** is formally an intramolecular Ritter reaction and has good precedent. [38]



scheme 33

In the event, bromination of **86** in methanol did not yield **88** but instead a complex mixture of products was formed which could not be further elaborated. It appeared from a spectroscopic analysis of the crude reaction mixture that the enol ether as well as the furan portion of **86** had reacted with the bromine.

A possible solution to this problem was recognized in the work of Urabe who showed that furan derivatives which were silylated in the 2-position can be transformed regioselectively to butenolides under mild conditions with peracetic acid (scheme 34).[39]

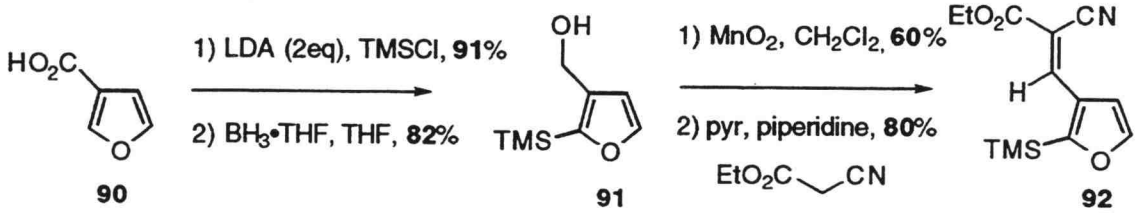


scheme 34

Butenolides (α,β-unsaturated γ-lactones) are Michael acceptors that react with many nucleophiles in a conjugate fashion. With this chemistry in mind, our plan evolved toward building the piperidine ring through an intramolecular Michael addition. For this purpose a nitrogen nucleophile derived from the cyano group and a butenolide Michael acceptor derived from the furan (for example, compound **89**, scheme 34) were needed.

First, 3-furoic acid (**90**) was silylated in the 2-position[40] and then reduced to the alcohol **91** (scheme 35). Benzylic oxidation of **91** yielded the furoic aldehyde which was condensed with ethyl α-cyanoacetate to afford **92**. The cis ring fusion of the hydroisoquinoline in ketone **61** requires that a

corresponding relationship exist between the furan and cyano group in the Diels-Alder dienophile **92**. Therefore, the geometry of the double bond in **92** was a critical issue.

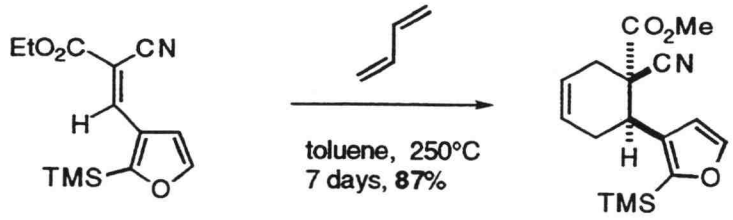


90 **91** **92**

scheme 35

While spectroscopic analysis, including ^{1}H and ^{13}C NMR, of **92** indicated that a single isomer was obtained, the configuration of the double bond could not be ascertained. Based on steric grounds it seemed reasonable to assume that **92** was the E-isomer shown, and this was subsequently confirmed by X-ray analysis of the Diels-Alder adduct **94** (*vide infra*).

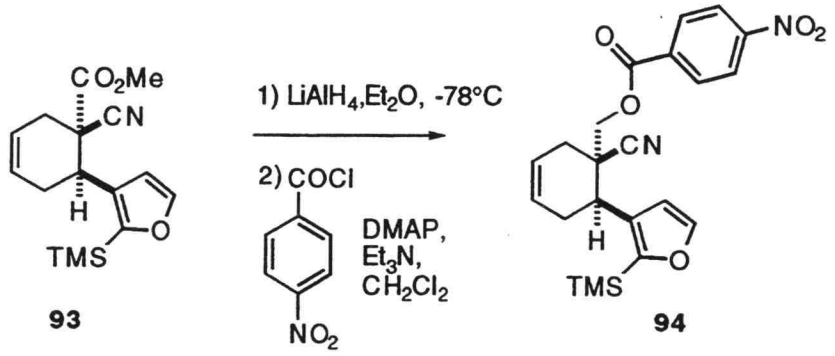
After considerable experimentation, **92** was found to give Diels-Alder adduct **93** using 1,3-butadiene in great excess (scheme 36). Extensive polymerization of the diene was the main side reaction.



92 **93**

scheme 36

With **93** in hand, efforts were undertaken to verify the assumed cis relationship of the furan and cyano group in the Diels-Alder adduct. A crystalline derivative **94** was obtained by selective reduction of the ester and acylation of the resulting primary alcohol with *p*-nitrobenzoyl chloride (scheme 37).



scheme 37

X-ray diffraction analysis of **94** fully confirmed the relative stereochemistry shown (Figure 1.1). The furan and the cyano group are attached to the same face of the cyclohexene ring.

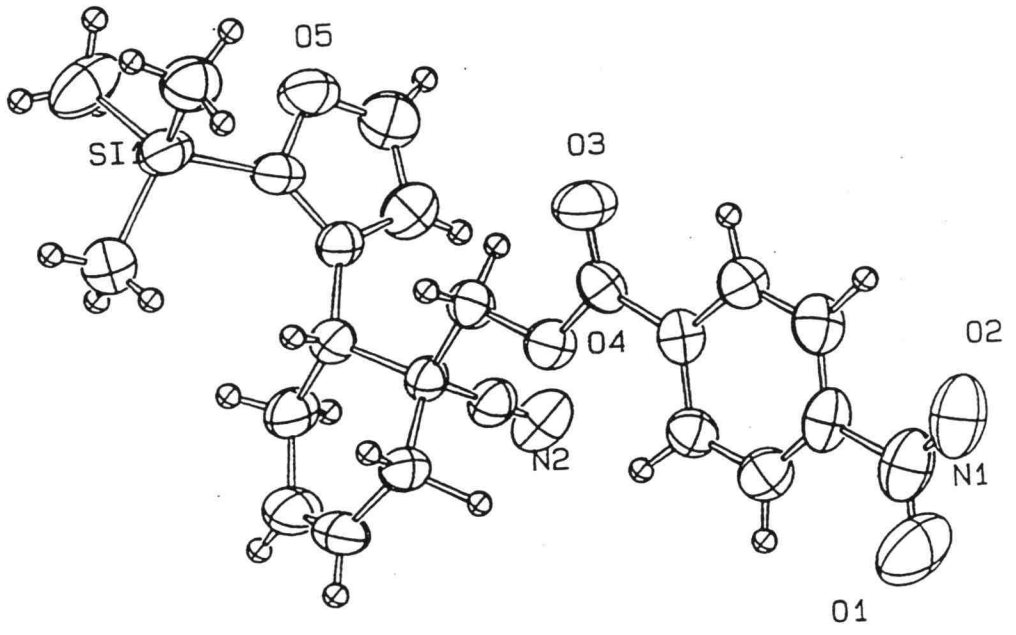
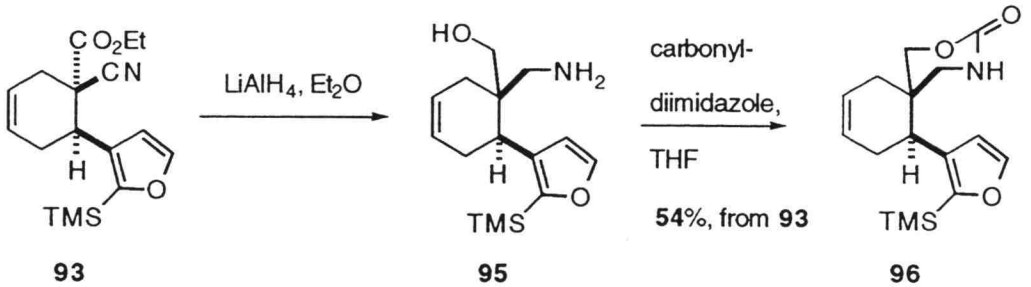
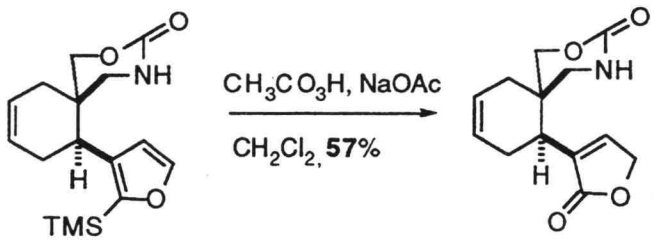


Figure 2.1: ORTEP Representation from X-ray Structure of **94**.

More complete reduction of **93** with lithium aluminum hydride gave an amino alcohol **95** which was converted without purification to the cyclic urethane **96** (scheme 38).

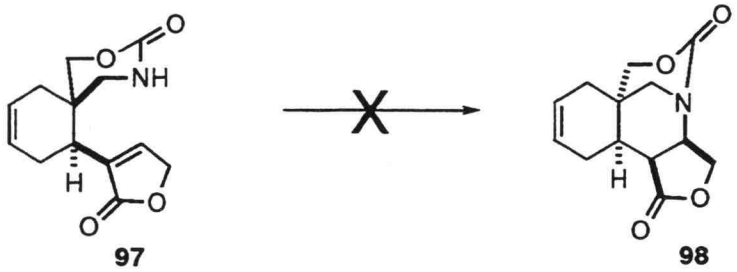




96 **97**

scheme 38

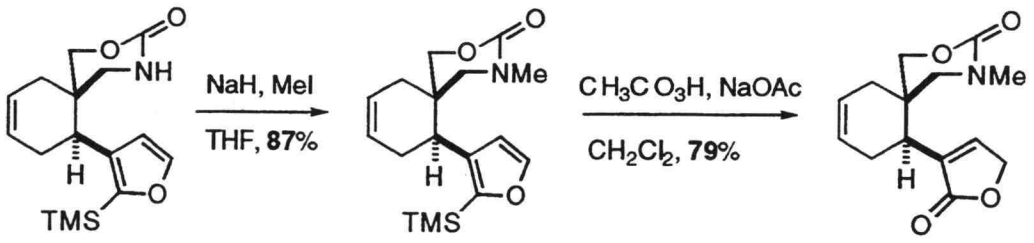
Oxidation of **96** following Urabe's conditions gave the butenolide **97** in modest yield. Much to our disappointment, **97** did not show any inclination to undergo spontaneous cyclization, nor were we able to bring about the intramolecular conjugate addition under any conditions that were tried.



97 **98**

scheme 39

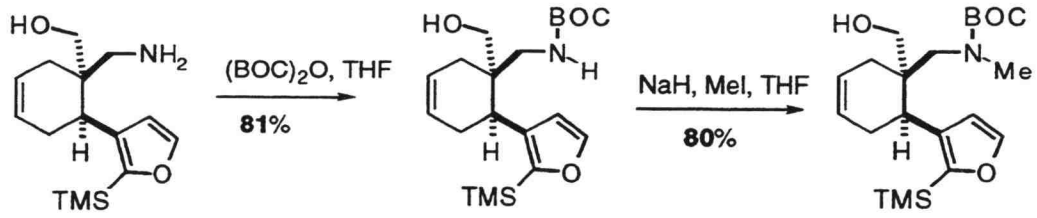
Due to the pronounced lability of **97** towards base, attempts to open the butenolide ring by alkaline hydrolysis also met with failure. However, the nitrogen of urethane **96** underwent smooth methylation with methyl iodide. Subsequent oxidation of the N-methyl urethane **99** afforded butenolide **100** in good yield (scheme 40).



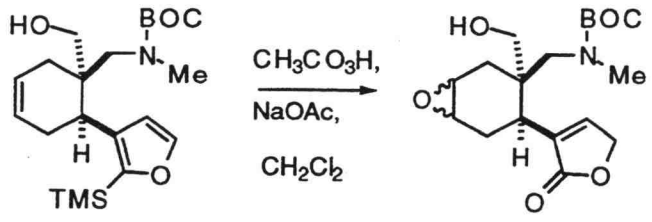
96 **99** **100**

scheme 40

Disappointingly, all attempts to cleave the cyclic carbamate of **100** were unsuccessful. Under conditions of basic hydrolysis, decomposition of **100** was observed as previously seen with **97**. In the presence of acidic reagents such as perchloric acid, Meerwein's salt or trimethylsilyl iodide, urethane **100** displayed surprising stability. In light of this result, efforts were undertaken to find alternative, more easily removed protection devices for the amino alcohol **95**. A *tert*-butoxycarbonyl group (BOC group) appeared to satisfy this requirement and was introduced without incident to afford compound **101**. The protected nitrogen was then methylated with methyl iodide to give **102**.



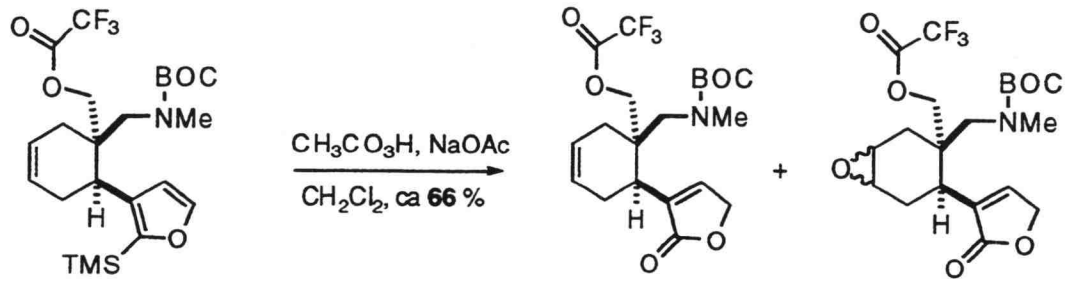
95 **101** **102**



102 **103**

scheme 41

Oxidation of the furan nucleus of **102**, unlike that of **99**, turned out to be problematic, and only a small amount of lactone epoxide **103** was isolated along with unreacted starting material (scheme 41). It was thought that the free primary hydroxyl group of **102** might have promoted epoxidation of the cyclohexene through hydrogen-bonding to the peracid. Accordingly, several attempts were made to block this sterically hindered alcohol but only a trifluoroacetate group could be introduced in practical yield, affording **104**. Oxidation of **104** again yielded an inseparable mixture of **105** and **106**, albeit in improved yield (scheme 42).

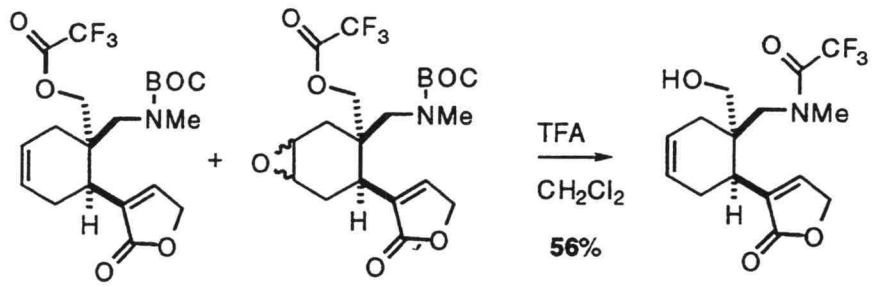


104 **105** **106**

scheme 42

Treatment of this unstable and base-sensitive mixture with trifluoroacetic acid resulted in the expected removal of the BOC group but was accompanied by unanticipated transfer of the trifluoroacetyl group to form the

trifluoroacetamide **107**. The lability of compound **107** toward base again precluded the removal of the trifluoroacetyl function from nitrogen (scheme 43).



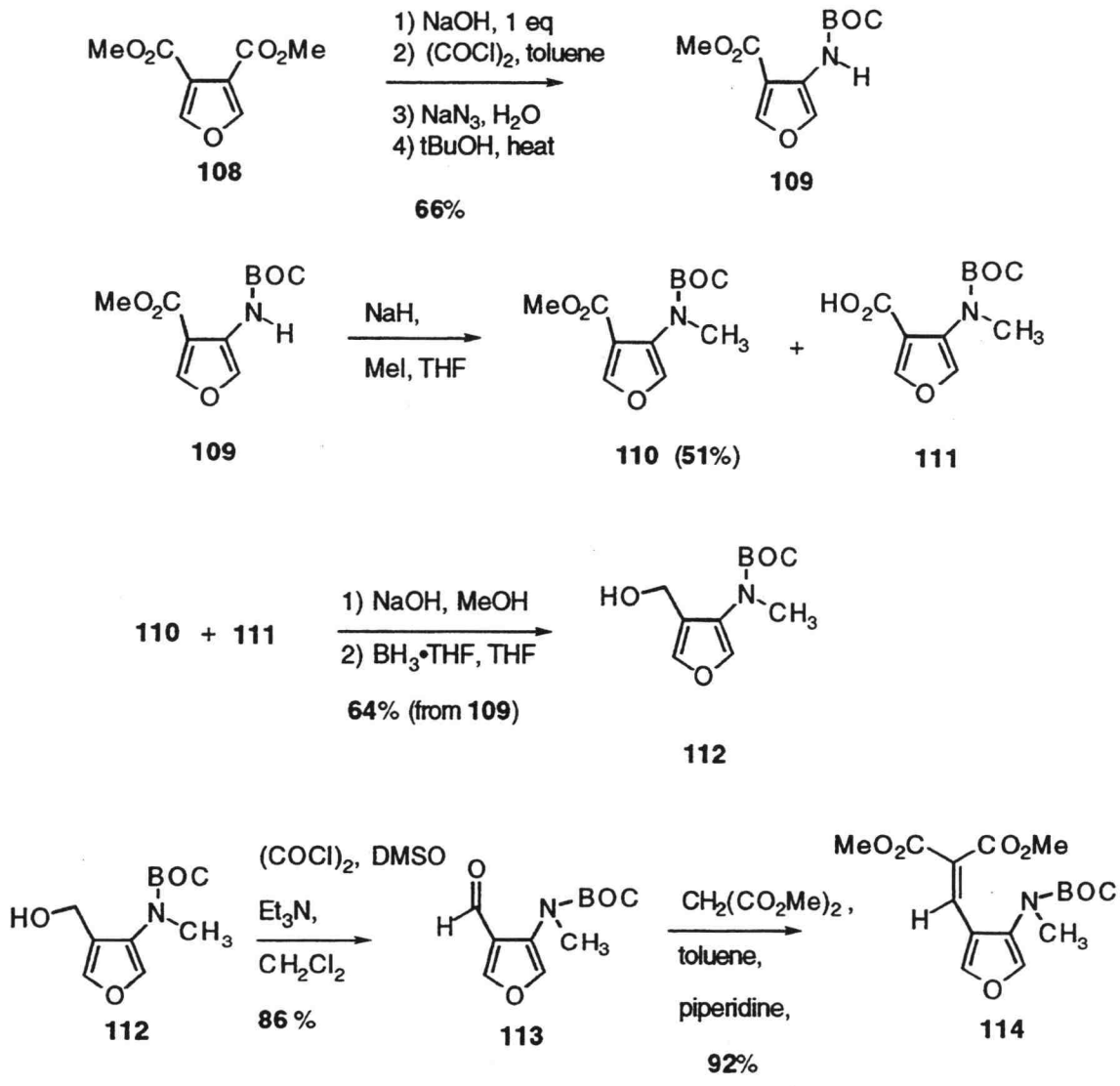
105 **106** **107**

scheme 43

These discouraging results prompted us to search for a new approach to **61** in which a potentially removable substituent is attached to nitrogen at the outset. This plan required complete revision of our original strategy and forced us to reevaluate the starting point of the synthesis. It was decided that a more fruitful approach would lie in attachment of the nitrogen function to the β-position of the furan dienophile, so that construction of the piperidine ring of **61** would now take place in the reverse sense from that envisioned previously.

The Curtius rearrangement came to mind as a convenient way to introduce a protected amino functionality into a furan precursor.[41] Dimethyl 3,4-furandicarboxylate (**108**) was subjected to monohydrolysis[42] and the

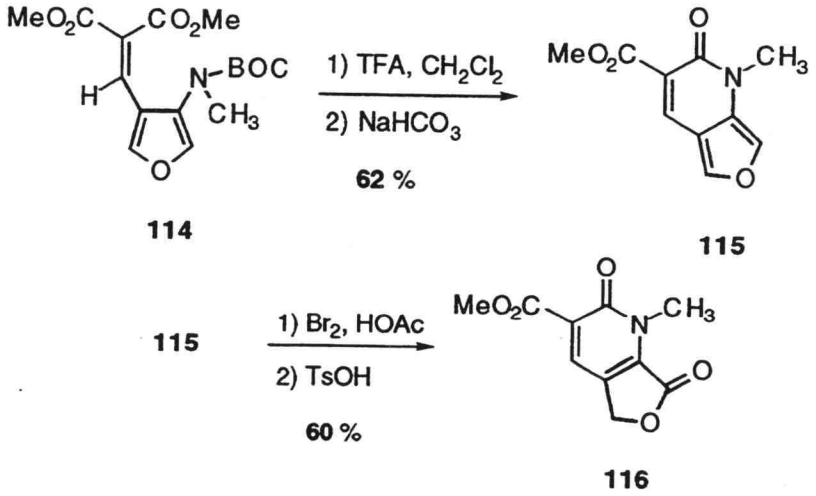
resultant carboxylic acid was converted to its acyl azide. Curtius rearrangement of this azide in the presence of *tert*-butanol yielded the BOC-protected 3-aminofuran **109** (scheme 44).



scheme 44

During the N-methylation of **109** the adjacent methyl ester was partially hydrolyzed to give the carboxylic acid **111**. Both ester **110** and acid **111** were reduced to the alcohol **112**, and the latter was oxidized under Swern

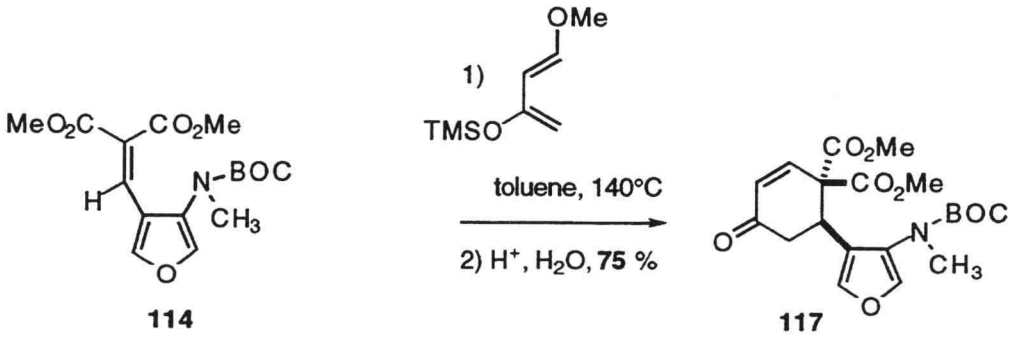
conditions to the aldehyde **113**. This aldehyde was condensed with dimethyl malonate to afford **114**. With an efficient route to **114** at hand, the next step was to identify an appropriate dienophile that would be accessible from **114** for the projected Diels-Alder reaction. Removal of the BOC group from **114** resulted in spontaneous cyclization to the unstable α,β-unsaturated amide **115** (scheme 45). However, **115** did not display dienophilic reactivity with 1,3-butadiene, 2-ethoxy-1,3-butadiene or Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene).[43] Hoping that transformation of the furan nucleus to an α,β-unsaturated lactone would enhance dienophilicity, **115** was oxidized with bromine in acetic acid[44] to **116**. Although the latter should , in principle, be a more reactive dienophile than **115** due to additional electron withdrawal by the lactone carbonyl, it also failed to undergo cycloaddition with 1,3-butadiene, 2-ethoxy-1,3-butadiene or Danishefsky's diene.



scheme 45

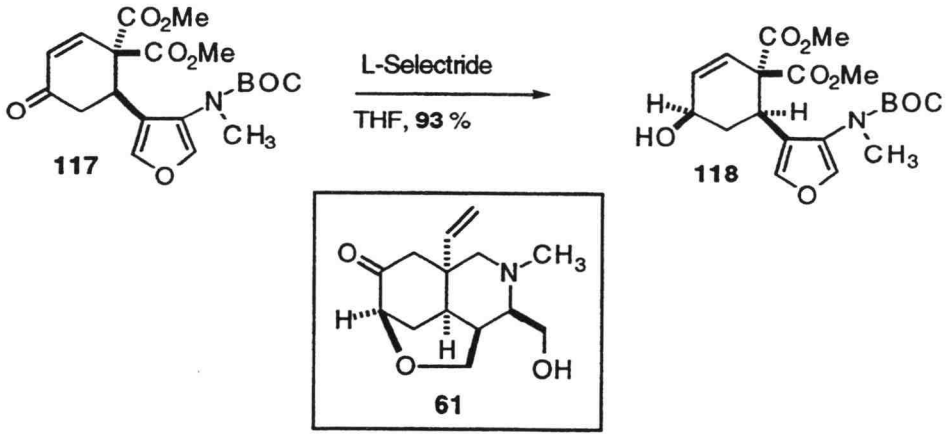
In contrast to **115** and **116**, **114** was reactive as a Diels-Alder dienophile, although its dienophilicity was found to be low, and only the highly

reactive Danishefsky diene gave a cycloadduct **117** in good yield (scheme 46).



scheme 46

Reduction of the enone **117** was examined under several conditions with the goal of preparing an allylic alcohol of β configuration. It was found that the use of *L*-Selectride produced a single allylic alcohol, **118**, the relative configuration of which was found to correspond to that required for the hydropyran moiety of **61** (scheme 47). The assignment of configuration was independently verified by X-ray analysis of a later intermediate.



scheme 47

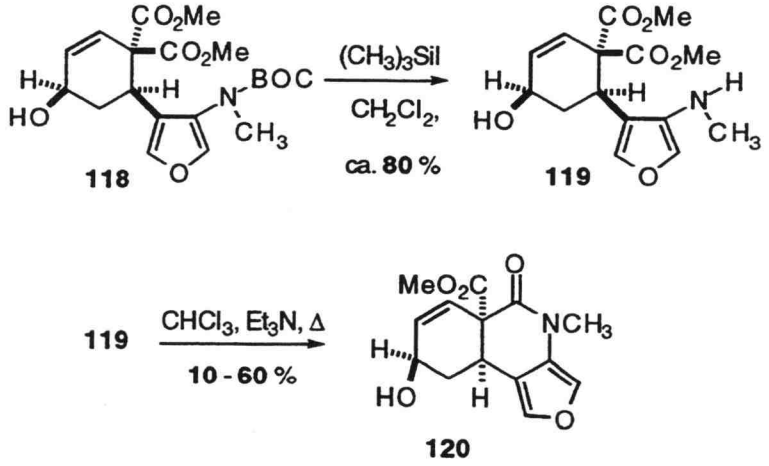
Our plan for **118** was to use this intermediate to advance the synthesis along three lines. These were:

a. Lactamization between the amino substituent of the furan and one of the geminal esters.

b. Hydropyran construction using the allylic alcohol and furan.

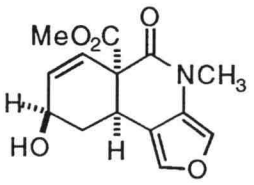
c. Transformation of the allylic alcohol to an α-alkoxy ketone.

Removal of the BOC group from **118** did not result in spontaneous lactamization as had been observed with compound **114**. Instead the amino alcohol **119** was isolated and could be characterized, although it proved to be a very unstable species (scheme 48). Amino ester **119** was found to undergo cyclization only very sluggishly to the stable δ-lactam **120**. A single isomer was formed in a reaction which proved to be very erratic with respect to yield.

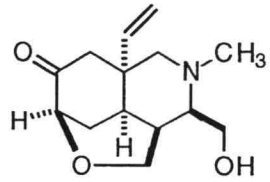


scheme 48

It was assumed that with the lactam **120** in hand the remaining functional group transformations toward **61** could be addressed. The first task, however, was to establish the ring fusion stereochemistry of **120**.

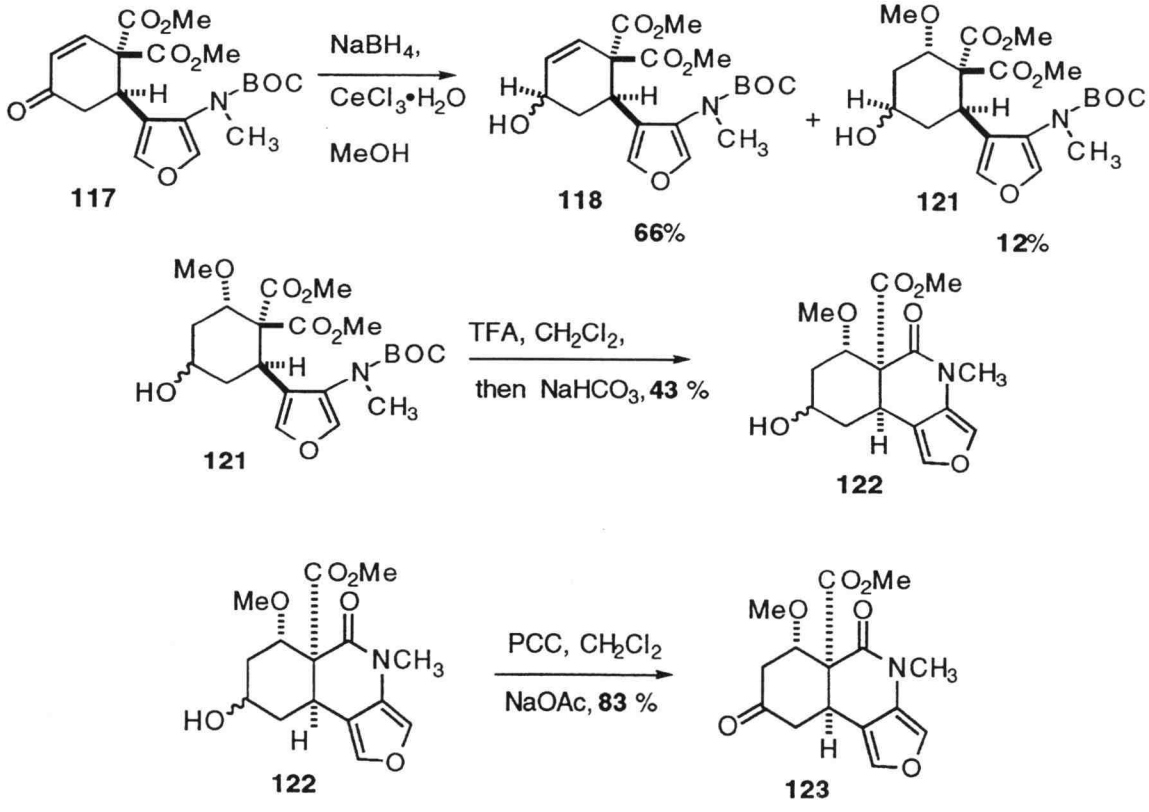


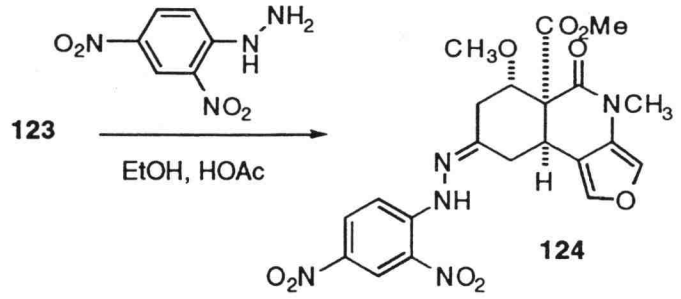
120



61

Proof of the cis ring fusion in **120**, which itself did not give rise to a crystalline derivative, was provided by X-ray analysis of **124**. The crystalline 2,4-dinitrophenylhydrazone **124** was prepared from the minor byproduct **121** obtained from Luche reduction of **117** (scheme 49). Thus, **121** was lactamized after removal of the BOC group, and the resulting hydroxy lactam **122** was oxidized with pyridinium chlorochromate to the β-methoxy ketone **123**. Treatment of **123** with 2,4-dinitrophenylhydrazine resulted in the formation of **124**.





scheme 49

X-ray diffraction analysis of the 2,4-dinitrophenylhydrazone derivative **124** fully confirmed the stereochemistry shown (figure 1.2).

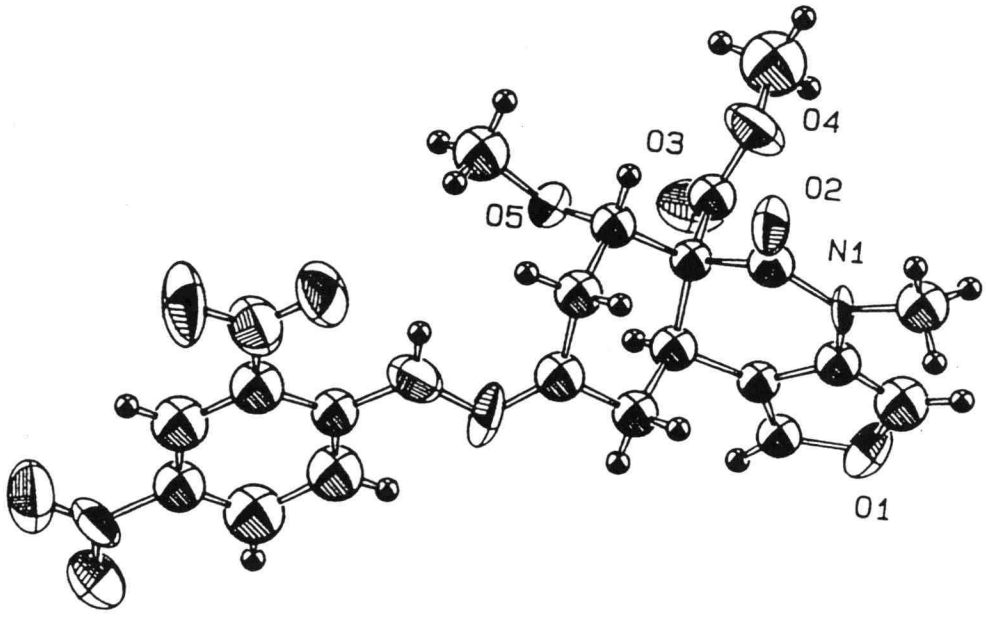
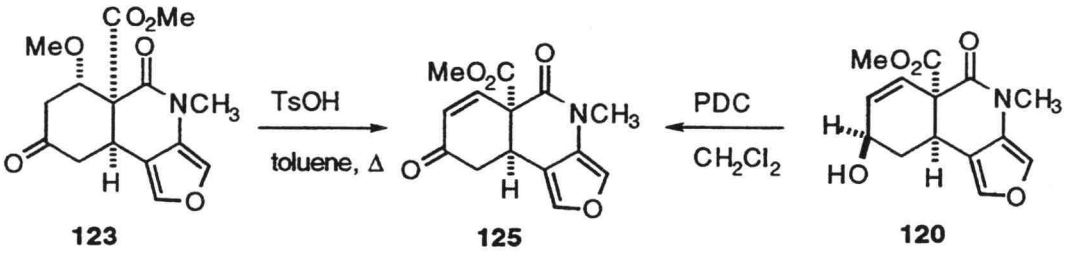


Figure 2.2: ORTEP Representation from X-ray Structure of **124**.

The structures of β-methoxy ketone **123** and allylic alcohol **120** were correlated by their conversion to the same enone **125** (scheme 50). Thus, **125** was obtained by straightforward oxidation of the alcohol **120** with pyridinium dichromate while acid-catalyzed elimination of methanol from **123** also gave **125**.

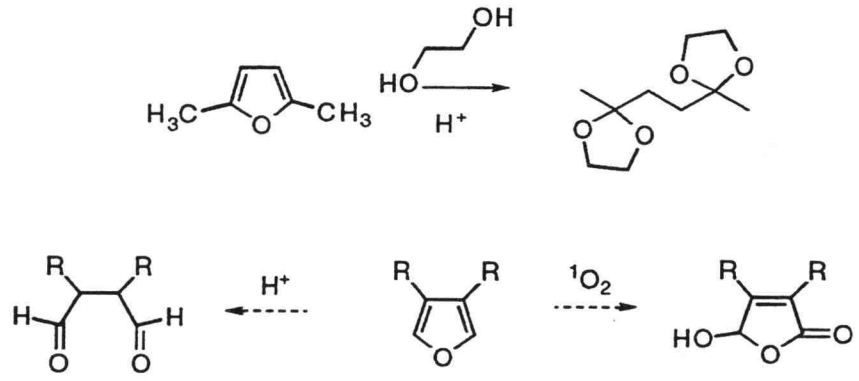


123 **125** **120**

scheme 50

Treatment of **120** with lithium aluminum hydride in an attempt to reduce the δ-lactam to a piperidine ring and also reduce the angular ester group afforded a very polar and unstable amino diol which could not be further characterized. It was therefore decided to defer the reduction of the δ-lactam **120** and study the furan opening next.

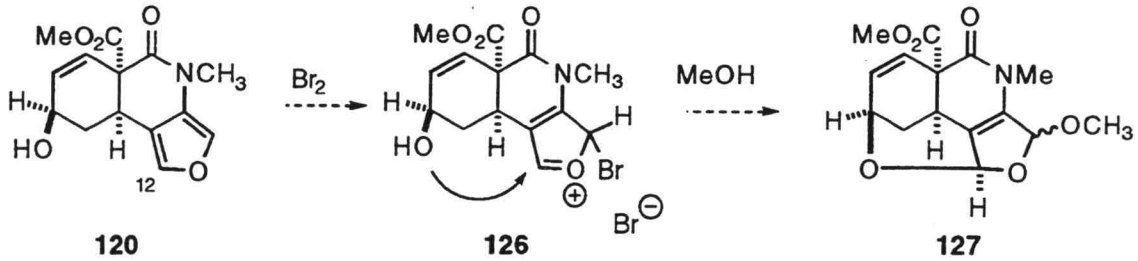
The reported use made of simple 2,5-dialkylfuran derivatives, for example 2,5-dimethylfuran, as 1,4-diketone equivalents (scheme 51)[45] suggested that the furan moiety of lactam **120** could be employed to generate a dialdehyde by acidic hydrolysis. Although unsubstituted in the 2- and 5-positions, it was assumed that the activating nitrogen substituent of **120** would enhance the acid lability of the furan.



scheme 51

Surprisingly, **120** proved to be quite stable toward acids, including formic acid and trifluoroacetic acid, and no products of hydrolytic ring opening were observed. An alternative means for opening the furan in **120** would be through the use of oxidative conditions,[46] but a disadvantage of this strategy over the hydrolytic opening is that a tetrasubstituted double bond is invariably formed when 3,4-disubstituted furans are oxidized (scheme 51).

