AN ABSTRACT OF THE DISSERTATION OF

Jungchul Kim for the degree of Doctor of Philosophy in Chemistry presented on November 2, 2000. Title: NATURAL PRODUCT SYNTHESIS VIA CYCLOBUTANES: PART I. ASYMMETRIC SYNTHESIS OF (+)-BYSSOCHLAMIC ACID. PART II. AN APPROACH TO THE NOOTROPIC AGENT HUPERZINE A.

Abstracted approved: Redacted for Privacy

James D. White

PART I. Asymmetric syntheses of both natural (+)- and nonnatural (-)-byssochlamic acid via a [2+2] photoaddition-cycloreversion strategy are described. X-ray crystallographic analysis of the cyclohexylamine salt **99** showed that the structure of the monomethyl ester **100** from esterase hydrolysis of **44** was originally misassigned as **56**. The enantiomeric relationship of the two diolides **106** and **70** permitted syntheses of nonnatural byssochlamic acid (-)-**3** and natural byssochlamic acid (+)-**3** from enantiopure alcohol (+)-**64** and from its enantiomer (-)-**110**, respectively. Through the use of (±)-**103** to reach both enantiomers of byssochlamic acid (**3**) and subsequent epimerization of the *n*-

propyl chain, it was proved that the cis configuration of the two alkyl substituents is strongly preferred in the natural product.

PART II. An asymmetric approach towards the nootropic agent huperzine A is described. Formation of cyclobutane **122** with the desired stereochemistry was accomplished using intramolecular [2+2] photoaddition of the enantiopure enone **121**. Attempts to prepare the methoxypyridine system via an azadiene Diels-Alder reaction were unsuccessful. However, intramolecular Michael addition of **181** produced silyl ether **182** which was converted into the pyridone **187** by treatment with hydrogen fluoride followed by selenoxide elimination. Attempts to effect the key sigmatropic rearrangement of ketone **197** into a direct precursor of huperzine A were unsuccessful.

NATURAL PRODUCT SYNTHESIS VIA CYCLOBUTANES: PART I. ASYMMETRIC SYNTHESIS OF (+)-BYSSOCHLAMIC ACID. PART II. AN APPROACH TO THE NOOTROPIC AGENT HUPERZINE A.

by

Jungchul Kim

A DISSERTATION

submitted to

Oregon State University

in partial fulfillment of

the requirements for the

degree of

Doctor of Philosophy

Completed November 2, 2000

Commencement June 2001

Doctor of Philosophy dissertation of Jungchul Kim presented on November 2, 2000

APPROVED:

Redacted for Privacy

Major Professor, representing Chemistry

Redacted for Privacy

Chair of the Department of Chemistry

Redacted for Privacy

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 the release of my dissertation to any reader upon request.

Redacted for Privacy

Jungchul Kim, Author

ACKNOWLEDGMENTS

I would like to sincerely thank professor James D. White for the support and guidance that made this thesis possible. I would also like to thank the present and past members of the White group, Jorg Deerberg, Duncan J. Wardrop, Carla Hassler, Sung-kee Kim, Christine S. Nylund, Scott J. Kemp, Roger Hanselmann, Volker K. Schulze, Eric Hong, Rich G. Carter, Bart Phillips, Paul Blakemore, Cindy Browder, Wolfgang Wenger, Uwe Grether, Laura Quaranta, Nicholas E. Drapela, Nadine Lee, Peter Hrnciar, Lonnie A. Robarge, Joshua D. Hansen, Kurt F. Sundermann, Sundaram M. Shanmugham, Christopher M. Lincoln, Punlop Kuntiyong and Eric Korf.

I would like to thank particularly Younggi Choi for his friendship at Oregon State University

I thank Alex Yokochi for X-ray crystallographic analysis and Rodger Kohnert for his advice and assistance on the NMR analysis.

The National Science Foundation and The National Institutes of Health are acknowledged for financial support.

Finally, I thank my wife, Eun-Young Suh, and my son, Colin Mugeun Kim, for their love.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF APPENDIX TABLES

LIST OF APPENDIX TABLES (Continued)

NATURAL PRODUCT SYNTHESIS VIA CYCLOBUTANES:

PART I. ASYMMETRIC SYNTHESIS OF (+)-BYSSOCHLAMIC ACID.

PART II. AN APPROACH TO THE NOOTROPIC AGENT HUPERZINE A.

PART I. ASYMMETRIC SYNTHESIS OF (+)-BYSSOCHLAMIC ACID.

Chapter I. GENERAL INTRODUCTION

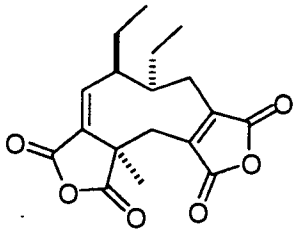
The importance of organic synthesis in contemporary chemistry cannot be overestimated. Organic synthesis can play a vital role in structure elucidation and stereochemical assignment of new compounds. In the case of biologically active natural products, organic synthesis can sometimes be the only means for obtaining sufficient quantities of the compounds. Organic synthesis can also aid in new drug development through the preparation of structural analogues derived from a parent compound. In general, the most important function of organic synthesis lies in the development of new methodologies and in expansion of the scope and utility of known reactions.

The dissertation presented in the following pages describes synthetic efforts directed toward two natural products. The first part of the thesis describes asymmetric syntheses of (+)-byssochlamic acid and its enantiomer (-)-byssochlamic acid. Byssochlamic acid is the simplest member of the family of the nonadrides, and was isolated from the Ascomycete, *Byssochlamys fulva.* The second part of the thesis presents an approach to the nootropic agent huperzine A. Huperzine A is a valuable naturally occurring substance used for the treatment of Alzheimer's dementia. It functions through inhibition of acetylcholinesterase.

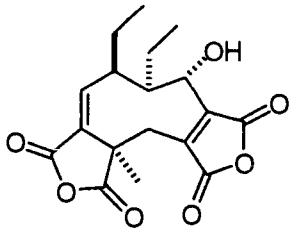
Chapter II. ASYMMETRIC SYNTHESIS OF (+)-BYSSOCHLAMIC ACID

History and Background

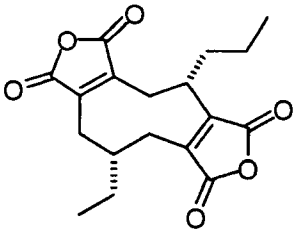
The natural products known collectively as nonadrides comprise a small structural class in which the core unit is a nine-membered carbocyclic ring.[1] Two five-membered anhydrides or an anhydride and a lactol are fused to the core, which also bears a pair of *n*-alkyl chains and, in some cases, one or more hydroxyl substituents (**Figure 1.1**). Glaucanic and glauconic acids, **1** and **2** respectively, were the first members of the class to be discovered,[2] and soon thereafter a "symmetrical" variant, byssochlamic acid (**3**), was isolated by Raistrick.[3] Subsequently, two hepatotoxic substances, rubratoxins A (**4**) and B (**5**), were obtained from extracts of the fungus *Penicillium rubrum*,[4] and more recently the nonadrides scytalidin (**6**),[5] heveadride (**7**),[6] and castaneiolide (**8**)[7] have been found in nature. The latest examples of this family of structures are CP-225,917 (**9**) and CP-263,114 (**10**), two metabolites isolated by a research group at Pfizer from an unidentified fungus which also produces zaragozic acid.[8] The powerful inhibition of ras farnesyl transferase by **9** and **10**[9] has made these nonadrides the objects of much interest,[10] and a synthesis of (±)-**9** and (±)-**10** was completed in 1999 by Nicolaou.[11]