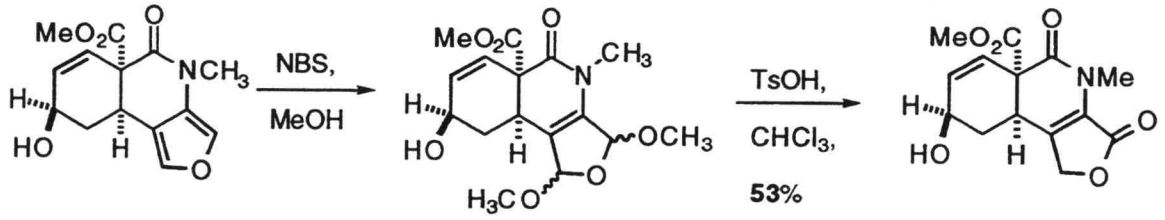
Inspection of a molecular model of lactam **120** indicated that there are accessible conformations in which the distance between the allylic alcohol and the C-12 atom of the furan is quite small. Since furans undergo rapid nucleophilic attack following electrophilic activation of the aromatic nucleus, the reaction of **120** with N-bromosuccinimide in methanol was investigated in the expectation that bromination of the furan would generate a cationic intermediate **126** which would react in an intramolecular fashion with the allylic alcohol and then with solvent to form **127** (scheme 52).



120 **126** **127**

scheme 52

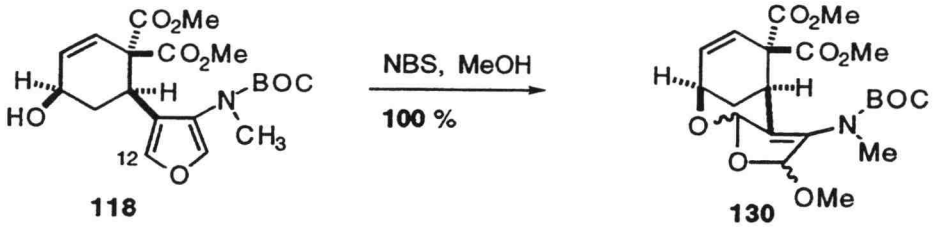
The tetracycle **127** was not observed when **120** was reacted under these conditions. Instead, dimethoxy adducts **128** were formed as a mixture of stereoisomers. When this unstable mixture was treated with *p*-toluenesulfonic acid, butenolide **129** was isolated in moderate yield (scheme 53).



120 **128** **129**

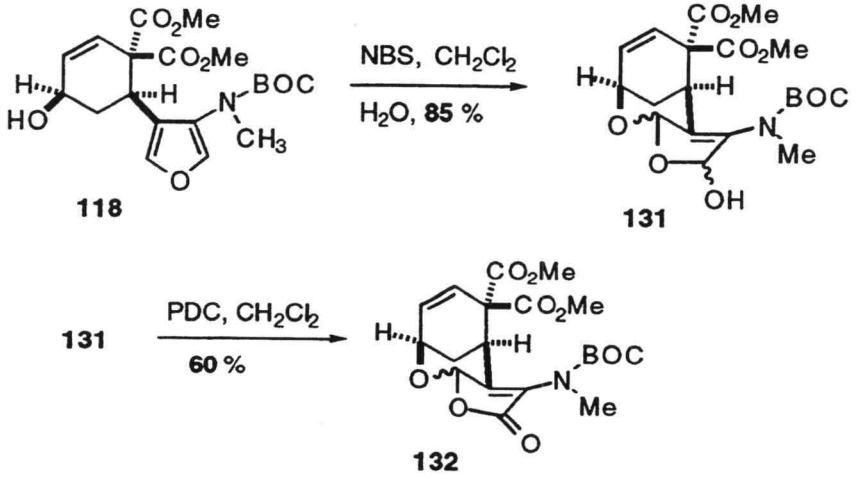
scheme 53

In order to determine whether there was any merit to the furan oxidation strategy, the allylic alcohol **118** was reacted under the same conditions as **120**. To our pleasure, **118** underwent quantitative intramolecular acetal formation between the allylic alcohol and C-12 of the furan to yield **130** (scheme 54). The proton NMR spectrum of **130** indicated the presence of at least two stereoisomers, but it was difficult to decide at this stage whether the multiple signals were due to rotameric isomers of the *tert*-butoxycarbonyl group or a diastereomeric mixture at the two newly formed acetal centers.



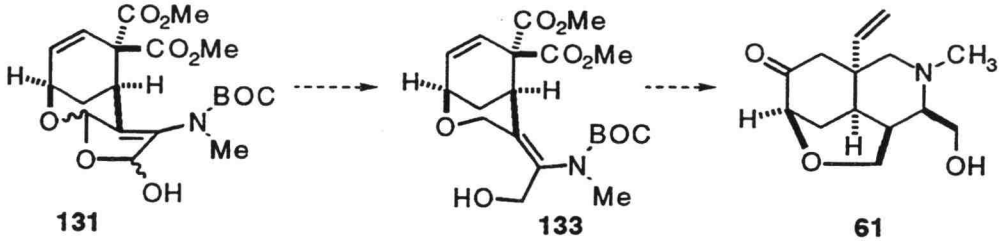
scheme 54

Subsequently, it was found that when the analogous reaction was carried out in water, hemiacetal **131** was isolated in good yield from **118**. Oxidation of **131** with pyridinium dichromate gave the butenolide **132** (scheme 55). Again, multiple peaks were observed for both **131** and **132** in the proton NMR spectrum. Unfortunately, none of the three compounds **130**, **131** or **132** were stable under the conditions required for removal of the BOC group.



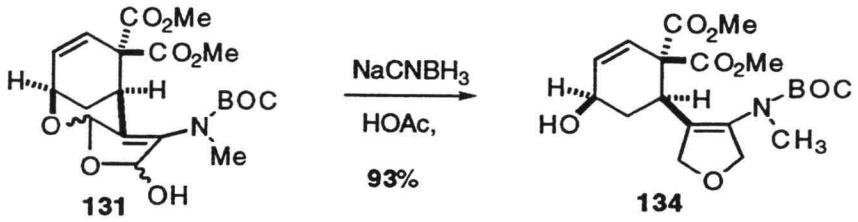
scheme 55

Several attempts were made with **130**, **131** and **132** to elaborate the pyran substructure of these acetals through reductive or hydrolytic cleavage of the acetal moiety but these too, were unsuccessful (scheme 56).



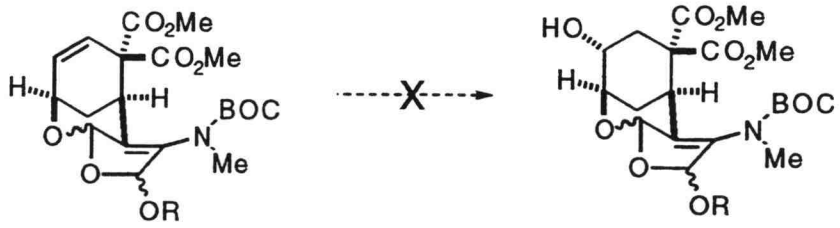
scheme 56

It appears that the acetal carbon-oxygen bonds of these structures are relatively weak and that cleavage occurs at the dihydrofuran rather than the pyran. This is reflected in the high-yielding conversion of **131** to **134** with sodium cyanoborohydride (scheme 57).



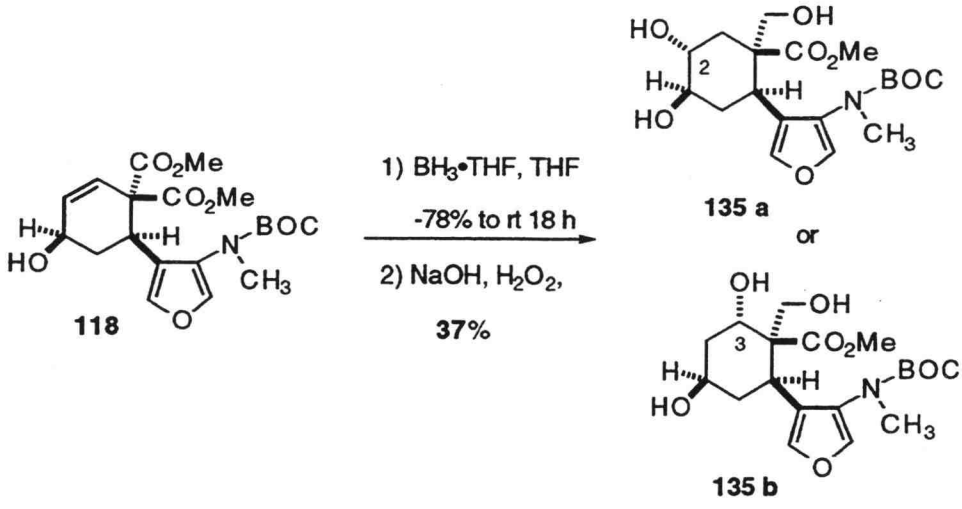
scheme 57

In tandem with these studies, efforts were also directed toward functionalization of the disubstituted double bond. Unfortunately, the tricyclic compounds **130**, **131** or **132** gave no useful result with either hydroboration, epoxidation, or oxymercuration (scheme 58).



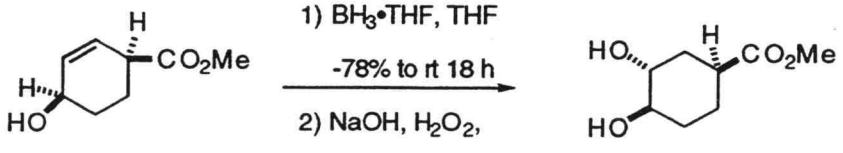
scheme 58

After investigating several hydroborating reagents, including 9-borabicyclo[3.3.1]nonane and thexylborane, it was discovered that the allylic alcohol **118** reacted with borane-tetrahydrofuran complex. Subsequent oxidation occurred with complete stereo- and regioselectivity to yield a triol. The structure **135 a** was tentatively assigned to this product (scheme 59).



scheme 59

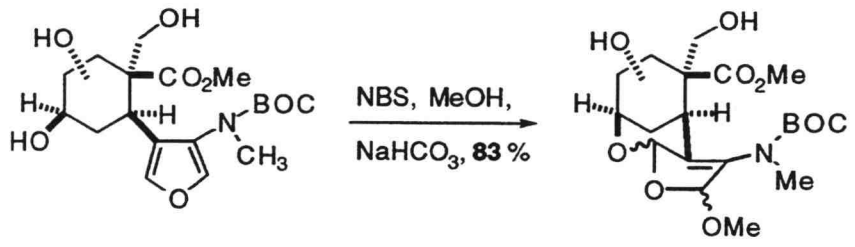
It was apparent from the proton NMR spectrum of the product that, in addition to hydroboration-oxidation of the double bond, reduction of one of the carbomethoxy groups had also occurred. High-resolution mass spectroscopy established that the molecular composition of the product was that expected for structure **135 a.** It was clear from spectroscopic analysis that a single diastereomer was formed and good precedent for formation of **135a** existed in the conversion of **136** to **137**,[47] (scheme 60).



136 137

scheme 60

Convincing physical evidence for the structure of **135 a**, however, was still lacking. In particular, the important question of the regiochemistry of the hydroboration, and hence the location of the newly formed secondary alcohol, could not be ascertained by spectroscopic analysis. Therefore, the regioisomeric structure **135 b** had to be considered.

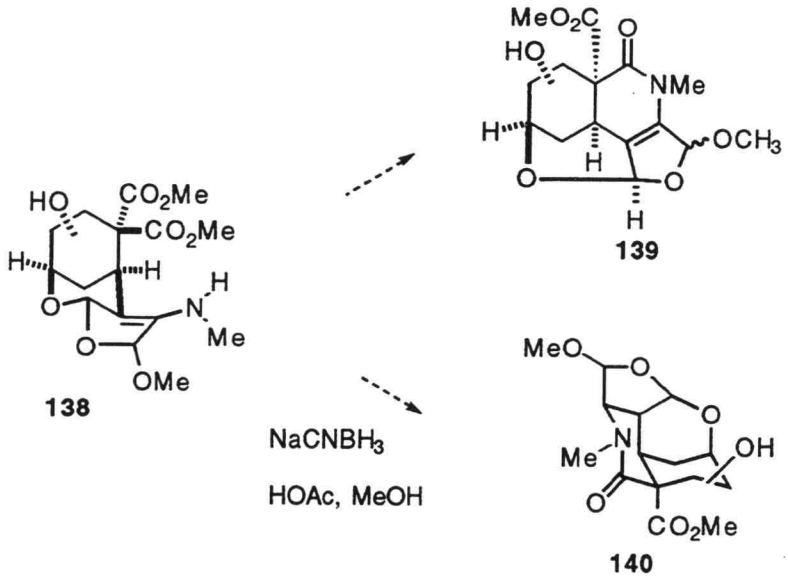


135 138

scheme 61

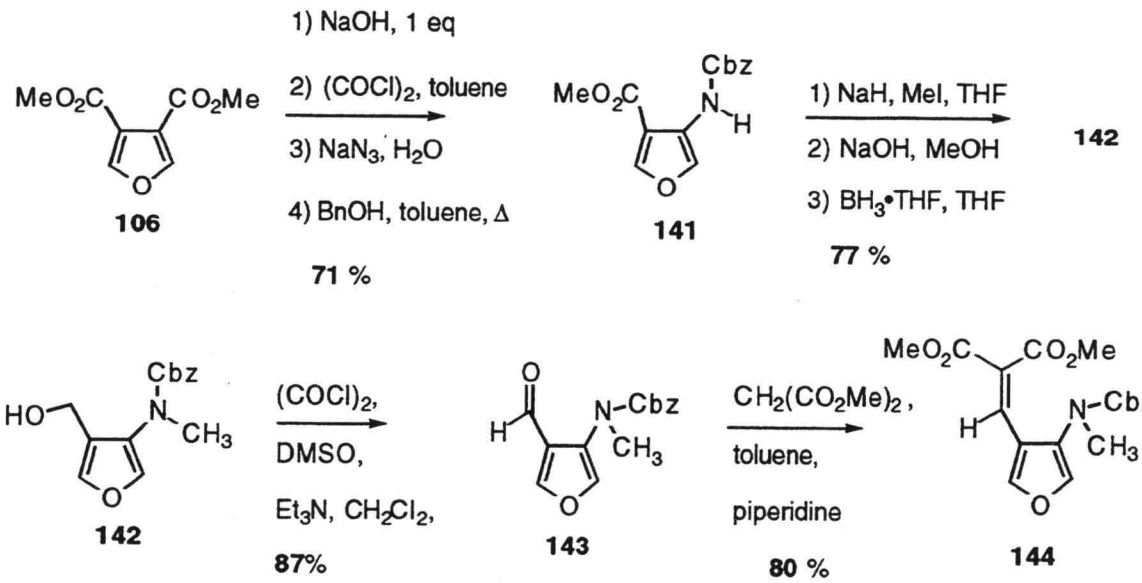
We were nevertheless encouraged by the fact that acetal formation with N-bromosuccinimide was unhampered by the additional hydroxyl groups in **135**, yielding **138** (scheme 61). For the tricyclic compounds **130**, **131**, **132**, and **138** it was assumed that, regardless of the configuration of the newly formed acetal moiety, the enamines produced upon cleavage of the nitrogen protecting group would be difficult to cyclize to a δ-lactam due to the strain associated with the tetrasubstituted double bond in **139** (see also scheme 52). However, the enamine function could, in principle, be reduced with sodium cyanoborohydride to the corresponding saturated amine, which

should be an excellent candidate for lactamization leading to **140** (scheme 62).



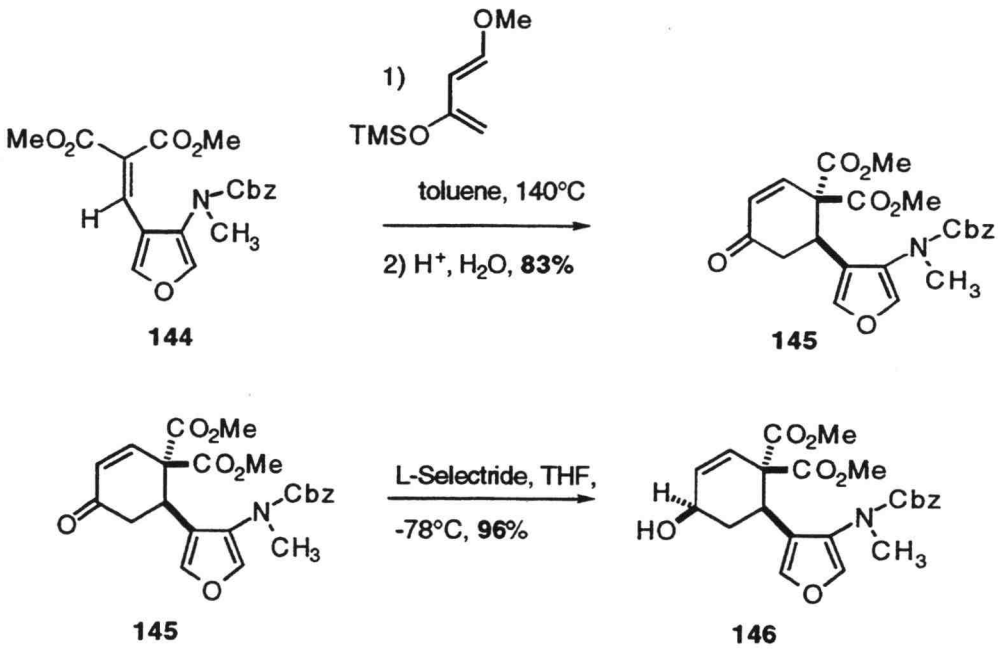
scheme 62

Since it had not been possible to cleave the BOC group of **130**, **131** or **132** in the presence of the acetal moiety, it was decided to modify this approach by installing a different protection group on nitrogen.



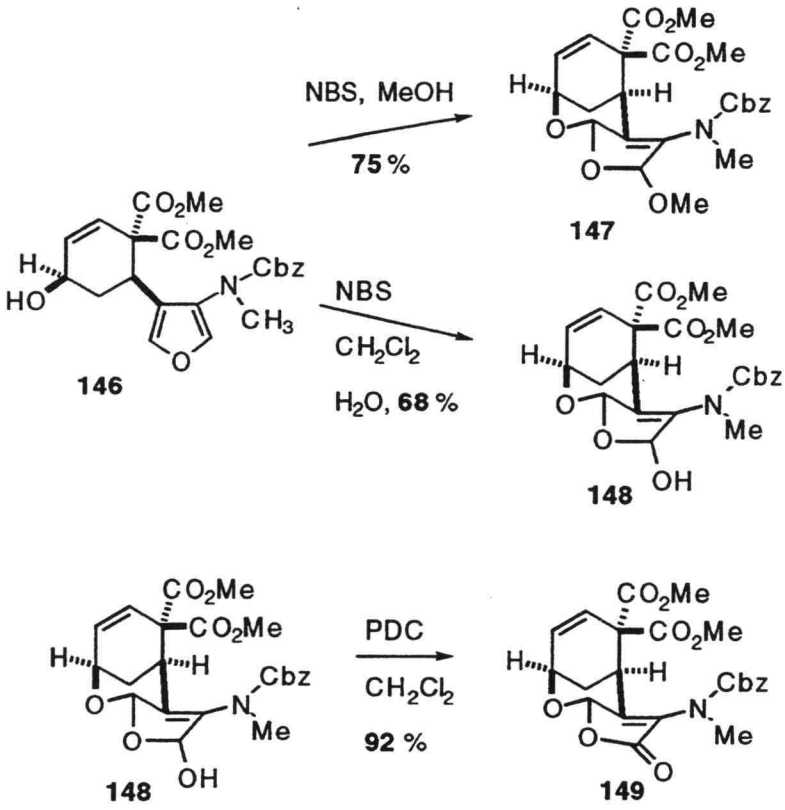
scheme 63

A carbobenzyloxy group (Cbz group) was introduced through a variation of the chemistry previously worked out for the preparation of dienophile **114**. Using benzyl alcohol instead of *tert*-butanol an analogous sequence led to the dienophile **144** (scheme 63).



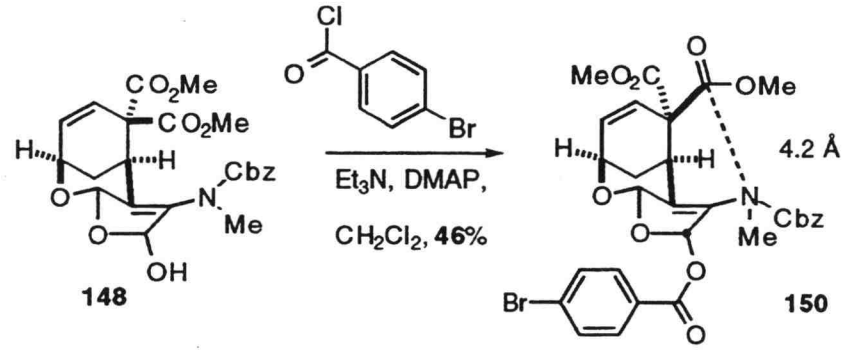
scheme 64

The Diels-Alder reaction of **144** (scheme 64) with Danishefsky's diene and reduction of the enone **145** proceeded uneventfully following the protocol previously described for **118** (see also scheme 46). The resulting allylic alcohol **146**, in turn, gave rise to the tricyclic intermediates **147**, **148** and **149** in analogy to the chemistry exhibited by **118** (scheme 65).



scheme 65

In order to determine the stereochemistry of the acetal ring system, and hence the prospects for lactamization, the crystalline *p*-nitrobenzoate derivative **150** of lactol **148** was prepared (scheme 66).



scheme 66

X-ray diffraction analysis of **150** fully confirmed the stereochemistry shown (figure 1.3).

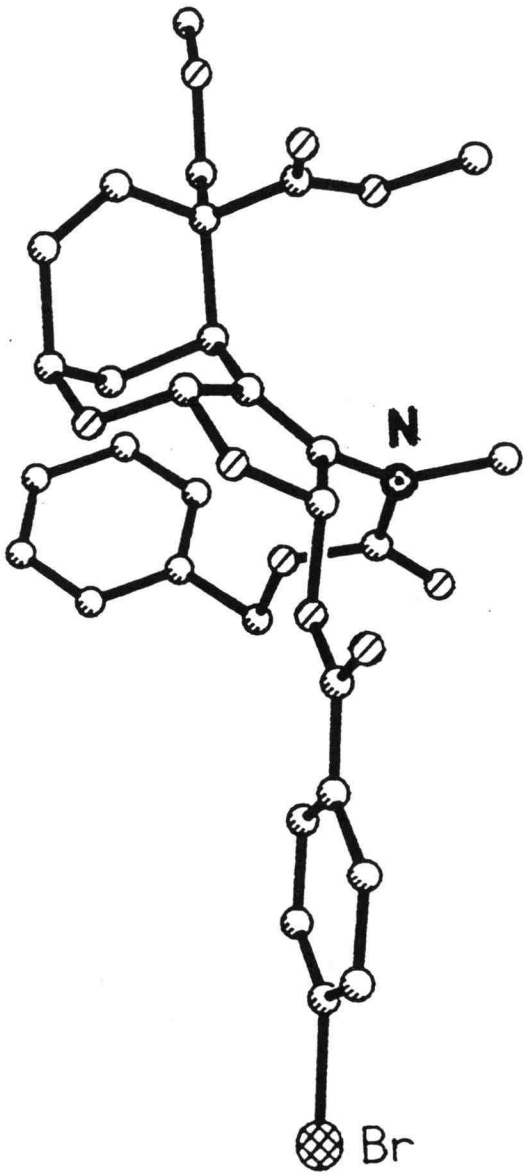
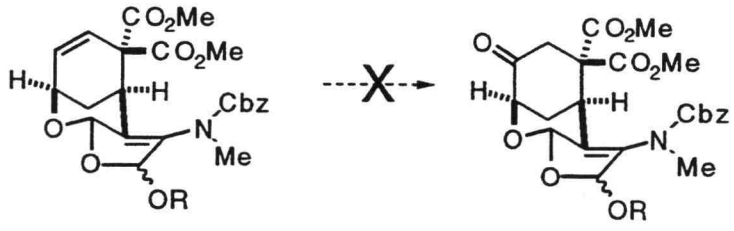


Figure 23: TELP Representation from X-ray Structure of **150**.

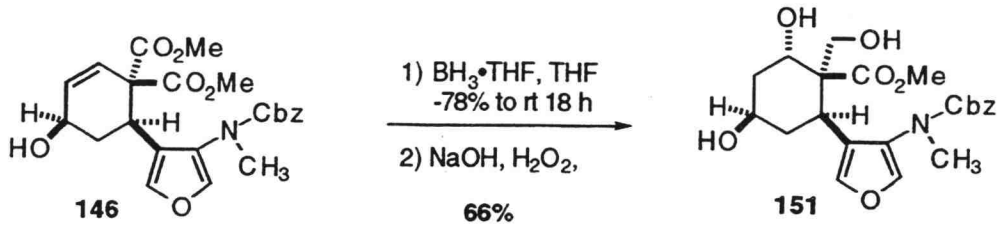
It can be seen that intramolecular addition of the allylic alcohol has taken place to the face of the furan opposite to that required for the formation of the tetracyclic lactam **127** (see schemes 52 and 62). The crystal structure also revealed the distance between the ester carbonyl and the protected nitrogen to be 4.2 Å (scheme 66). With this geometry, there is no reason to expect spontaneous cyclization to a δ-lactam after cleavage of the Cbz group of **148**.

Although hydrogenolytic cleavage of the Cbz-group in **147**, **148** and **149** was found to be straightforward, the disubstituted double bond in these structures was sacrificed in the process. It was therefore decided to forego deprotection of the nitrogen atom at this stage, and to reexamine the disubstituted double bond as a locus for the regioselective installation of the ketone which would be needed for indolization.



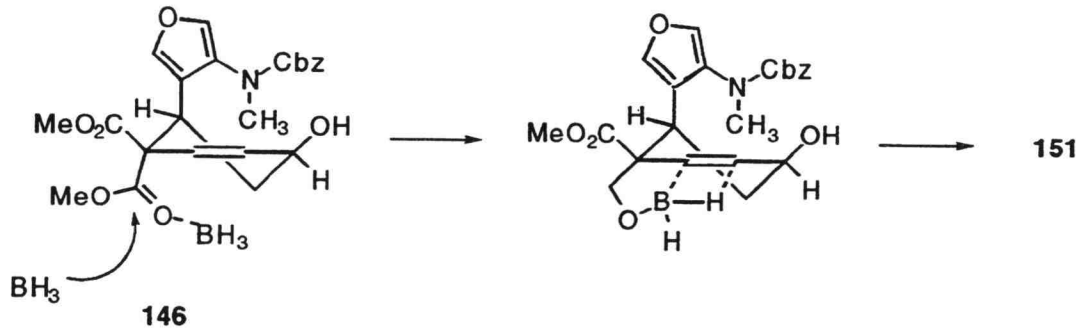
scheme 67

Unfortunately, all attempts to bring about functionalization of the cyclohexene double bond in these structures met with failure, presumably due to the high degree of steric hindrance afforded by the tricyclic ring system (scheme 67). This left only hydroboration of **146** as a viable option. The alcohol **146** was hydroborated and oxidized using the same conditions as decribed for **118** (scheme 68).



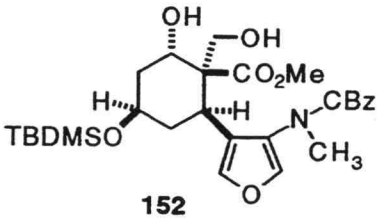
scheme 68

A triol was isolated which displayed very similar chemical and spectroscopic properties to those observed with **135** (scheme 59). Closer examination of the triol, however, revealed that, contrary to our original assignment for **135 a** and to literature precedent,[46] it was the more hindered carbon adjacent to the quaternary center that carried the hydroxyl substituent (scheme 68). The structure of the triol could therefore be assigned as **151**. The regiochemistry of the hydroboration of **146** suggests that a directive complexation of borane with one of the carbomethoxy groups may be operative in the hydroboration step. In this way, the borane is delivered to the proximal carbon of the olefin from the α-face of the cyclohexene, and one of the carbomethoxy groups is reduced in the process leading to **146** (scheme 69).

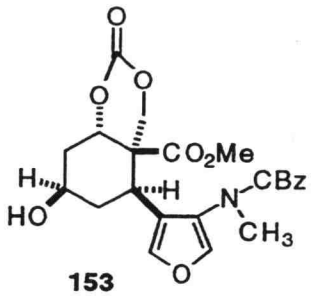


scheme 69

All attempts to reverse the regiochemical preference of the hydroboration of **146** through the use of other hydroborating reagents were unsuccessful. Protection of the sterically hindered allylic alcohol **146** did not affect the outcome of the reaction. The acetate of **146**, for example, could be prepared in good yield but did not withstand the basic conditions of the hydroboration-oxidation, and only the triol **151** could be isolated. The *tert*-butyldimethylsilyl ether of **146** was prepared in low yield and gave after hydroboration-oxidation the monoprotected triol **152**. Deprotection of the silyl ether again yielded **151**.



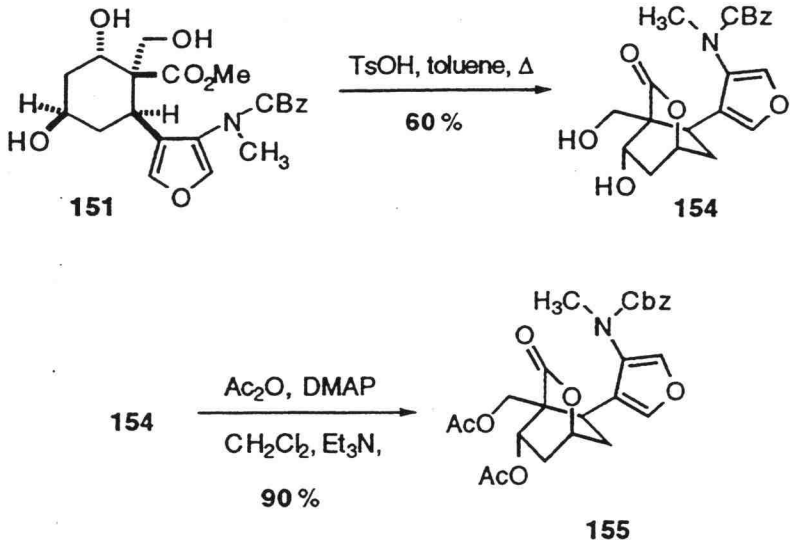
152



153

The ready formation of a cyclic carbonate **153** from **151** clearly supported the syn relationship of the two newly created alcohols. Furthermore, the regiochemical sense of the hydroboration is suggested by the six-membered cyclic carbonate since seven-membered carbonates are very rare.

The structure of **151** was subsequently verified by crystallographic analysis. The lactone **154** could be isolated either directly as a byproduct of the hydroboration of **138**, or through treatment of **146** with *p* -toluenesulfonic acid (scheme 70).



scheme 70

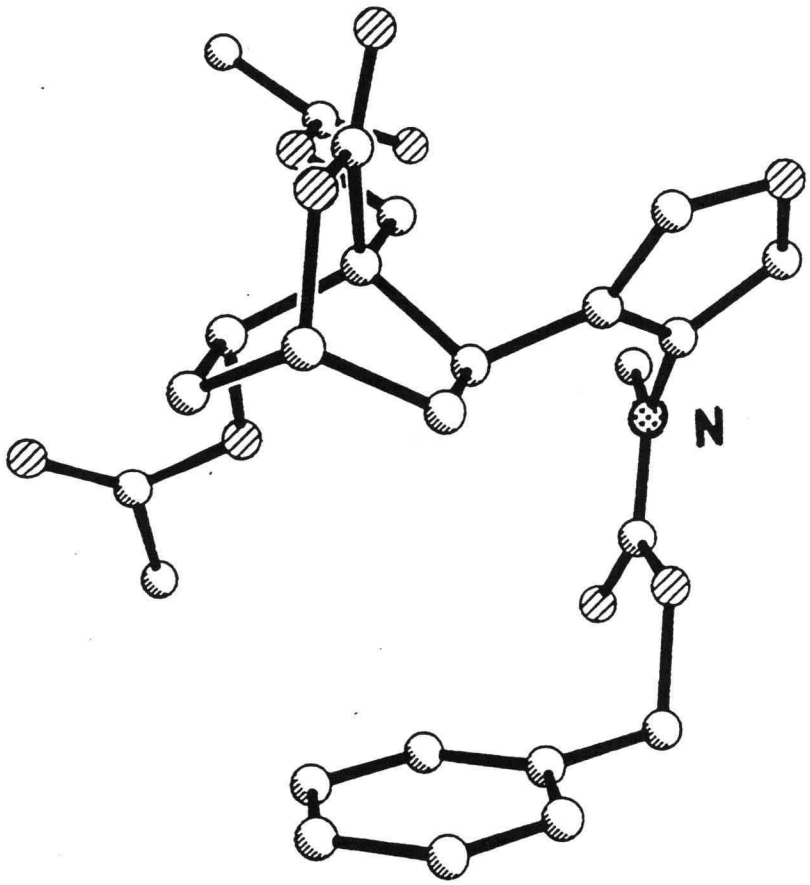
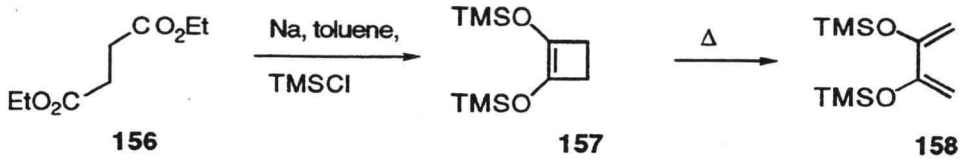


Figure 2.4: TELP Representation from X-ray Structure of **155**.

When **154** was acetylated with acetic anhydride in the presence of 4-dimethylaminopyridine the crystalline diacetate **155** was obtained. An X-ray crystal structure of this substance confirmed that it had originated from **151** and that hydroboration-oxidation of **146** had taken place to give the alcohol resulting from addition of boron to the more sterically congested terminus of the cyclohexene double bond (figure 1.4).

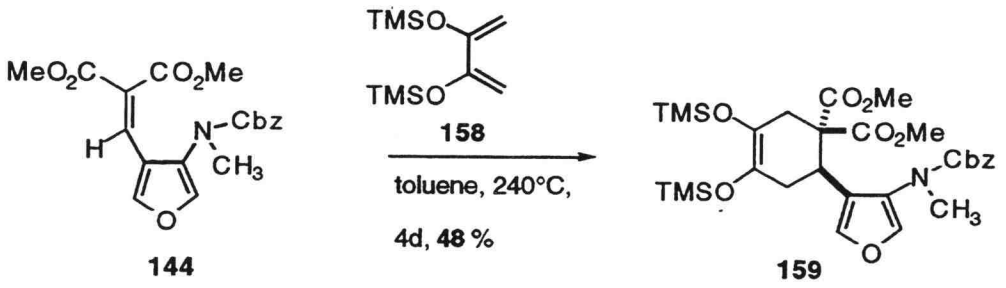
The unfavorable outcome of the hydroboration-oxidation led us to explore other Diels-Alder reactions of the dienophile **144** in the hope that it would allow for a more direct transformation of the Diels-Alder adduct to the desired α-alkoxy ketone. However, the poor dienophilic properties of **144** imposed a serious constraint on this endeavor, and it was recognized that an exceptionally reactive diene would be needed for a successful cycloaddition. 2,3-Bis(trimethylsiloxy)-1,3-butadiene (**158**) was selected for this purpose, since it is readily available through acyloin condensation of diethyl succinate (**156**) followed by pericyclic opening of the resulting 1,2-bis(trimethylsilyloxy)-1,3-butadiene (**157**) (scheme 71).[48]



156 **157** **158**

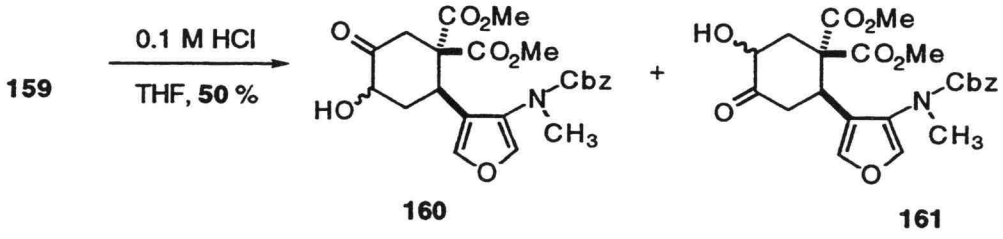
scheme 71

The dienophile **144** reacted only very sluggishly with diene **158**, but the cycloadduct **159** could be obtained in modest yield (scheme 72).



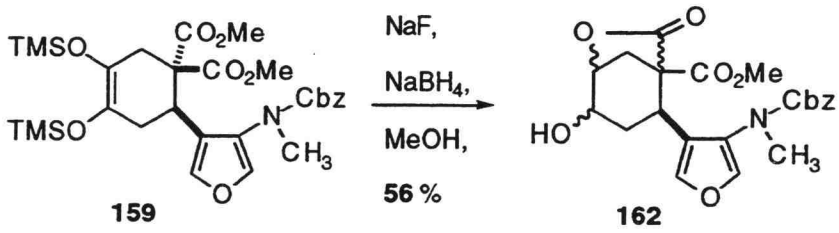
scheme 72

Unfortunately, although **159** bears oxygen substituents in the correct position of the cyclohexane, selective conversion of the protected acyloin functionality to the desired α-hydroxy ketone could not be achieved. After removal of the silyl groups from **159**, an inseparable and unstable mixture of regiosomeric and diastereomeric α-hydroxy ketones **160** and **161** was obtained (scheme 73).



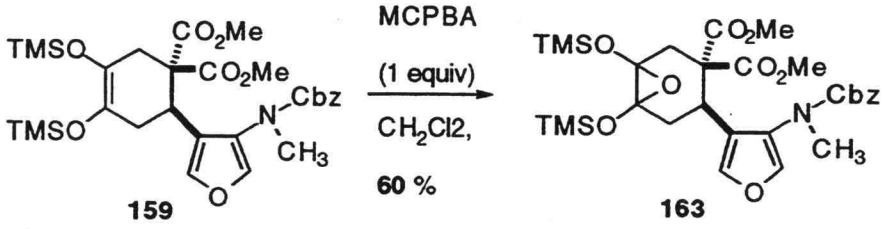
scheme 73

Cleavage of the protected enediol of **159** with sodium fluoride, followed by reduction of the mixture *in situ* with sodium borohydride, gave a diastereomeric mixture of hydroxy γ-lactones **162** whose stereochemistry could not be defined (scheme 74).



scheme 74

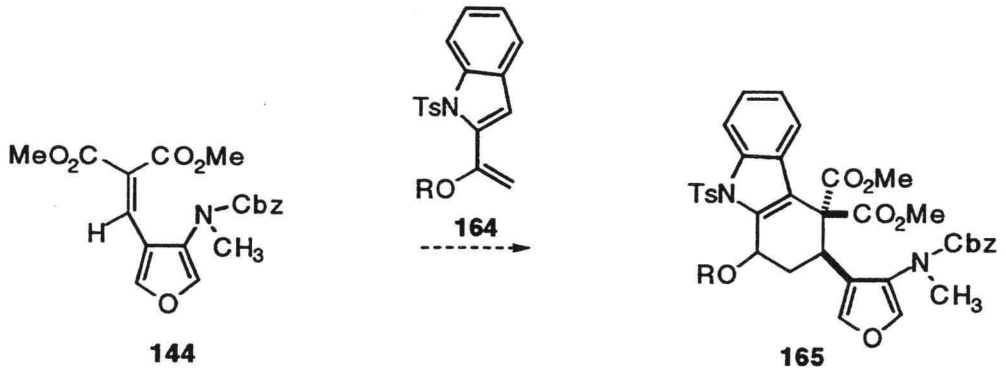
Attempts to elaborate the mixture of lactones **162** towards workable compounds met with failure. Futhermore, although **159** could be epoxidized to **163** with *m*-chloroperbenzoic acid, further transformation of this substance to an α-diketone or an α-hydroxy ketone could not be accomplished (scheme 75).



scheme 75

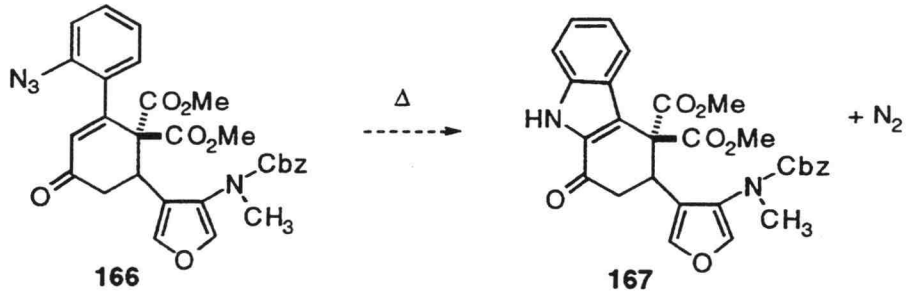
In summary, there are several features of the chemistry described above that warrant comment. We were able to develop direct access to several functionalized Diels-Alder adducts that contain all but one of the carbon atoms of the target structure **61**. However, transformation of these adducts to a substance which could lead to koumine remains to be completed. In particular, the manipulation of the furan moiety in these adducts and the elaboration of the α-alkoxy ketone in the carbocyclic ring were identified as steps that will require extensive study.

In light of the difficulties that were encountered with the installation of the ketone needed for eventual Fischer indolization, it may be fruitful to consider alternative indolization methods for the future. Along these lines, some preliminary experiments have pointed at the possibility that the indole moiety may be introduced by a Diels-Alder reaction of an indole diene such as **164** with dienophile **144**.[49] Although the synthesis of dienes similar to **164** is possible,[50] the low dienophilic reactivity of **144** and potential problems of regio and stereocontrol in the Diels-Alder reaction would have to be overcome (scheme 76).



scheme 76

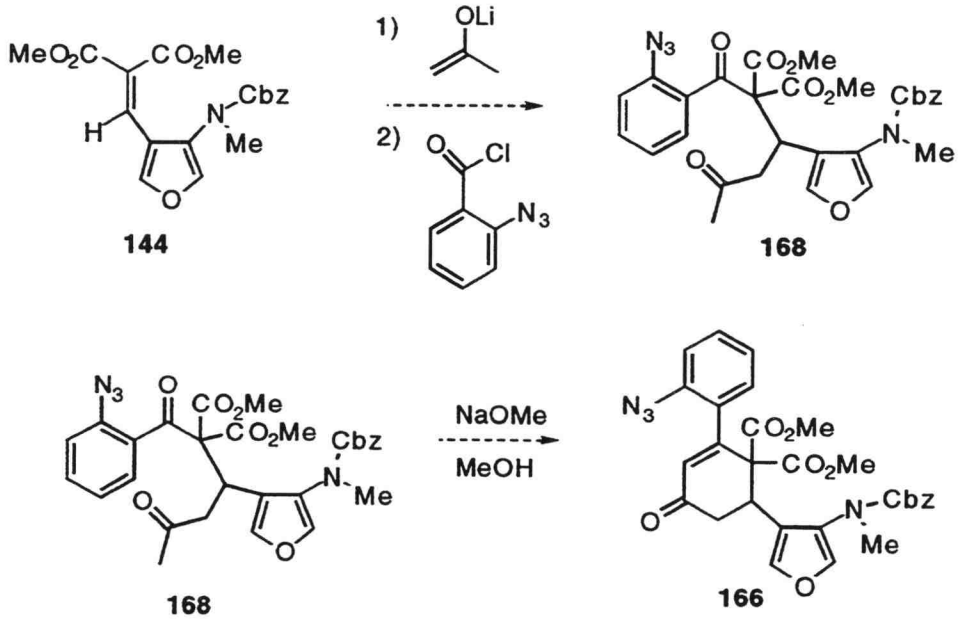
An alternative strategy would entail introduction of the indole at some later stage through manipulation of an *o*-azidoaryl substituent connected to the β-carbon of an enone **166**. Thermolysis of **166**, for example, could yield a reactive nitrene intermediate that would insert into the carbon hydrogen bond of the enone to afford indole **167** (scheme 76).[51]



166 **167**

scheme 76

Synthesis of **166** can be envisioned through a Michael addition-acylation sequence using enoate **144** as a substrate. Thus, conjugate addition of acetone enolate, followed by acylation of the resulting enolate with *o*-azidobenzoyl chloride, would yield diketone **168** which could undergo intramolecular aldol condensation leading to **166** (scheme 77).



144 **168** **168** **166**

scheme 76

Except for the *o*-azidophenyl group, structure **166** is identical to the enone **145** obtained in the Diels-Alder reaction between **144** and

Danishefky's diene (scheme 64). Thus, it is conceivable that the chemistry worked out in that series may offer some valuable direction for synthetic efforts toward koumine in the future.

Experimental Section

General

Starting materials and reagents were obtained from commercial sources and, unless stated otherwise, were used without further purification. Solvents were dried by distillation from the appropriate drying agent immediately prior to use. Toluene, tetrahydrofuran, and ether were distilled from potassium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, diisopropylethylamine, dimethylformamide, acetonitrile, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Moisture and air sensitive reactions were carried out under an atmosphere of argon.

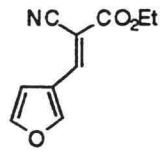
Unless otherwise stated, the combined organic layers obtained during the workup of a reaction were dried over magnesium sulfate. Concentration *in vacuo* refers to the use of a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at pressures less than 2 torr. Reaction flasks were flame dried under a stream of argon. Syringes were oven dried at 200 °C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Analytical thin layer chromatography (TLC) was conducted using E. Merck precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Spots were visualized by ultraviolet light, or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, 10% ammonium

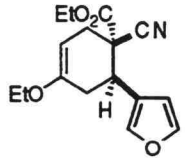
molybdate, or a 1% solution of vanillin in 0.1M H_2SO_4 in methanol. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors with layer thickness of 1, 2 or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

Melting points were measured using a Büchi melting point apparatus. Infared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300, or Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^1H NMR spectral data are reported in the order: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (J) in Hertz, and number of protons.

Chemical ionization mass spectra MS(CI) were obtained using a Finnigan 4023 quadrupole GC-MS 4500 spectrometer with a source temperature of 140 °C and a pressure of 0.7 torr. Electron impact mass spectra MS(EI) were obtained using a Varian MAT311 spectrometer with an ionization potential of 70 eV. High resolution mass spectra were obtained using a Kratos MS-50 RF spectrometer. X-ray crystallographic data were collected using a Rigaku AFC6R or a Siemens P4 diffractometer. Structures were solved using the direct methods programs contained in the TEXAN (VAX/VMS) and SHELXTL (Silicon Graphics/UNIX) software packages. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.



3-(-Ethyl-2-cyano-3-(furanyl)-acrylate (85). A mixture of 3-furaldehyde (**84**) (100 mg, 1.0 mmol) and ethyl α-cyanoethyl acetate (226 mg, 2 mmol) and a catalytic amount of piperidine (10 μL) in pyridine (2.5 mL) was stirred at room temperature for 12 h. The mixture was cooled to ice bath temperature, 10% H_2SO_4 (10 mL) was added, and the mixture was extracted with ether (3 x 10 mL). The separated organic layer was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 10:1) afforded 165 mg (83%) of **85** as a white solid: mp 88°C; IR (KBr) 3190, 2996, 2226, 1717, 1645, 1292, 1162, 1105, 876, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.35 (3 H, t, J = 8.0 Hz); 4.30 (2 H, q, J = 8.0 Hz), 7.26 (1 H, s), 7.55 (1 H, s), 8.05 (1 H, s), 8.15 (1 H, s), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 62.5, 101.9, 108.5, 115.6, 120.8, 145.3, 145.4, 149.8, 162.4 ; MS (EI) m/z 191, 146, 135, 63.



1-Ethoxy-4-cyano-4-carboethoxy-5-(3-furanyl)cyclohexene (86). A mixture of **85** (17 mg, 0.09 mmol) and 2-ethoxy-1,3-butadiene (130 mg, 2 mmol) in toluene (20 mL) was heated in a screw cap flask at 180°C for 20 h. Solvent and residual diene were removed in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 9:1) afforded 24 mg (95%) of **86** as a yellow oil that slowly turned solid: mp 60 °C; IR (KBr) 2980, 2929, 1739, 1673, 1242, 1029, 657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15

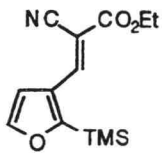
(3H, t, J=8.0 Hz), 1.3 (3H, t, J=8.0 Hz), 2.39 (1H, dd, J=13.0, 5.6 Hz), 2.65 (2H, m), 2.91 (1H, m), 3.40 (1H, dd, J=12.0, 5.6 Hz), 3.75 (2H, q, J = 8.0 Hz), 4.12 (2H, m), 4.60 (1H, d, J = 4.0 Hz), 6.50 (1H, s), 7.35 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7; 14.5, 32.1, 32.8, 36.7, 50.0, 62.4, 62.6, 88.4, 109.6, 118.0, 122.9, 140.2, 143.1, 153.4, 168.7; MS(EI) *m/z* 289 (M^+, 100), 260, 164, 136; HRMS *m/z* calcd for $C_{16}H_{19}O_4N$ (M^+): 289.1314. Found: 289.1314.

2-Trimethylsilylfuran-3-carboxylic Acid. A flame dried 50 mL three-neck flask was charged with diisopropylamine (1.4 mL, 10 mmol). To this was added via syringe 1.6 M butyllithium solution (5.3 mL) followed by tetrahydrofuran (16 mL). The mixture was cooled to -78°C and 3-furanoic acid (600 mg, 5.0 mmol) was added in tetrahydrofuran (10 mL) while stirring. The mixture was kept at -78°C for 0.5 h after which chlorotrimethylsilane (1.6 mL) was added. The mixture was allowed to warm to room temperature and then water (6 mL) was added followed by 10% aqueous sulfuric acid (20 mL). The resulting mixture was stirred for 0.5 h after which water (50 mL) was added and the mixture was extracted with ether (4 x 30 mL portions). The combined ether layers were washed with brine and dried over magnesium sulfate. There was obtained 905 mg (91%) of the title compound as a white amorphous powder: mp 88 °C (lit[40]: 89-90 °C); IR (KBr) 3450, 3444, 1685, 1682, 1673, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.36 (9H, s), 6.80 (1H, d, J = 1.0 Hz), 7.26 (1H, d, J = 1.0 Hz).

2-Trimethylsilyl-3-furanmethanol (91). To a cold (0°C) solution of 2-trimethylsilylfuran-3-carboxylic acid (598 mg, 3.2 mmol) in tetrahydrofuran (15 mL) was added 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran (6 mL). After 1 h the ice bath was removed and the mixture was stirred at room temperature for another 3h. Ammonium chloride solution (15 mL) was

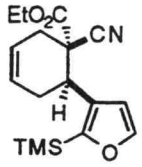
carefully added and the mixture was stirred for 0.5 h and extracted into ether (3 x 30 mL). The separated organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) yielded 450 mg (82%) of the title compound: IR (neat) 3327 (br), 3313, 2957, 1508, 1250, 1008, 841, 807, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.30 (9H, s), 4.6 (2H, d, J = 5 Hz), 6.45 (1H, d, J = 1 Hz), 7.57 (1H, d, J = 1 Hz).

2-Trimethylsilyl-3-furaldehyde. To a suspension of active manganese (IV) oxide (2 g, 23 mmol) in hexane (30 mL) was added 2-trimethylsilyl-3-furanmethanol (433 mg, 2.5 mmol) in hexane (1 mL). The mixture was stirred at room temperature for 6h and then filtered over Celite. The filter cake was thoroughly washed with ether and the solvent carefully removed in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 260 mg (60 %) of the title compound: IR (neat) 3400 (br), 2957, 1668, 844, 762, 632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s),6.80 (1H, d, J = 0.5 Hz) 7.60 (1H, d, J = 1 Hz), 10.1 (1H, s).



3-(-Ethyl-2-cyano-3-(2-trimethylsilyl-3-furanyl)-acrylate (92). A mixture of 2-trimethylsilyl-3-furaldehyde (180 mg, 1.0 mmol), ethyl α-cyano acetate (220 mg, 2 mmol), and a catalytic amount of piperidine in pyridine (2.5 mL) was stirred at room temperature for 10 h. The mixture was cooled to 0°C, 10% aqueous sulfuric acid (10 mL) was added, and the mixture was extracted with ether (3 x 10 mL). The separated organic layer was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue

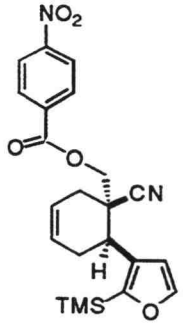
(hexane-ethyl acetate, 20:1) afforded 230 mg (80%) of **92** as a white solid: mp 106°C; IR (KBr) 3190, 2996, 2226, 1722, 1609, 1267, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 1.40 (3H, t, J = 8.0 Hz) 4.40 (2H, q, J = 8.0 Hz), 7.40 (1H, d, J = 0.5 Hz), 7.68 (1H, d, J = 0.5 Hz), 8.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.1, 14.1, 62.3, 100.7, 108.0, 115.8, 129.7, 146.4, 148.1, 162.8, 171.2; MS (EI) m/z 263, 248, 177, 100, 75, 73. HRMS *m/z* calcd for $C_{13}H_{17}O_3NSi$: 263.0978. Found: 263.0978.



4-Cyano-4-carboethoxy-5-(2-trimethylsilyl-3-furanyl) cyclohexene (93). To a solution of **92** (61 mg, 0.23 mmol) in toluene (3 mL) was added an undefined amount of 1,3-butadiene which was bubbled through the solution in a gas stream. The mixture was heated in a sealed flask at 250°C for 7 days (progress of the reaction was monitored by TLC and 1,3-butadiene was added to the reaction vessel several times). The mixture was poured into 5 mL of methanol and the polymeric material was removed by filtration over Celite. Solvent and residual diene were removed in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 63 mg (87%) of **93** as a colorless oil: IR (neat) 2958, 2929, 1741, 1281, 1261, 1252, 1230, 843, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 1.03 (3H, t, J=8.0 Hz), 2.35 (2H, m), 2.58 (2H, m), 2.91 (1H, m), 3.35 (1H, dd, J=12, 5.6 Hz), 4.05 (2H, m), 5.8 (2H, m), 6.80 (1H, d, J = 0.5 Hz), 7.60 (1H, d, J = 0.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.0, 13.4, 31.5, 34.6, 37.3, 48.4, 62.3, 108.6, 118.8, 121.9, 127.1, 133.3, 146.7, 156.1, 168.5; MS(EI) *m/z* 317 (M^+), 303,

302, 274, 248, 230, 220, 73 ; HRMS *m/z* calcd for $C_{17}H_{23}O_3N$ Si :317.1447. Found: 317.1447.

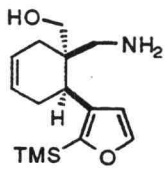
4-Cyano-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl)-cyclohexene. To a suspension of lithium aluminum hydride (20 mg, 0.5 mmol) in dry ether (8 mL) was added **93** (90 mg, 0.28 mmol) in ether (5 mL) via cannula. The mixture was stirred at -78°C for 1.5 h after which water (20 µL) was added followed by 10% aqueous sodium hydroxide (20 µL) and water (60 µL). The resulting suspension was filtered over Celite and the filtercake was washed with ether. The filtrate was dried and the solvent was evaporated. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 54 mg (30%) of the title compound and 42 mg (21%) of **93** was recovered: IR (neat) 3400, 2920, 1250, 840, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 9H), 1,85-2.4 (m, 4 H), 3.25 (dd, J=11Hz, 11 Hz, 1H), 3.58 (d, J=11 Hz, 1H), 3.67 (d, J=11 Hz, 1H), 5.78 (m, 2 H), 6.80 (d, J = 0.7 Hz, 1 H), 7.61(d, J = 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.8, 32.1, 33.5, 35.1, 42.6, 66.6, 108.3, 122.0, 123.0, 127.1, 134.6, 147.4, 155.5.



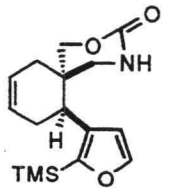
4-Cyano-nitrobenzoyl-4-hydroxymethyl-5-(2-trimethyl-silyl-3-furanyl)cyclohexene (94). To a solution of 4-Cyano-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl)-cyclohexene (50 mg, 0.17 mmol) in dichloromethane (5 mL) was added *p*-nitrobenzoyl chloride (40 mg, 0.21

mmol), triethylamine (60 μL, 0.6 mmol) and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 15 h, after which 0.1 N hydrochloric acid (10 mL) was added and the mixture was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 40 mg (52%) of **94** as a yellow solid and 10 mg (20%) of starting material was recovered: IR (KBr) 2920, 1732, 1529, 1347, 1269, 1100, 840, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 2.30-2.80 (4H, m), 3.05 (1H, dd, J=11Hz, 5 Hz), 4.22 (1H, d, J=11 Hz), 4.30 (1H, d, J=11 Hz), 5.78 (2H, m), 6.80 (1H, d, J=1 Hz), 7.59 (1H, d, J=1 Hz), 8.15-8.31 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -0.7, 31.9, 34.5, 36.2, 40.6, 66.8, 108.3, 120.8, 122.0, 123.6, 127.7, 130.9, 133.4, 134.5, 147.6, 150.8, 155.8, 164.0; Anal. calcd for $C_{22}H_{24}N_2O_5Si$ C; 62.24; H; 5.70; N; 6.60. Found: C; 61.86; H; 5.63; N; 6.46.

Compound **94** crystallized in the monoclinic space group c2/c with a=30.400 (2) Å, b=10.351(4) Å, c=13.999 (6) Å, β=95.44 (7), V=4386 (4) $Å^3$, Z=8, D_{calc}=1.322 g/cm^3. All 3111 nonequivalent reflection in the range of 3.5° < 2Θ < 50° were measured on a Rigaku AFC6R diffractometer with graphite monochromated Mo Kα radiation (λ=0.71069 Å). The structure was solved with direct methods (SHELXS) using 3052 unique reflections with F > 3 σ(F). Full matrix least squares refinement with anisotropic temperature factors for all non-hydrogen atoms and calculated hydrogen atom positions led to the final discrepancy indices of R=0.058 and R_w=0.065.

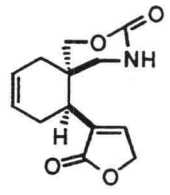


4-Aminomethyl-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl)cyclohexene (95). To a suspension of lithium aluminum hydride (20 mg, 0.5 mmol) in of dry ether (2 mL) was added a solution of Diels-Alder adduct **93** (26 mg, 0.08 mmol) in ether (5 mL) via cannula. The mixture was stirred at room temperature for 14 h, after which water (20 μL) was added followed by 10% aqueus sodium hydroxide (20 μL) and water (60 μL). The resulting suspension was filtered over Celite and the filtercake was washed with ether and methanol. Due its very polar properties, **95** was used without further purification: IR (KBr) 3030 (br), 2957, 2923, 2907, 1249, 840, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (9H, s), 2.4-1.85 (4H, m), 2.70 (1H, d, 10 Hz), 2.80 (1H, d, 10 Hz), 3.25 (1H, dd, J=18Hz, 5.6 Hz), 3.62 (1H, d, 10 Hz), 3.69 (1H, d, 10 Hz), 5.72 (2H, m), 6.30 (1H, d, J = 0.5 Hz), 7.55 (1H, d, J = 0.5 H).



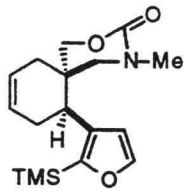
4-Aminomethyl-4-hydroxymethylureido-5-(2-trimethylsilyl-3-furanyl)cyclohexene (96). To a solution of crude **95** (ca. 0.08 mmol) in tetrahydrofuran (5 mL) was added 1,1'-carbonyldiimidazole (15 mg, 0.09 mmol) in 3 mg portions over a period of 3h. The mixture was stirred for 12 h, after which 5 mL of water were added and the mixture was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried, and

concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 13 mg (54%, from **93**) of **96** as a colorless oil: IR (KBr) 2899, 1715, 1487, 1250, 1115, 840, 762, 654 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) 0.29 (9H, s), 2.1 (2H, m), 2.35 (2H, m), 2.95 (1H, m), 3.05 (1H, t, J=5Hz), 3.2 (1H, d, J=9Hz), 4.01 (1H, d, 11 Hz), 4.07 (1H, d, 11 Hz), 5.75 (2H, m), 6.32 (1H, d, J = 1.5 Hz),7.55 (1H, d, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.6, 29.5, 29.9, 32.2, 32.5, 47.1, 73.6, 109.6, 124.1, 126.0, 134.7, 147.0, 153.9, 155.7; MS (CI) m/z 306 (M^{+1}), 290, 59; HRMS *m/z* calcd for $C_{16}H_{24}O_3NSi$ (M^{+1}): 306.15255 Found: 306.15250.

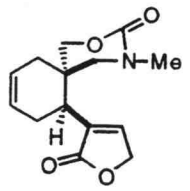


4-Aminomethyl-4-hydroxymethylureido-5-(2-furanonyl)-cyclohexene (97). To a suspension of **96** (101 mg, 0.33 mmol) and sodium acetate (50 mg) in dichloromethane (20 mL) was added 38% peracetic acid (250 μL, 1.4 mmol). The resulting mixture was stirred at 9°C for 36 h. Solid sodium thiosulfate (50 mg) was added, and the mixture was filtered over Celite and the filtercake washed with ether. The filtrate was dried and the solvent was evaporated. Column chromatography of the residue (ethyl acetate-methanol, 1:4) afforded 56 mg (57%) of **97** as a colorless oil: IR (neat) 3400, 2899, 1746, 1724, 1702, 1692, 1686, 1582, 1575, 1566, 1490, 1443, 1419 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95-2.45 (4H, m), 2.91 (2H, m), 3.28 (1H, d, J=15Hz), 4.07 (1H, d, 18 Hz), 4.10 (1H, d, 18 Hz), 4.81 (2H, m), 5.79 (2H, m), 6.00 (1H, s), 7.37 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 29.0, 32.3, 32.6, 47.0, 70.5, 72.8, 124.7, 125.1, 134.4, 147.0,153.7, 174.3; MS (CI) m/z 250

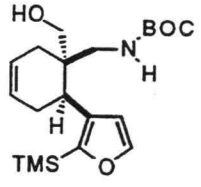
(M^{+1}), 232, 206, 189, 143; HRMS *m/z* calcd for $C_{13}H_{16}NO_4$ (M^{+1}): 250.1079 Found: 250.1079.



N-Methyl-4-aminomethyl-4-hydroxymethylureido-5-(2-trimethylsilyl-3-furanyl)cyclohexene(99). To a suspension of 60% sodium hydride dispersion in mineral oil (15 mg, 0.37 mmol) in dry tetrahydrofuran (1.5 mL) was added **96** (44 mg, 0.14 mmol) in tetrahydrofuran (3 mL) via cannula. The mixture was cooled to 0°C and iodomethane (300 µL, 5.3 mmol) was added via syringe. The mixture was stirred at room temperature for 5 h, after which 0.1 N aqueous sodium hydroxide solution (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:4) afforded 40 mg (87%) of **99** as an amorphous white solid: IR (KBr) 2899, 1686, 1492, 1250, 1144, 840, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (9H, s), 2.0-2.45 (4H, m), 2.35 (2H, m), 2.80 (1H, d, J = 11Hz), 2.88 (3H, s), 3.16 (1H, d, J = 18Hz), 3.96 (1H, d, 10.8 Hz), 3.98 (1H, d, 10.8 Hz), 5.75 (2H, m), 6.32 (1H, d, J = 4 Hz), 7.50 (1H, d, J = 4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.6, 29.5, 30.2, 32.6, 33.5, 36.8, 54.9, 73.1, 109.7, 124.1, 126.0, 134.9, 147.1, 153.4, 155.7; MS (EI) m/z 319 (M^+), 304, 238, 198, 73, HRMS *m/z* calcd for $C_{17}H_{26}NO_3Si$ (M^{+1}):320.1682. Found: 320.1680.

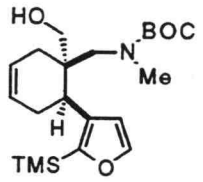


N-Methyl-4-aminomethyl-4-hydroxymethylureido-5-(2-furanonyl) cyclohexene (100). To a suspension of **99** (217 mg, 0.68 mmol) and sodium acetate (50 mg) in dichloromethane (20 mL) was added 38% peracetic acid (250 μL, 1.4 mmol). The resulting mixture was stirred at 9°C for 36 h. Solid sodium thiosulfate (50 mg) was added, the mixture was filtered over Celite and the filtercake was washed with ether. The filtrate was dried and the solvent was evaporated. Column chromatography of the residue (ethyl acetate-methanol, 1:4) afforded 103 mg (57%, 79% based on recovered starting material) of **100** and 61 mg (28%) of **99**: IR (neat) 3400, 2899, 1750, 1700, 1692, 1687, 1582, 1576, 1566, 1490, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95-2.45 (4 H, m), 2.80 (1H, d, J=15Hz), 2.90 (3H, s), 3.28 (1H, d, J=15Hz), 4.15 (2H, m), 4.80 (1H, d, 18 Hz), 4.85 (1H, d, 18 Hz), 5.79 (2H, m), 7.39 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 29.1, 32.2, 33.8, 36.8, 54.6, 70.4, 72.2, 124.7, 125.1, 134.6, 147.0, 153.7, 174.2; MS (CI) m/z 264 (M^{+1}), 117, 59, 57, HRMS *m/z* calcd for $C_{14}H_{18}NO_4(M^{+1})$: 264.1236. Found: 264.1235.



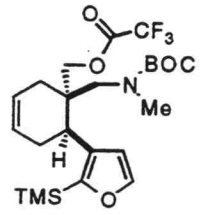
N-*tert*-Butoxycarbonyl-4-aminomethyl-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl)cyclohexene (101). To a solution of crude **95** (290 mg, 1.04 mmol) in dry tetrahydrofuran (8 mL) was added di-*tert*-butyl dicarbonate (250 mg, 1.1 mmol). The mixture was stirred at room temperature

for 4 h, after which water (20 mL) was added and the mixture was extracted into ether (3 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 320 mg (81%) of **101**: IR (KBr) 3380, 3283, 2960, 1678, 1559, 1347, 1250, 1172, 840, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (9H, s), 1.43 (9H, s), 1.90 (3H, m), 2.50 (1H, m), 2.90 (1H, dd, J = 18Hz, 12Hz), 3.10 (1H, d, J=12 Hz), 3.41 (2H, m), 3.95 (1H, t, J=12Hz), 4.59 (1H, bt, J=8Hz), 5.75 (2H, m), 6.32 (1H, d, J = 0.5 Hz), 7.53 (1H, d, J = 0.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.6, 28.3, 28.4, 29.7, 30.6, 40.6, 44.7, 64.3, 80.0, 110.2, 124.6, 125.5, 137.7, 147.0, 154.5, 157.7; MS (EI) *m/z* 379 (M^+), 308, 172, 102, 73, HRMS *m/z* calcd for $C_{20}H_{33}NO_4Si$ (M^+):379.2179 Found: 379.2180.



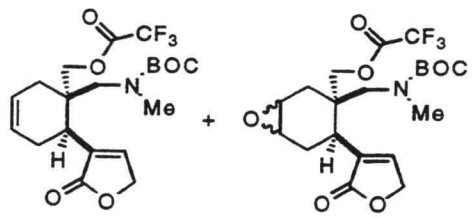
N-Methyl-N-*tert*-butoxycarbonyl-4-aminomethyl-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl)cyclohexene (102). To a solution of **101** (222 mg, 0.59 mmol) in dry tetrahydrofuran (8 mL) was added 60% sodium hydride dispersion in mineral oil (25 mg, 0.65 mmol). The mixture was cooled to 0°C and iodomethane (0.5 mL, 8.0 mmol) was added via syringe. The mixture was stirred at room temperature for 8 h, after which aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 320 mg (80%) of **102**: IR (KBr) 3734, 2960, 1701, 1505, 1250, 1172, 840, 718 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) 0.29 (s, 9H), 1.40 (s, 9H), 1.85-2.40 (4H, m), 3.10 (2H, m), 3.25 (2H, m), 3.30 (3H, s), 4.95 (1H, bs), 5.75 (2H, m), 6.35 (1H, s), 7.52 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.6, 28.4, 29.4, 30.4, 32.9, 39.1, 45.3, 59.4, 78.7, 110.3, 125.1, 125.7, 136.6, 146.7, 154.8, 156.3; MS (EI) *m/z* 393 (M^+), 322, 216, 172, 159.1, 74, 73, HRMS *m/z* calcd for $C_{21}H_{35}NO_4Si$ (M^+): 393.2335. Found: 393.2336.

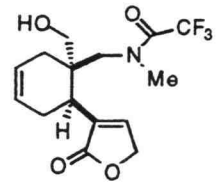


N-Methyl-N-*tert*-butoxycarbonyl-4-aminomethyl-trifuoroacetyl-4-hydroxymethyl-5-(2-trimethylsilyl-3-furanyl) cyclohexene (104). To a solution of the **102** (156 mg, 0.39 mmol) in dry dichloromethane (2 mL) was added triethylamine (0.5 mL) and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was cooled to 0°C and freshly distilled trifluoroacetic anhydride (0.25 mL) was added via syringe. The resulting mixture was stirred for 1 h and was diluted with cold water (30 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 119 mg (78%) of **104**: IR (KBr) 3734, 2960, 1760, 1718, 1371, 1281, 1255, 1198, 1127, 1101, 840, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (9H, s), 1.49 (9H, s), 3.02-3.12 (2H, m), 3.18 (3H, s), 3.22 (1H, d, J=9 Hz), 3.58 (1H, d, J=14Hz), 4.02 (1H, d, J=14Hz), 5.75 (2H, m), 6.38 (1H, d, J=3 Hz), 7.56 (1H, d, J=3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.6, 27.5, 29.4, 30.2, 33.7, 40.4, 50.0, 59.1, 85.4, 110.1, 125.0, 125.5, 136.0, 146.9, 151.9, 155.2; MS (EI) m/z 489

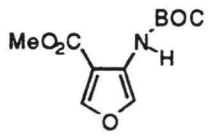
(M+), 374, 204, 203, 193, 143, 122, 118, 81, 75, 73; HRMS *m/z* calcd for $C_{23}H_{34}NO_5SiF_3$ (M+):489.2158. Found: 489.2159.



N-Methyl-N-*tert*-butoxycarbonyl-4-aminomethyl-trifuoroacetyl-4-hydroxymethyl-5-(3-furanoyl)cyclohexene (105) and its epoxide 106. To a solution of **104** in dichloromethane (2 mL) was added sodium acetate (20 mg). The mixture was cooled to 0°C and 38% peracetic acid was added in two portions (80 μL, 0.08 mmol) over a period of 6 h. The resulting mixture was stirred for 12 h at 9°C, diluted with aqueous sodium thiosulfate (10 mL) and aqueous sodium bicarbonate solution (10 mL), and was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 4:1) afforded 17 mg (66%) of a mixture of **105** and **106**: IR (neat) 3734, 2960, 1756, 1714, 1283, 1198, 1131, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.01-2.31 (m, 4H), 2.91-3.22 (m, 6H), 3.65 (m, 1H), 4.02 (m, 2H), 4.81 (m, 2H), 5.75 (m, 2H), 7.32 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 27.5, 28.1, 29.7, 29.9, 33.0, 34.2, 39.3, 40.9, 46.1,47.7, 50.3, 51.7, 58.8, 70.0, 70.3, 85.7, 86.1, 124.7, 125.6, 135.1, 145.5, 147.1, 151.8,174.6.

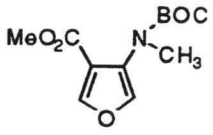


N-Methyl-N-trifuoroacetamido-4-aminomethyl-4-hydroxymethyl-5-(3-furanoyl)cyclohexene (107). To a solution of a mixture of **105** and **106** (48 mg, 0.11 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.75 mL) dropwise over a period of 1h. Aqueous sodium bicarbonate (20 mL) was carefully added and the mixture was extracted into ether. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 4:1) afforded 20 mg (56%) of **107**: IR (neat) 3349, 2923, 1724, 1447, 1209, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.7 (1H, m), 1.92 (2H, m), 2.31(1H, m), 2.10 (1H, m), 2.75 (1H, dd, J=5Hz, 1Hz), 3.07 (1H, dd, J=5Hz, 1Hz), 3.30 (3H, s), 3.41 (2H, m), 3.65 (1H, dd, J=14Hz, 8Hz), 4.81 (2H, m), 5.70 (2H, m), 7.39 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 28.9, 31.2, 39.2, 39.4, 44.7, 59.1, 70.7, 77.5, 124.8, 125.4, 135.7, 146.7, 175.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -76.63; MS (CI) m/z 334 (M^{+1}), 314, 302, 220, 207, 188, 175, 143, 129; HRMS *m/z* calcd for $C_{15}H_{19}F_3NO_4$ (M^+): 334.1266. Found: 334.1267.



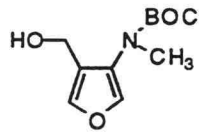
Methyl-4-N-*tert*-Butoxycarbonylamino-3-furoate (109). To a solution of 4-carbomethoxy-3-furoic acid[42] (718 mg, 4.22 mmol) in dry toluene (7 mL) was added oxalyl chloride (0.4 mL, 4.3 mmol) via syringe. The mixture was refluxed for 1 h and the toluene was removed in vacuo. The residue was

taken up in ether (10 mL), cooled to 0°C, and a solution of sodium azide (1g, 15.4 mmol) in water (10 mL) was added. The resulting two phase system was stirred at 0°C for 2 h, after which the layers were separated and the aqueous layer was back extracted with ether (3 x 15 mL). The combined organic layers were washed with brine and aqueous sodium bicarbonate, dried, and concentrated in vacuo. The crude acyl azide was taken up in dry *tert*-butanol (20 mL) and the solution was refluxed for 3 h. Evaporation of the *tert*-butanol and column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 680 mg (66%) of **109**: IR (KBr) 3399, 1709, 1705, 1561, 1510, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.50 (9H, s), 3.85 (3H, s), 7.83 (1H, s), 7.91 (2H, bs); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 51.5, 80.6, 109.9, 124.9, 131.5, 146.2, 152.2, 164.4; MS (EI) m/z 241 (M^+), 185, 168, 154, 141, 109; HRMS *m/z* calcd for $C_{11}H_{15}NO_5$ (M^+): 241.0950. Found: 241.0950.



Methyl-4-N-*tert*-Butoxycarbonyl-N-methylamino-3-furoate (110). To a suspension of 60% sodium hydride dispersion in mineral oil (116 mg, 2.9 mmol) in dry tetrahydrofuran (4 mL) was added a solution of **109** (470 mg, 1.93 mmol) in tetrahydrofuran (8 mL). The mixture was cooled to 0°C and iodomethane (0.5 mL, 8.05 mmol) was added via syringe. The mixture was stirred at room temperature for 3 h after which aqueous sodium hydroxide solution (20 mL) was added and the mixture was extracted with ether (3 x 25 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 20:1) afforded 253 mg (51%) of **110**: IR (neat) 2960, 1730, 1708, 1435, 1388, 1362, 1389, 1160, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50

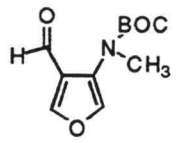
(9H, s), 3.12 (3H, s), 3.79 (3H, s), 7.37 (1H, bs), 7.91 (1H, d, J=1Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 38.0, 51.5, 80.2, 116.3, 129.7, 139.2, 139.9, 145.8, 148.0, 154.9, 162.5.



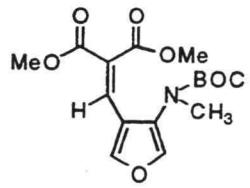
4-N-*tert*-Butoxycarbonyl-N-methylamino-3-furanmethanol (112). Method A: The combined aqueous layers from the preparation of **110** described above were carefully acidified with aqueous 1N hydrochloric acid and extracted with ether (3 x 15 mL). The ether combined layers were washed with brine, dried, and concentrated in vacuo, and the residue was taken up in tetrahydrofuran (3 mL). To this solution was added 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran (0.6 mL). The mixture was stirred at room temperature for 3h. Saturated aqueous ammonium chloride (0.6 mL) was carefully added and the mixture was stirred for 0.5 h and was extracted into ether (3 x 15 mL). The separated organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) yielded 85 mg (20%, from **110**) of **112**.

Method B: To a suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in dry ether (2 mL) was added **110** (253 mg, 0.98 mmol) in ether (5 mL) via cannula. The mixture was stirred at 0°C for 1 h, after which water (80 μL) was added followed by 10% aqueous sodium hydroxide (80 μL) and water (240 μL). The resulting suspension was stirred at room temperature for 0.5 h and filtered over Celite. The filtercake was washed with ether and the ether evaporated. Column chromatography of the residue (hexane-ethyl acetate, 20:1) gave 151 mg (64%) of **112**: IR (neat) 3464, 3457, 2977, 1701, 1686, 1476, 1368, 1362, 1251, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s),

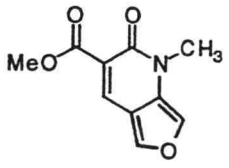
3.19 (3H, s), 4.35 (2H, m), 7.37 (1H, s), 7.39 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 38.9, 53.7, 81.3, 122.7, 130.3, 136.9, 141.0, 155.6; MS (EI) m/z 227 (M^+), 171, 154, 127, 109, 108, 80.1, 66; HRMS *m/z* calcd for $C_{11}H_{17}NO_4$ (M^+): 227.1158. Found: 227.1158.