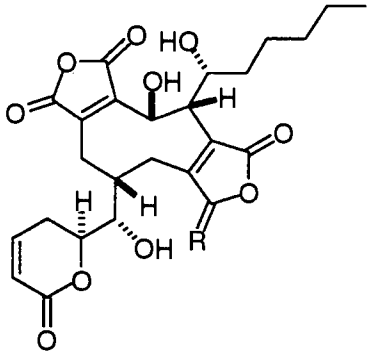
Glaucanic acid (**1**)



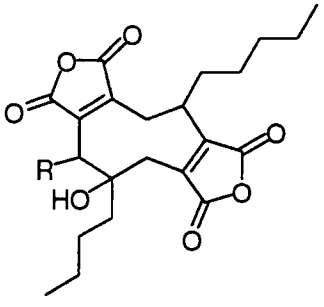
Glauconic acid (**2**)



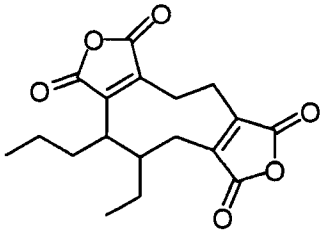
Byssochlamic acid (**3**)



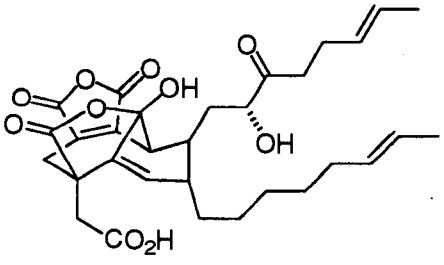
Rubratoxin A (**4**), R = H, OH
Rubratoxin B (**5**), R = O



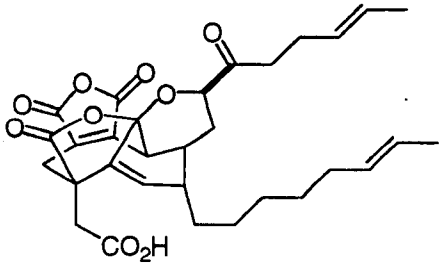
Scytalidin (**6**), R = H
Castaneiolide (**8**), R = OH



Heveadride (**7**)



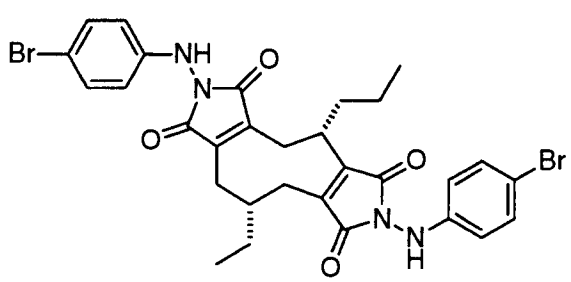
CP-225,917 (**9**)



CP-263,114 (**10**)

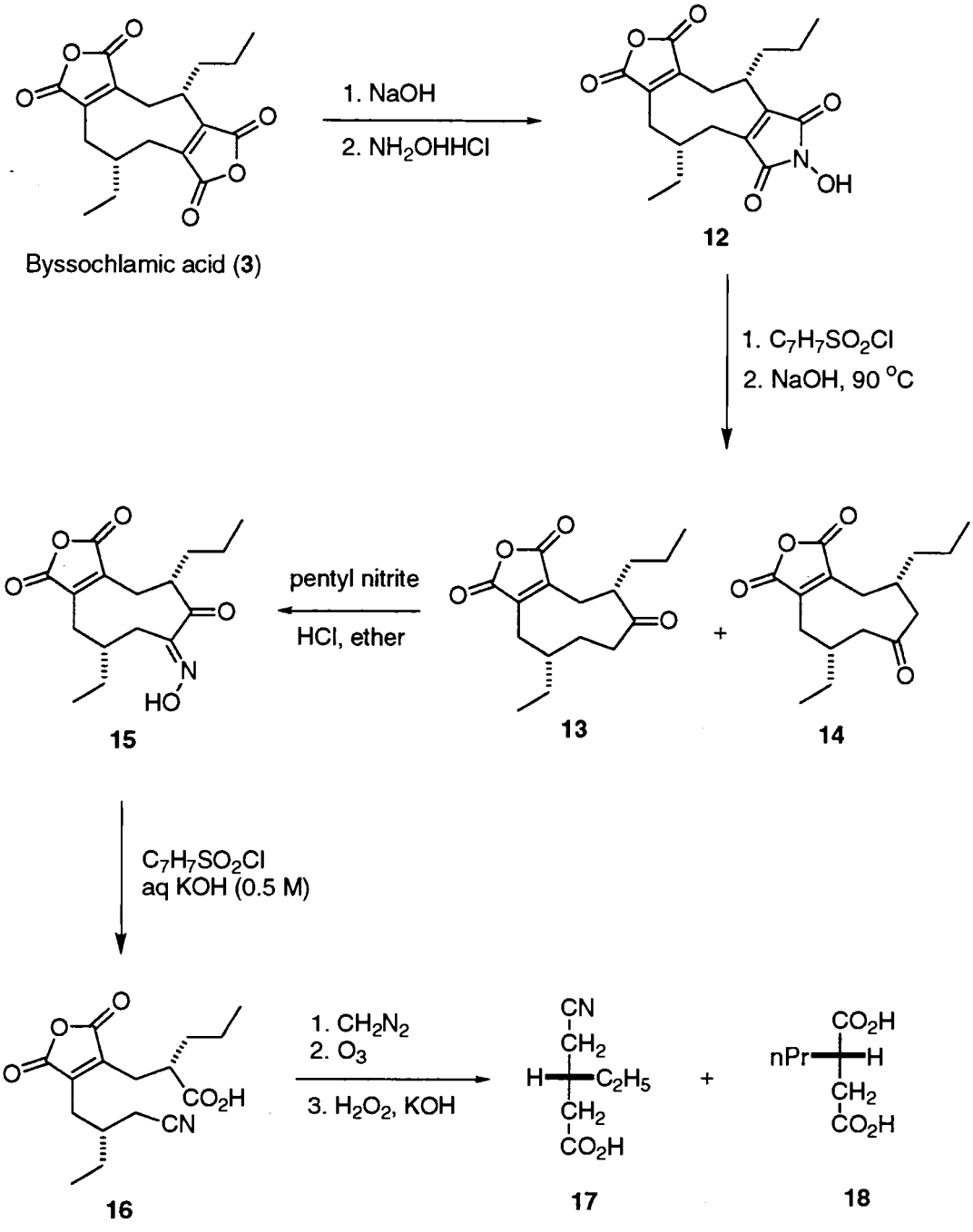
Figure 1.1 The nonadrides

Byssochlamic acid (**3**) was isolated in 1933 during an investigation into the natural metabolites of a new Ascomycete, *Byssochlamys fulva.*[12] This organism was noteworthy due to its frequent occurrence as a cause of spoilage among processed fruits. Its spores were determined to be unaffected by the normal fruit sterilizing process in which the temperature obtained exceeds 90 °C. After several weeks of incubation of the fungus on a synthetic medium, it was found that acidification of the mixture produced an ether soluble precipitate. Recrystallization of this solid from ether-benzene yielded pure byssochlamic acid.