4-N-*tert*-Butoxycarbonyl-N-methylamino-3-furaldehyde (113). To a solution of oxalyl chloride (0.14 mL, 1.6 mmol) in dry dichloromethane (2 mL) at -78°C was added a solution of dimethylsulfoxide (0.24 mL, 3.4 mmol) in dichloromethane (3 mL). A solution of **112** (279 mg, 1.22 mmol) in dichloromethane (8 mL) was added dropwise over a period of 0.5 h. The mixture was stirred at -78°C for an additional 0.5 h, after which triethylamine (0.85 mL, 6.1 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with aqueous 0.1N hydrochloric acid (10 mL), the layers were separated, and the aqueous layer was back extracted with ether (2 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 240 mg (86%) of **113**: IR (neat) 2978, 1698, 1693, 1597, 1429, 1386, 1363, 1311, 1253, 1162, 1052, 869, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (9H, s), 3.19 (3H, s), 7.45 (1H, bs),7.92 (1H, d, J=1Hz), 9.89 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 37.95, 80.88, 124,4, 128.7, 139.1, 150.5, 154.4, 183.9; MS (CI) m/z 226 (M^{+1}), 210, 198, 170, 133, 101; HRMS *m/z* calcd for $C_{11}H_{15}NO_4$ (M^+): 225.1001. Found: 225.1001.

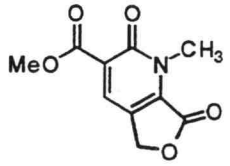


Dimethyl-4-N-*tert*-Butoxycarbonyl-N-methylamino-3-furylidenemalonate (114). To a solution of aldehyde **113** (616 mg, 2.72 mmol) in toluene (30 mL) was added diethyl malonate (0.36 mL, 3.0 mmol) and a catalytic amount of piperidine (50 μL). The mixture was heated to reflux for 3 h and the water formed during the reaction was removed with a Dean-Stark trap. The mixture was cooled to 0°C and diluted with cold aqueous 2N sulfuric acid (30 mL). The layers were separated and the aqueous layer was back extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 860 mg (92%) of **114**: IR (neat) 2978, 1709, 1363, 1270, 1230, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (9H, s), 3.18 (3H, s), 3.81 (3H, s),3.86 (3H, s), 7.36 (1H, s), 7.40 (s, 1H), 7.72 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 39.2, 52.6, 52.7, 81.2, 117.3, 117.5, 124.3, 131.0, 132.0, 137.4, 143.6, 164.4, 166.8; MS (CI) m/z 340 (M^{+1}), 312, 298, 284, 277, 254, 208, 187, 170; HRMS *m/z* calcd for $C_{16}H_{21}NO_7$ (M^+): 339.1319. Found: 339.1319.



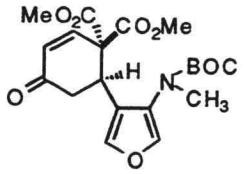
5-Carbomethoxy-6-oxo-7-N-methyl-3,8-pyridinefuran (115). To a solution of (**114**) (30 mg, 0.09 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred at 0°C for 15 min and diluted with cold aqueous sodium bicarbonate (10 mL). The layers were

separated and the aqueous layer was back extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 4:1) afforded 12 mg (62%) of **115**: IR (neat) 2980, 1732, 1648, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 3.89 (3H, s), 3.91 (3H, s), 7.39 (1H, s), 7.85 (1H, s), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.9, 52.5, 112.5, 123.2, 123.8, 131.1, 132.0, 135.1, 140.8, 158.6, 166.4; MS (EI) m/z 207 (M^+), 190, 188, 177, 176, 175.

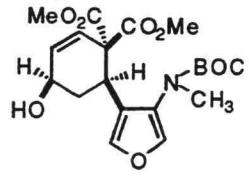


6-Carbomethoxy-5-oxo-4-N-methyl-3,8-pyridinefuranone (116). To a solution of **115** (14 mg, 0.07 mmol) in glacial acetic acid (1 mL) buffered with potassium acetate (30 mg) was added neat bromine (5 μL, 0.07 mmol). The mixture was stirred at 0°C for 15 min and diluted with cold aqueous sodium bicarbonate (10 mL) and chloroform (5 mL). The layers were separated and the aqueous layer was back extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 4:1) afforded 9 mg (60%) of **116**: IR (neat) 2980, 1732, 1648, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 3.89 (3H, s), 3.91 (3H, s), 7.39 (1H, s), 7.85 (1H, s), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.9, 52.5, 112.5, 123.2, 123.8, 131.1, 132.0, 135.1, 140.8, 158.6, 166.4; MS (EI) m/z 207 (M^+), 190, 188, 177, 176, 175: IR (neat) 2980, 1765, 1741, 1715, 1664, 1217; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (3H, s), 3.95 (3H, s), 5.15 (2H, s), 8.11 (1H, s); ^{13}C

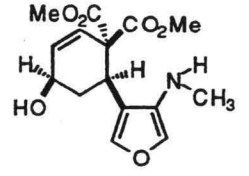
NMR ($CDCl_3$, 75 MHz) δ 29.0, 29.7.53.0, 66.9, 126.3, 126.9, 133.6, 135.6, 159.4, 164.2, 166.8.



4,4-Dicarbomethoxy-5-[3-N-*tert*-butoxycarbonyl-N-methylamino-4-furanyl]cyclohex-2-en-1-one (117). To a solution of **114** (272 mg, 0.80 mmol) in toluene (4 mL) was added 1-methoxy-3-(trimethylsilyloxyl)-1,3-butandiene (0.60 mL, 2.8 mmol) and the mixture was heated in a sealed tube at 140°C for 18 h. After evaporation of the toluene the residue was taken up with a 1:1 mixture of tetrahydrofuran and aqueous 0.1 M hydrochloric acid and was stirred at room temperature for 0.5 h. Saturated aqueous bicarbonate solution was added and the mixture was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 233 mg (75%) of **117**: IR (neat) 2977, 1737, 1434, 1366, 1328,1310, 1257, 1237, 1214, 1154, 1091, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76 (1H, m), 1.44 (9H, s), 3.06 (1H, d, J=6Hz), 3.12 (3H s), 3.60 (3H, s), 3.80 (3H, s), 4.05 (1H, m), 6.19 (1H, d, J=10Hz), 7.10 (1H, s), 7.27 (1H, s), 7.30 (1H, d, J=10Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.6, 28.1, 34.2, 40.6, 53.0, 53.5, 58.0, 80.7, 121.6, 130.6, 137.7, 139.4, 142.9, 154.9, 163.1, 167.4, 168.0, 196.0; MS (EI) m/z 407 (M^+), 308, 307, 248, 216, 159, 109, 94, 85; HRMS *m/z* calcd for $C_{20}H_{25}NO_8$ (M^+): 407.1581. Found: 407.1581.

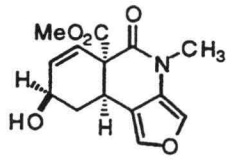


4,4-Dicarbomethoxy-5-[3-N-*tert*-butoxycarbonyl-N-methylamino-4-furanyl]cyclohex-2-en-1-ol (118). To a solution of **117** (16 mg, 0.039 mmol) in tetrahydrofuran (1 mL) was added a 1.0 M solution of L-selectride in tetrahydrofuran (45 μL, 0.041 mmol). The mixture was stirred at 0°C for 15 min, after which saturated aqueous ammonium chloride (2 mL) was added and the mixture was extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 15 mg (93%) of **118**: IR (neat) 2957, 1735, 1700, 1452, 1369, 1264, 1208, 1154, 1091, 1068, 874, 801, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.25-2.38 (m, 2H), 3.14 (s, 3H), 3.58 (s, 3H), 3.65 (m, 1H), 3.71 (s, 3H), 4.12 (m, 1H), 6.09-6.28 (m, 2H), 7.21 (s, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 30.9, 33.7, 52.6, 53.0, 57.9, 64.1, 80.6, 123.9, 125.4, 130.4, 133.2, 136.9, 137.9, 140.0, 155.1, 169.5; MS (EI) m/z 309 (M^+-$C_5H_8O_2$, 65), 246, 216, 119, 103.

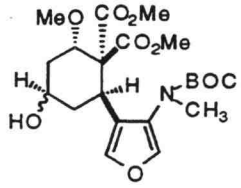


4,4-Dicarbomethoxy-5-[3-N-methyl-4-furanyl]cyclohex-2-en-1-ol (119). To a solution of **118** (52 mg, 0.127 mmol) in dichloromethane (2 mL) was added neat trimethylsilyl iodide (20 μL, 0.13 mmol). After 5 min the mixture was quenched with a few drops of 10% methanolic potassium carbonate. The solvent was evaporated and the residue was taken up with

deuterated chloroform (0.24 mL): IR (neat) 3400, 2977, 1729, 1450, 1444, 1435, 1267, 1245, 916, 880, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (2H, m), 2.45-2.68 (3H, s), 3.50 (3H, s), 3.65 (1H, m), 3.72 (3H, s), 4.12 (1H, m), 6.10 (2H, m),6.95 (1H, s), 7.15 (1H, s).

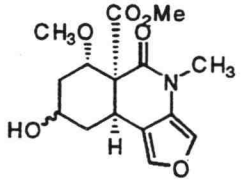


8a-Carbomethoxy-3,4-[3,4-furanyl]-2-N-methyl-6-hydroxy hexahydroisoquinolin-2-one (120). To a solution of the **118** (52 mg, 0.127 mmol) in dichloromethane (2 mL) was added neat trimethylsilyl iodide (20 μL, 0.13 mmol). After 5 min the mixture was quenched with a few drops of methanolic 10% potassium carbonate. The solvent was evaporated and the residue was taken up with chloroform (2 mL) and triethylamine (0.1 mL) and the solution was heated to reflux for 12 h. The mixture was allowed to cool to room temperature and washed with aqueous 0.1 N hydrochloric acid (2 mL). The layers were separated and the aqueous layer back extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 23 mg (63%) of **120**: IR (neat) 3400, 2977, 1733, 1664, 1637, 1221, 1121, 1003, 915, 887, 804, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (2H, m), 2.22-3.26 (3H, s), 3.64 (3H, s), 3.65 (1H, m), 3.68 (3H, s), 4.37 (1H, m), 6.07 (2H, m),7.11 (1H, s), 7.23 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.1, 31.1, 31.7, 36.2, 53.2, 65.7, 115.1, 125.1, 126.3, 129.7, 133.5, 138.0, 166.2, 170.9; MS (EI) m/z 277 (M^+), 232, 218, 200, 176, 91, 69. HRMS *m/z* calcd for $C_{14}H_{15}NO_5$ (M^+): 277.0950. Found: 277.0949.



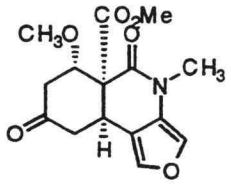
4-4-Dicarbomethoxy-3-methoxy-5-[3-N-*tert*-butoxycarbonyl-N-methylamino-4-furanyl]cyclohexan-1-ol (121). To a solution of **117** (317 mg, 0.77 mmol) in 0.4 M aqueous cerium chloride (1.5 mL) was added sodium borohydride (57 mg, 1.4 mmol) in small portions. The mixture was stirred at room temperature for 15 min, treated with aqueous 0.1 N hydrochloric acid and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 209 mg (66%) of **118** (see above for the preparation of **118** as a single epimer) and 42 mg (12%) of **121**.

121: IR (neat) 3398, 2957, 1758, 1729, 1697, 1435, 1368, 1258, 1205, 1154, 1068, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.55-2.38 (5H, m), 3.31 (6H, m), 3.70 (6H, m), 3.91 (1H, m), 4.02 (1H, m), 6.91 (1H, s), 7.26 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 31.1, 38.9, 39.0, 52.0, 52.0, 57.0, 57.8, 62.1, 65.7, 66.0, 80.0, 125.2, 131.0, 136.8, 139.3, 155.2, 169.4, 169.6; MS (EI) m/z 441 (M^+), 342, 341, 232, 200, 137.



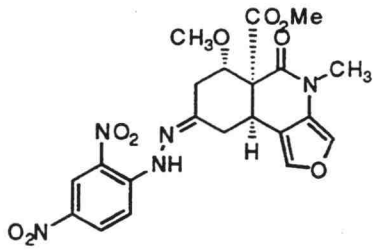
8a-Carbomethoxy-3,4-[3,4-furanyl]-2-N-methyl-8-methoxy-6-hydroxy-1-octahydroisoquinolin-2-one (122). To a solution of **121** (30 mg, 0.09 mmol) in dichloromethane (2.5 mL) was added trifluoroacetic acid (0.5 mL). After 5 min the mixture was quenched with aqueous sodium

bicarbonate (5 mL). The resulting mixture was diluted with tetrahydrofuran (3 mL) and stirred at room temperature for 0.5 h. The layers were separated and the aqueous layer was back extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 12.1 mg (43%) of **122**: IR (neat) 3437, 2946, 1743, 1672, 1639, 1456, 1437, 1358, 1282, 1230, 1183, 1109, 1083, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (m, 1H) 1.38 (m, 1H), 1.55 (m, 1H), 2.05 (m, 1H); 3.26 (s, 3H), 3.33 (s, 3H), 3.47 (m, 1H), 3.65 (s, 3H), 3.70 (m, 1H), 4.0 (m, 1H), 4.50 (m, 1H), 7.06 (d, J=1.5Hz, 1H), 7.20 (d, J=1.5 Hz, 1H); MS (EI) m/z 309 (M^+), 277, 251, 250, 219, 218, 208, 176, 147, 85.9, 83, 69.



8a-Carbomethoxy-3,4-[3,4-furanyl]-2-N-methyl-8-methoxy-1-octahydroisoquinolin-2,6-one (123). To a cold (0°C) suspension of pyridinium chlorochromate (15 mg, 0.07 mmol) and sodium acetate (20 mg) in dichloromethane (1 mL) was added a solution of **122** (12 mg, 0.038 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 3 h, after which the mixture was diluted with ether (5 mL) and filtered over Celite. The filtercake was washed with ether and the filtrate was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 10 mg (83%) of **123**: IR (neat) 2925, 1743, 1725, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21-2.50 (2H, m), 2.80 (2H, m), 3.27 (3H, s), 3.32 (3H, s), 3.68 (3H, s), 4.11 (1H, dd, J=18.0, 6.0 Hz),

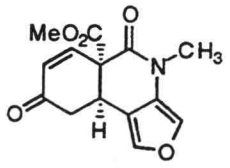
4.71 (1H, m), 7.13 (1H, s), 7.22 (1H, s); MS (EI) m/z 307 (M^+), 275, 248, 216, 208, 176.1, 150, 134, 84, 77.



8a-Carbomethoxy-3,4-[3,4-furanyl]-2-N-methyl-8-methoxy-6-[2,4-dinitrophenylhydrazinyl]-1-octahydroisoquinolin-2-one (124). To a solution of **123** (2.8 mg, 0.009 mmol) in ethanol (0.2 mL) was added 2,4-dinitrophenylhydrazine (2 mg, 0.01 mmol) and acetic acid (2 μL). The mixture was stirred for 4 h and the solvent was evaporated. Chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 1 mg (22%) of **124**: IR (neat) 2915, 1742, 1671, 1615, 1612, 1585, 1506, 1460, 1340, 1109, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (m, 1H), 2.32 (m, 1H), 2.51 (m, 1H), 2.75 (m, 1H), 3.40 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 3.92 (m, 1H), 4.75 (m, 1H), 7.15 (s, 1H), 7.28 (s, 1H), 7.95 (d, J=1Hz, 10H), 8.30 (d, J=1Hz, 10H), 9.14 (d, J=1Hz, 1H).

Compound **124** crystallized in the triclinic space group P-1 with a=11.975 (3) Å, b=12.399 (4) Å, c=8.308 (6) Å, a=91.23 (6)°, β=95.44 (7)°, γ=117.24 (5)°, V=1077.8 (8) $Å^3$, Z=2, D_{calc}=1.19 g/cm^3. There were 3381 reflections measured in the range of 2.0° < 2Θ < 45° using a Rigaku AFC6R diffractometer with graphite monochromated Mo Kα radiation (λ=0.71069 Å). Of the 1998 unique reflections 1000 were considered observed with F > 3 σ(F). The structure was solved with direct methods (SHELXS) and refined using a full matrix least squares routine with anisotropic temperature factors

for all oxygen and nitrogen atoms and calculated hydrogen atom positions. The final discrepancy indices were R=0.078 and R_w=0.084.

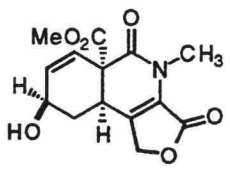


8a-Carbomethoxy-3,4-[3,4-furanyl]-2-N-methyl-6-one-1-hexahydroisoquinolin-2,6-one (125).

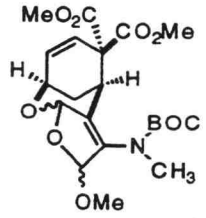
Method A.: To a cold (0°C) suspension of pyridinium chlorochromate (20 mg, 0.06 mmol) and sodium acetate (20 mg) in dichloromethane (1 mL) was added a solution of **120** (6 mg, 0.029 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 3 h, after which it was diluted with ether (5 mL) and filtered was over Celite. The filtercake was washed with ether and the filtrate washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 7 mg (88%) of **125**.

Method B.: To a solution of **123** (2 mg, 0.006 mmol) in toluene (2 mL) was added *p*-toluenesulfonic acid (ca. 0.2 mg) and the mixture was heated to reflux for 12 h. The mixture was allowed to cool to room temperature and was washed with 2 mL of aqueous sodium bicarbonate. The layers were separated and the aqueous layer was back extracted with ether (3 x 2 mL). The combined organic layers were dried and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 1 mg (55%) of **125**: IR (neat) 1739, 1672, 1638, 1244, 1150, 1091, 1033, 884, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 2H), 3.25 (3H, s), 3.83 (3H, s), 4.15 (1H, m), 6.13 (1H, d, J=10Hz), 6.82 (1H, d, J=10Hz), 7.15 (1H, d, J=1Hz),7.18 (1H, d, J=1Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.3, 33.5, 34.2,

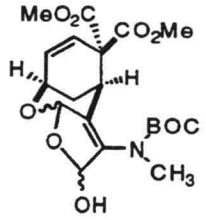
39.7, 53.7, 65.7, 113.7, 125.9, 130.7, 138.4, 143.2, 166.1, 169.6, 195.0; MS (EI) m/z 277 (M^+), 216, 188, 158, 123; HRMS *m/z* calcd for $C_{14}H_{13}NO_5$ (M^+): 275.0794. Found: 275.0794.



8a-Carbomethoxy-3,4-[3,4-furanonyl]-2-N-methyl-6-hydroxy hexahydroisoquinolin-2-one (129). To a solution **120** (15 mg, 0.05 mmol) in methanol (2 mL) was added solid sodium bicarbonate (5 mg) and N-bromosuccinimide (9 mg, 0.05 mmol). The methanol was evaporated after 5 min and the residue was taken up with chloroform (3 mL). The resulting solution was washed with aqueous sodium thiosulfate, dried over sodium sulfate and heated at reflux with a catalytic amount of *p*-toluenesulfonic acid for 4 h. The mixture was allowed to cool to room temperature, washed with aqueous sodium bicarbonate (2 mL), dried over sodium sulfate, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 8.4 mg (53%) of **129**: IR (neat) 3396, 2977, 1761, 1736, 1678, 1221, 1058, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (2H, m), 3.45 (3H, s), 3.70 (1H, m), 3.76 (3H, s), 4.32 (1H, m), 4.90 (2H, m), 6.07 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.9, 31.9, 33.2, 53.7, 55.1,64.6, 68.0, 125.8, 126.2, 133.8, 139.4, 166.3, 166.4, 169.8; MS (EI) m/z 293 (M^+), 248, 234, 216, 160, 77; HRMS *m/z* calcd for $C_{14}H_{15}NO_6$ (M^+): 293.0899. Found: 293.0899.

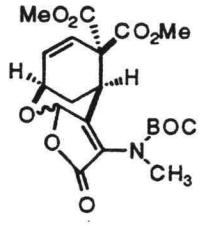


9,9-Dicarbomethoxy-6N-*tert*-butoxycarbonyl-N-methylamino--5-methoxytricyclo-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (130). To a solution of **118** (48 mg, 0.12 mmol) in methanol (3 mL) was added sodium bicarbonate (10 mg) and N-bromosuccinimide (23 mg, 0.13 mmol). The mixture was stirred at room temperature for 5 min and the solvent was evaporated. The residue was taken up with aqueous sodium thiosulfate (5 mL) and the mixture was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 51 mg (99%) of **130**: IR (neat) 2959, 1737, 1698, 1437, 1153, 998 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.11 (2H, m), 2.97-3.11 (3H, m), 3.66-3.78 (6H, m), 4.38 (1H, m), 5.78-6.34 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 31.5, 31.7, 33.9, 36.0, 36.8, 52.9, 53.1, 54.1, 54.7, 57.6, 57.8, 64.9, 65.4, 81.0, 99.4, 100.4,106.2, 106.9, 127.9, 128.1, 128.7, 129.0, 135.2, 153.7, 168.2, 169.0, 169.7; MS (EI) m/z 439 (M^+), 308, 280, 279, 279, 278, 264. HRMS *m/z* calcd for $C_{21}H_{29}NO_9$ (M^+): 439.1843. Found: 439.1843.



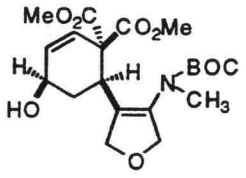
9,9-Dicarbomethoxy-6-N-*tert*-butoxycarbonyl-N-methylamino-5-hydroxytricyclo-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (131). To a solution of **118** (52 mg, 0.13 mmol) in "wet"

dichloromethane (3 mL) was added solid sodium bicarbonate (ca. 10 mg) and N-bromosuccinimide (24 mg, 0.14 mmol). The mixture was stirred at room temperature for 5 min after which aqueous sodium thiosulfate (5 mL) was added and the mixture was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 46 mg (85%) of **131**: IR (neat) 3330, 2959, 1737, 1714, 1262, 1153, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.11 (2H, m), 3.04 (3H, m), 3.75 (6H, m), 3.85 (1H, m), 4.95 (1H, m), 5.25-6.10 (2H, m), 6.20 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 28.2, 29.5, 29.6, 31.4, 34.0, 36.6, 53.0, 53.2, 57.7, 60.3, 81.5, 99.5, 100.4, 128.0, 129.0, 137.0, 171.1, 177.6.

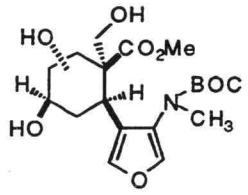


9,9-Dicarbomethoxy-6-N-*tert*-butoxycarbonyl-N-methylamino-5-oxotricyclo-2,4-dioxa[6.3.1.$0^{3,7}$]dodeca-6,10-diene (132). To a cold (0°C) suspension of pyridinium dichromate (177 mg, 0.45 mmol) and crushed 4 Å molecular sieves (100 mg) in dichloromethane (3 mL) was added hemiacetal **131** (67 mg, 0.16 mmol) in dichloromethane (4 mL). The mixture was stirred at room temperature for 3 h, after which it was diluted with ether (5 mL) and filtered over Celite. The filtercake was washed with ether and the filtrate was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 41 mg (60%) of **132**: IR (neat) 2959, 1789, 1739, 1698, 1436, 1366, 1229, 1154, 1091, 1068, 942 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 2.18

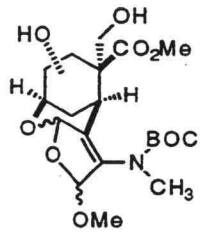
(2H, m), 3.05 (3H, s), 3.75 (6H, m), 4.10 (1H, m), 4.50 (1H, m), 5.93 (1H, m), 6.30 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 31.1, 34.7, 35.4, 53.4, 53.5, 57.5, 60.4, 65.3, 81.9, 94.6, 127.3, 129.5, 153.6, 166.9, 167.6, 168.9; MS (EI) m/z 422 (M^{-1+}), 421, 321, 277, 217, 152, 136, 124; HRMS *m/z* calcd for (M^+): 423.1529. Found: 423.1528.



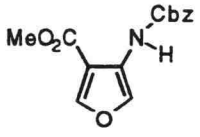
4,4-Dicarbomethoxy-5-[3-N-*tert*-butoxycarbonyl-N-methylamino-4-dihydrofuranyl]cyclohex-2-en-1-ol (134). To a solution of **131** (10 mg, 0.02 mmol) in glacial acetic acid (0.3 mL) was added sodium cyanoborohydride (15 mg, 0.24 mmol) in small portions. The mixture was stirred at room temperature for 0.5 h, treated with aqueous 1 N potassium hydroxide (3 mL), and extracted with ether (4 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 9 mg (93%) of **134**: IR (neat) 2957, 1735, 1706, 1702, 1452, 1259, 1155, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s), 2.11 (1H, m), 2.30 (1H, m), 2.92 (3H, s), 3.35 (1H, m), 3.71 (3H, s), 3.72 (3H, s), 4.31 (1H, m), 4.40 (1H, m), 4.55 (1H, m), 4.75 (1H, m), 5.99 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 35.1, 35.1, 52.9, 57.1, 65.3, 71.6, 75.0, 80.6, 125.0, 126.3, 131.5, 133.8, 164.7, 169.5.



4-Carbomethoxy-4-hydroxymethyl-3-hydroxy-5-[3-N-*tert*-butoxycarbonyl-N-methylamino-4-furanyl]cyclohexan-1-ol (135). To a solution of **118** (90 mg, 0.22 mmol) in tetrahydrofuran (1 mL) was added 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran (0.7 mL). The mixture was heated at reflux for 0.5 h, cooled to 0°C and aqueous 1M sodium hydroxide (1 mL) followed by 30% Hydrogen peroxide (0.3 mL) were added. The resulting mixture was stirred at 0°C for 1.5 h, diluted with water (6 mL) and extracted into ether and ethyl acetate (5 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8 to ethyl acetate-methanol 9:1) afforded 10 mg (11%) of recovered starting material and 28 mg (33%) of **135**: IR (neat) 3330, 2932, 1709, 1660, 1438, 1368, 1343, 1251, 1197, 1156, 1063, 1043, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.95 (2H, m), 2.20 (2H, m), 3.16 (3H, s), 3.65-3.80 (5H, m), 3.85 (1H, m), 4.01 (1H, m), 4.22 (1H, m,), 4.59 (m, 1H), 7.39 (s, 1H),7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 38.9, 39.1, 39.4, 52.0, 54.9, 65.7, 65.8, 66.4, 81.9, 123.0, 130.7, 137.3, 137.5, 142.0, 156.4, 173.0; MS (EI) m/z 309 (M^+), 326, 300, 299, 268, 204, 115; HRMS *m/z* calcd for $C_{19}H_{29}NO_8$ (M^+): 399.1893. Found: 399.1892.

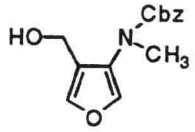


Acetal 138. To a solution of **135** (18 mg, 0.045 mmol) in methanol (2 mL) was added sodium bicarbonate (10 mg) and N-bromosuccinimide (9 mg, 0.05 mmol). The mixture was stirred at room temperature for 5 min and the solvent was evaporated. Column chromatography of the residue (hexane-ethyl acetate, 2:8 to ethyl acetate-methanol 9:1) afforded 16 mg (83%) of **138**: IR (neat) 3379, 2937, 1704, 1661, 1437, 1369, 1337, 1250, 1208, 1157, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s,), 2.11-2.42 (3H, m), 3.05 (3H, m), 3.45 (5H, m), 3.75 (3H, s), 3.78 (1H, m,), 4.10 (2H, m), 4.41 (1H, m),5.45 (2H, m), 5.67 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 35.9, 39.1, 39.4, 52.0, 53.1, 54.4, 54.5, 54.7, 55.0, 66.1, 66.4, 82.0, 107.1, 125.1, 138.0, 139.8, 173.5; MS (EI) m/z 429 (M^+), 373, 330, 329, 312, 300, 298, 270, 268, 238, 220, 176, 154.



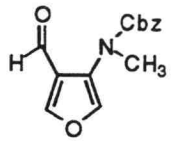
Methyl-4-N-Carbobenzyloxyamino-3-furoate (141). To a solution of 4-carbomethoxy-3-furoic acid[42] (2.40 g, 14 mmol) in dry toluene (7 mL) was added oxalyl chloride (1.2 mL, 15 mmol) via syringe. The mixture was refluxed for 1 h and the toluene was removed in vacuo. The residue was taken up in ether (40 mL) and cooled to 0°C. A solution of sodium azide (4.0 g, 61 mmol) in water (20 mL) was added and the resulting two phase mixture was stirred at 0°C for 2 h after which the layers were separated and the aqueous layer was back extracted with ether (3 x 40 mL). The combined

organic layers were washed with brine and aqueous sodium bicarbonate, dried, and concentrated in vacuo. The crude acyl azide was taken up in toluene (40 mL) and benzyl alcohol (1.6 mL, 16 mmol) and the solution was refluxed for 3 h. Evaporation of the solvent and recrystallisation of the residue from hexane afforded 3.91 g (71%) of **141** as a colorless solid; mp 65°C: IR (KBr) 3390, 2996, 1731, 1717, 1561, 1513, 1263, 1042, 742, 698 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (3H, s), 5.21 (2H, s), 7.38 (5H, m), 7.84 (1H, s), 7.97 (1H, s), 8.15 (1H, bs); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.6, 67.3, 110.0, 124.7, 128.1, 128.3, 128.5, 131.9, 135.8, 146.3, 153.2, 164.2; MS (EI) m/z 275 (M^+), 231, 136, 92, 91; HRMS *m/z* calcd for $C_{14}H_{13}NO_5$ (M^+): 275.0794. Found: 275.0793. Anal. Calcd for $C_{14}H_{13}NO_5$ C; 61.09; H; 4.76; N; 5.09. Found: C; 61.12; H; 4.63; N; 5.17.



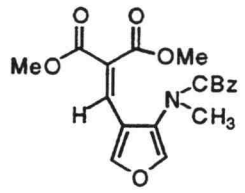
4-N-Carbobenzyloxy-N-methylamino-3-furanmethanol (142). To a suspension of 60% sodium hydride dispersion (460 mg, 12 mmol) in dry tetrahydrofuran (20 mL) was added a solution of **141** (1.60 g, 5.8 mmol) in tetrahydrofuran (30 mL) via cannula. The mixture was cooled to 0°C and iodomethane (2 mL, 60 mmol) was added via syringe. The mixture was stirred at room temperature for 5 h, after which aqueous 3 N sodium hydroxide (50 mL) was added and the mixture was stirred for 4 h at room temperature. The mixture was diluted with ether and acidified with aqueous 10% sulfuric acid. The layers were separated and the aqueous layer was back extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. The residual crude acid was taken up in tetrahydrofuran (50 mL), cooled to 0°C, and reduced with 1.0 M borane-

tetrahydrofuran complex in tetrahydrofuran (10 mL). The mixture was stirred at room temperature for another 3 h. Aqueous ammonium chloride (30 mL) was carefully added and the mixture was stirred for 0.5 h, after which it was extracted with ether (3 x 50 mL). The separated organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) yielded 1.21 g (77%) of **142**: IR (neat) 3300, 2988, 1705, 1476, 1163, 1013, 759, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 4.35 (d, 2H, J=6Hz), 5.20 (s, 2H),7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.9, 53.9, 62.6, 70.8, 128.1, 128.3, 128.6, 136.0, 137.1, 137.8, 141.0, 156.2; MS (EI) m/z 261 (M^+), 108, 92, 91, 64; HRMS *m/z* calcd for $C_{14}H_{15}NO_4$ (M^+): 261.1001. Found: 261.1001; Anal. calcd for $C_{14}H_{15}NO_5$ C; 64.36; H; 5.79; N; 5.36. Found: C; 64.19; H; 5.64; N; 4.98.

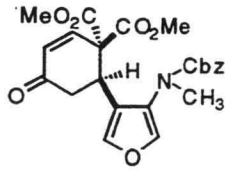


4-N-Carbobenzyloxy-N-methylamino-3-furaldehyde (143). To a solution of oxalyl chloride (4.9 mL, 30 mmol) in dry dichloromethane (4 mL) at -78°C was added a solution of dimethyl sulfoxide (2.8 mL, 69 mmol) in dichloromethane (5 mL). A solution of **142** (7.50 g, 29 mmol) in dichloromethane (40 mL) was added dropwise over a period of 0.5 h. The mixture was stirred at -78°C for an additional 0.5 h, after which triethylamine (20 mL, 150 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with aqueous 10% sulfuric acid (40 mL), the layers were separated, and the aqueous layer was back extracted with ether (2 x 30 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 0.50g (7%) of recovered **142** and 6.0 g

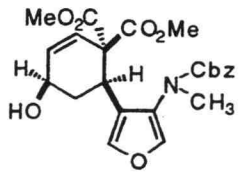
(87%) of **143**: IR (neat) 2951, 1721, 1715, 1705, 1693, 1597, 1545, 1447, 1369, 1216, 1162, 870, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.24 (3H, s), 5.13 (2H, s), 7.30 (6H, m), 7.97 (1H, s), 9.85 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 67.7, 124.4, 127.8, 128.0, 128.4, 136.1, 139.8, 151.2, 155.4, 183.6; MS (EI) m/z 259 (M^+), 92, 91, 65; Anal. Calcd for $C_{14}H_{13}NO_4$ C; 64.86; H; 5.05; N; 5.40. Found: C; 64.81; H; 5.48; N; 5.02.



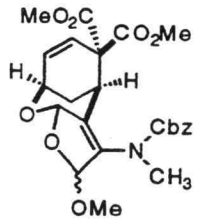
Dimethyl-4-N-Carbobenzyloxy-N-methylamino-3-furylidene malonate (144). To a solution of **143** (478 mg, 1.80 mmol) in toluene (30 mL) was added diethyl malonate (0.30 mL, 3.6 mmol) and a catalytic amount of piperidine (50 μL). The mixture was heated at reflux for 3 h and the water produced during the reaction was removed with a Dean-Stark trap. The mixture was cooled to 0°C and diluted with aqueous cold 2N sulfuric acid (30 mL). The layers were separated and the aqueous layer was back extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 545 mg (80%) of **144**: IR (neat) 2964, 1719, 1604, 1438, 1363, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.74 (3H, s), 3.79 (3H, s), 5.12 (2H, s), 7.28 (1H, s), 7.43 (1H, s), 7.74 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.8, 52.5, 52.7, 67.8, 125.1, 127.9, 128.4, 131.2, 142.0, 143.9, 155.4, 164.2; MS (EI) m/z 373 (M^+), 180, 120, 92, 91, 66, 65; HRMS *m/z* calcd for $C_{19}H_{19}NO_7$ (M^+): 373.1161. Found: 373.1161. Anal. calcd for $C_{19}H_{19}NO_7$ C; 61.12; H; 5.13; N; 3.75. Found: C; 61.46; H; 5.11; N; 3.84.



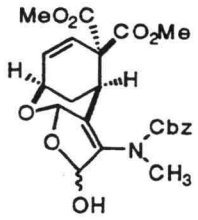
4,4-Dicarbomethoxy-5-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]cyclohex-2-en-1-one (145). To a solution of **144** (463 mg, 1.24 mmol) in toluene (4 mL) was added 1-methoxy-3-(trimethylsilyloxyl)-1,3-butadiene (0.60 mL, 2.8 mmol) and the mixture was heated in a sealed tube at 140°C for 18 h. After evaporation of the toluene the residue was taken up with a 1:1 mixture of tetrahydrofuran and 0.1 M hydrochloric acid (50 mL) and was stirred at room temperature for 0.5 h. Saturated aqueous bicarbonate (30 mL) was added and the mixture was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 423 mg (83%) of **145**: IR (neat) 2954, 1749, 1737, 1705, 1694, 1643, 1436, 1351, 1271, 1257, 1217, 1154, 1094, 1054, 915, 817, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (m, 1H), 2.96 (m, 1H), 3.20 (s, 3H), 3.52 (s, 3H), 3.77 (s, 3H), 4.02 (m, 1H), 5.19 (m, 2H), 6.19 (d, J=10Hz, 1H), 7.10 (s, 1H), 7.11 (s, 1H), 7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.2, 39.2, 40.8, 53.1, 53.5, 53.6, 58.3, 67.7, 121.8, 127.0, 128.1, 128.5, 130.7, 136.2, 137.9, 139.8, 143.0, 155.8, 167.4, 168.1, 196.0; MS (EI) m/z 441 (M^+), 382, 338, 306, 94, 91; HRMS *m/z* calcd for $C_{23}H_{23}NO_8$ (M^+): 441.1424. Found: 441.1423.



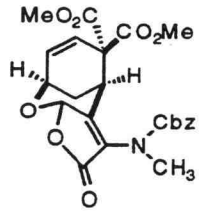
4,4-Dicarbomethoxy-5-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]cyclohex-2-en-1-ol (146). To a cold (-78°C) solution of **145** (740 mg, 1.63 mmol) in tetrahydrofuran (18 mL) was added a 1.0 M solution of L-selectride in tetrahydrofuran (2 mL). The mixture was stirred at -78°C for 30 min, after which it was allowed to warm to room temperature and saturated aqueous ammonium chloride (20 mL) was added. The mixture was then extracted with ether (3 x 20 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8) afforded 720 mg (96%) of **146**: IR (neat) 2953, 1733, 1706, 1452, 1336, 1391, 1354, 1326, 1208, 1106, 1091, 1106, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (2H, m), 3.22 (3H, s), 3.52 (3H, s), 3.67 (3H, s), 3.87 (1H, m), 4.30 (1H, m), 5.10 (2H, m), 6.10 (2H, m), 7.30 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.0, 34.2, 39.0, 52.5, 52.9, 58.2, 64.3, 67.5, 123.8, 125.4, 128.1, 128.4, 137.6, 140.4, 155.8, 196.5; MS (EI) m/z 443 (M^+), 340, 308, 306, 92, 91; HRMS *m/z* calcd for $C_{23}H_{25}NO_8$ (M^+): 443.1580. Found: 443.1580. Anal. calcd for $C_{23}H_{25}NO_8$ C; 62.30; H; 5.68; N; 3.16. Found: C; 62.15; H; 5.44; N; 2.97.