11

Structural elucidation of **1**, **2**, and **3** by the Barton group[13] at Imperial College built upon earlier degradative work addressed at **1** and **2** by Sutter[14] and Kraft,[15] and led to the proposal **3**, exclusive of stereochemistry, for byssochlamic acid. Confirmation of this assignment and designation of cis relative configuration was obtained through X-ray crystallographic analysis of the bis-*p*-bromophenylhydrazide **11**of byssochlamic acid.[16]


1. NaOH
2. NH2OHHCl
Byssochlamic acid (3)
12
1. C7H7SO2Cl
2. NaOH, 90 °C
pentyl nitrite
HCl, ether
15
13
14
C7H7SO2Cl
aq KOH (0.5 M)
1. CH2N2
2. O3
3. H2O2, KOH
16
17
18

Scheme 1

The absolute configuration of byssochlamic acid was determined by degradative experiments which caused fission of the nine-membered ring and gave products of known stereochemistry (**Scheme 1**).[17] When byssochlamic acid tetrasodium salt was reacted with one mole of hydroxylamine hydrochloride, the generated mono-N-hydroxyimide **12** undergoes degradation with *p*-toluenesulfonyl chloride and sodium hydroxide to give ketones **13** and **14**. Nitrosation of **13** gave the oximino ketone **15** which, upon treatment with *p*-toluenesulfonyl chloride and sodium hydroxide underwent a Beckman fragmentation yielding the nitrile acid **16**. Subsequent ozonolysis followed by oxidative work up gave (*S*)-(-)-*n*-propylsuccinic acid **18** and the nitrile **17**. Identification of these products established the absolute configuration of byssochlamic acid.

On inspecting the structures of glaucanic and byssochlamic acids, it is striking that each contains two identical nine-carbon unit. Accepting that this structural feature has biogenetic significance, it was postulated that these nonadrides are derived from two units having essentially identical carbon skeletons, and that the anion of one subunit is coupled to the other in forming the nine-membered ring (**Figure 1.2**).[18]

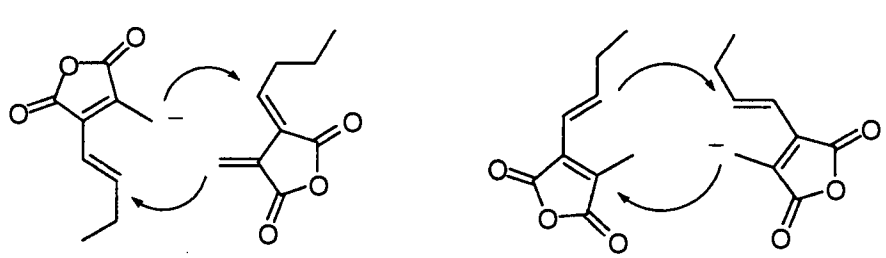


Figure 1.2 Dimerization of two C_9 units to form a nonadride.

The anhydride subunits, in turn, could be derived by decarboxylation and elimination of water from a tricarboxylic acid **19** formed via a modified citric acid cycle. The citric acid derivative **19** could presumably arise by condensation of oxaloacetic acid **20** with hexenoic acid (**Figure 1.3**). This hypothesis was strengthened by precedent in the biosynthesis of other microbial products.[19]

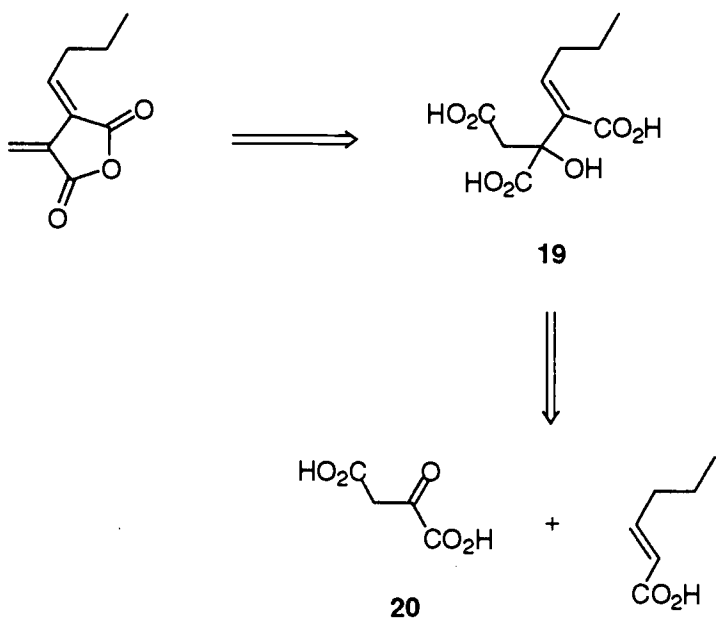
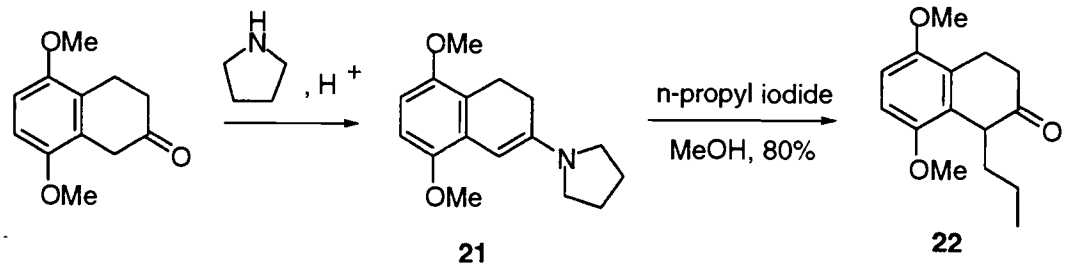


Figure 1.3 Proposed biosynthesis of the C_9 units of byssochlamic acid.

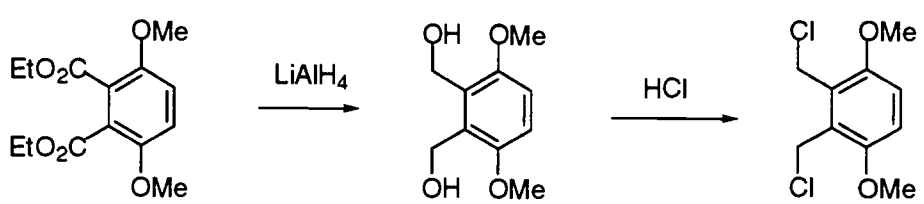
The first synthesis of a member of the nonadride family was that of (±)-**3** by Stork in 1972.[20] Stork's strategy employs two hydroquinone dimethyl ethers as latent maleic anhydride systems; the aryl rings of these hydroquinone are also sufficiently sterically demanding to induce the correct cis relationship of the two alkyl chains across the nine-membered ring, The Stork synthesis is convergent, with the central ring formed from ketone **22** and dichloride **25** via enolate dialkylation. The synthesis begins as shown in **Scheme 2**.



21 22

Scheme 2

Commencing with 5,8-dimethoxy-2-tetralone, alkylation of its pyrrolidine enamine with *n*-propyl iodide produced **22**. Fragment **25** was made via lithium aluminum hydride (LAH) reduction of diethyl 3,6-dimethoxyphthalate (**23**) followed by treatment with hydrochloric acid (**Scheme 3**).