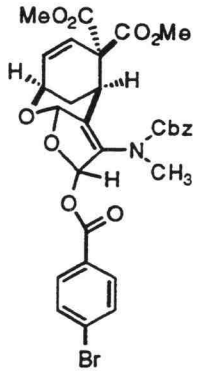
9,9-Dicarbomethoxy-6-N-carbobenzyloxy-N-methylamino-5-methoxytricyclo-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (147). To a solution of **146** (108 mg, 0.24 mmol) in methanol (3 mL) was added sodium bicarbonate (20 mg) and N-bromosuccinimide (45 mg, 0.25 mmol). The mixture was stirred at room temperature for 5 min and the solvent was evaporated. The residue was taken up with aqueous sodium thiosulfate (10 mL) and the mixture was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 90 mg (75%) of **147**: IR (neat) 2955, 1720, 1437, 1394, 1331, 1267, 1165, 968, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (1H, m), 2.01 (1H, m), 3.03 and 3.13 (3H, 2s), 3.30 and 3.48 (3H, 2 s,), 3.72 (6H, m), 3.85 (1H, m), 4.35 (1H, m), 5.18 (2H, m), 5.74 (1H, m), 5.94 (1H, m), 6.20 (2H, m), 7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.1, 54.4, 54.6, 57.6, 57.8, 64.9, 65.4, 67.7, 99.6, 100.4, 105.8, 107.1, 127.9, 128.0, 128.1, 128.3, 128.5, 128.7, 129.0, 132.3,134.1, 135.9, 154.5, 167.0, 168.1, 196.0, 196.6; MS (EI) m/z 473 (M$^+$), 382, 383, 214, 169, 91, 91, 84; HRMS *m/z* calcd for $C_{24}H_{27}NO_9$ (M$^+$): 473.1686. Found: 473.1685.



9,9-Dicarbomethoxy-6-N-carbobenzyloxy-N-methylamino-5-hydroxytricyclo-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (148). To a solution of **146** (184 mg, 0.41 mmol) in "wet" dichloromethane (6 mL) was added sodium bicarbonate (10 mg) and N-bromosuccinimide (75 mg, 0.42 mmol). The mixture was stirred at room temperature for 5 min, after which aqueous sodium thiosulfate (5 mL) was added. The mixture was extracted with ether (4 x 20 mL) and the combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 130 mg (68%) of **148**: IR (neat) 3404, 2955, 1733, 1437, 1393, 1332; 1266, 1231, 1210, 1074, 1007, 873, 763, 733, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (m, 2H), 3.11 (3H, s), 3.54 (3H, s), 3.80 (1H, s), 4.32 (1H, m), 4.75 (3H, s), 5.15 (2H, m), 6.01 (4H, m), 7.35 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.0, 36.4, 36.6, 52.9, 53.2, 57.7, 60.4, 65.0, 65.5, 67.9, 68.1, 99.7, 100.1, 101.2, 127.9, 128.1, 128.4, 128.6, 128.9, 129.1, 134.9, 135.7, 155.1, 168.0, 169.2; MS (EI) m/z 459 (M^+), 306, 274, 216, 186, 105, 91, 77; HRMS *m/z* calcd for $C_{23}H_{25}NO_9$ (M^+): 459.1529. Found: 459.1528.



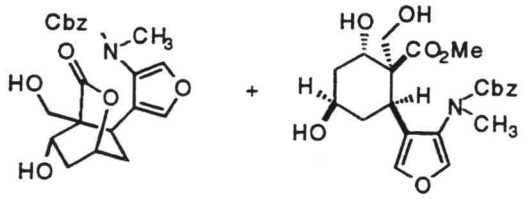
9,9-Dicarbomethoxy-6-N-carbobenzyloxy-N-methylamino-5-oxo-tricyclo-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (149). To a cold (0°C) suspension of pyridinium dichromate (80 mg, 0.18 mmol) and crushed 4 Å molecular sieves (50 mg) in dichloromethane (1.5 mL) was added a solution of hemiacetal **148** (28 mg, 0.06 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 3 h, after which it was diluted with ether (5 mL) and filtered over Celite. The filtercake was washed with ether and the filtrate was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 26 mg (92%) of **149**: IR (neat) 2972, 1786, 1732, 1326, 1267, 1230, 1150, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (2H, m), 3.14 (3H, s), 3.62 (3H, s), 3.77 (3H, s), 4.01 (1H, s), 4.40 (1H, s), 5.15 (2H, m), 5.89 (1H, s), 6.25 (2H, m), 7.34 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.4, 34.8, 35.4, 53.3, 53.4, 57.5,65.4, 68.4, 94.6, 127.3, 127.8, 128.4, 128.6,129.4, 135.5, 154.1, 154.3, 166.8, 167.4, 168.8; MS (EI) m/z 457 (M^+), 366, 322, 278, 158, 91, 65; HRMS *m/z* calcd for $C_{23}H_{23}NO_9$ (M^+): 457.1373. Found: 457.1372.



9,9-Dicarbomethoxy-6-N-carbobenzyloxy-N-methylamino-5-bromobenzyloxy-2,4-dioxa[6.3.1.0^{3,7}]dodeca-6,10-diene (150). To a solution of **148** (5 mg, 0.01 mmol) in dichloromethane (5 mL) was added *p*-bromobenzoyl chloride (10 mg, 0.045 mmol), triethylamine (10 μL, 0.1 mmol) and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 15 h, after which aqueous 0.1 N hydrochloric acid (10 mL) was added and the mixture was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 3 mg (46%) of **150** as a yellow solid: IR (KBr) 2920, 1733, 1269, 718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (2H, m), 3.16 (3H, s), 3.50 (3H, s), 3.75 (3H, s), 3.92 (1H, m), 4.40 (1H, m), 5.15 (2H, m), 5.91-6.40 (4H, m), 7.06 (1H, s), 7.34 (5H, m), 7.55 (2H, d, J=8Hz), 7.84 (2H, d, J=8Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 36.4, 36.6, 52.9, 53.2, 57.7, 60.4, 65.0, 65.5, 67.9, 68.1, 99.7, 100.1, 101.2, 127.9, 128.1, 128.4, 128.6, 128.9, 129.1, 134.9, 135.7, 155.1, 168.0, 169.2, 172.9.

Compound **150** crystallized in the monoclinic space group C2/C with a=26.140 (5) Å, b=10.389 (2) Å, c=24.814 (5) Å, β=117.94° (3), V=5953.23 Å^3, Z=8, D_{calc}=1.434 g/cm^3. All 4454 non equivalent reflections in the range of 3.5° < 2Θ < 95° were measured on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å). The structure was solved by

direct methods (SHELXTL) using 3411 unique reflections of which 2253 were considered observed with $F > 4\ \sigma(F)$. Full matrix least squares refinement with anisotropic temperature factors for all non-hydrogen atoms and calculated hydrogen atom positions led to the final discrepancy indices of R=0.054 and $_wR$ =0.051.

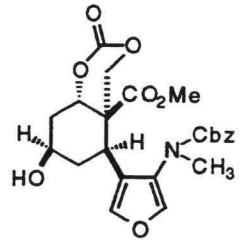


1-Hydroxymethyl-2-oxo-3-oxa-6-hydroxy-7-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]bicyclo[2.2.2]octane (146) and 4-Carbomethoxy-4-hydroxymethyl-3-hydroxy-5-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]cyclohexan-1-ol (154). To a cold (-78°C) solution of **146** (601 mg, 1.36 mmol) in tetrahydrofuran (60 mL) was slowly added 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran (10 mL). The mixture was allowed to warm to room temperature and was stirred for 12 h. The mixture was cooled to 0°C and aqueous 3M sodium hydroxide (3 mL), followed by 30% hydrogen peroxide (0.5 mL) were added. The resulting mixture was stirred at 0°C for 3 h and poured into aqueous ammonium chloride (60 mL). The mixture was extracted with ether (4 x 15 mL) and ethyl acetate (6 x 15 mL)and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 2:8 to ethyl acetate-methanol 9:1) afforded 123 mg (23%) of **154** and 251 mg (43%) of **151**.

154: IR (neat) 3448, 3434, 2945, 1727, 1709, 1686, 1471, 1455, 1436, 1394, 1354, 1322, 1212, 1153, 1082, 1022, 914, 754, 699, 615, 604 cm^{-1}; ^1H

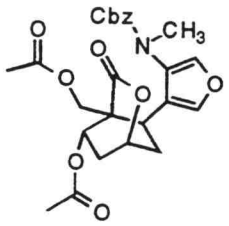
NMR (300 MHz, $CDCl_3$) δ 1.59 (1H, m), 1.85 (1H, m), 2.38 (1H, m), 2.42 (1H, m), 3.19 (3H, s), 3.60 (2H, m), 3.85 (1H, m), 4.39 (1H, m), 4.67 (1H, m), 5.19 (2H, m), 7.35 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.7, 36.1, 39.3, 49.6, 57.9, 60.4, 65.3, 67.6, 73.3, 123.8, 128.3, 128.5, 136.3, 137.5, 139.9, 155.6, 171.2; MS (EI) m/z 401 (M^+), 342, 134, 91; HRMS *m/z* calcd for $C_{21}H_{23}NO_7$ (M^+): 401.1474. Found: 401.1474.

151: IR (neat) 3402, 3395, 3391, 3368, 2945, 1694, 1444, 1438, 1394, 1352, 1211, 1160, 1088, 1048,764, 735, 699, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (2H, m), 2.01 (2H, m), 3.19 (3H, s), 3.65 (5H, m),3.85 (1H, m), 4.45 (1H, m), 4.91 (1H, m), 5.20 (2H, m), 7.31 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 18.8, 20.9, 29.6, 38.6, 50.3, 60.3, 62.4, 67.8, 69.5, 123.1, 128.01, 128.1, 128.5, 130.0, 135.9, 137.0, 139.8, 141.8, 155.7, 171.1; MS (EI) m/z 433 (M^+), 404, 342, 91; HRMS *m/z* calcd for $C_{22}H_{27}NO_8$ (M^+): 433.1737 Found: 433.1736.



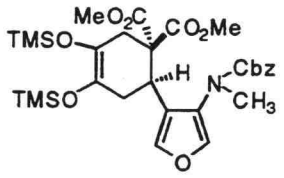
4-Carbomethoxy-4-hydroxymethyl-3-hydroxy-5-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]cyclohexane-1-ol (153). To a solution of triol **151** (3 mg, 0.006 mmol) in tetrahydrofuran (1 mL) was added triethylamine (3 μL, 0.03 mmol) and triphosgene (3 mg, 0.011 mmol). The mixture was heated to reflux for 20 min after which the mixture was allowed to cool to room temperature and water (3 mL) was added and the mixture extracted with ether (3 x 3 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column

chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 1.6 mg (56%) of **153**: IR (neat) 3396, 2945, 1772, 1731, 1707, 1450, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90-2.61 (5H, m), 3.21 (3H, s), 3.70 (3H, s), 4.12 (1H, m), 4.42 (2H, m), 4.80-5.25 (3H, m), 7.33 (1H, s), 7.34 (7H, m), 7.44 (1H, s).



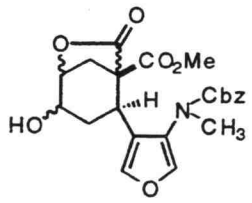
6-Acetoxy-1-acetoxymethyl-2-oxo-3-oxa-7-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]-bicyclo[2.2.2]octane (155). To a solution of **154** (20 mg, 0.05 mmol) in dichloromethane (2 mL) was added acetic anhydride (10 mg, 0.10 mmol), triethylamine (20 μL, 0.2 mmol) and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 5 h, after which aqueous 0.1 N hydrochloric acid (10 mL) was added and the mixture was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 16 mg (66%) of **155**: IR (neat) 2945, 1751, 1708, 1450, 1432, 1364, 1319, 1239, 1151,1125, 1083, 1046, 599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (1H, m), 1.69 (1H, m), 1.81 (1H, m), 2.03 (3H, s), 2.07 (3H, s), 2.65 (1H, m), 3.28 (3H, s), 3.95 (1H, m), 4.12 (1H, m), 4.65 (1H, m), 4.92 (1H, m), 5.20 (2H, m), 5.26 (2H, m), 7.36 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 22.0, 33.7, 36.1, 39.3, 49.6, 57.9, 60.4, 65.3, 67.6, 73.3, 123.8, 128.3, 128.5, 136.3, 137.5, 139.9, 155.6, 169.6, 170.5, 171.2; MS (EI) m/z 485 (M^+), 338, 248, 91; HRMS *m/z* calcd for $C_{25}H_{27}NO_9$ (M^+): 485.1686. Found: 485.1685.

Compound **155** crystallized in the orthorhombic space group P2(1)2(1)2(1) with a=15.779 (3) Å, b=8.880 (2) Å, c=17.227 (3) Å, V=2413.80 $Å^3$, Z=4, D_{calc}=1.434 g/cm^3. All 1792 non equivalent reflections in the range of $3.5° < 2\Theta < 95°$ were measured on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å). The structure was solved with direct methods (SHELXTL) using 1482 unique reflections with $F > 4\sigma(F)$. Full matrix least squares refinement with anisotropic temperature factors for all non-hydrogen atoms and calculated hydrogen atom positions led to the final discrepancy indices of R=0.032 and $_wR$ =0.030.

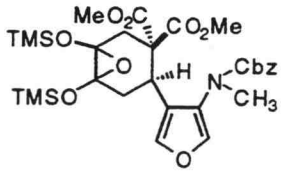


1,2-Bistrimethylsilyloxyl-4,4-dicarbomethoxy-5-[3-N-carbo benzyloxy-N-methylamino-4-furanyl]cyclohexene (159). To a solution of **144** (820 mg, 2.20 mmol) in toluene (4 mL) was added 2,3-bis(trimethylsilyloxy)-1,3-butadiene (1.0 g, 4.94 mmol) and the mixture was heated in a sealed tube at 240°C for 4d. After evaporation of the toluene the residue was chromatographed (hexane-ethyl acetate, 3:1) to afforded 264 mg (32%) of recovered **144** and 643 mg (48%) of **159**: IR (neat) 2958, 1735, 1711, 1436, 1390, 1350, 1307, 1255, 1220, 1154, 1054, 912, 887, 843, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (m, 18H), 2.04 (1H, m), 2.50 (1H, m), 2.80 (2H, m), 3.20 (3H, s), 3.46 (1H, s), 3.61 (3H, s), 3.64 (3H, s), 5.15 (2H, m), 7.34 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.71, 1.3, 15.2, 32.9, 33.4, 34.2, 39.1, 52.6, 52.7, 57.2, 60.3, 65.8, 67.5, 122.8, 127.8, 128.0, 128.4, 129.0, 130.4, 136.3, 136.8, 140.9, 155.8, 169.6, 170.4; MS (EI) m/z 603 (M^+), 404,

378, 304, 149, 94, 91; HRMS *m/z* calcd for $C_{29}H_{41}NO_9Si_2$ (M^+): 603.2320. Found: 603.2319.



1-Carbomethoxy-2-[3-N-carbobenzyloxy-N-methylamino-4-furanyl]-4-hydroxy-6-oxa-7-oxo-bicyclo[3.2.1]octane (162). To a solution of **159** (30 mg, 0.05 mmol) in methanol (2 mL) was added sodium fluoride (15 mg, 0.35 mmol) and sodium borohydride (5 mg, 0.13 mmol). The mixture was stirred for 1h at room temperature and the methanol was evaporated. The residue was taken up with water (5 mL) and the solution was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 12 mg (56%) of **162**: IR (neat) 3520, 3477, 2958, 1785, 1732, 1704, 1436, 1393, 1354, 1331, 1299, 1256, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51-2.90 (5H, m), 3.19 (3H, s), 3.31 (3H, s), 3.40 (1H, m), 3.51 (3H, s), 3.61 (3H, s), 3.75 (3H, s), 4.65 (1H, m), 5.15 (2H, m), 7.33 (1H, s), 7.34 (7H, m), 7.44 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.9, 36.2, 37.6, 39.0, 39.2, 40.7, 52.3, 52.6, 54.5, 58.6, 67.5, 69.0, 79.2, 122.8, 128.3, 128.6, 136.5, 136.9, 139.6, 142.7, 155.9, 168.6, 170.2, 172.3; MS (EI) m/z 429 (M^+), 91; HRMS *m/z* calcd for $C_{22}H_{23}NO_8$ (M^+): 429.1424. Found: 429.1423.



Epoxide 163. To a solution of **159** (10 mg, 0.016 mmol) in dichloromethane (1 mL) was added *m*-chloroperbenzoic acid (4 mg, 0.017 mmol) and the mixture was stirred at 0°C for 4h. The mixture was diluted with water (3 mL) and extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 7 mg (71%) of unstable **163**: IR (neat) 2958, 1731, 1711, 1436, 1391, 1352, 1289, 1253, 1204, 1121, 1042, 993, 845, 740, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (m, 18H), 2.60 (2H, m), 2.90 (1H, m), 3.50 (1H, m), 3.61 (3H, s), 5.15 (2H, m), 7.34 (7H, m), 7.51 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 1.5, 1.8, 2.2, 2.3, 39.1, 39.9, 52.0, 52.5, 57.5, 67.3, 96.7, 97.5, 120.9, 127.7, 128.3, 129.6, 129.8, 132.6, 133.3, 136.5, 143.7, 155.9, 170.1, 171.0; MS (EI) m/z 619 (M^+), 593, 529, 438, 394, 366, 330, 213, 91.

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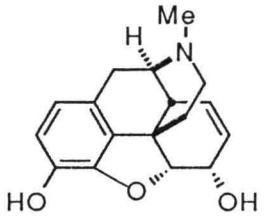
PART II: AN APPROACH TOWARD THE SYNTHESIS OF (±)-MORPHINE

Chapter III. An Approach toward the Synthesis of (±)-Morphine

Background and History

The opium poppy (*Papaver somniferum*) has been known since prehistoric times as the source of opium, an air dried milky exudate from the incised unripe capsules of the plant. Due to its sedative and euphoriant properties opium has had a prominent position as a therapeutic and recreational drug since antiquity. Opium contains more than twenty alkaloids, of which (-)-morphine (**1**), (-)-codeine (**2**) and (-)-thebaine (**3**) are the most important.



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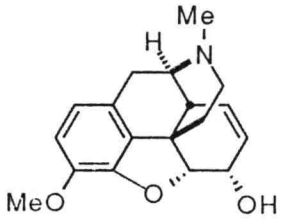

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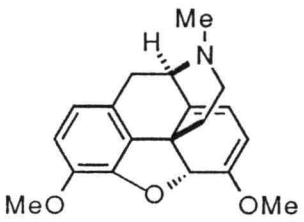

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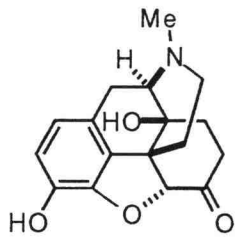
After morphine was isolated as a pure substance by Sertürmer in 1806 the use of the pure alkaloid rather than crude opium preparations began to spread throughout the medical world. With the invention of the hypodermic syringe in the eighteenth century, morphine could be administered by a route that allowed a far better expression of its potent analgetic and euphoriant activity. This also led to very severe compulsive drug abuse, and the drug's propensity to cause profound physical dependence became widely recognized. The abuse of morphine-based narcotics, especially heroin, is still a serious problem today.

The now accepted structure of morphine was first proposed by Robinson[1] in 1925, and it was confirmed by a total synthesis of (±)-morphine reported by Gates in 1952.[2] The absolute configuration of natural (-)-morphine was established in 1968 by X-ray crystallographic analysis.[3]

The search for analgetic drugs and their synthetic preparation has long represented an important area of research within the pharmacological sciences. In this context, the total synthesis of morphine has been an alluring goal since the days of Liebig. In 1870 the Prussian Academy of Science in Berlin held out a prize of 100 ducats for a solution to this problem, and in 1925 a rich manufacturer in New York offered $ 100,000 for the same purpose.[4] Today, after decades of research, a practical route to synthetic morphine has yet to be discovered.

The structural complexity of morphine, particularly the presence of the nitrogen-containing ring which bridges the phenanthrene nucleus, has frustrated many attempts at the total synthesis of this molecule and its close relatives. For this reason the search for clinically useful analgesics has focused mainly on the derivatization of morphine alkaloids obtained from plant sources. Thebaine is still the most important starting material in the synthesis of more recent analgetic drugs based on the full morphine nucleus. Oxymorphone (**4**), for example, has between six and eight times the activity of morphine in man.[5] Etorphine (**5**), also obtained from thebaine, is among the most potent opiates. Owing to its high potency it is used primarily for the immobilization of large zoo animals, such as elephants.



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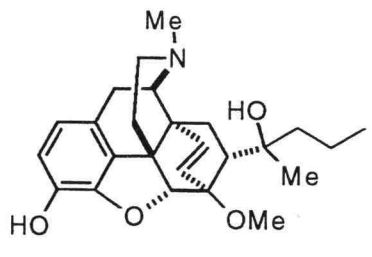
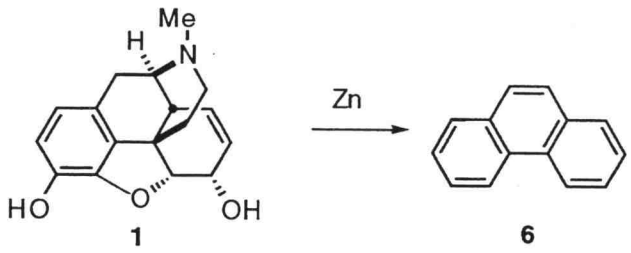


5

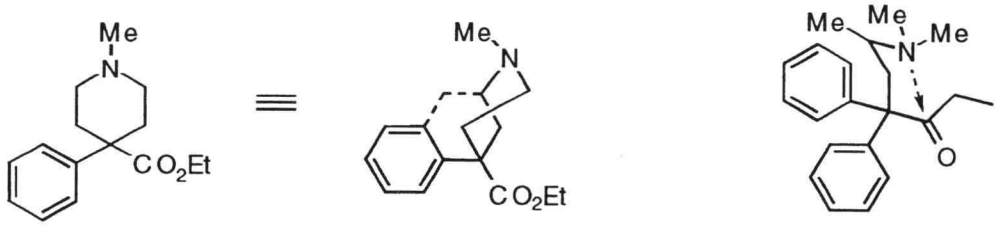
In the absence of a practical total synthesis, medicinal chemists have developed a long-standing interest in "simplifying" the morphine structure to identify the minimum pharmacophore necessary for analgetic activity. Research towards this end was started in the 1880's following the observation that the reduction of morphine (**1**) with zinc dust yielded phenanthrene (**6**) (scheme 1).[6]



1 **6**

scheme 1

Phenanthrene was unsuccessfully used as a starting material in this endeavor. It was discovered serendipitously in the 1940's that meperidine (**7**), a compound originally designed as an antispasmodic agent, showed potent analgetic activity. This led the way to the preparation of new synthetic analgetic agents with structural complexity far below that of morphine.[5]



7 **8**

Acyclic analgesics such as methadone represent a further "simplification" of the morphine structure. Methadone (**8**) is used today primarily as a treatment for heroin addiction. Unlike meperidine, methadone is chiral and has been resolved. Most, but not all of the analgesic activity of the racemate is associated

with the *S*-form. Its enantiomer, *R*-methadone lacks significant respiratory-depressant action and addiction liability.

In 1954 Beckett and Casy[7] formulated a set of empirical rules which attempted to define the structural elements required for analgetic activity. The structural requirements were

1. an *aromatic ring*, preferably axially disposed; if connected to a piperidine
2. ring, a *quaternary carbon center* connected via the equivalent of an
3. ethylene chain to a *basic amine*.

The assumption underlying these rules was that, in order for a drug to be analgetic, it must bind to a specific receptor located in the central nervous system. More recently, binding studies with radiolabelled opioid drugs in brain and other tissue such as mouse *vas deferens* have suggested the existence of distinct populations of receptors that can interact with opioid drugs or endogenous opioid peptides. The latter are natural opioid receptor ligands produced in the body in response to extreme stress and pain.

In the mammalian central nervous system, three major classes of opioid receptors can be distinguished based on their pharmacological profile. These are μ,κ and δ -types.[8] These are proteins of about 60 kDa which belong to a broader class of receptors that are coupled to G proteins and have seven transmembrane segments. About 80% of all known receptors belong to this family, for which extensive homology in the amino acid sequence has been reported.[9] Functional and regulatory homology within this family of receptors seems very likely. For example, all G protein-coupled receptors have a common mechanism of desensitization that is caused by reversible phosphorylation of the receptor by regulatory kinases such as protein kinase C. The desensitization of opioid receptors is responsible for the gradual increase in drug consumption typically seen with morphine addicts.

The overall effect of opioid drugs on the nervous system is determined by which cells express μ,κ or δ -receptors. The receptor distributions have been extensively mapped by autoradiography.[10] Since morphine is mainly selective for μ-receptors, the distribution of μ-receptors largely corresponds to the spectrum of its pharmacological action such as analgesia, drowsiness, change of mood, respiratory depression and decreased gastrointestinal motility. Since other sensory modalities, such as touch, are not affected by the drug, the mechanism of opiate induced analgesia must involve the selective inhibition of nociceptive reflexes in the spinal cord and the substantia gelatinosa. At the cellular level, the potassium and calcium ion channels and the enzyme adenylyl cyclase are the immediate targets of opioid action. Adenylyl cyclase produces cyclic AMP (cAMP), a common second messenger. Opiates reduce the levels of cellular cAMP through inhibition of adenyl cyclase. After prolonged opiate exposure, the cell responds by increasing the production of acetylcholine which in turn raises the cAMP levels in order to maintain normal cell functions. If the use of the drug is interrupted, there is a sudden surge in the cellular cAMP-production which precipitates a multitude of serious withdrawal symptoms.

Although the mechanism of opiate induced analgesia is not completely understood, changes in the ion channel conductivity of the affected nerve tissue, and the reduction of neurotransmitter release from those nerve cells appear to be the main functional consequences of morphine administration. For pain therapy it is therefore important to distinguish between pain that is caused by stimulation of nociceptive nerve cells which is transmitted over intact neural pathways and pain that is caused by damage to neural structures. Morphine is reportedly ineffective for treatment of the latter type of pain.[11]

In addition to its analgesic properties, morphine acts as a powerful respiratory depressant even at subtherapeutic doses. This effect is mediated by

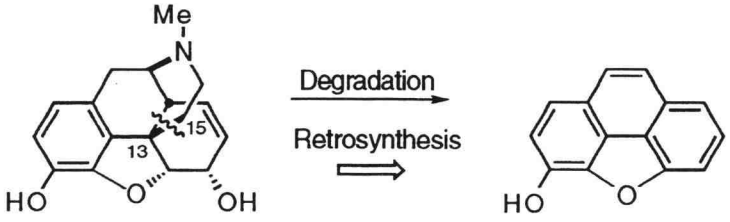
a subpopulation of μ-receptors in the medullary areas of the brain stem responsible for ventilary control. Respiratory depression represents a limitation to the therapeutic use of opioid analgesics since human fatalities through morphine poisoning is always a result of respiratory arrest. Other species, for example dogs, are much less sensitive in this respect.

The neurobiological changes that are produced in the mammalian brain by morphine addiction are very complex. Drug abuse alters the metabolism of both opioid receptors and endogenous peptides. This interferes with a variety of other physiological processes such as mood, learning, thermoregulation, ingestive behavior, motor activity and the perception of reward. There is evidence that the mesolimbic dopamine pathway and various γ-aminobutyric acid (GABA) interneurons are affected by morphine abuse.[12]

The genetic cloning and overexpression of opioid receptors is currently an active area of investigation. Isolation and sequencing of all three receptor types has now been accomplished.[8] The technique makes macroscopic quantities of the receptors available-for example NG108-15 cells express ca 300,000 δ receptors per cell- and this has created new opportunities in biological research, particularly that involving endogenous peptide ligands. Biochemical and molecular genetic studies are currently being conducted to assign structural domains in these receptors to specific functions such as agonist and antagonist binding, coupling to the G-proteins, and phosphorylation by kinases. With further examination of these receptors more detailed structural information should become obtainable which could eventually influence the design of analgesic drugs.

The numerous approaches that have been directed toward synthesis of the molecular skeleton of morphine represent a vast area of synthetic chemistry that cannot be covered here in any detail. A diverse array of synthetic concepts and methods have been used to construct the carbocyclic and heterocyclic rings of the molecule. Some of the more innovative approaches will be described below. Most of them are racemic and, in fact, there have been very few attempts to design chiral syntheses in this area.[13] Only very recently has the first asymmetric total synthesis of morphine been completed which did not involve resolution.[14]

Early routes to morphine were often influenced by degradative studies which all yielded phenanthrene derivatives (scheme 2). Before the structure of morphine was fully elucidated, it was assumed that this hydrocarbon represented the "primeval form" of morphine and was thus regarded as the appropriate starting material for synthetic studies. In spite of extensive efforts along this line very few examples can be found in the literature of successful morphine syntheses in which carbon-carbon bond formation between carbon 13 and 15 is used to construct the morphine ring system.[15]

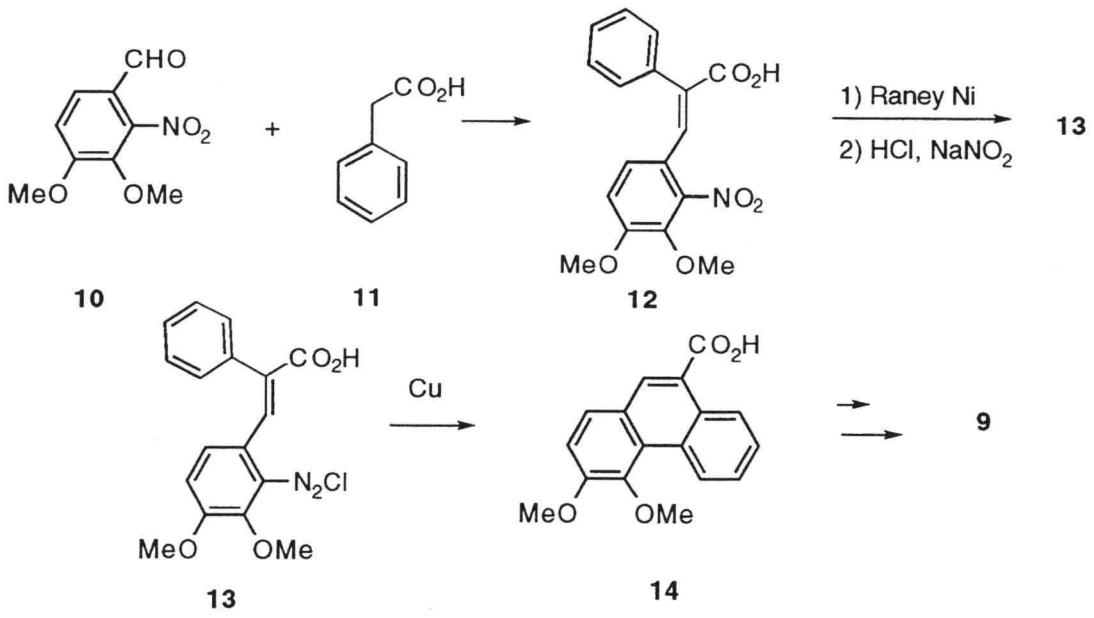


1 9

scheme 2

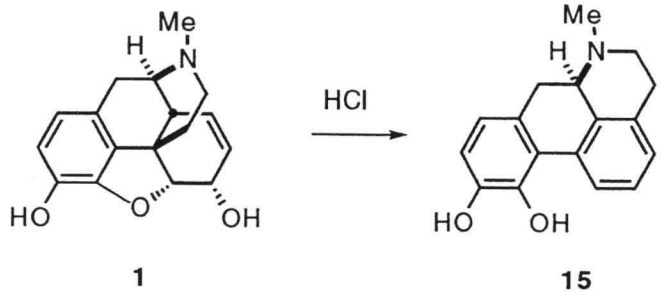
Several of the intermediates that were prepared following the "phenanthrene approach" were useful in the identification of degradation products obtained from morphine alkaloids. For example, in 1896 Pschorr

developed a general method for the synthesis of phenanthrene derivatives that was applied to a proof of the structure of morphenol (**9**) (scheme 3). [16]



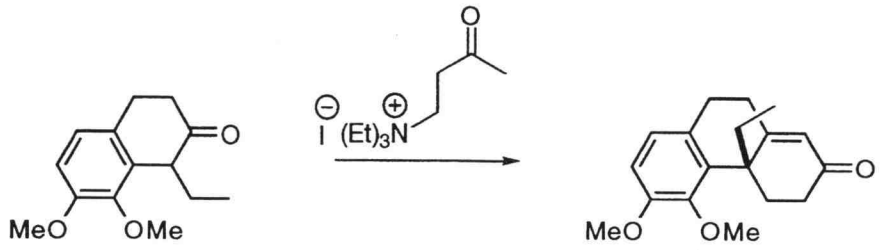
scheme 3

The Pschorr synthesis of **14** was also used to determine the structure of apomorphine (**15**), which can be obtained from morphine through an acid catalyzed rearrangement (scheme 4). It was believed by Pschorr that knowledge of the structure of apomorphine would clarify the structure of morphine since it was not recognized at the time that a rearrangement takes place in the conversion of morphine (**1**) to apomorphine (**15**).



scheme 4

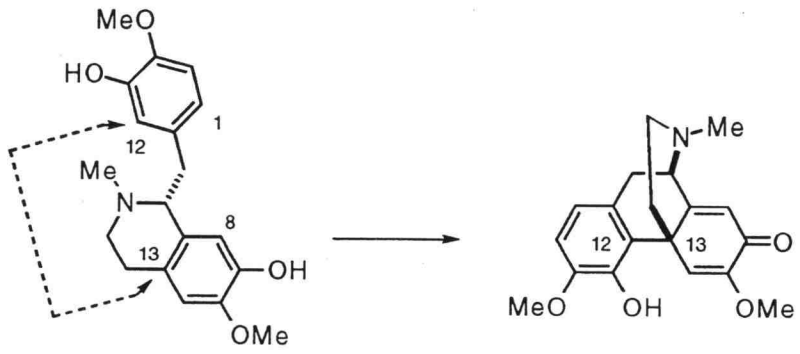
Robinson who was first to propose the correct structure of morphine reported the synthesis of an intermediate **17** which shares with morphine the phenanthrene skeleton and the quaternary carbon center (scheme 5).[17] Although no further synthetic progress could be achieved with **17**, it closely resembles certain degradation products of morphine.



16 **17**

scheme 5

The elucidation of the detailed biosynthesis of morphine[18] has prompted many attempts to simulate the key biosynthetic transformation which converts reticuline (**18**) to salutaridine (**19**) in the poppy plant (scheme 6).

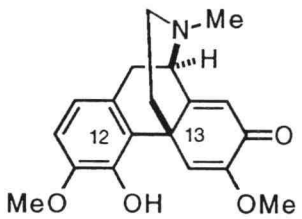


18 **19**

scheme 6

Salutaridine, the immediate precursor to the morphine alkaloids, is produced in *Papaver Somniferum* by an intramolecular oxidative coupling that

establishes the tetracyclic framework with great efficiency. By contrast, this process when carried out under non enzymatic conditions in the laboratory has proved to be an exceedingly difficult reaction. Chemical yields are often low and the coupling frequently gives mixtures of all possible coupling products: isosalutaridine (**20**), isoboldine (**21**), corytuberine (**22**) and only a minor quantity of the desired salutaridine (**19**). Efforts to find efficient oxidative phenolic coupling procedures have been a challenging problem for chemical synthesis, although considerable progress has been made in the development of coupling reagents[19] as well as in the regio- and stereochemical control of the reaction.[20] A total synthesis of (±)-codeine has been completed following this biomimetic approach.[21]



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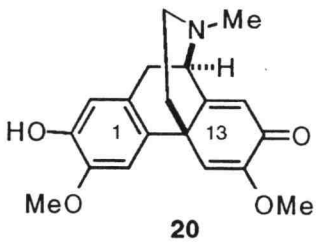

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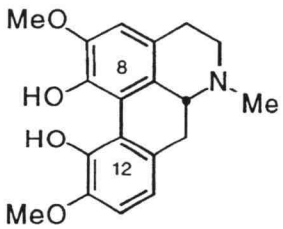

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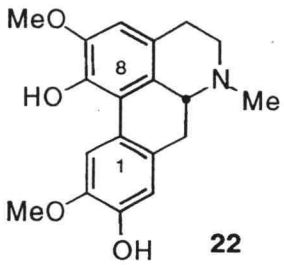
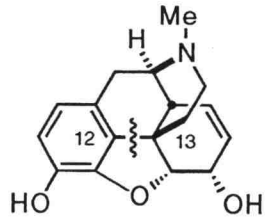


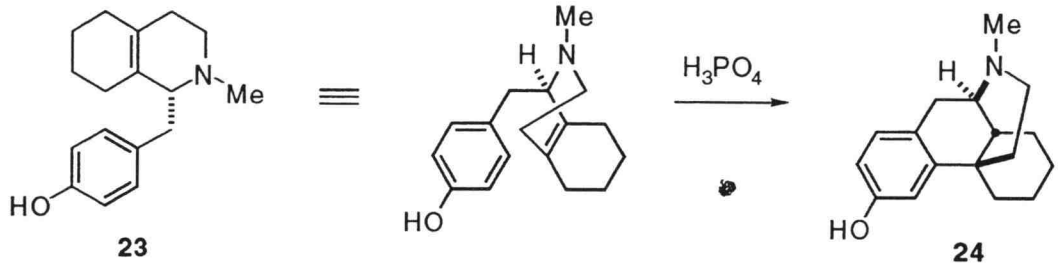
22

In spite of their diverse nature, almost all other successful synthetic approaches toward the morphine nucleus have in common with the biosynthesis the fact that the creation of a bond between carbons 12 and 13 is the crucial step which establishes the morphine ring system.



1

In formal analogy to the biosynthesis (although through a very different mechanism), a variety of 1-benzylhydroisoquinoline derivatives such as **23** have been cyclized under acidic conditions to the morphinan nucleus (scheme 7).



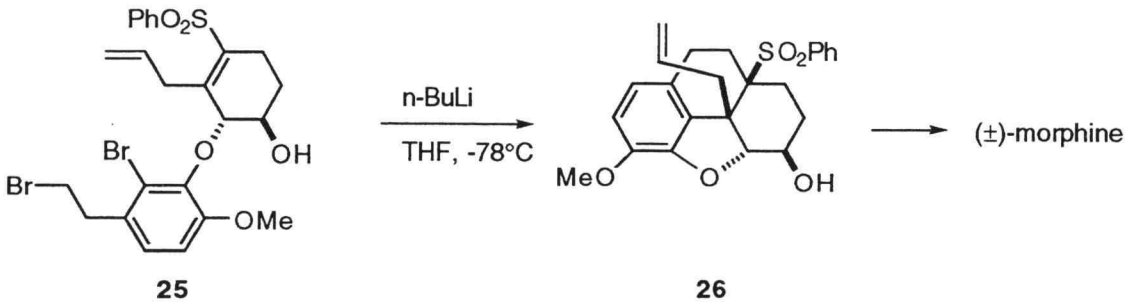
23 **24**

scheme 7

This approach is known as the Grewe cyclization[22] and has proven to be a quite flexible process and has provided access to some commercially important morphinan derivatives. It has also permitted a formal total syntheses of (±)-morphine.[23] The hydroisoquinoline precursor can be resolved on an industrial scale to afford, after Grewe cyclization, levorphanol (**24**), an orally active analgesic, and its enantiomer dextrorphan, a useful antitussive agent.

Using a quite different concept, Fuchs[24] has reported a total synthesis of (±)-morphine based on vinyl sulfone chemistry which connects the carbocyclic framework as shown in scheme 8. The ether linkage of **25** becomes the prospective hydrofuran oxygen of the morphine structure in this plan. The key step here is an intramolecular conjugate addition of an aryloxy anion derived from

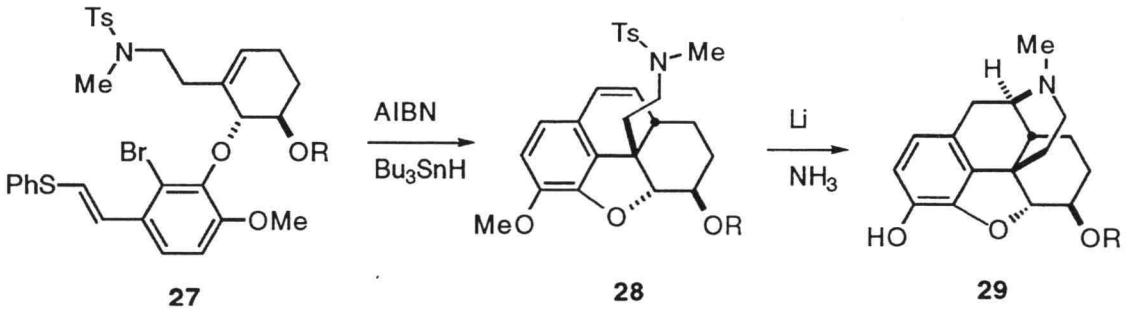
25 to the vinyl sulfone, thereby providing an incipient α-sulfonyl anion which undergoes intramolecular alkylation. The tetracyclic sulfone **26** is obtained in a single operation as a beautifully crystalline material.



25 **26**

scheme 8

Quite recently, studies by Parker have culminated in a formal total synthesis of (±)-morphine which features a very elegant tandem radical cyclization strategy (scheme 9).[25]



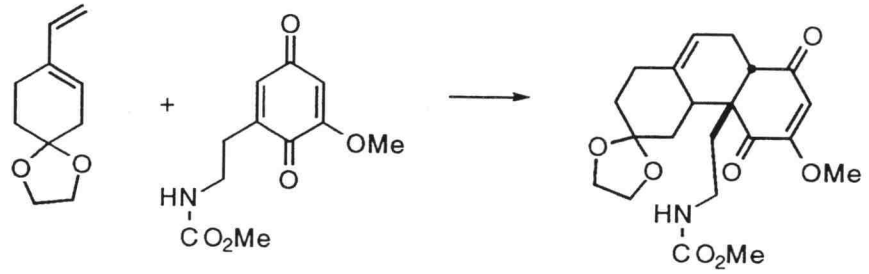
27 **28** **29**

scheme 9

As in the Fuchs strategy, the ether linkage in **27** serves as a tether to hold the coupling partners in close proximity. In the second step, a reductive detosylation effects concomitant formation of a carbon-nitrogen bond across the styrene moiety of **28**. This unprecedented cyclization is probably facilitated by

the close proximity of the reactive nitrogen species (radical or anion) with the styrene double bond.

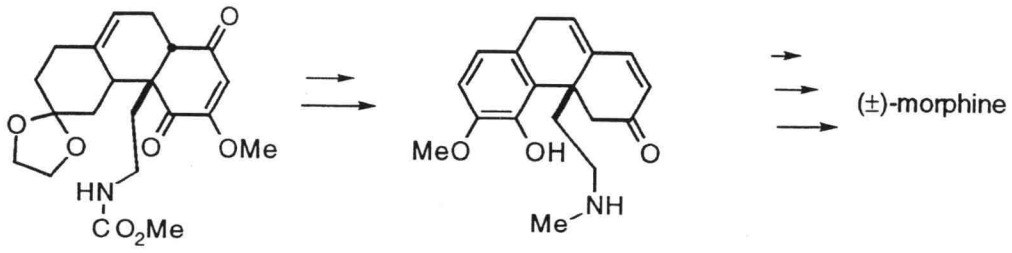
Recent work by Tius has demonstrated the practicality of a Diels-Alder reaction between **30** and **31** in an unconventional formal synthesis of (±)-morphine (scheme 10).[26]



30 **31** **32**

scheme 10

The Diels-Alder adduct **32** was transformed in a number of steps that involved hydroxylation and aromatization of the A ring and reduction of the C ring to the intermediate **33** which condensed to the morphine nucleus through an intramolecular Michael addition (scheme 11).



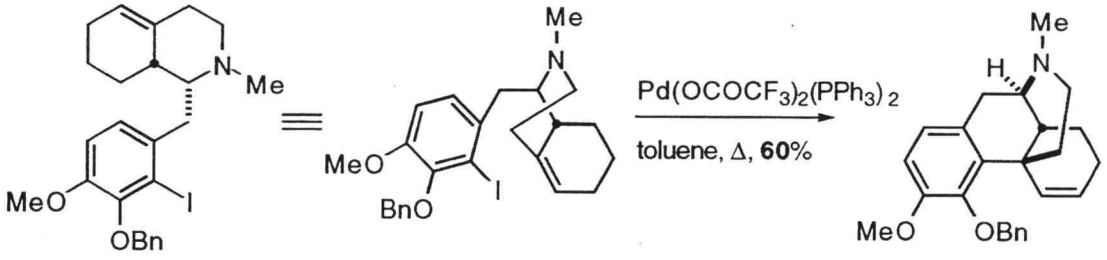
32 **33**

scheme 11

In 1993 Overman reported the first asymmetric total synthesis of (-)-morphine by applying an intramolecular Heck arylation reaction to the

enantiomerically pure octahydroisoquinoline **34**.[13] In terms of bond connection, this approach is very similar to the traditional Grewe cyclization (scheme 7).

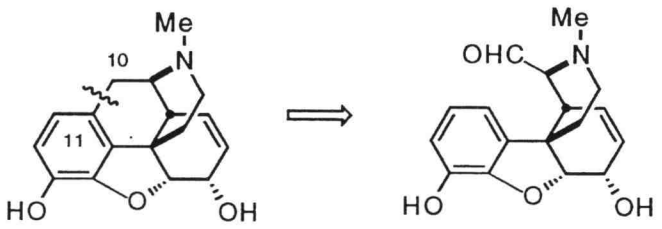
The Heck arylation has broad scope and tolerates a variety of functional groups, so that potentially a wide range of previously unavailable morphinans could be assembled by this route.



34 **35**

scheme 12

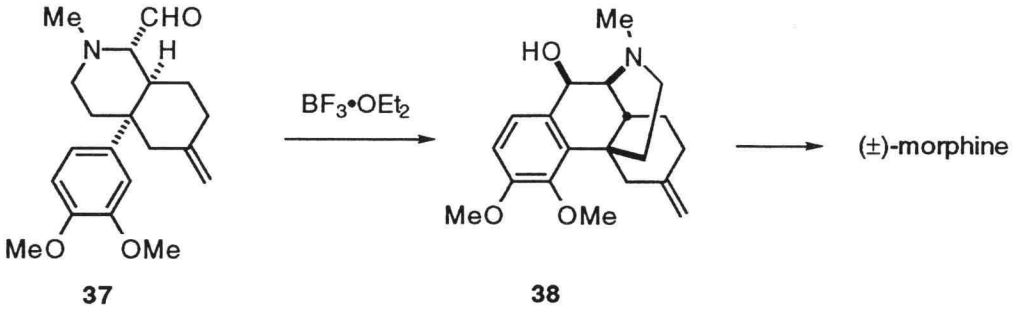
A conceptually different approach centers on the use of aryldecahydroisoquinoline derivatives that have become available following the methodological studies of Rapoport[27] and Evans.[28] Here, the crucial bond connection is made between carbon 10 and 11 (scheme 13). An inherent advantage of this strategy is the improved control over the regiochemical outcome of the coupling step.



1 **36**

scheme 13

Thus, Evans[29] has reported the cyclization of the aryl substituted amino aldehyde **37** to morphinan **38** which has been taken on to (±)-morphine (scheme 14).



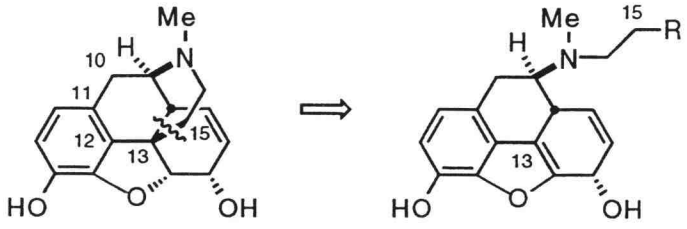
37 **38**

scheme 14

As can be seen from the examples shown above, morphine and its derivatives continue to hold the fascination of chemists and neuroscientists alike. Although many creative approaches have been reported, nature's ability to synthesize this small but intrinsically complex molecule is still unsurpassed. Apart from the academic challenge, any total synthesis of morphine provides a source of interesting material for biological testing and pharmacological research. As more information about the opioid receptors is gathered, synthesis of biological probe molecules related to morphine (for example, for affinity labeling) may become a useful tool in the study of these receptors.

Results and Discussion

As outlined in the previous chapter, the successful synthetic routes to morphine alkaloids most often involved bond formation between carbon atoms 12 and 13 (biomimetic, Grewe and Overman approaches) or between carbon atoms 10 and 11 (Evans and Rapoport approaches). By contrast, strategies which envision bonding between carbon atoms 13 and 15 (the phenanthrene approach) have so far not usually proven useful in spite of a long history of attempts along this line (scheme 15).[15]



1 **39**

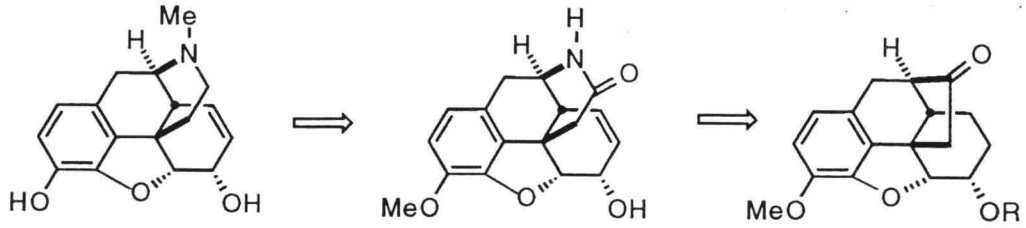
scheme 15

Perhaps the most compelling reason for this failure is the high degree of steric hindrance around carbon 13 in the "bay region" of the phenanthrene skeleton which makes the formation of a carbon-carbon bond at this position a difficult process. Aside from this fundamental problem, however, there are a number of inherent advantages to this strategy. These include the fact that the nitrogen can be introduced late in the synthesis and that a variety of potentially useful phenanthrene templates can be constructed with relative ease.

It can be inferred from accounts in the older literature that attempts to create a bond between the quarternary center at carbon 13 and carbon 15 by conventional methods, for example using enolate chemistry, would most likely

fail. Less conventional methods of carbon-carbon bond construction that were developed in the recent past have not been examined in the context of this particular problem. This led us to propose a "modernized" strategy for the phenanthrene approach involving an intramolecular process where carbon-carbon bond formation takes place in a highly reactive organic intermediate such as a carbenoid species or a free radical.[30]

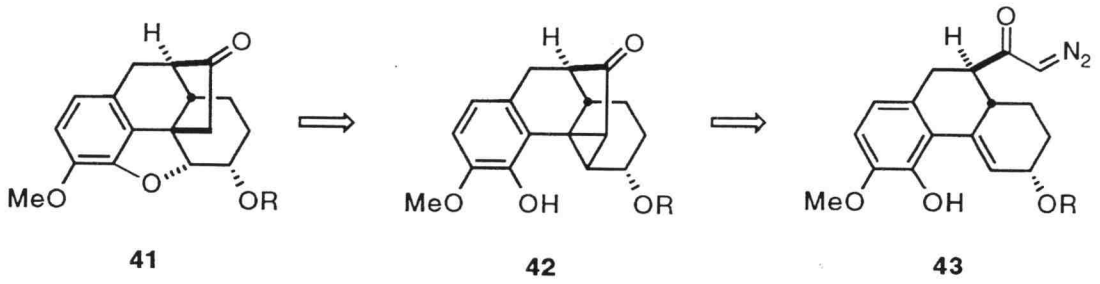
Examination of a molecular model of morphine (**1**) conveys the fact that the nitrogen-containing ring which bridges the phenanthrene nucleus represents the most flexible part of an otherwise rigid framework. It was concluded that this part of the molecule could arise from a more strained precursor such as ketone **41** via Beckmann rearrangement[31] and subsequent reduction of the lactam **40** (scheme 16).[32]



1 **40** **41**

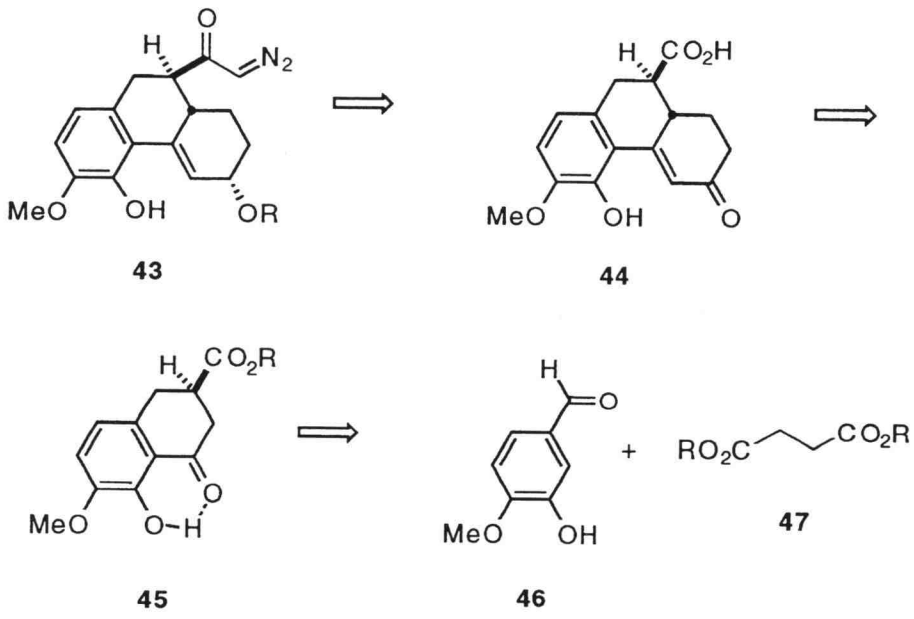
scheme 16

Synthesis of ketone **41** was envisioned from a strained cyclopropyl ketone intermediate **42** that would undergo ring fragmentation with concomitant closure of the furan ring of the morphine structure. Cyclopropyl ketones are frequently prepared by the decomposition of diazoketones. Cyclopropane ring formation has been postulated to occur via the reaction between the intermediate carbenoid species and the π-electrons of a carbon-carbon double bond (scheme 17).[33]



scheme 17

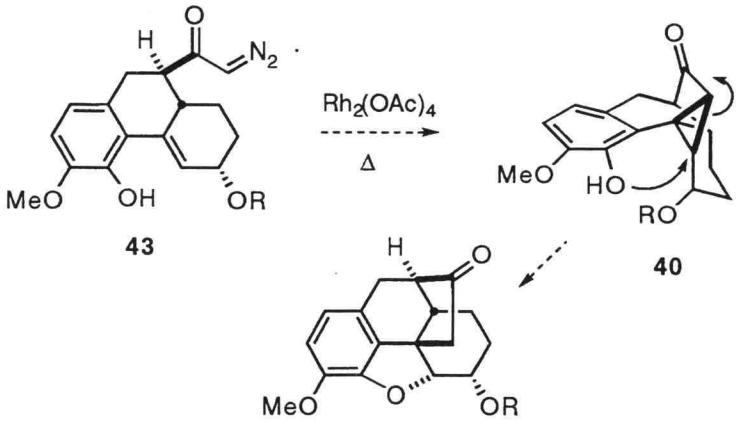
The diazoketone **43** could be obtained from the phenanthrenone-carboxylic acid **44** which in turn arises from the tetralone **45** through a Robinson annulation. The tetralone **45** can be prepared, in principle, from isovanillin (**46**) and dialkyl succinate **47** (scheme 18) via a Stobbe condensation, followed by reduction of the resulting cinnamate and a Friedel-Crafts cyclization.



scheme 18

While the steps leading to the phenanthrenonecarboxylic acid **44** can be considered relatively straightforward, the intramolecular cyclopropanation of **43** has no direct precedent. It was surmised that diazoketone **43** could be induced

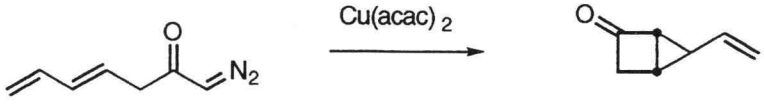
to undergo a rhodium diacetate-catalyzed carbenoid addition to the olefinic bond to afford the strained cyclopropyl ketone **40**. This could subsequently suffer homoconjugate addition of the free phenol (scheme 19).

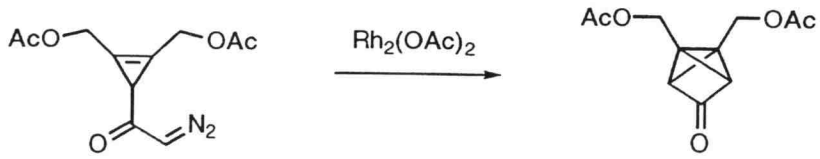


43 **40** **41**

scheme 19

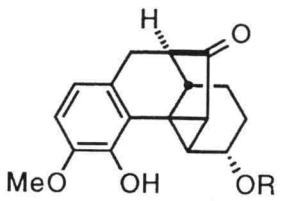
Many examples in the literature confirm that the addition of ketocarbenoid species to π-bonds is a very general and direct entry to highly functionalized cyclopropane-containing structures. For intramolecular cyclopropanation, reactions which generate the [3.1.0] and the [4.1.0] bicyclic frameworks are the most common. However, very strained [2.1.0] and [1.1.0] bicyclic systems are also accessible via this pathway. The reaction appears to be insensitive toward strain in the resultant ring system and the degree of substitution of the olefin substrate (scheme 20).[34]



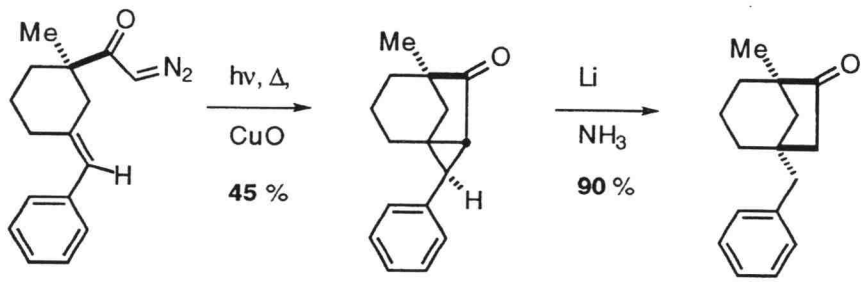


scheme 20

The ring system present in the strained cyclopropyl ketone **40** is not known. However, Wenkert has reported the synthesis of an analogous cyclopropanobicyclo[3.2.1]octanone **49** from diazoketone **48**.[35] The cyclopropane of **49** underwent facile reductive ring opening to afford **50**. A highly selective cleavage of the bond most nearly parallel to the neighboring ketone π-orbital was observed (scheme 21).



40

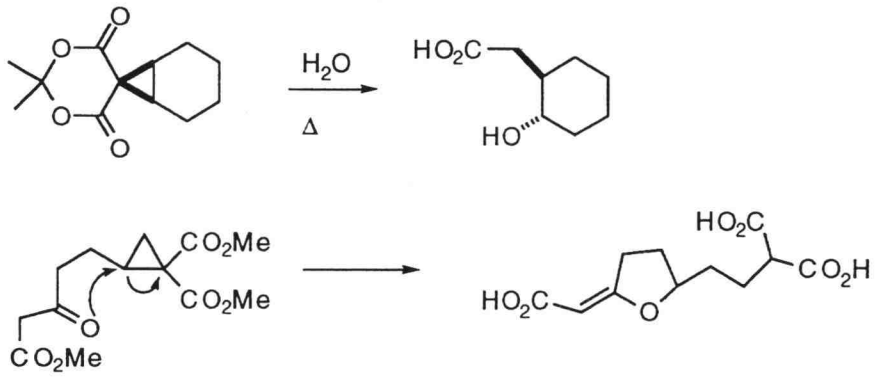


48 **49** **50**

scheme 21

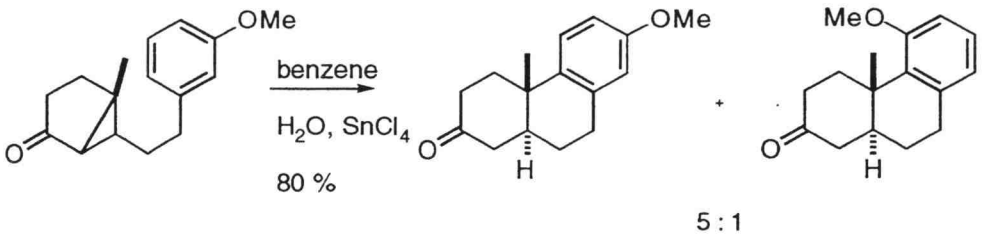
The inherent strain associated with the cyclopropane ring within a bicyclic system such as **40** can lead to a variety of ring-opening transformations after the carbenoid insertion step. Apart from rearrangement,[36] fragmentation[37] and

reductive ring opening,[38] there are a number of examples which demonstrate that electrophilic cyclopropanes can undergo homoconjugate addition. In these reactions ring opening occurs in the presence of an external or internal nucleophile. In particular, doubly activated cyclopropanes, such as those resulting from the reaction between an olefin and diazomalonate, react with nitrogen, sulfur and oxygen nucleophiles in a homoconjugate fashion. This reaction has been reviewed by Danishefsky,[39] of which two examples are shown below for oxygen nucleophiles (scheme 22).



scheme 22

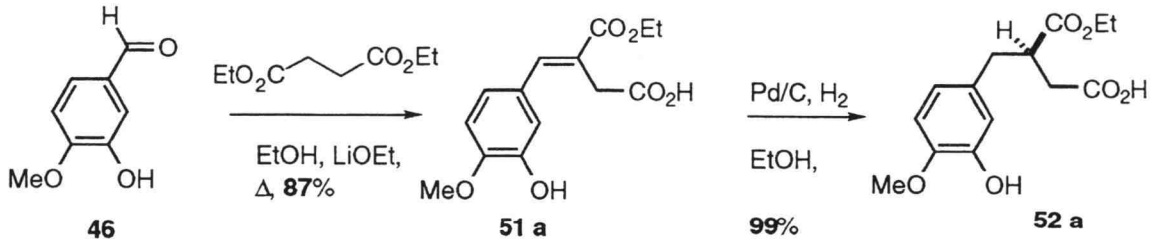
By contrast, monoactivated systems are much less reactive so that powerful nucleophiles and electrophilic assistance are often needed to promote homoconjugate addition. Intramolecular cleavage of monoactivated cyclopropanes are rare, except in cases where a cyclopropyl cation is intercepted through the involvement of a π-system. The latter is generally an aromatic ring or a double bond. An example of such a process is found in a "polyene cyclization" reported by Stork which proceeds in high yield and with good stereoselectivity (scheme 23).[40]



scheme 23

The synthetic approach towards morphine presented here is most straightforward in its racemic form. However, a chiral version may be feasible. This would involve preparation of the first chiral intermediate of the sequence **52** in enantiomerically pure form either through a resolution or via enantioselective synthesis.

Isovanillin (**46**) was treated with diethyl succinate under Stobbe condensation conditions to afford *E*-cinnamate half ester **51 a**.[41] Racemic carboxylic acid **52 a** was readily available through hydrogenation of **51 a** (scheme 24).



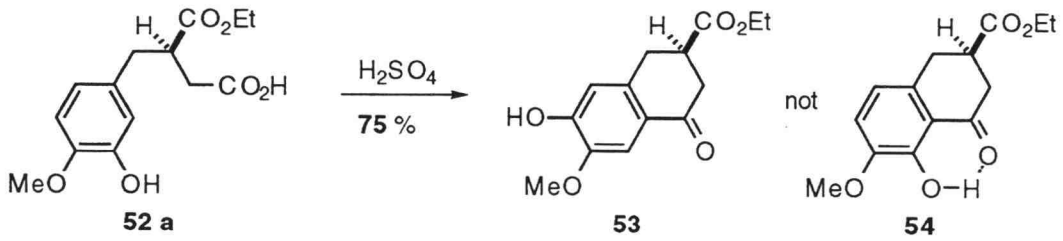
46 **51 a** **52 a**

scheme 24

Isovanillin (**46**) has not been previously studied in this context. However both steps have been carried out in excellent yield with vanillin (3-methoxy-4-hydroxybenzaldehyde) as a starting material. Protection of the phenolic hydroxy group is not needed during the Stobbe condensation and the carboxylic acid isomeric with **52 a** can be readily resolved with a chiral amine.[42] The same compound is available in enantiomerically pure form through asymmetric

hydrogenation using a chiral rhodium(I)-catalyst,[43] thus suggesting two options for obtaining **52** in a version suitable for asymmetric synthesis.

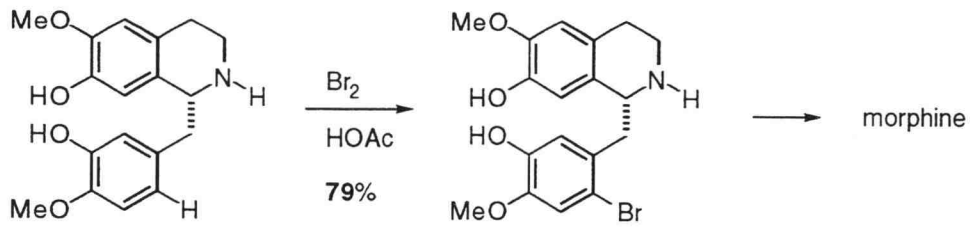
Carboxylic acid **52 a** was subjected to concentrated sulfuric acid in order to promote an intramolecular Friedel-Crafts acylation. Not unexpectedly, the acylation was found to be completely *para* selective, affording the undesired tetralone **53** in good yield (scheme 25). For steric and electronic reasons **53** is strongly favored over the desired ortho coupled product **54** .



52 a **53** **54**

scheme 25

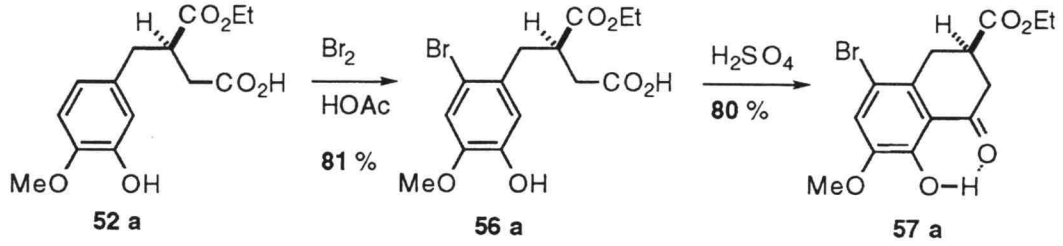
The outcome of this reaction necessitated the blockage of the reactive *para* -position preferably by a group that could easily be removed at a later stage in the synthesis. A *para* selective bromination reaction of N-norreticuline (**19**) has been described in the literature where the product **55** was taken forward to morphine (scheme 26).[20] The removal of the bromine from the alkaloid nucleus has been successful under a number of conditions.



19 **55**

scheme 26

Hence, bromination of carboxylic acid **52 a** followed by Friedel Crafts acylation of **56 a** yielded the bromo tetralone **57 a** with the desired regiochemistry (scheme 27).



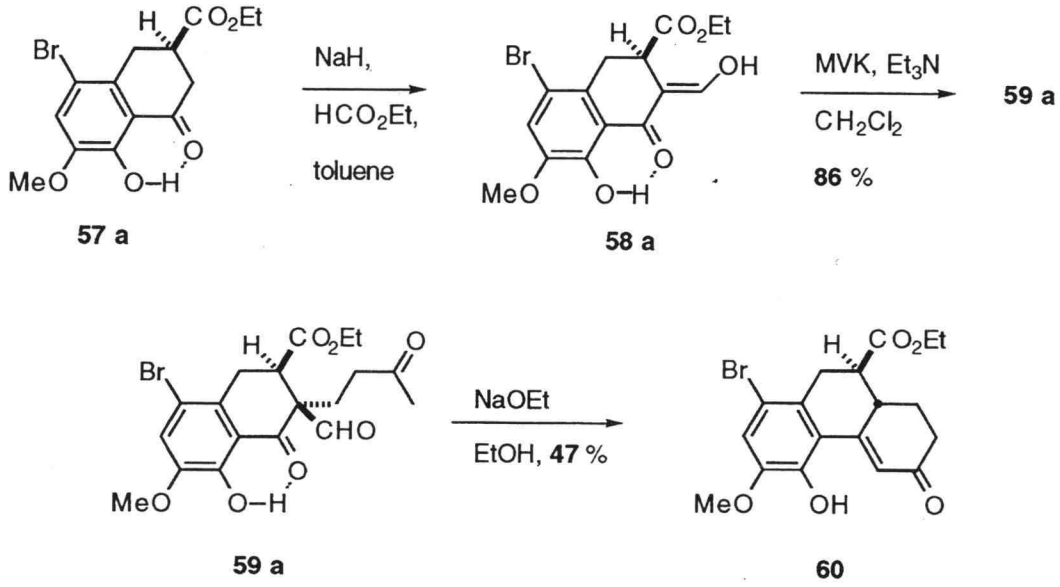
52 a **56 a** **57 a**

scheme 27

The tetralone **57 a** was then to be subjected to a Robinson annulation, a classical ring construction procedure which condenses a ketone with methyl vinyl ketone to yield cyclohexenone derivatives.[44] Attempts to effect the Robinson annulation of **57 a** directly by treating the compound with methyl vinyl ketone under either acidic or basic conditions or with 5-diethylamino-2-pentanone failed. The latter compound forms methyl vinyl ketone under basic conditions at a slow rate. Presumably, the slow rate of formation of either the enol or the enolate anion derived from **57 a** put these species at a disadvantage in the Michael addition step which therefore failed to compete effectively with polymerization of the electrophile.

To circumvent this problem, α-formylation of tetralone **57 a** was carried out using ethyl formate and sodium hydride.[45] Purification of the resulting α- formyl tetralone **58 a** proved to be difficult due to lability of the compound. However, the reaction of crude **58 a** with methyl vinyl ketone in the presence of triethylamine resulted in smooth Michael addition and formation of the alkylated product **59 a** in high yield. Intramolecular aldol condensation, dehydration and deformylation was achieved in one step by treating **59 a** with refluxing sodium

ethoxide in ethanol. The Robinson adduct **59 a** was obtained in modest yield, but as a single diastereomer (scheme 28).



scheme 28

The relative configuration of the latter was confirmed by X-ray diffraction analysis of its acetate derivative **61**. The crystal structure of **61** reveals some interesting conformational features. For example, the carboethoxy group is pseudoaxially oriented, and the carbon-carbon bond of the enone is bent out of the plane of the aromatic ring by 11.6 °.

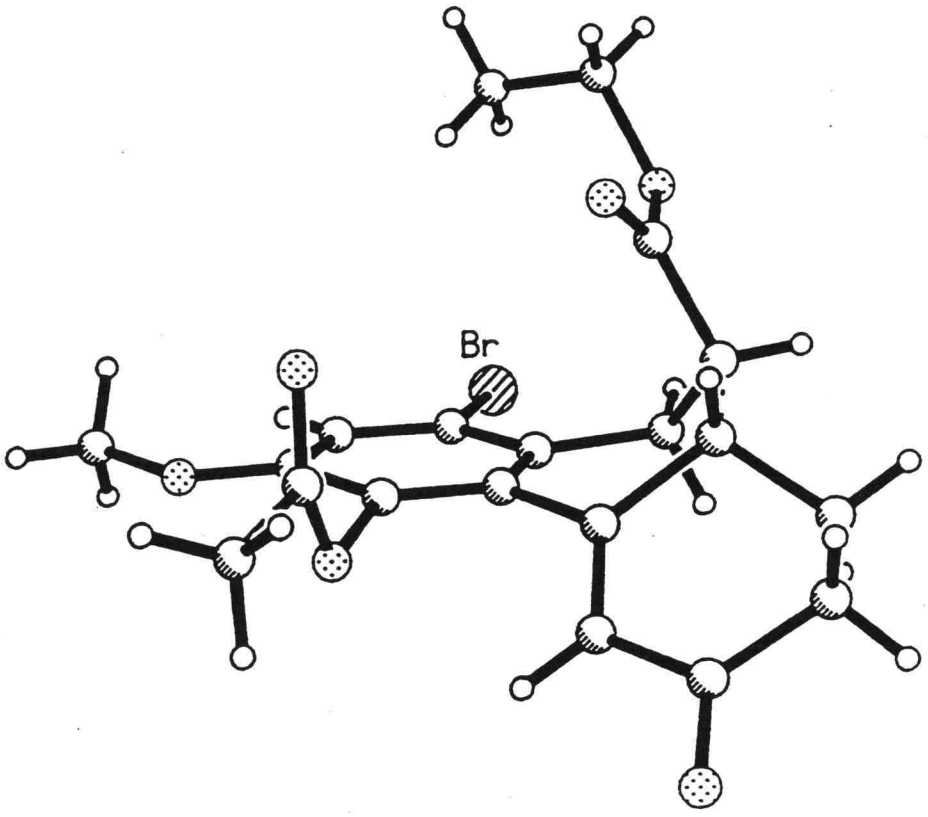
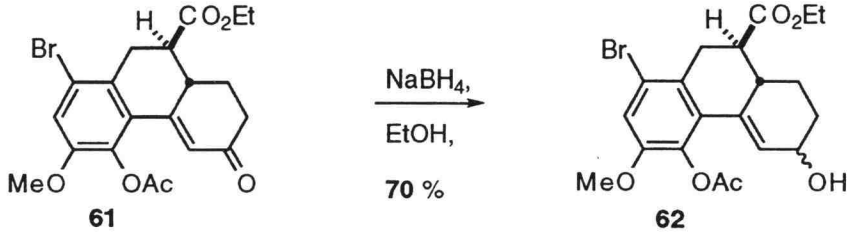


Figure 3.1: TELP Representation from X-ray Structure of **61**.

With compounds **60** and **61** in hand, an opportunity for examining reduction of the enone became available. Our hope was that the existing stereochemistry of **60** would direct reduction of the ketone to give a secondary alcohol at C-15 corresponding in configuration to that of the morphine structure.

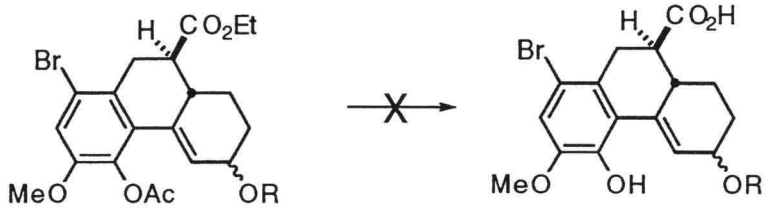
While the free phenol **60** was found to react very sluggishly with sodium borohydride to give a hydroxy phenol in low yield, its acetate **61** could be reduced more efficiently under a variety of conditions that included sodium borohydride, L-selectride, lithium borohydride and lithium aluminum hydride. However, the stereoselectivity was found to be disappointingly low. Changes in the protecting

group of the phenol did not appear to have any effect on the selectivity of the reduction (scheme 29).



scheme 29

The epimeric mixture of alcohols **62** proved to be unstable in the presence of acid or base. Even after protection of the secondary alcohol in **62** as the *tert*-butyldimethylsilyl ether **63** or the methoxyethoxymethyl ether **64**, hydrolysis of the carboethoxy group could not be accomplished without extensive decomposition of the starting materials (scheme 30).