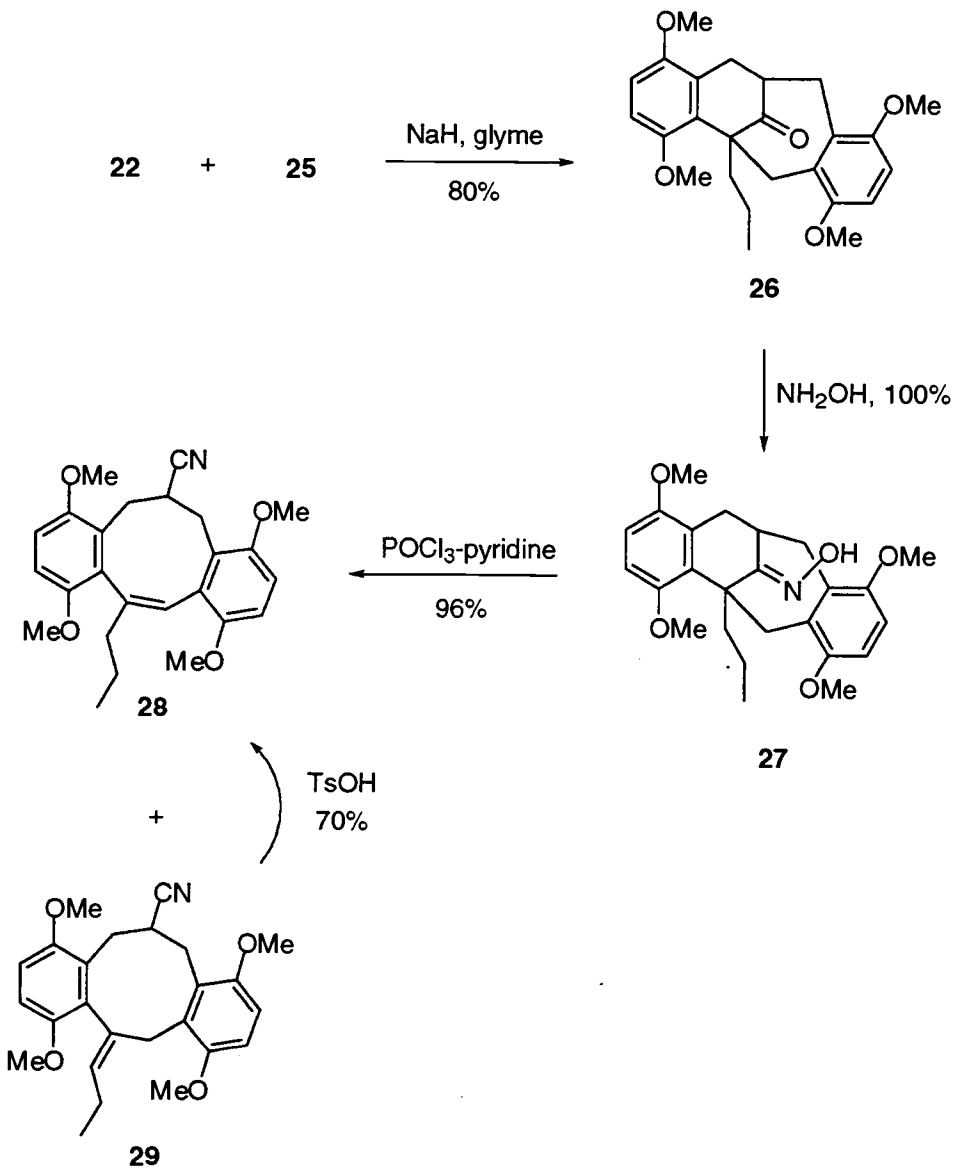


23 24 25

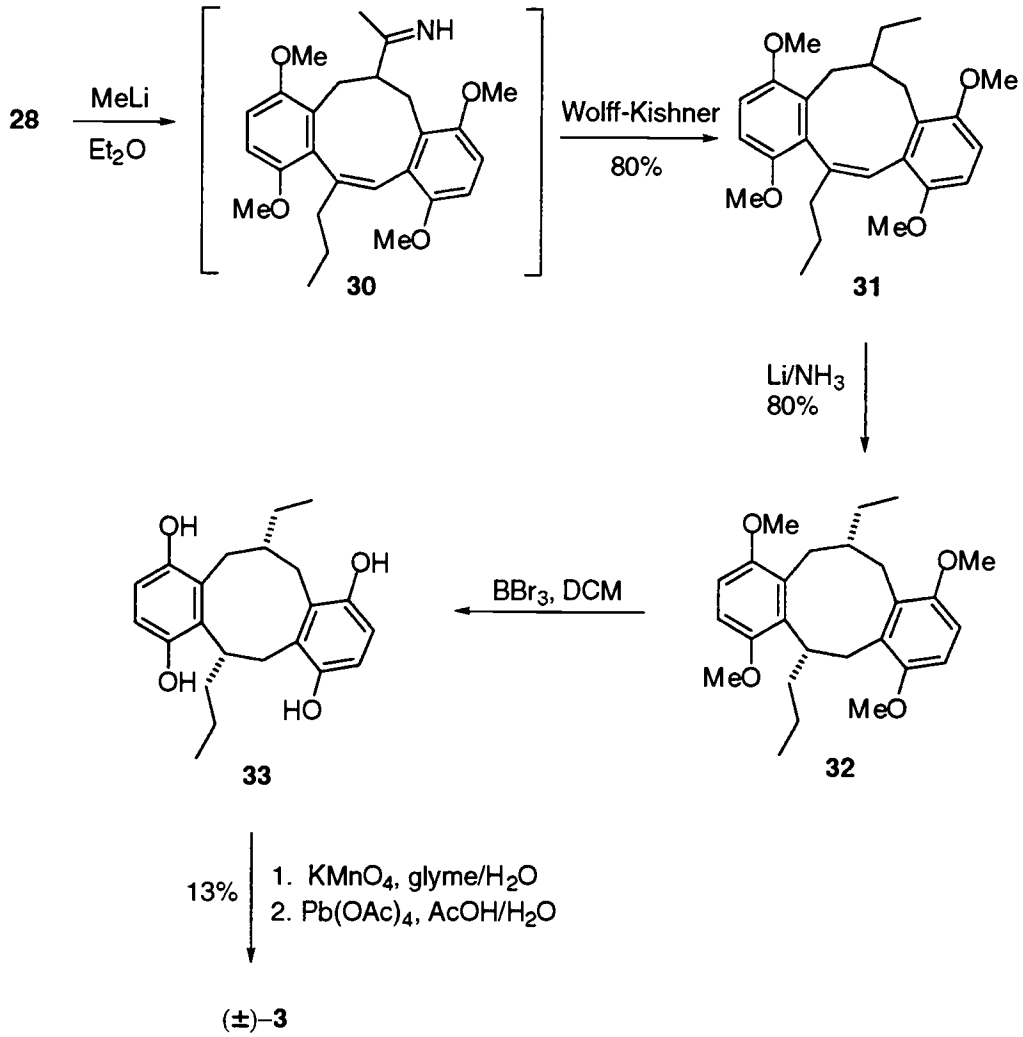
Scheme 3

The coupling of **22** and **25** was accomplished using sodium hydride in glyme at reflux to furnish the tetracycle **26** (**Scheme 4**). Hydroxylamine treatment of **26** gave oxime **27** which underwent Beckmann fragmentation with phosphorus oxychloride-pyridine to give an approximately 1:1 ratio of tricyclic nitriles **28** and **29**. The yield of the desired isomer **28** could be increased by transformation of

exo alkene **29** into the more thermodynamically stable endo **28** using *p*-toluenesulfonic acid.