R=H, **62**

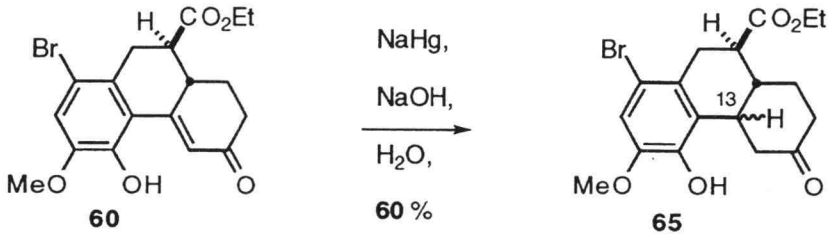
R=TBDMS, **63**

R=MEM, **64**

scheme 30

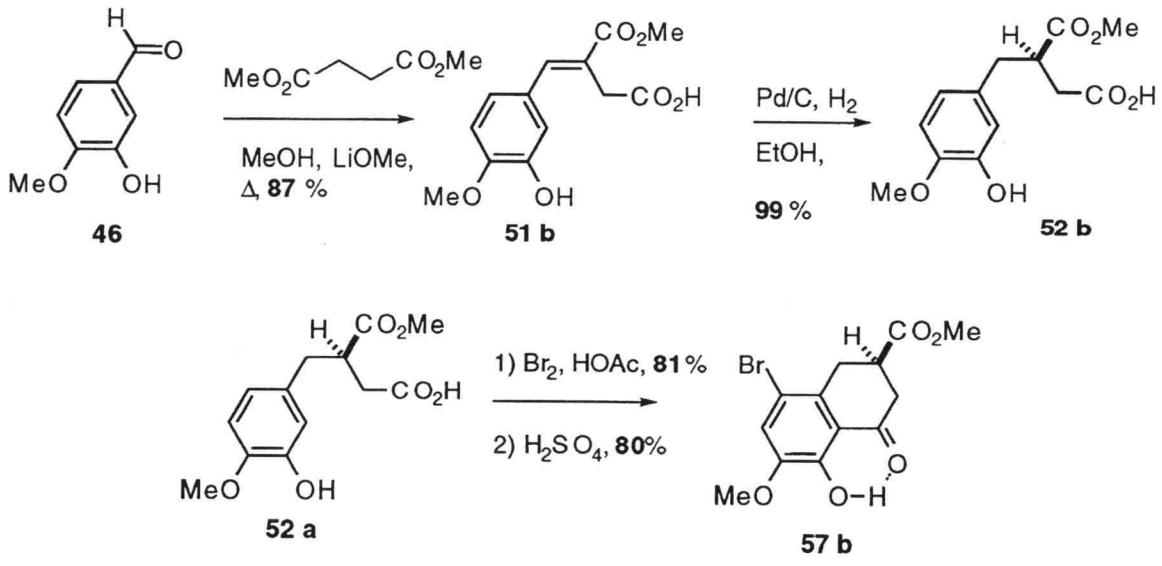
Saturation of the enone double bond in **60** could be accomplished smoothly with sodium amalgam, but unfortunately, a 1:1 mixture of diastereomers was obtained (scheme 31). It was originally intended to take **65** on to a diazoketone that would have been capable of C-H insertion into the benzylic

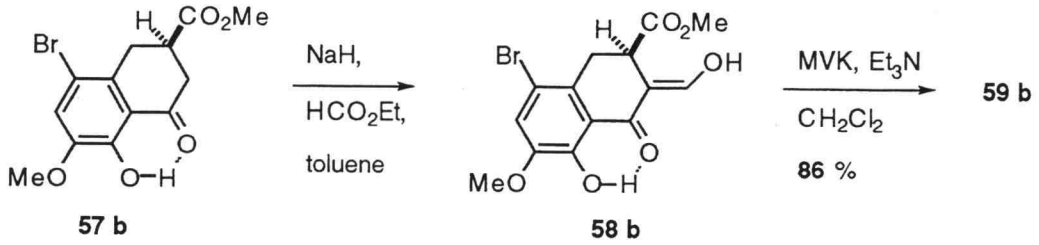
methine C13. However, the hydrolysis of **65** was found to be difficult. These results made any approach to morphine from **65** unattractive, and this line of attack was not pursued further.



scheme 31

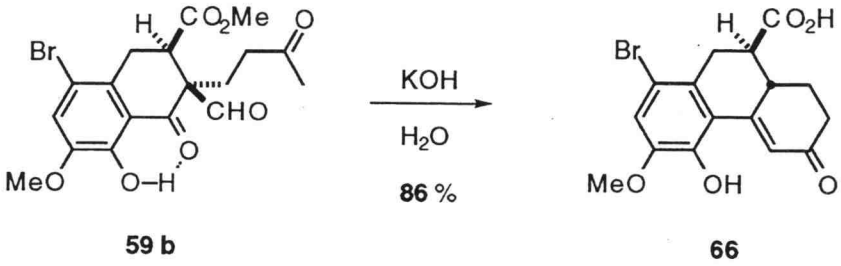
The difficulties encountered with the hydrolysis of the carboethoxy group in **61-63** and in **65** indicated that a more tractable ester was needed, and for this reason it was decided to replace this functionality by a methyl ester. Dimethyl succinate was used in the Stobbe condensation leading to compound **59 b** through the steps previously described (scheme 32).





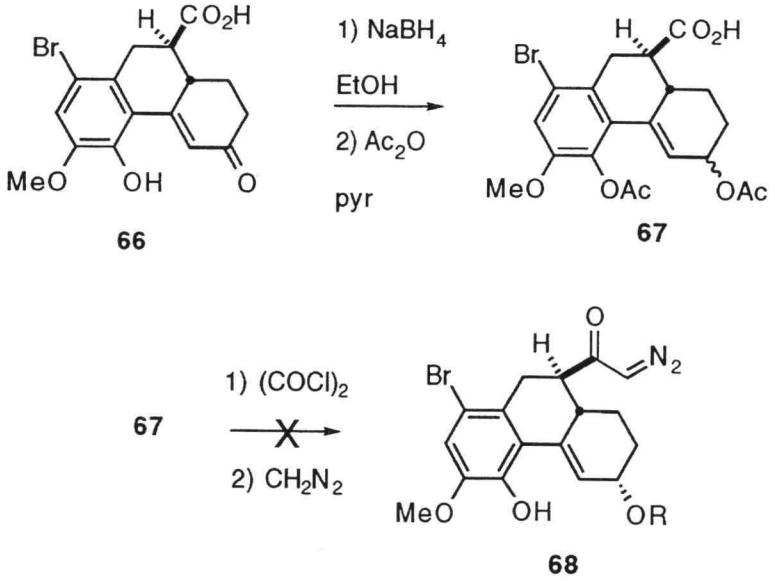
scheme 32

It was observed that during the Robinson annelation the hydrolysis of the carbomethoxy group occurred as a side reaction. Following up on this observation, we could obtain the phenanthrenonecarboxylic acid **66** directly by simple treatment of **59 b** with a 1M potassium hydroxide solution. Compound **66** was thus available in much better yield than was the case when the corresponding ester was isolated (scheme 33).



scheme 33

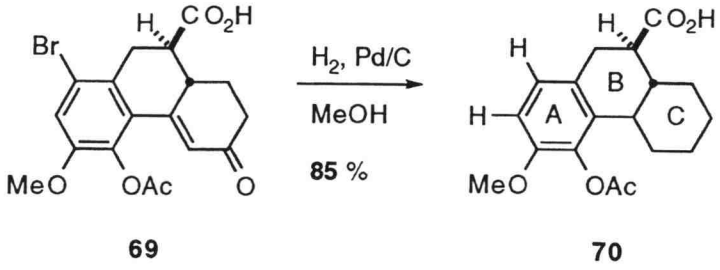
Several attempts were made to transform this unusually polar and insoluble material to a diazoketone of the type **68** that was envisioned in our original plan (see retrosynthetic analysis scheme 15). While the reduction of **66** with sodium borohydride and the acetylation could be carried out to afford **67** in low yield, activation of the carboxyl group with oxalyl chloride resulted in decomposition (scheme 34).

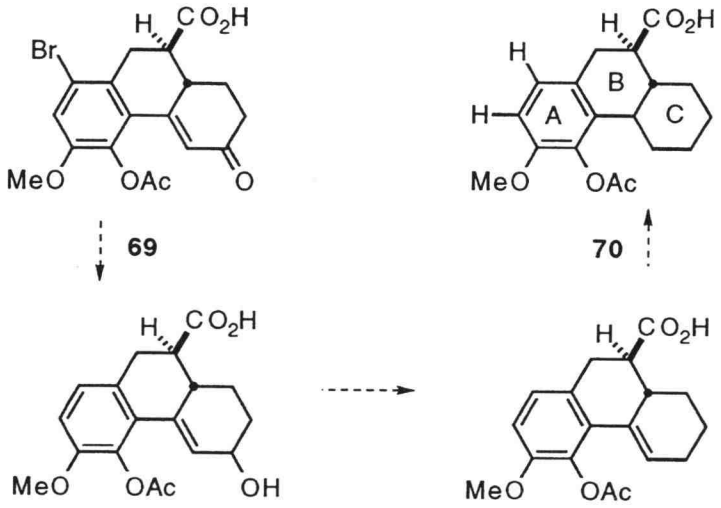


scheme 34

Although **66** was uncooperative it was hoped that structural changes could be introduced which would lead to a more stable series of compounds and which would allow for the elaboration of the diazoketone from the carboxylic acid. Acetylation of **66** greatly improved the solubility and stability of the compound.

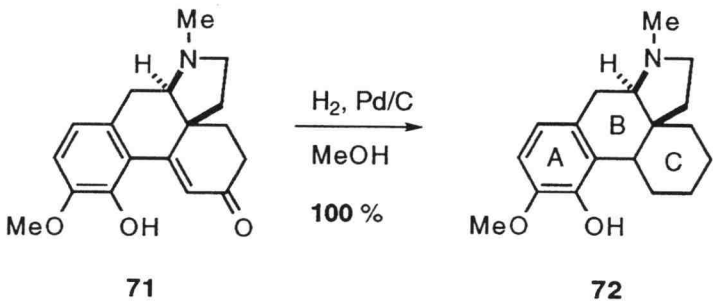
However, in an attempt to remove bromine from the tricyclic nucleus, hydrogenation of the acetate **69** unexpectedly yielded **70** (scheme 35). In addition to debromination, conversion of the enone to a saturated C ring occurs, presumably via 1,2-reduction of the ketone and hydrogenolysis of the resultant allylic alcohol. The latter then undergoes further reduction of the trisubstituted double bond.





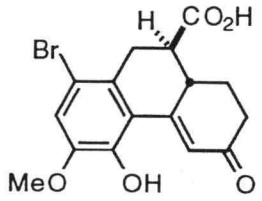
scheme 35

An analogous result was reported by Gates *et al.* [46]while studying the hydrogenation of the thebaine derived product **71** (scheme 36).

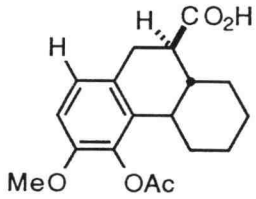


scheme 36

After more experimentation with carboxylic acids **66** and **70**, it was concluded that only protected carboxylic acid **69** could be converted in a satisfactory manner to a diazoketone.

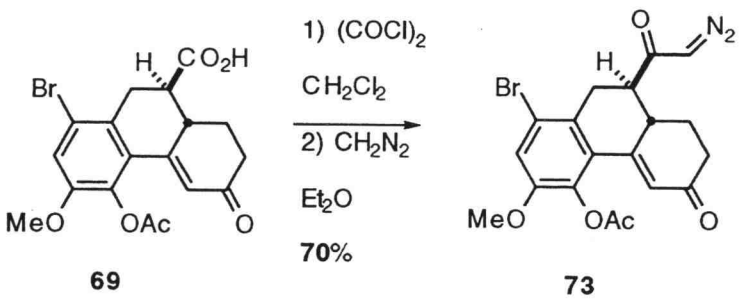


66



70

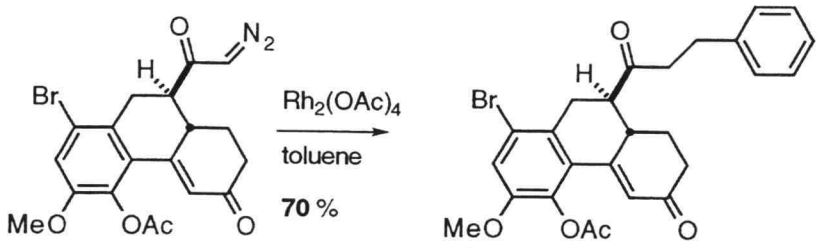
This was accomplished by treatment of **69** with oxalyl chloride, followed by reaction of the unisolated acyl chloride with diazomethane. The diazoketone **73** was found to be relatively stable (scheme 37).



69 **73**

scheme 37

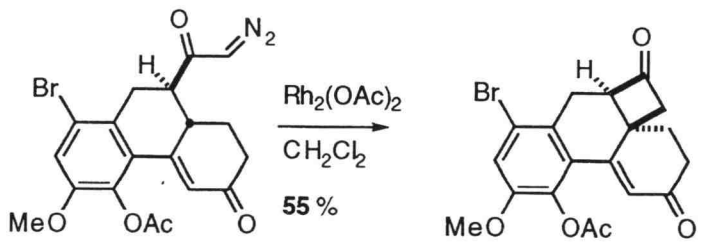
First experiments with **73** were not encouraging, for exposure of **73** to rhodium acetate in toluene resulted in reaction with the solvent to afford **74** as the sole product (scheme 38). This *intermolecular* insertion into the benzylic methyl group is not without precedent[47] but was surprising in view of the several alternative pathways which appeared to be accessible to **73**.



73 **74**

scheme 38

By contrast, when diazoketone **73** was reacted in dichloromethane, *intramolecular* C-H insertion was the main pathway leading to the cyclobutanone **75** as a beautifully crystalline material (scheme 39). Formation of **75** was not the desired outcome, and the insertion into the γ-hydrogen of the enone moiety was unexpected. Although studies have shown that methine protons are the preferred site for rhodium (II) catalyzed intramolecular C-H insertions,[48] the formation of a cyclobutanone is typically observed only as a minor side reaction rather than the main reaction pathway.[49]



73 **75**

scheme 39

The identity of **75** was independently verified by X-ray diffraction analysis (figure 2.2). The crystal structure reveals interesting conformational details including the fact that the cyclobutanone ring stands out perpendicularly with respect to the π-system of the aromatic ring and the enone.

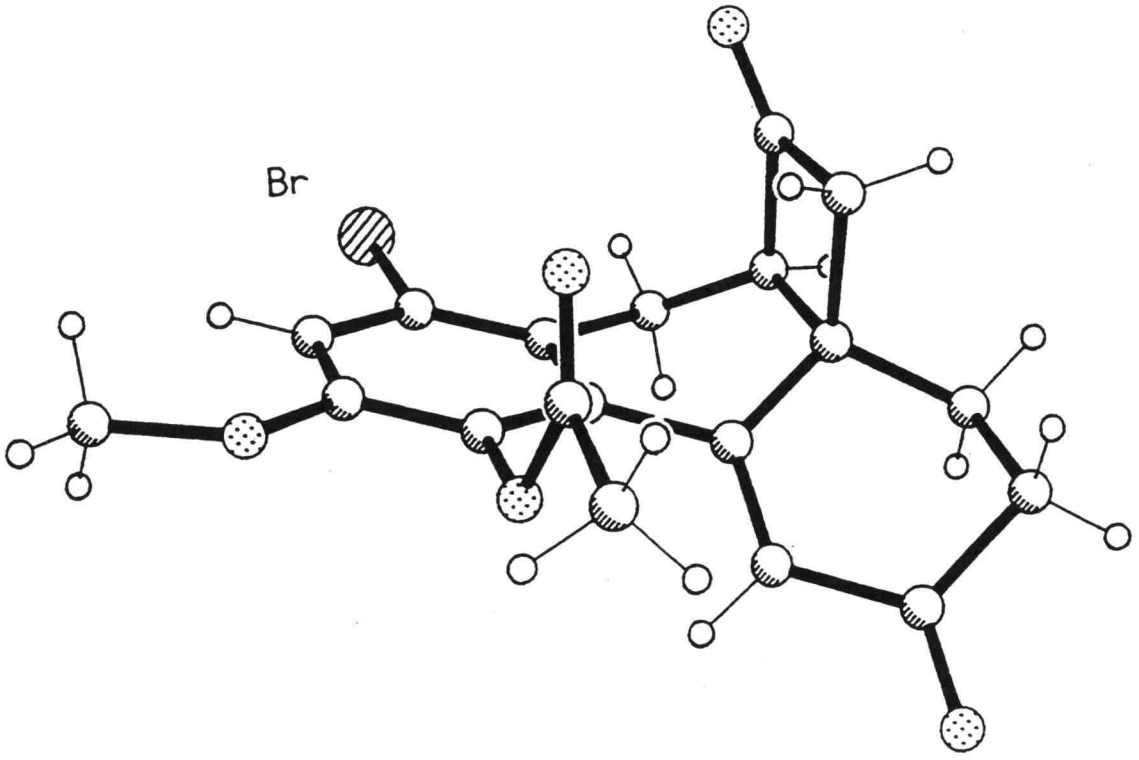
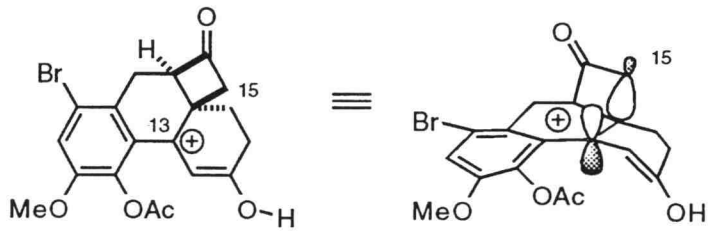


Figure 3.2: TELP Representation from X-ray Structure of **75**.

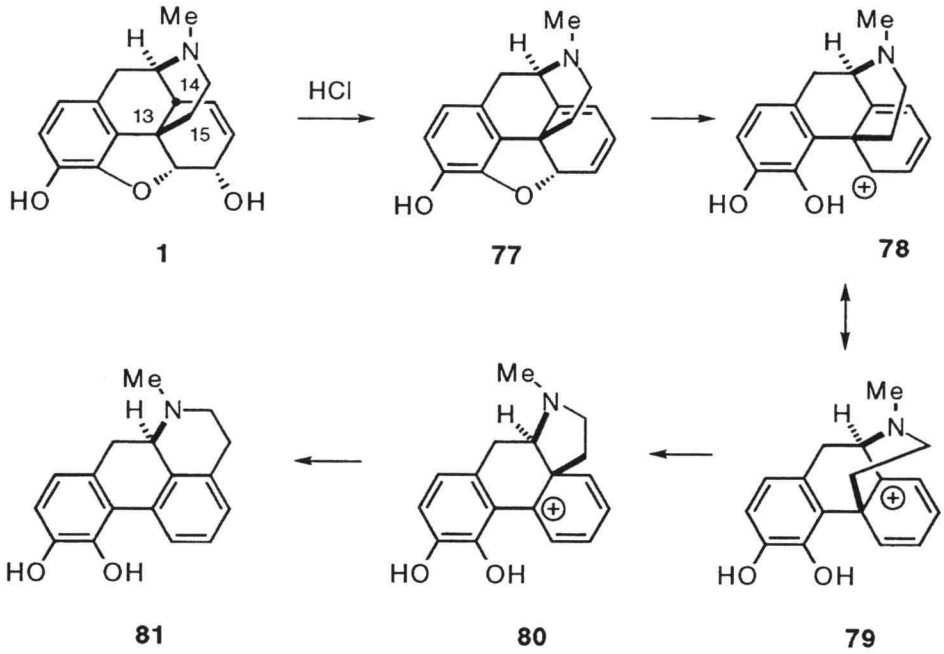
The C-H insertion process which leads to **75** and which creates a quaternary carbon center, generates a new carbon-carbon bond between the carbons 14 and 15 rather than carbon 13 and 15 as had been hoped. Access to the morphine skeleton thus appeared to be blocked by the propensity of diazoketone **73** to form a cyclobutanone rather than a cyclopentanone.

This predicament led us to examine the prospects for a rearrangement of **75** involving a 1,2-alkyl shift of carbon 15 to carbon 13 (morphine numbering). The geometry of **75**, as revealed by its crystal structure is clearly conducive to a rearrangement with the cyclobutanone placed perpendicular to the π-system of the aromatic ring and the enone. This implies that the σ-bond between carbon 14 and carbon 15 should be in position to overlap favorably with the vacant p-orbital of carbon 13 during this Wagner-Meerwein rearrangement.[50]



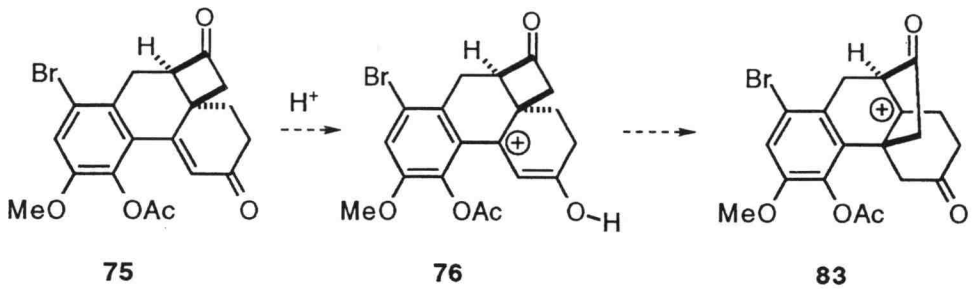
76

There should, in principle, be substantial driving force for this rearrangement since it would relieve ring strain of the cyclobutanone, which is approximately 30 kcal/mol.[51] On the other hand, a well known skeletal rearrangement of morphine offers precedence for the reverse event since it has been noted that during the acid-catalyzed conversion of morphine (**1**) to apomorphine (**81**), a ring contraction occurs in which carbon 15 migrates from carbon 13 to 14.[52] This would appear to be driven by the increased stability of carbocation **80** relative to **79** (scheme 40).



scheme 40

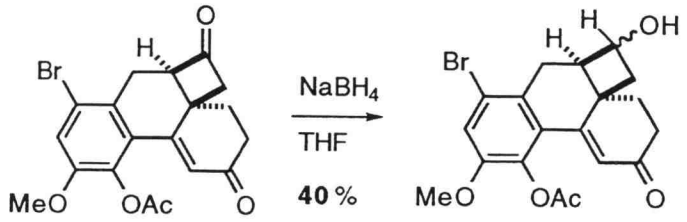
In the conversion of **1** to **80**, where ring contraction of a piperidine to a pyrrolidine takes place, ring strain clearly is less important than carbocationic stability. On the other hand, relief of ring strain associated with the rearrangement of **75** should be the dominant factor and should outweigh the difference in stability of carbocations **76** and **83**. Thus, expansion of the cyclobutanone should provide significant thermodynamic driving force in the direction of **83** (scheme 41).



scheme 41

Much to our disappointment, however, **75** did not show any inclination to undergo the expected rearrangement. A variety of mineral and Lewis acids were combined with **75** but to no avail. Cleavage of the acetate in **75** was the only reaction observed after extended exposure to acids, including *p*-toluenesulfonic acid in refluxing toluene.

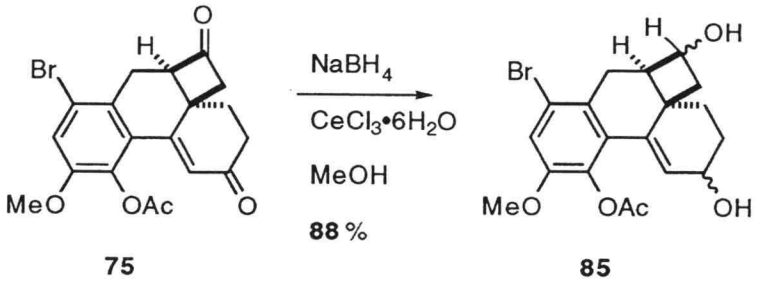
It was reasoned that, because the carbonyl group of the cyclobutanone decreases the migratory aptitude of carbon 15, rearrangement could be effected if this ketone were reduced. While studying the reduction of **75** it was found that the cyclobutanone is reduced at a faster rate than the cyclohexenone with sodium borohydride in tetrahydrofuran. By this means, the alcohol **84** was available in modest yield and was subjected to the same conditions as had been explored with **75**. Again, no rearrangement of **84** could be induced (scheme 42).



75 **84**

scheme 42

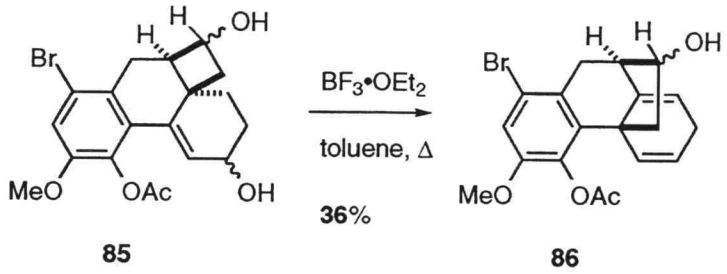
Reduction of both keto groups of **75** could be carried out under Luche conditions[53] and gave a diastereomeric mixture of four diols **85** in variable yields (scheme 42). The mixture of diols **85** was unstable and consequently difficult to handle. Chromatographic purification, for example, led to decomposition and low mass recovery.



75 85

scheme 43

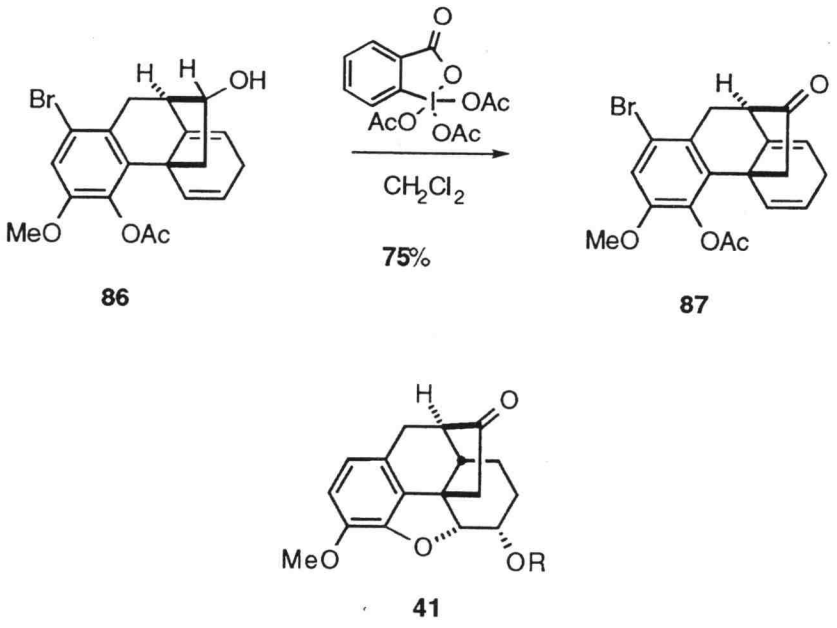
When the diols **85** were treated with Lewis acids (boron trifluoride etherate, titanium tetrachloride, stannic chloride or, diethylaluminum chloride) at low temperature in dichloromethane, slow decomposition of the starting material and no rearrangement was observed. Eventually, it was found that **85** could be rearranged in the presence of a catalytic amount of boron trifluoride etherate in refluxing toluene. An epimeric mixture of dienyl alcohols **86** was thus obtained in 36% yield (scheme 43).



85 86

scheme 44

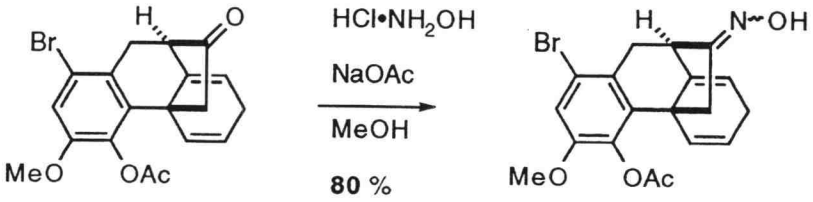
The mixture of alcohols **86** was oxidized to a single ketone **87** in good yield (scheme 45).[54] Tetracycle **87** possesses the complete carbon framework of morphine and structurally resembles the ketone **41** which, according to our original plan (scheme 16), was to be converted to lactam **40** via Beckmann rearrangement.



86 **87** **41**

scheme 45

Several unsuccessful attempts were made to obtain a crystalline sample of **87** or a derivative suitable for X-ray analysis. It was decided therefore to continue forward from **87**, and its oxime derivative **88** was prepared in the hope that it could be subjected to the Beckmann rearrangement to yield the desired δ-lactam (scheme 45).

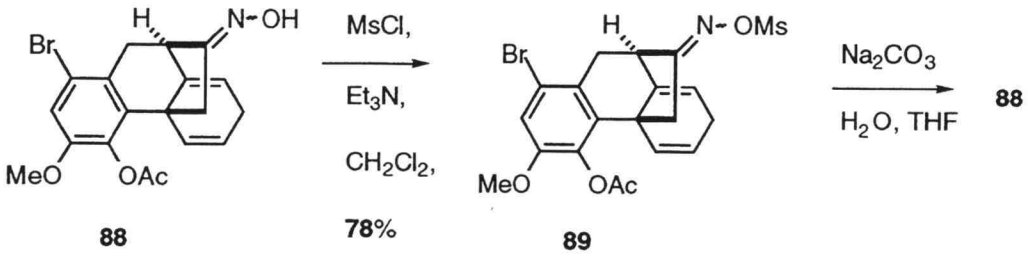


87 **88**

scheme 46

Tosylation of the hydroxyl group of oxime of **88** proved difficult and gave no useful result. However, an unstable mesylate **89** was prepared in good yield.[55] Unfortunately, attempted rearrangement of **89** under basic conditions led

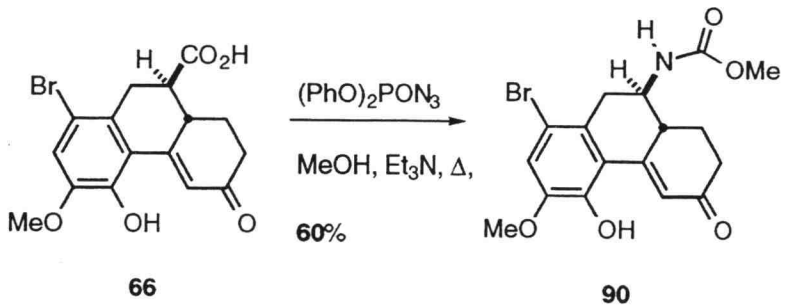
to hydrolysis of the oxime mesylate, resulting in recovery of **88** (scheme 47). The oxime **88** was found to decompose after prolonged exposure to base. Attempts to induce Beckmann rearrangement of **88** or its mesylate **89** under acidic conditions, for example with trimethylsilyl iodide, were also unsuccessful.



scheme 47

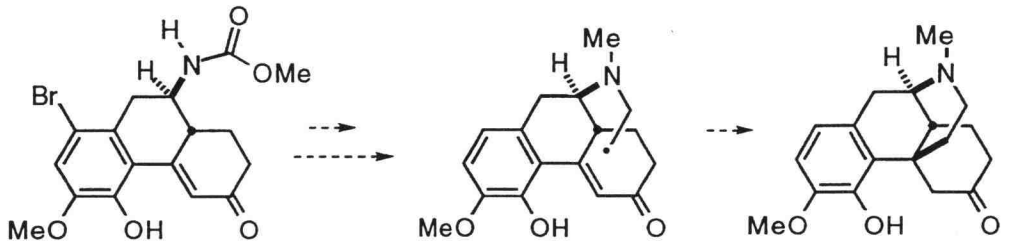
Although a negative result has to be viewed with caution, we must conclude that the Beckmann rearrangement of oxime **88** is not feasible by conventional methods and further experimentation is required to establish a route from **87** to morphine. Changes in the structure of ketone **87**, for example, by debromination or dihydrofuran ring closure, or a variation in the conditions of the Beckmann rearrangement could lead to the desired product.

In a different approach to the morphine structure, it has been possible to perform a Curtius rearrangement at the stage of the tricyclic phenanthrenone carboxylic acid **66**.



scheme 48

Initial experiments with **66** have been promising and have led to **90** (scheme 48). It is hoped that the urethane **90** can be transformed to the tetracyclic morphinan skeleton along the lines of a radical cyclization strategy shown in scheme 49.[56]



90

scheme 49

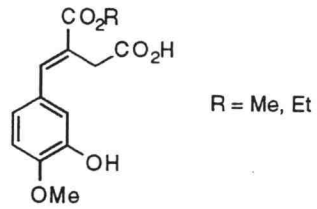
In summary, we have demonstrated that a new series of tetracyclic "carbomorphinan" compounds are available from a phenanthrenone precursor **63**. The route to these novel structures involves cyclobutanone formation by intramolecular insertion of a diazoketone and a subsequent ring expansion via Wagner-Meerwein rearrangement.

These tetracyclic compounds may ultimately be useful for a total synthesis of morphine and related alkaloids. In addition, these intermediates provide access to potentially valuable analogs of morphine which cannot easily be made through synthetic modification of natural morphine alkaloids.[57]

Experimental Section

General

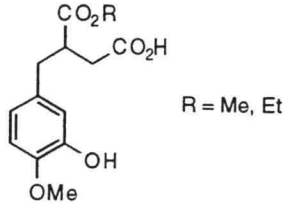
General experimental techniques and instrumentation used in this work are outlined in part I chapter IV.



4-[3-Hydroxy-4-methoxyphenyl]-3-carbomethoxy-3-butenoic acid (51 b). A solution of sodium methoxide was prepared from sodium metal (2.3 g, 0.10 mol) and methanol (100 mL). To that solution was added isovanillin (**46**) (5.01 g, 0.032 mol) and dimethyl succinate (5.02 g, 0.034 mol) followed by lithium chloride (10 g, 0.23 mol). The resulting yellow suspension was refluxed for 18 h. The color of the mixture changed from yellow to dark orange. The mixture was allowed to cool to room temperature and was taken up with aqueous 10% sulfuric acid (400 mL) and extracted with ether (4 x 150 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Recrystallization of the residue from methanol afforded 7.61 g (86%) of **51 b** as a orange solid: mp 183°C; IR (KBr) 3347, 2883, 2939, 1733, 1687, 1606, 1588, 1511, 1444, 1278, 1212, 1163, 1126, 1022, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (2H, m), 3.82 (3H, s), 3.90 (3H, s), 6.60-6.95 (3H, m), 7.81 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.5, 52.3, 55.9, 110.7, 115.3, 121.9, 123.4, 127.9, 142.4, 145.6, 147.5, 168.2, 177.0; MS(EI) *m/z* 266 (M^+, 27), 222, 175, 167, 163, 162, 162, 147, 131, 119, 103, 91;

HRMS *m/z* calcd for $C_{13}H_{14}O_6$ (M^+): 266.0790. Found: 266.0790. Anal. Calcd for $C_{13}H_{14}O_6$ C; 58.65; H; 5.30. Found: C; 58.54; H; 5.27.

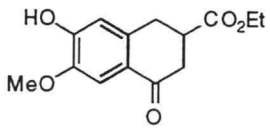
4-[3-Hydroxy-4-methoxyphenyl]-3-carboethoxy-3-butenoic Acid (51 a). The ethyl ester **51 a** was prepared in a manner analogous to that used for the methyl ester **51 b** described above: IR (KBr) 3343, 2883, 2939, 1734, 1687, 1606, 1588, 1511, 1441, 1278, 1212, 1163, 1126, 1022, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3 H, t, J=7Hz), 3.61 (2H, m), 3.80 (3H, s), 4.23 (2H, q, J=7Hz), 6.60-6.95 (3H, m), 7.81 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 28.9, 56.1, 60.8, 110.2, 114.1, 125.6, 130.5, 146.1, 151.9, 145.6, 147.5, 172.2, 172.3, 177.0; MS(EI) *m/z* 280 (M^+), 236, 175, 162, 147, 131, 119, 103, 103, 91; HRMS *m/z* calcd for $C_{14}H_{16}O_6$ (M^+): 280.0947. Found: 280.0946.



4-[3-Hydroxy-4-methoxyphenyl]-3-carbomethoxybutanoic Acid (52 b). To a solution of **51 b** (5.50 g, 0.020 mol) in ethanol (200 mL) was added 10% palladium on carbon (300 mg, 1.4 mol%). The flask was flushed with hydrogen gas and the mixture was stirred vigorously. After 3 h the mixture was filtered over Celite, and the filtercake was washed with ether. After evaporation of the filtrate there was obtained 5.51g of crude **52 b**: IR (neat) 3447, 3234, 2980, 1724, 1715, 1513, 1274, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (1H, m), 2.68 (2H, m), 3.05 (2H, m), 3.46 (1H, s), 3.66 (3H, s), 3.83 (3H, s), 6.65 (3H, m), 7.30 (1H, bs); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.9, 42.8, 52.0, 55.9, 110.8, 115.2, 120.5, 131.1, 145.4, 145.5, 174.7, 177.0;

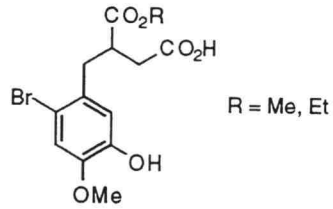
MS(EI) *m/z* 268 (M^+), 208, 137, 131, 122, 103, 94, 77; HRMS *m/z* calcd for $C_{13}H_{16}O_6$ (M^+): 268.0947. Found: 268.0947.

4-[3-Hydroxy-4-methoxyphenyl]-3-carboethoxybutanoic Acid (52 a). The ethyl ester **52 a** was prepared in a manner analogous to that used for the methyl ester **52 b** described above: IR (neat) 3447, 3234, 2980, 1724, 1715, 1513, 1274, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3 H, t, J=7Hz), 2.4-3.0 (5H, m), 3.85 (3H, s), 4.14 (2H, q, J=7Hz), 6.60 (d, 1H, J=8Hz), 6.71 (d, 1H, J=1Hz), 6.75 (d, 1H, J=8Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 34.6, 37.0, 42.9, 56.0, 60.8; 110.7, 115.2, 120.5, 131.2, 145.4, 145.6, 174.1, 177.4; MS(EI) *m/z* 282.2 (M^+), 208, 191, 137, 122, 103, 94, 77; HRMS *m/z* calcd for $C_{14}H_{18}O_6$ (M^+): 282.1103. Found: 282.1102.



3-Carboethoxy-6-hydroxy-7-methoxy-1-tetralone (53). To a solution of **52 a** (10 mg, 0.035 mmol) in ether (1 mL) was added 100% sulfuric acid (30 μL). The resulting mixture was stirred at room temperature for 2 h and diluted with water (3 mL). The phases were separated, and the aqueous layer was back extracted with ether (2 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 5 mg (53%) of **53**: IR (neat) 3385, 3380, 2996, 1730, 1669, 1610, 1580, 1308, 1280, 1213, 1188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 (3H, t, J=7Hz), 3.13 (3H, m), 3.92 (3H, s), 4.16 (1H, q, J=7Hz), 6.13 (1H, bs), 6.77 (1H, s), 7.51 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8, 173.2, 151.0, 145.9, 137.2, 125.0, 113.9, 108.3, 61.0, 56.2, 40.5, 40.2, 31.5, 14.1; MS (EI) *m/z* 264 (M^+), 192,

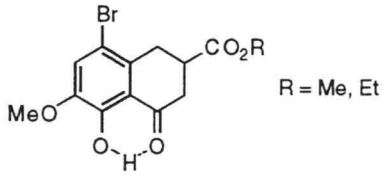
191, 131, 103, 91. HRMS *m/z* calcd for $C_{14}H_{16}O_5$ (M^+): 264.0998. Found: 264.0997.



4-[6-bromo-3-Hydroxy-4-methoxyphenyl]-3-carbomethoxy-3-butanoic Acid (56 b). To a stirred solution of **52 b** (2.50 g, 9.33 mmol) in glacial acetic acid (50 mL) was added dropwise a solution of bromine (0.50 mL, 9.4 mmol) in acetic acid (1 mL). The mixture was stirred at room temperature for 0.5 h, after which aqueous sodium thiosulfate (50 mL) and water (200 mL) were added. The resulting mixture was extracted with ether (4 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. There was obtained 2.10 g (65%) of crude **56 b**. Due its very polar nature, **56 b** was used without further purification: IR (neat) 3315, 3238, 2983, 1715, 1502, 1441, 1277, 1230, 1183, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (1H, s), 2.75 (2H, m), 3.15 (2H, m), 3.68 (3H, s), 3.86 (3H, s), 6.00 (1H, s), 6.75 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.7, 37.0, 41.4, 52.1, 56.2, 113.5, 115.2, 116.7, 130.2, 145.0, 146.1, 174.4, 177.4; MS(EI) *m/z* 348, 346 (M^+), 269, 267, 271, 216, 215, 214, 191, 159, 127, 118; HRMS *m/z* calcd for $C_{13}H_{15}O_6Br$ (M^+): 346.0052. Found: 346.0054.

4-[6-bromo-3-Hydroxy-4-methoxyphenyl]-3-carboethoxy-3-butanoic Acid (56 a). The ethyl ester **56 a** was prepared in a manner analogous to that used for the methyl ester **56 b** described above: IR (neat) 3315, 3238, 2983, 1715, 1502, 1441, 1277, 1230, 1183, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3 H, t, J=7Hz), 2.4 (2H, m), 2.80 (1H, m), 3.10 (2H,

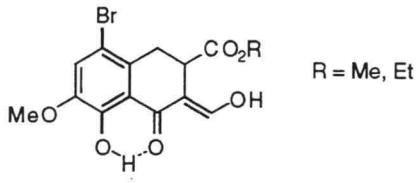
m); 3.88 (3H, s), 4.14 (2H, q, J=7Hz), 6.75 (s, 1H), 6.98 (s, 1H); MS(EI) *m/z* (rel. intensity) 362, 360 (M^+), 288, 281, 271, 235, 217, 193, 172, 162, 147, 131, 103, 91; HRMS *m/z* calcd for $C_{14}H_{17}O_6Br$ (M^+): 360.0209. Found: 360.0208.



5-Bromo-3-carbomethoxy-8-hydroxy-1-oxo-7-methoxy-1, 2, 3, 4-tetrahydronaphthalene (57 b). To crude **57 b** (11.50 g, 34.0 mmol) was added 100% sulfuric acid (30 mL). The resulting syrup was stirred at room temperature for 4 h, cooled to 0°C, diluted with methanol (100 mL), and stirred at room temperature for 2 h. The mixture was diluted with brine (200 mL) and extracted with ether (6 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Recrystallization of the residue from methanol afforded 7.40 g (65%) of **57 b** as a yellow solid: mp 95°C; IR (KBr) 2928, 1731, 1643, 1465, 1435, 1281, 1245, 1181, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85-3.30 (5H, m), 3.74 (3H, s), 3.87 (3H, s), 7.20 (1H, s), 12.7 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.8, 39.0, 39.9, 52.3, 56.3, 111.4, 116.9, 121.3, 131.0, 147.6, 152.7, 172.9, 202.9; MS(EI) *m/z* (rel. intensity) 330, 328 (M^+), 298, 296, 271, 269, 253, 239, 191, 189, 175, 119; HRMS *m/z* calcd for $C_{13}H_{13}O_5Br$ (M^+): 327.9946. Found: 327.9946. Anal. Calcd for $C_{13}H_{13}O_5Br$ C; 47.44; H; 3.98. Found: C; 47.52; H; 3.76.

5-Bromo-3-carboethoxy-8-hydroxy-1-oxo-7-methoxy-1, 2 ,3, 4-tetrahydronaphthalene (57 a). The ethyl ester **57 a** was prepared in a manner analogous to that used for the methyl ester **57 b** described above: IR (KBr) 2928, 1731, 1643, 1465, 1435, 1281, 1245, 1181, cm^{-1}; ^1H NMR (300

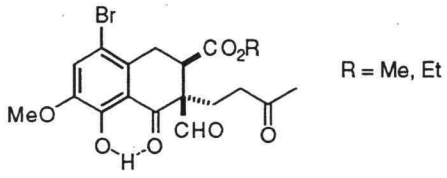
MHz, $CDCl_3$) δ 1.26 (3H, t, J=7Hz), 2.90-3.20 (5H, m), 3.88 (3H, s), 4.17 (2H, t, J=7Hz), 7.20 (1H, s), 12.7 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 32.0, 39.3, 40.1, 56.4, 61.3, 111.4, 117.0, 123.3, 131.1, 151.4, 152.9, 172.5, 203.0; MS(EI) *m/z* 344, 342 (M^+), 298, 296, 282, 280, 269, 255, 192, 190, 159, 127; HRMS *m/z* calcd for $C_{14}H_{15}O_5Br$ (M^+): 342.0103. Found: 342.0103.



5-Bromo-3-carbomethoxy-2-formyl-8-hydroxy-1-oxo-7-methoxy-1, 2 ,3, 4-tetrahydronaphthalene (58 b). To a suspension of 60% sodium hydride dispersion in mineral oil (38 mg, 1.0 mmol) in toluene (0.5 mL) was added methyl formate (1 mL, 12.4 mmol). To the foamy suspension was added **57 b** (101 mg, 0.31 mmol) in toluene (3 mL). The resulting mixture was stirred at room temperature for 18 h, after which aqueous 0.1 N hydrochloric acid (10 mL) was added. The layers were separated, and the aqueous layer was back extracted with ether (3 x 5 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. There was obtained 110 mg of crude **58 b**. Due to its oxygen sensitivity, **58 b** was used directly without further purification: IR (neat) 2928, 1726, 1613, 1467, 1439, 1409, 1356, 1242, 1215, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90 (1H, dd, J=4.0, 1 Hz), 3.60 (2H, m), 3.74 (3H, s), 3.94 (3H, s), 7.16 (1H, s), 7.53 (1H, d, J=10Hz), 12.18 (1H, s).

5-Bromo-3-carboethoxy-2-formyl-8-hydroxy-1-oxo-7-methoxy-1, 2 ,3, 4-tetrahydronaphthalene (58 a). The ethyl ester **58 a** was prepared in a manner analogous to that used for the methyl ester **58 b**

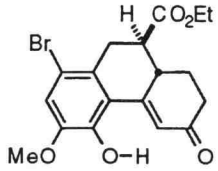
described above: IR (neat) 2928, 1726, 1613, 1467, 1439, 1409, 1356, 1242, 1215, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, t, J=7Hz), 2.90 (1H, dd, J=4.0, 1 Hz), 3.62 (2H, m), 3.87 (3H, s), 4.10 (2H, m), 7.16 (1H, s), 7.53 (1H, d, J=10Hz), 12.18 (1H, s).



5-Bromo-3-carbomethoxy-2-[1-(3-butanone)]-2-formyl-8-hydroxy-1-oxo-7-methoxy-1, 2 ,3, 4-tetrahydronaphthalene (59 b). To a cold (0°C) solution of crude **58 b** (110 mg, 0.28 mmol) in dichloromethane (4 mL) was added freshly distilled methyl vinyl ketone (300 μL, 5 mmol) followed by triethylamine (10 μL, 0.14 mmol). The resulting mixture was stirred at room temperature for 5 h, after which the volatile components were evaporated in vacuo. Chromatography of the residue afforded 116 mg (86%) of **59 b**: IR (neat) 2928, 1721, 1638, 1465, 1435, 1311, 1258, 1206, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (1H, s), 2.10 (3H, s), 2.90 (1H, m), 3.15 (1H, m),3.45 (1H, m), 3.60-3.80 (3H, m), 3.94 (3H, s),7.20 (1H, s), 10.31 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 28.7, 30.0, 36.9, 45.6, 52.8, 56.4, 57.0, 60.4, 111.8, 121.8, 127.8, 148.2, 153.5, 171.1, 173.2, 200.0, 202.1; MS(CI) m/z 428, 426 (M^+), 383, 381, 368, 366, 343, 341, 283, 281; HRMS *m/z* calcd for $C_{18}H_{19}O_7Br$ (M^+): 426.0314. Found: 426.0313.

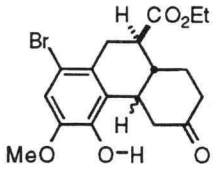
5-Bromo-3-carboethoxy-2-[1-(3-butanone)]-2-formyl-8-hydroxy-1-oxo-7-methoxy-1, 2, 3, 4-tetrahydronaphthalene (59 a). The ethyl ester **59 a** was prepared in a manner analogous to that used for the methyl ester **59 b** described above: IR (neat) 2928, 1721, 1638, 1465, 1435,

1311, 1258, 1206, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, t, J=7Hz), 2.07 (3H, s), 2.41 (2H, m), 2.80 (1H, m), 3.01 (2H, m), 3.45 (2H, m), 3.85 (3H, s), 4.02 (1H, m), 4.20 (2H, m), 3.94 (3H, s),7.20 (1H, s), 10.31 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 26.5, 29.9, 30.0, 37.0, 37.8, 45.9, 56.9, 61.7, 111.8, 115.8, 121.8, 128.0, 148.2, 153.5, 172.6, 200.0, 202.1, 202.7.

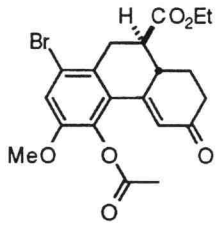


8-Bromo-10-carboethoxy-5-hydroxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydrophenanthrene (60). To a solution of sodium ethoxide prepared from sodium (200 mg, 8.70 mmol) and ethanol (50 mL) was added a solution of **59 a** (1.20 g, 2.72 mmol) in ethanol (20 mL), and the mixture was refluxed for 1 h. Most of the ethanol was carefully evaporated in vacuo, and the residue was acidified by addition of aqueous 10 % hydrochloric acid (50 mL). The mixture was extracted with ether (3 x 40 mL) and ethyl acetate (4 x 40 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 512 mg (47%) of **60** as a colorless solid: IR (KBr) 2919, 2850, 1728, 1657, 1466, 1284, 1181, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, J=7Hz), 1.81 (1H, m), 2.20 (1H, m), 2.55 (3H, m), 2.95 (2H, m), 3.14 (1H, dd, J=16, 6Hz), 3.91 (3H, s), 4.19 (2H, m), 6.62 (1H, s), 7.10 (1H, s), 7.38 (1H, d, J=2Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 27.7, 33.6, 36.6, 38.6, 46.3, 56.6, 61.0, 113.5, 115.9, 120.2, 128.7, 129.1, 145.3, 145.6, 152.4, 174.0, 200.3; MS(EI) *m/z* 396, 394 (M^+), 368, 366, 323, 321, 294, 292, 265, 263, 241, 186, 171, 143, 115, 89; HRMS *m/z* calcd for $C_{18}H_{19}O_5Br$ (M^+): 394.0416.

Found: 394.0416. Anal. Calcd for $C_{18}H_{19}O_5Br$ C; 54.70; H; 4.85. Found: C; 54.58; H; 4.66.



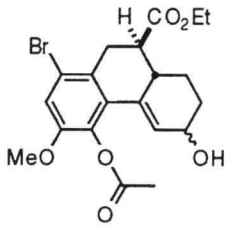
8-Bromo-10-carboethoxy-5-hydroxy-6-methoxy-3-oxo-1, 2, 4, 4a, 9, 10-hexahydrophenanthrene (65). To a solution of **60** (220 mg, 0.55 mmol) in aqueous 0.1 N sodium hydroxide (50 mL) was added 2% sodium amalgam (6 g, 0.6 mmol), and the mixture was stirred at room temperature until the red color of the solution disappeared. The mixture was filtered and the filtrate was acidified by careful addition of aqueous 1 N hydrochloric acid . The mixture was extracted with ether (3 x 40 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuo. There was obtained 180 mg (84%) of **65**: IR (KBr) 3389, 3383, 2938, 1722, 1702, 1478, 1435, 1285, 1239, 1179, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.3 (3H, m), 1.65 (1H, m), 2.01-2.25 (3H, m), 2.31-2.65 (2H, m), 2.81-3.20 (3H, m), 3.60 (1H, m), 3.87 (3H, s), 3.90 (1H, m), 4.23 (2H, m), 5.90 (1H, bs), 6.98 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 27.8, 28.4, 33.3, 34.3, 34.9, 36.3, 36.7, 38.9, 41.0, 42.1, 42.3, 42.8, 45.2, 45.6, 56.3, 60.7, 60.8, 113.3, 113.5, 124.9, 125.7, 126.4, 127.9, 141.8, 143.4, 144.9, 145.2, 171.7, 174.8, 210.4, 211.0; MS(EI) *m/z* 398, 396 (M^+), 324, 322, 318, 317, 307, 305, 279, 267, 265, 244, 243, 227, 226, 213, 201, 187, 183, 175, 167, 160, 149, 144, 143, 131, 128, 115, 103, 84; HRMS *m/z* calcd for $C_{18}H_{21}O_5Br$ (M^+): 396.0572. Found: 396.0572.



5-Acetoxy-8-bromo-10-carboethoxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydrophenanthrene (61). To a solution of **60** (90 mg, 0.23 mmol) in dichloromethane (4 mL) was added acetic anhydride (30 mg, 0.30 mmol), triethylamine (40 μL, 0.4 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 5 h, after which aqueous 0.1 N hydrochloric acid (20 mL) was added and the mixture was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 81 mg (80%) of **61**: IR (KBr) 2942, 1770, 1730, 1670, 1601, 1558, 1472, 1287, 1262, 1124, 912, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, J=7Hz), 1.85 (1H, m), 2.18 (1H, s), 2.26 (3H, s), 2.50 (2H, m), 2.71 (1H, m), 2.98 (2H, m), 3.20 (1H, dd, J=16, 10Hz), 3.80 (3H, s), 4.15 (2H, q, J=7Hz), 6.55 (1H, s), 7.18 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.2, 20.7, 27.5, 31.9, 36.0, 37.3, 45.7, 56.4, 61.1, 117.6, 121.0, 128.0, 128.6, 129.3, 136.9, 150.5, 152.6, 168.2, 173.2, 199.0; MS(EI) *m/z* 438, 436 (M^+), 396, 394, 323, 321, 279, 277, 265, 263, 242, 240, 214, 213, 185, 128; HRMS *m/z* calcd for $C_{20}H_{21}O_6Br$ (M^+): 436.0521. Found: 436.0521.

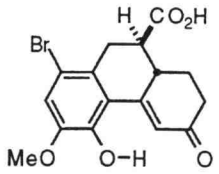
Compound **61** crystallized in the tetragonal space group I4(1)/a with a=26.878 (4) Å, b=26.878 (4) Å, c=10.870 (3) Å, V=7852.78 $Å^3$, Z=16, D_{calc}=1.479 g/cm^3. All 2187 nonequivalent reflections in the range of 3.5° < 2Θ < 95° were measured on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å). The structure was solved

with direct methods (SHELXTL) using 1536 unique reflections with F > 4 σ(F). Full matrix least squares refinement with anisotropic temperature factors for all non-hydrogen atoms and calculated hydrogen atom positions led to the final discrepancy indices of R=0.0749 and $_wR$ =0.0776.

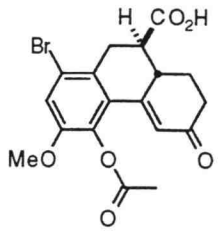


5-Acetoxy-8-bromo-10-carboethoxy-6-methoxy-3-hydroxy-1, 2, 3, 9, 10-tetrahydrophenanthrene (62). To a solution of **61** (150 mg, 0.34 mmol) in methanol (4 mL) was added sodium borohydride (20 mg, 0.4 mmol) in small portions. The mixture was stirred at room temperature for 15 min, treated with aqueous 0.1 N hydrochloric acid, and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 111 mg (75%) of **62**: IR (KBr) 3426, 2938, 1761, 1728, 1471, 1437, 1371, 1286, 1190, 1127, 1103, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, m), 1.65 (m, 1H), 1.82 (m, 2H), 2.08 (m, 1H), 2.26 (s, 3H), 2.30, 2.51 (m, 1H), 2.70 (m, 1H), 3.00 (m, 2H), 3.30 (m, 1H),3.39, 3.79 (s, 3H), 3.80, 4.15 (m, 2H), 6.32, 6.41 (s, 1 H), 7.07 (s, 1 H), 7.09; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 20.7, 20.9, 21.0, 25.0, 28.6, 29.9, 32.5, 32.8, 35.9, 36.0, 46.4, 47.7, 56.3, 60.4, 60.8, 66.1, 66.8, 115.4, 115.6, 121.4, 127.4, 127.5, 130.5, 130.6, 132.8, 134.2, 136.2, 150.2, 150.2, 168.7, 173.2, 174.3, MS(EI) *m/z* 440, 438 (M^+), 422, 420, 402, 380, 378, 348, 307, 306, 305, 304, 303, 291, 289, 287, 280, 279, 278, 227, 226, 225, 224, 211, 210, 208, 198, 194, 193, 183,

165, 153, 152, 139, 128, 115; HRMS *m/z* calcd for $C_{20}H_{23}O_6Br$ (M^+): 438.0678. Found: 438.0678.

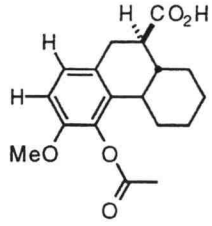


8-Bromo-5-hydroxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydro phenanthrene-10-carboxylic Acid (66). A solution of **59 b** (2.0 g, 4.54 mmol) in aqueous 1.0 M potassium hydroxide (100 mL) was stirred at room temperature for 7 h. The mixture was acidified with aqueous 10 % hydrochloric acid (50 mL) during which the red color of the solution disappeared and a white precipitate formed. Filtration of the mixture through a Büchner funnel provided 1.40 g (86%) of crude **66** as a colorless solid: mp 264°C; IR (KBr) 2928, 1702, 1609, 1466, 1245, 1181, cm^{-1}; ^1H NMR (400 MHz, D_6-DMSO) δ 1.75 (1H, m), 2.11 (1H, m), 2.41 (2H, m), 2.85 (2H, m), 3.82 (3H, s), 7,15 (1H, s), 7.27 (1 H, s), 9.71 (1H, s); ^{13}C NMR (D_6-DMSO, 100 MHz) δ 27.6, 32.8, 36.3, 37.8, 45.2, 56.5, 112.0, 116.5, 120.9, 127.5, 128.4, 145.9, 146.9, 153.2, 174.9, 199.2,; MS(EI) *m/z* 368, 366 (M^+), 323, 321, 242, 240, 215, 214, 209, 199, 186, 185, 153, 152, 139, 119; HRMS *m/z* calcd for $C_{16}H_{15}O_5Br$ (M^+): 366.0103. Found: 366.0103. Anal. Calcd for $C_{16}H_{15}O_5Br$ C; 52.34; H; 4.12. Found: C; 52.74; H; 4.00.



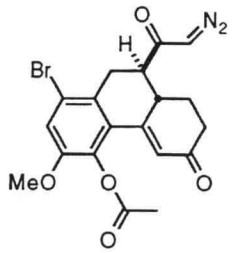
5-Acetoxy-8-bromo--6-methoxy-3-oxo-1, 2, 9, 10-tetrahydro phenanthrene-10-carboxylic Acid (69). To a suspension of **66** (238

mg, 0.65 mmol) in dichloromethane (20 mL) was added acetic anhydride (200 mL, 2.0 mmol), triethylamine (0.5 mL, 7 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at room temperature for 12 h after which aqueous 0.1 N hydrochloric acid (50 mL) was added and the mixture was extracted with ether (4 x 40 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Recrystallisation of the residue from ether afforded 250 mg (92%) of **69** as a colorless solid: mp: 196°C; IR (KBr) 2946, 1769, 1733, 1664, 1470, 1436, 1284, 1263, 1185, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (1H, m), 2.18 (1H, m), 2.50 (2H, m), 2.28 (3H, s), 3.05 (2H, m), 2.78 (1H, m), 3.20 (1H, dd, J=16, 7Hz), 3.82 (3H, s), 6.62 (1H, s), 7.22 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 27.4, 32.0, 36.4, 39.9, 45.6, 56.4, 117.9, 121.3, 128.1, 128.4,129.0, 137.1, 150.6, 152.6, 168.3, 178.0, 199.4; MS(EI) *m/z* 410, 408 (M^+), 368, 366, 323, 321, 214, 212, 186, 185, 171, 169; HRMS *m/z* calcd for $C_{18}H_{17}O_6Br$ (M^+): 408.0208. Found: 408.0207.

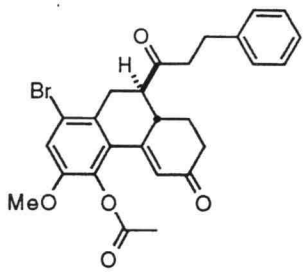


5-Acetoxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydro phenanthrene-10-carboxylic Acid (70). To a suspension of 69 (250 mg, 0.61 mmol) in methanol (10 mL) was added 10% palladium on carbon (9 mg, 1.4 mol%). The flask was flushed with hydrogen gas and the mixture was stirred vigorously. After 3 h the mixture was filtered over Celite, and the filtercake was washed with ether. After evaporation of the filtrate, there was obtained 165 mg (85%) of crude **70**: IR (KBr) 2931, 1765, 1740, 1705, 1490, 1283, 1193, 1090, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, m), 1.65 (1H, m), 1.90 (1H,

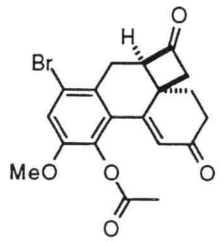
m), 2.31 (3H, s), 2.45 (2H, m), 2.71 (1H, m), 2.91 (1H, m), 3.10 (2H, m), 3.78 (3H, s), 6.92 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 26.5, 27.3, 31.2, 31.9, 34.1, 43.4, 45.0, 45.6, 56.0, 110.2, 126.7, 128.5, 132.4, 138.8, 149.7, 168.7, 181.4; MS(CI) m/z 408 (M^+), 301, 276, 231; HRMS *m/z* calcd for $C_{18}H_{22}O_5$ (M^+): 318.1467. Found: 318.1467.



5-Acetoxy-8-bromo-10-[2'-diazoacetyl]-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydrophenanthrene (73). To a solution of **69** (85 mg, 0.21 mmol) in dichloromethane (2 mL) was added oxalyl chloride (50 μL, 0.60 mmol). The mixture was stirred at room temperature for 18 h. Solvent and residual oxalyl chloride were evaporated in vacuo, and the residue was taken up in ether (3 mL) and treated with diazomethane solution in ether (1 mL). The resulting yellow solution was stirred for 1 h at room temperature and the solvent was evaporated. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 63 mg (70%) of **73**: IR (neat) 2918, 2108, 1769, 1666, 1640, 1469, 1375, 1288, 1260, 1184, 1123, 1019, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (1H, m), 2.20 (1H, m), 2.28 (3H, s), 2.49 (2H, m), 2.61 (1H, m), 3.05 (3H, m), 3.81 (3H, s), 5.39 (1H, s), 6.66 (1H, s), 7.21 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 27.1, 33.1, 35.9, 37.4, 50.7, 55.5, 56.4, 117.8, 121.3, 128.2, 128.6, 128.7, 137.3, 150.6, 152.8, 168.2, 194.3, 199.1; Anal. Calcd for $C_{19}H_{17}O_5BrN_2$ C; 52.77; H; 3.97; N; 6.48. Found: C; 52.59; H; 3.94; N; 5.78.

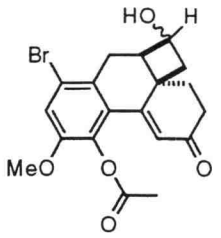


5-Acetoxy-8-bromo-10-[3-phenylpropanoyl]-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydrophenanthrene (74). To a suspension of rhodium (II) acetate dimer (3 mg, 0.007 mmol) in toluene (1 mL) was added dropwise over a period of 4 h a solution of **73** (50 mg, 0.11 mmol) in toluene (20 mL). After the addition was complete, the solvent was evaporated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 40 mg (70%) of **74**: IR (neat) 2920, 1769, 1714, 1671, 1601, 1470, 1436, 1369, 1331, 1262, 1186, 1124, 1020, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (2H, m), 2.0 (2H, m), 2.15 (1H, m), 2.28 (3H, s), 2.35 (1H, m), 2.50 (2H, m), 3.11 (3H, m), 3.80 (3H, s), 4.13 (1H, m), 6.01-6.30 (4H, m), 6.56 (1H, s), 7.17 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 20.7, 23.0, 23.1, 27.6, 32.0, 36.2, 36.7, 51.4, 56.4, 65.8, 117.6, 120.9, 126.3, 126.4, 127.1, 127.6, 127.9, 128.0, 128.4, 129.4, 150.6, 153.2, 168.2, 199.0, 199.1; MS(EI) *m/z* 498, 496 (M^+), 456, 454, 410, 408, 364, 362, 324, 323, 322, 321, 320, 263, 242, 128, 119, 106, 105, 91; HRMS *m/z* calcd for $C_{26}H_{25}O_5Br$ (M^+): 496.0885. Found: 496.0885.

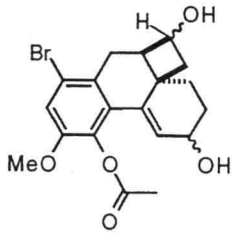


8-Acetoxy-11-bromo-2, 3, 4, 5, 6, 7-hexadehydro-9-methoxy-4-oxo-15-oxo-tetracyclo[12.2.0^{1,6}.0^{7,12}.0^{1,14}]-5-hexadecene (75). To a suspension of rhodium (II) acetate dimer (10 mg, 0.02 mmol) in dichloromethane (20 mL) was added dropwise over a period of 4 h a solution of **73** (340 mg, 0.78 mmol) in dichloromethane (60 mL). After the addition was complete, the solvent was evaporated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:1) afforded 170 mg (53%) of **75**: IR (neat) 2925, 1781, 1668, 1470, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.50 (4H, m), 2.92 (1H, m), 3.20 (1H, dd, J=18, 4Hz), 3.55 (2H, m), 3.83 (3H, s), 6.38 (1H, s), 7.22 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 27.3, 34.1, 34.7, 35.3, 56.4, 56.6, 63.9, 118.0, 121.0, 127.9, 128.7, 129.3, 137.4, 150.9, 153.4, 168.5, 198.2, 206.9; MS(EI) *m/z* 406, 404 (M^+), 364, 362, 322, 320, 307, 305, 279, 277, 265, 263, 261, 242, 240, 213, 211, 198, 197, 169, 167, 116, 113; HRMS *m/z* calcd for $C_{19}H_{17}O_5Br$ (M^+): 404.0259. Found: 404.0259.

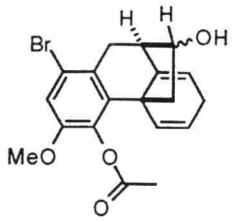
Compound **75** crystallized in the triclinic space group P-1 with a=9.489 (2) Å, b=11.102 (2) Å, c=16.969 (3) Å, V=1786.28 Å^3, Z=2, D_{calc}=1.507 g/cm^3. All 2340 nonequivalent reflections in the range of 3.5° < 2Θ < 95° were measured on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å). The structure was solved with direct methods (SHELXTL) using 2155 unique reflections with F > 4 σ(F). Full matrix least squares refinement with anisotropic temperature factors for all non-hydrogen atoms and calculated hydrogen atom positions led to the final discrepancy indices of R=0.1093 and $_w$R =0.1051.



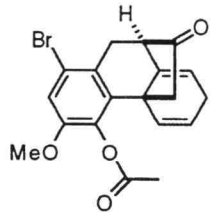
8-Acetoxy-11-bromo-2, 3, 4, 5, 6, 7-hexadehydro-15-hydroxy-4-oxo-9-methoxy-tetracyclo[12.2.0^{1,6}.0^{7,12}.0^{1,14}]-5-hexadecene (84). To a solution of **75** (52 mg, 0.13 mmol) in tetrahydrofuran (2.5 mL) at -78°C was added sodium borohydride (10 mg, 0.27 mmol) in small portions. The mixture was stirred at -78°C for 15 min, treated with aqueous 0.1 N hydrochloric acid (5 mL), and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 1:4) afforded 21 mg (40%) of **85** and 13 mg (25%) of recovered starting material: IR (neat) 3444, 3426, 3414, 2928, 1766, 1662, 1471, 1436, 1280, 1191, 1145, 1118, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (1H, m), 2.21 (3H, s), 2.32-2.60 (5H, m), 2.80 (2H, m), 3.42 (1H, m), 3.83 (3H, s), 4.50 (1H, m), 6.27 (1H, s), 7.12 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.4, 14.1, 21.0, 26.5, 33.1, 34.1, 34.5, 41.1, 43.1, 56.2, 56.3, 58.3, 60.4, 64.4, 67.4, 115.6, 117.7, 120.6, 129.3, 130.9, 132.2, 137.4, 150.4, 154.8, 168.6, 199.1; MS(EI) *m/z* 408, 406 (M^+), 366, 365, 364, 348, 346, 322, 320, 307, 305, 279, 241, 225, 213, 198, 182, 169, 165, 153, 115, 91; HRMS *m/z* calcd for $C_{19}H_{19}O_5Br$ (M^+): 406.0416. Found: 406.0416.



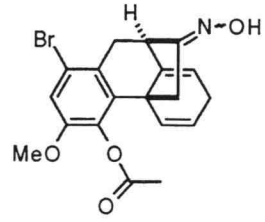
8-Acetoxy-11-bromo-2, 3, 4, 5, 6, 7-hexadehydro-4-hydroxy-15-hydroxy-9-methoxytetracyclo[12.2.0^{1,6}.0^{7,12}.0^{1,14}.]-5-hexadecene (85). To a solution of **75** (95 mg, 0.23 mmol) in 0.4 M cerium chloride (0.5 mL) was added sodium borohydride (20 mg, 0.54 mmol) in small portions. The mixture was stirred at room temperature for 15 min, treated with aqueous 0.1 N hydrochloric acid (5 mL), and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. There was obtained 83 mg (88%) of crude product. Column chromatography of the crude residue (hexane-ethyl acetate, 1:4) afforded 58 mg (60%) of **85**: IR (neat) 3392, 2927, 1760, 1469, 1198 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (2H, m), 2.02 (2H, m), 2.27 (4H, m), 2.47 (1H, m), 2.69 (1H, m),3.35 (1H, m), 3.40 (1H, m), 3.82 (3H, s), 4.35 (1H, m), 6.00 (1H, s), 7.11, 7.13 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 150.5, 150.4, 137.0, 135.5, 133.1, 130.5, 130.4, 129.1, 120.0, 119.9, 115.4, 115.2, 67.1, 66, 64.8, 64.7, 56.2, 46.5, 43.5, 43.0, 35.0, 34.7, 34.1, 32.5, 29.6, 29.4, 26.9, 26.6, 20.8, 20.6; MS(EI) *m/z* 410, 408 (M^+), 392, 390, 366, 364, 350, 287, 251, 226, 224, 193, 192, 181, 178, 153, 152, 115, 197, 169, 167, 116, 113; HRMS *m/z* calcd for $C_{19}H_{21}O_5Br$ (M^+): 408.0572. Found: 408.0572.



3-Acetoxy-6-bromo-2, 3, 4, 5, 6, 7-hexadehydro-15-hydroxy-4-methoxytetracyclo[7.5.2.0^{2,7}.0^{1,10}]-10,13-hexadecadiene (86). To a solution of **85** (21 mg, 0.05 mmol) in refluxing toluene (2 mL) was added a 0.1 M solution of boron trifluoride diethyl etherate (10 μL) in dichloromethane. After 30 sec the mixture was poured into ice water, the layers were separated, and the aqueous layer was back extracted with ether (2 x 10 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 7 mg (36 %) of **86**: IR (neat) 3312, 2927, 1761, 1472, 1198, 1169, 1143, 1017 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (3H, s), 2.52-2.80 (3H, m), 3.01 (1H, m), 3.30 (1H, m), 3.80 (3H, s), 3.82 (2H, m), 5.74 (3H, m), 7.13 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 20.8, 27.0, 27.4, 29.3, 31.4, 38.3, 38.5, 45.7, 46.0, 47.7, 48.5, 56.2, 56.3, 65.2, 115.8, 123.5, 124.1, 125.7, 129.4, 130.8, 132.9, 133.6, 137.1, 137.4, 150.3, 151.3, 168.2, 168.8; MS(EI) *m/z* 392, 390 (M^+), 330, 304, 258, 207, 178, 165, 152, 139, 131, 120, 117, 107, 106, 105; HRMS *m/z* calcd for $C_{19}H_{19}O_4Br$ (M^+): 390.0467. Found: 390.0457.

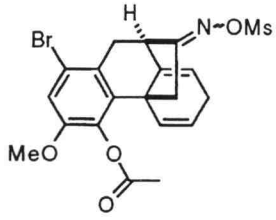


3-Acetoxy-6-bromo-2, 3, 4, 5, 6, 7-hexadehydro-4-methoxy-15-oxo-tetracyclo-[7.5.2.0^{2,7}.0^{1,10}]-10,13-hexadecadiene (87). To a solution of **86** (7 mg, 0.018 mmol) in dichloromethane (1 mL) was added Dess-Martin periodinane (15 mg, 0.054 mmol). The mixture was stirred at room temperature for 0.5 h and was diluted with ether (2 mL) and aqueous sodium thiosulfate (2 mL). After separation of the layers, the aqueous layer was back extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 5 mg (72%) of **87**: IR (neat) 2971, 2933, 2929, 1768, 1752, 1477, 1195, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (3H, s), 2.80-3.25 (4H, m), 3.75 (3H, s), 3.80 (1H, m), 5.80 (3H, m), 6.97 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 27.5, 34.7, 44.4, 57.8, 60.4, 60.7, 115.0, 115.7, 116.4, 120.0, 124.8, 126.4, 127.6, 135.4, 139.4, 151.6, 168.2, 216; MS(EI) *m/z* 390, 388 (M^+), 348, 346, 306, 304, 267, 225, 224; 223, 207, 165, 152, 139, 115, 91; HRMS *m/z* calcd for $C_{19}H_{17}O_4Br$ (M^+): 388.0310. Found: 388.0310.



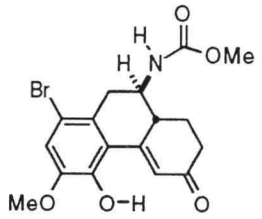
3-Acetoxy-6-bromo-2, 3, 4, 5, 6, 7-hexadehydro-15-hydroxyimino-4-methoxytetracyclo-[7.5.2.0^{2,7}.0^{1,10}]-10,13-hexadecadiene (88). To a solution of **87** (20 mg, 0.05 mmol) in methanol

(0.5 mL) was added ammonium chloride (20 mg, 0.38 mmol) followed by hydroxylamine hydrochloride (11 mg, 0.15 mmol). The mixture was stirred at room temperature for 3 h, after which the methanol was evaporated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 15 mg (71 %) of **88** as a colorless amorphous solid: IR (neat) 3312, 2971, 2933, 2861, 1767, 1476, 1192, 1171, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (3H, s), 2.32 (2H, m), 2.60-2.98 (2H, m), 3.01-3.25 (2H, m), 3.49 (1H, m), 3.80 (m, 1H), 5.75 (3H, m), 6.99 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 21.0, 26.1, 33.8, 37.2, 37.4, 56.3, 56.5, 58.3, 114.7, 115.5, 116.2, 116.5, 119.0, 124.1, 124.5, 125.2, 126.3, 126.6, 127.8, 135.9, 136.2, 139.5, 151.4, 164.5, 168.2; MS(EI) *m/z* 405, 403 (M^+), 363, 361, 346, 345, 344, 343, 330, 306, 305, 304, 302, 165, 153, 151, 139; HRMS *m/z* calcd for $C_{19}H_{18}NO_4Br$ (M^+): 403.0419. Found: 403.0419.



3-Acetoxy-6-bromo-2, 3, 4, 5, 6, 7-hexadehydro-15-methansulfonyloxyimino-4-methoxytetracyclo-[7.5.2.$0^{2,7}$.$0^{1,10}$]-10,13-hexadecadiene (89). To a solution of **88** (5 mg, 0.012 mmol) in dichloromethane (1 mL) and triethylamine (10 μL, 0.05 mmol) was added methanesulfonyl chloride (10 μL, 0.062 mmol). The mixture was stirred at 0°C for 3 h, after which it was diluted with aqueous 0.1 N hydrochloric acid (2 mL) and extracted into ether (3 x 2 mL). Column chromatography of the residue (hexane-ethyl acetate, 3:1) afforded 4 mg (67 %) of **89** as a colorless oil: IR (neat) 3170, 3165, 3020, 2924, 2853, 1764, 1477, 1437,1192, 1171,1110,

1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (3H, s), 2.82 (2H, m), 3.05 (1H, m), 3.10 (3H, s), 3.20-3.51 (4H, m), 3.77 (m, 1H), 5.80 (m, 3H), 7.01 (s, 1 H).



8-Bromo-10-methoxycarbonylamino-5-hydroxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydro-phenanthrene (90). To a solution of 8-bromo-10-carboxyl-5-hydroxy-6-methoxy-3-oxo-1, 2, 9, 10-tetrahydro-phenanthrene **89** (20 mg, 0.055 mmol) in dry methanol (1.5 mL) was added diphenylphosphoryl azide (35 μL, 0.16 mmol) and triethylamine (20 μL, 0.10 mmol). The mixture was heated to reflux for 2 h after which it was diluted with aqueous 0.1 N hydrochloric acid (2 mL) and extracted into ether (3 x 2 mL). Column chromatography of the residue (hexane-ethyl acetate, 1:4) afforded 13 mg (60 %) of **90** as a white solid: IR (KBr) 3992, 3316, 3290, 2941, 1768, 1689, 1642, 1466, 1287, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (1H, m), 2.41-2.80 (5H, m), 3.20 (1H, dd, J=16, 6 Hz), 3.70 (3H, s), 3.77 (1H, m), 3.92 (3H, s), 4.65 (1H, bd, J=9Hz), 6.55 (1H, s), 7.10 (1 H, s), 7.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.2, 29.69, 36.5, 37.1, 42.8, 51.3, 56.6, 113.7, 115.8, 120.5, 128.9, 129.0, 145.0, 145.7, 152.4, 156.5, 200.3; MS(CI) m/z 397, 395 (M^{+1}), 380, 322, 320, 243, 241, 169, 158, 152, 142, 124, 106, 100, 95, 83; HRMS *m/z* calcd for $C_{17}H_{18}NO_5Br$ (M^{+1}): 395.0368. Found: 395.0369.

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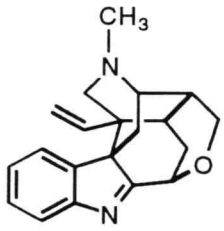
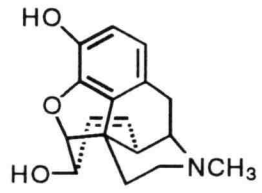
Chapter IV. General Conclusion

This dissertation describes the synthetic approaches toward two complex alkaloids, koumine, a herbal drug used in China, and morphine, an important analgesic widely used in the practice of medicine throughout the world.



(-)-Koumine



(-)-Morphine

Although structurally unrelated, both substances have been used to alleviate pain. Leitmotiv for the synthetic planning has been to approach these complex structures starting from simple heterocyclic or aromatic compounds. We then sought to gain entry to the appropriate ring system by applying organic transformations that have precedence in the literature (for example, the Diels-Alder Reaction or Robinson annulation). Further study is needed to complete both syntheses.

Although both koumine and morphine occur in nature as single enantiomers, the synthetic approaches described here are racemic. However, both routes are potentially amenable to asymmetric synthesis.

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