Scheme 4



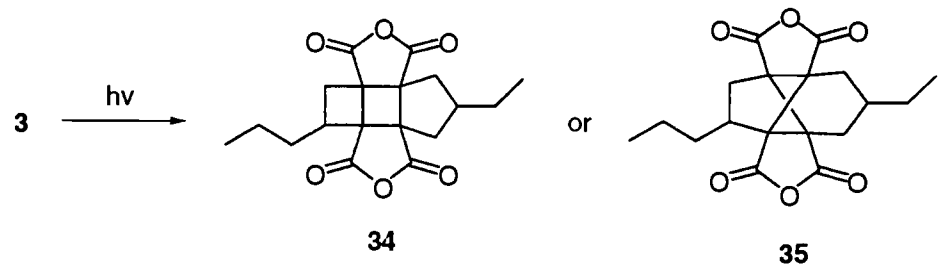
Scheme 5

Treatment of **28** with excess methyllithium presumably formed the unisolated imine **30**, which was then subjected to Wolff-Kishner reduction to produce **31** (**Scheme 5**). Reduction of **31** under thermodynamic conditions using lithium in ammonia afforded cis diastereomer **32** in high yield, a result which can be readily understood if nine-membered ring of **32** adopts a U-shaped conformation similar to that seen in the X-ray crystal structure of the bis-*p*-bromophenylhydrazide of byssochlamic acid (**Figure 1.2**). Formation of the trans

isomer would move the propyl group into a serious eclipsing interaction with one of the anhydride residues. The transformation of **31** to **32** suggested a strong preference by the alkyl chains in this system for the cis configuration over the trans.

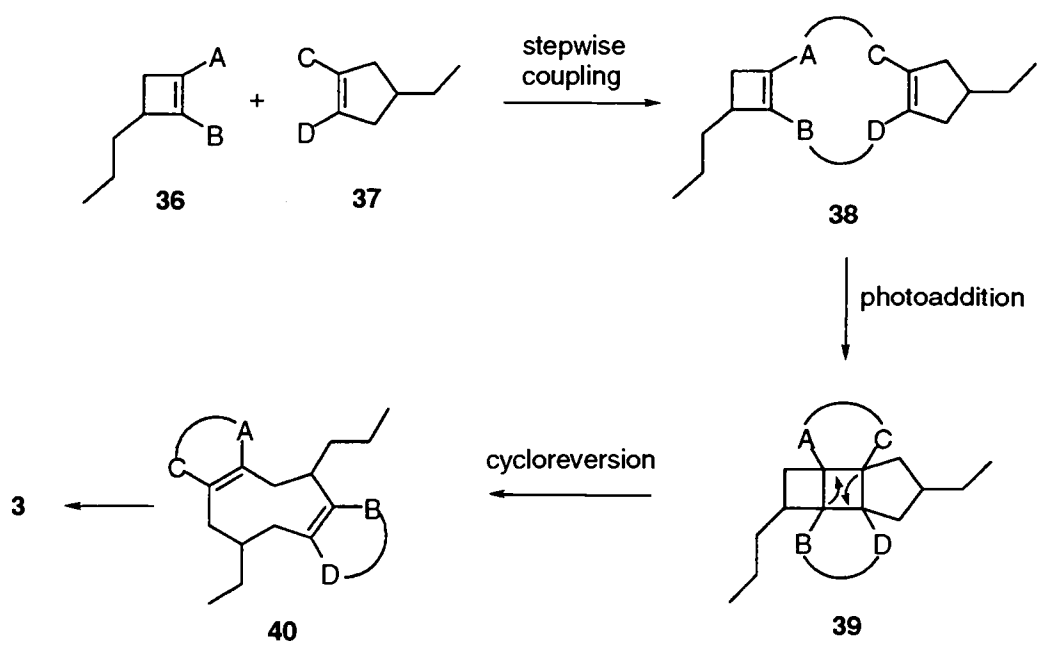
Final conversion of the two hydroquinone ethers into the anhydrides of byssochlamic acid proved to be problematic. Methyl ether cleavage with boron tribromide provided the bisdihydroquinone **33** which was oxidized in a two-step operation with potassium permanganate and lead tetraacetate to give racemic byssochlamic acid in 13% yield (**Scheme 5**). In spite of low yield at its finale, Stork's synthesis was relatively concise and convergent, and it broke new ground in the area of nonadride chemistry.

A seemingly inconsequential addendum to the Imperial College structural elucidation of byssochlamic acid by the Barton group[17] was the disclosure that the natural product undergoes a reaction to give a saturated isomer when irradiated in tetrahydrofuran (**Scheme 6**). Two structures were considered for "photobyssochlamic acid," one (**34**) derived from intramolecular, parallel [2+2] cycloaddition and the other (**35**) corresponding to a crossed photoaddition. Since pyrolysis of the photoisomer of byssochlamic acid failed to regenerate **3**, the conclusion was drawn that its structure was **35**. The implication that **34** should have reverted to byssochlamic acid upon thermolysis was a proposition which played an important role in guiding our approach to byssochlamic acid.[21]



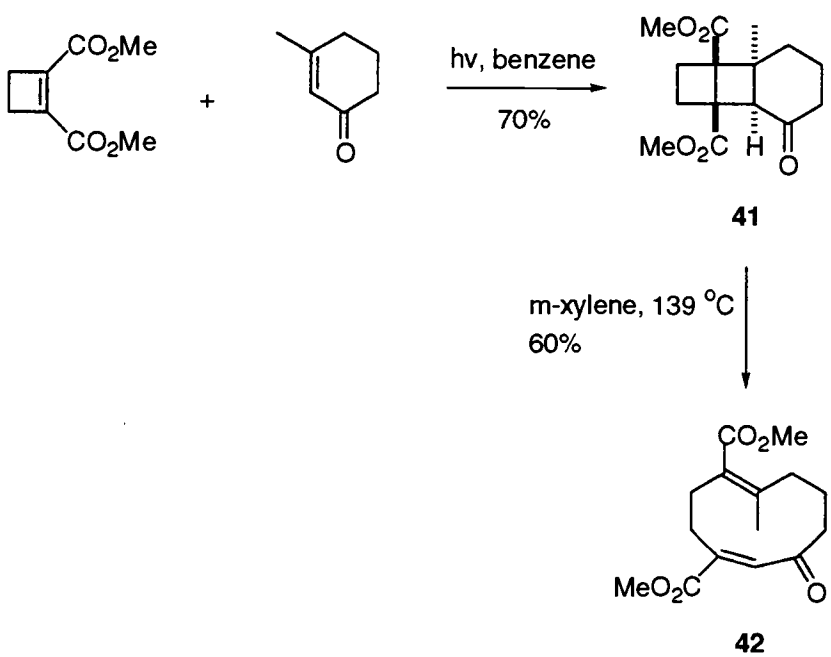
Scheme 6

Our plan for constructing the 1,5-cyclononadiene nucleus of **3** (**Scheme 7**) hinged upon connection of two photo partners, a cyclobutene **36** and a cyclopentene **37**, to produce a substrate **38** which upon irradiation would be expected to yield **39**. Subsequent cycloreversion of **39** would provide the carbocyclic structure **40**.



Scheme 7

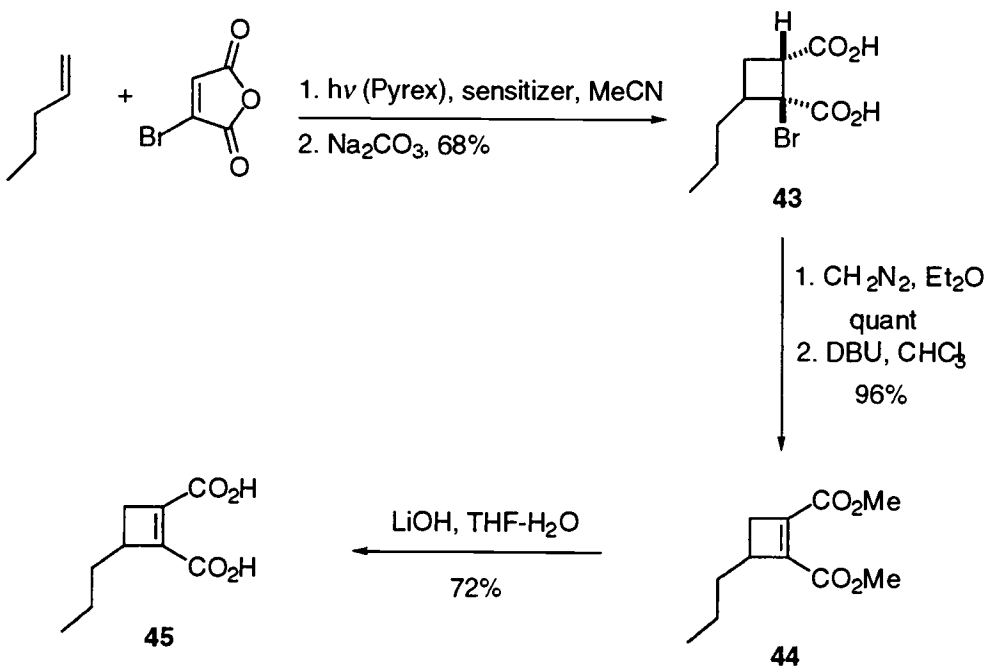
The concept of a [2+2] photoaddition-cycloreversion strategy for assembling carbocyclic structures has long been recognized as a powerful paradigm in medium-ring synthesis.[22] It was first exemplified in the context of natural product synthesis by Lange[23] (**Scheme 8**) and Wender[24] in their approaches to germacranolide sesquiterpenes, and others soon followed their lead.[25] In Lange's work, irradiation of dimethyl cyclobutene-1,2-dicarboxylate and 3-methyl-2-cyclohexenone in benzene resulted in the formation of the cycloadduct **41** which was heated to produce the 1,5-cyclodecadiene **42**.



Scheme 8

In White's synthesis of racemic **3**, formation of the cyclobutene component **36** required for coupling with **37** was also accomplished by a [2+2] photoaddition

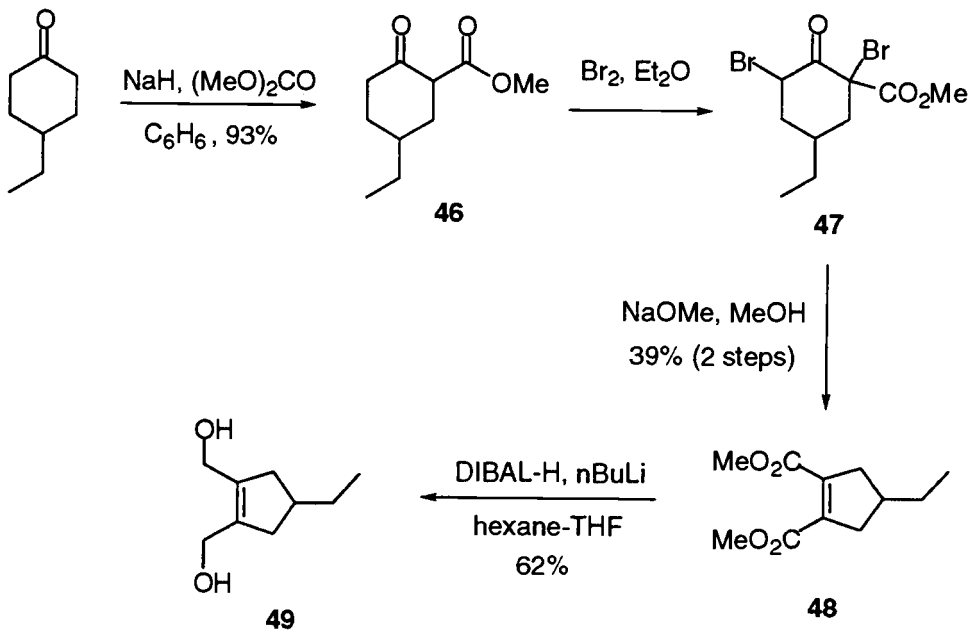
(**Scheme 9**). A mixture of 1-pentene and bromomaleic anhydride was irradiated in the presence of a sensitizer, then treated with aqueous sodium carbonate to give a mixture of cyclic diacids **43**. Treatment of this mixture with diazomethane, followed by 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) induced dehydrobromination, and afforded the cyclobutene dimethyl ester **44**. This compound was then saponified to provide the diacid **45**.



Scheme 9

The cyclopentene partner **49** required for coupling to **45** was prepared by acylation of 4-ethylcyclohexanone with dimethyl carbonate to give the keto ester **46** (**Scheme 10**). This was brominated and the the resulting dibromide **47** was subjected to a Favorski rearrangement-elimination[26] to yield the cyclopentene

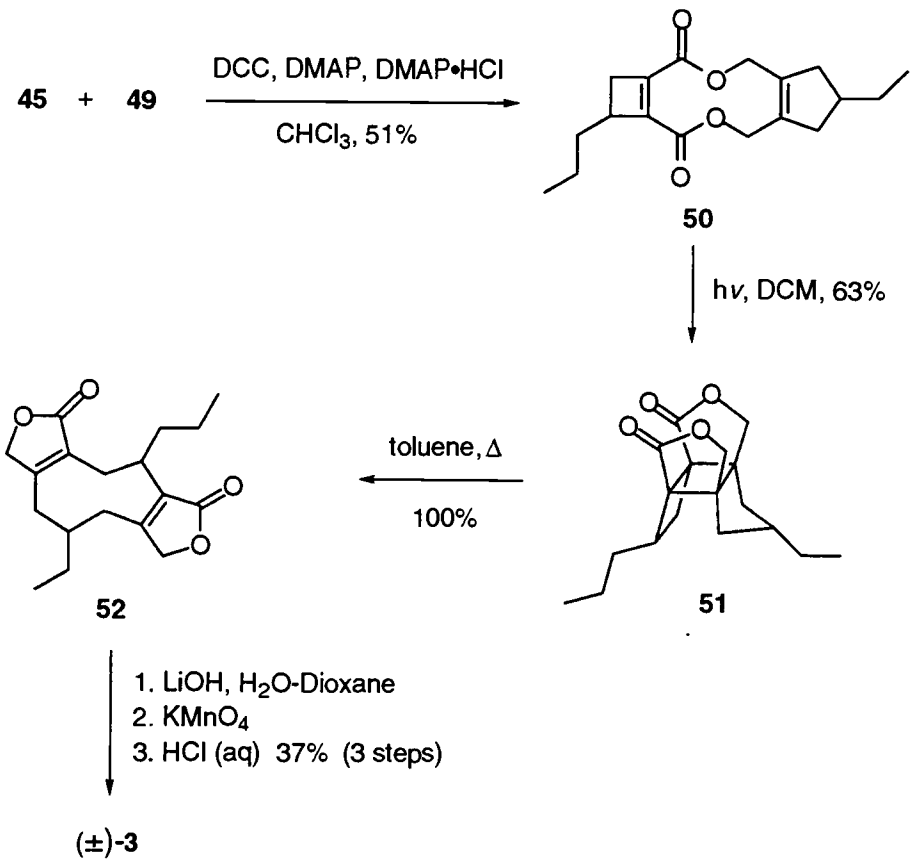
dimethyl ester **48**. Finally, treatment with the "ate" complex of diisobutylaluminum hydride provided diol **49**.



Scheme 10

Coupling of **44** and **49** to yield the diolide **50** was accomplished using Steglich-Keck conditions (**Scheme 11**).[27] Irradiation of **50** in dichloromethane afforded the highly strained structure **51** which, when refluxed in toluene, opened quantitatively to produce the dilactone **52** as a mixture of the cis and trans diastereomers. Saponification of **52** with lithium hydroxide, followed by potassium permanganate oxidation and an acidic work-up afforded racemic byssochlamic acid **3**. Only a single diastereomer was produced in this sequence, the propyl chain again showing a marked preference for the cis over the trans configuration

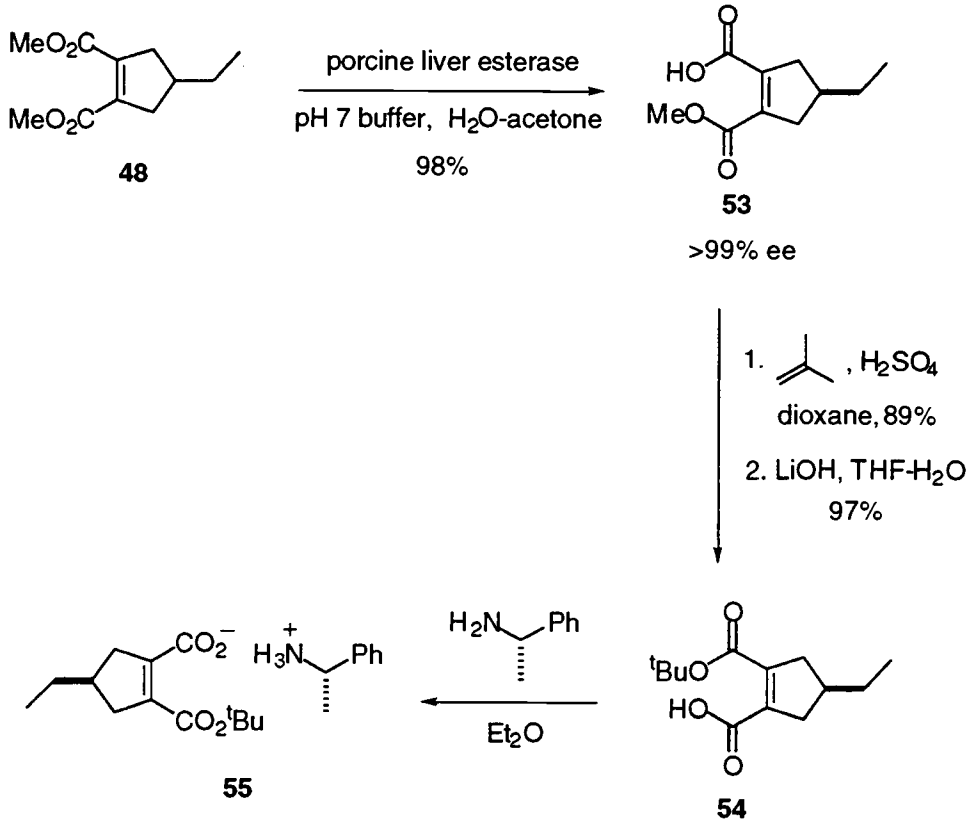
in this system. Presumably, epimerization occurred during conversion of **52** to **3** to give exclucively the more stable natural diastereomer.



Scheme 11

In 1996, an effort to extend this photoaddition-cycloreversion approach to an asymmetric synthesis of natural (+)-byssochlamic acid was initiated by Nick Drapela[28] in these laboratories. Synthesis of the chiral, differentiated cyclopentene component **54** began from dimethyl ester **48** (**Scheme 12**). Desymmetrization of dimethyl ester **48** with buffered (pH 7) porcine liver esterase[29] gave a half acid **53** (>99% ee) in virtually quantitative yield. The

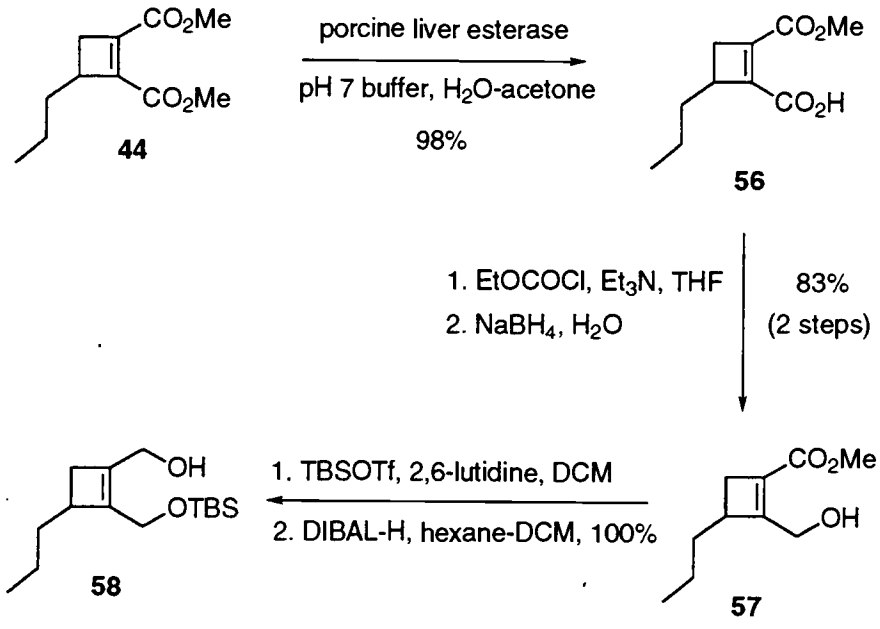
absolute configuration of **53** was determined as (*R*) by X-ray crystallographic analysis of the (*S*)-(–)-α-methylbenzylamine salt **55** of carboxylic acid **54**, prepared via the *tert*-butyl ester of **53**.



Scheme 12

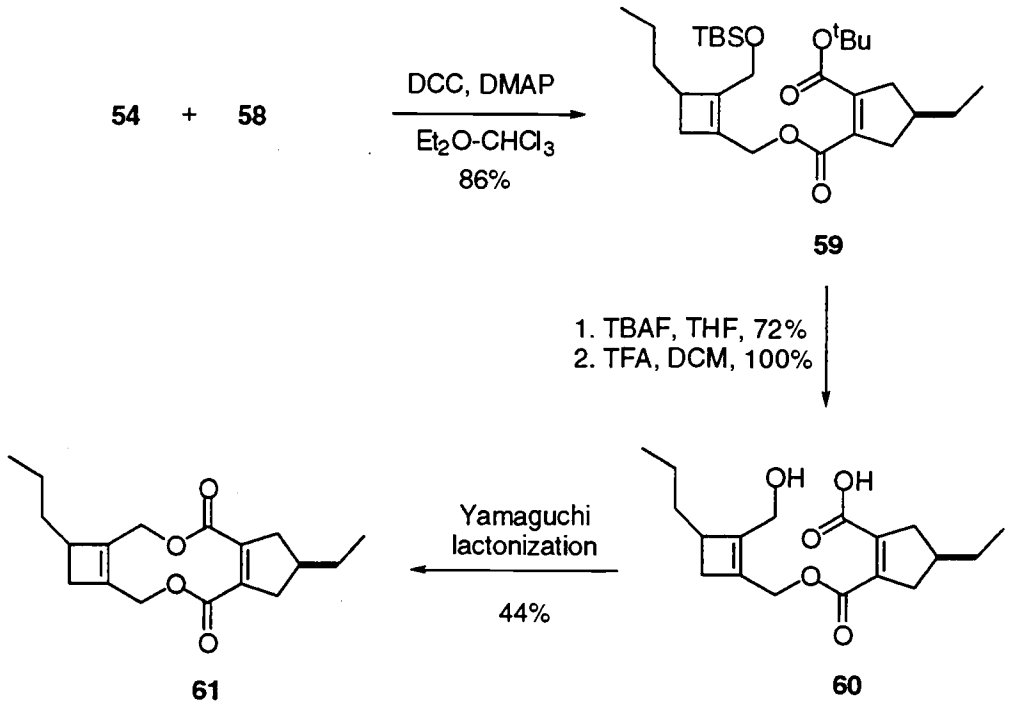
The cyclobutene component **58** was prepared from diester **44**. Treatment of this dimethyl ester with buffered porcine liver esterase furnished a carboxylic acid **56** (**Scheme 13**). The nearly quantitative yield of **56** implied that the esterase had failed to distinguish enantiomers in the racemate **44** while effecting a completely regioselective ester hydrolysis. This unexpected result will be discussed in the next chapter in greater detail. Selective reduction of the

carboxylic acid of **56** was achieved by using the mixed anhydride method to give hydroxy ester **57**.[30] Protection of the free alcohol in **57** followed by reduction of the resulting ester furnished alcohol **58**.



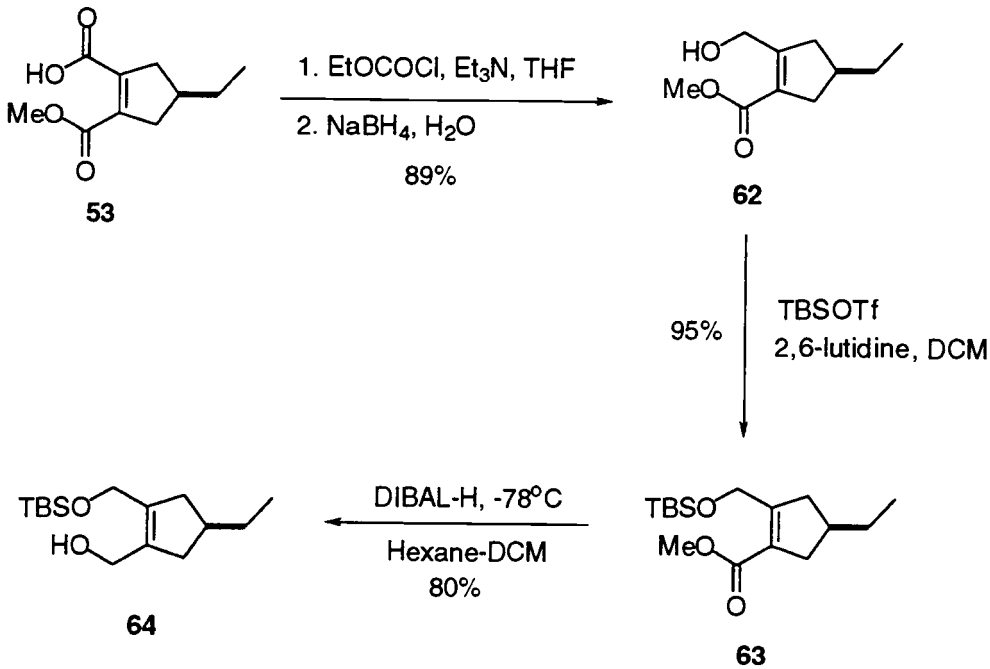
Scheme 13

Coupling of **58** with *tert*-butyl ester **54** proceeded efficiently to yield ester **59** (**Scheme 14**). Removal of the silyl ether from **59** followed by acidic cleavage of the *tert*-butyl ester afforded hydroxy acid **60**, which underwent Yamaguchi lactonization[31] to produce diolide **61**. To Drapela's suprise, all attempts to effect intramolecular photoaddition of **61** by irradiation through Pyrex resulted only in recovered starting material, and after measurement of the UV spectrum of **61** which showed an extinction coefficient (ϵ) of only 500 at 313 nm, it became clear that insufficient light absorption by **61** was responsible for this lack of reactivity.



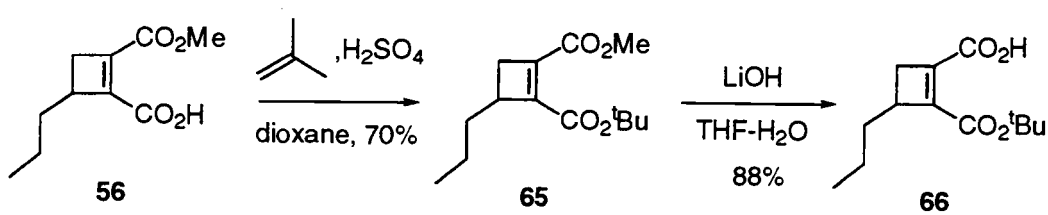
Scheme 14

An alternative approach investigated by Drapela, in which the cyclobutene and cyclopentene functionality was reversed, was intended to produce the diolide **50** in asymmetric form. Thus, reduction of the carboxylic acid **53** via its mixed anhydride provided primary alcohol **62** which was protected as its silyl ether **63**. Reduction of **63** with DIBAL-H gave the mono protected diol **64** (**Scheme 15**).



Scheme 15

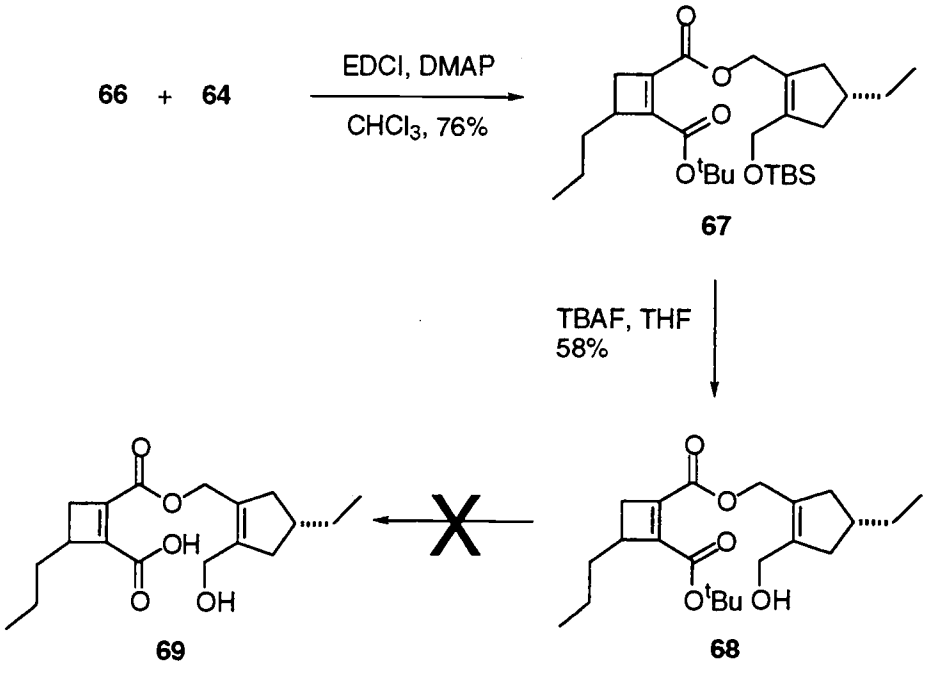
Esterification of methyl ester **56** by reaction with isobutylene and sulfuric acid in dioxane gave the mixed diester **65**. The methyl ester of **65** was then selectively saponified to afford the half acid **66**.



Scheme 16

Esterification of carboxylic acid **66** with alcohol **64** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-

dimethylaminopyridine gave the ester **67** in 76% yield, and deprotection of the silyl ether in **67** with tetrabutylammonium fluoride produced alcohol **68**. However, attempts to remove the *tert*-butyl group in **68** to obtain the free acid required for subsequent lactonization to the diolide **50** gave an intractable mixture of products. This disappointing outcome brought an end to Drapela's efforts to devise an asymmetric route to **3**.



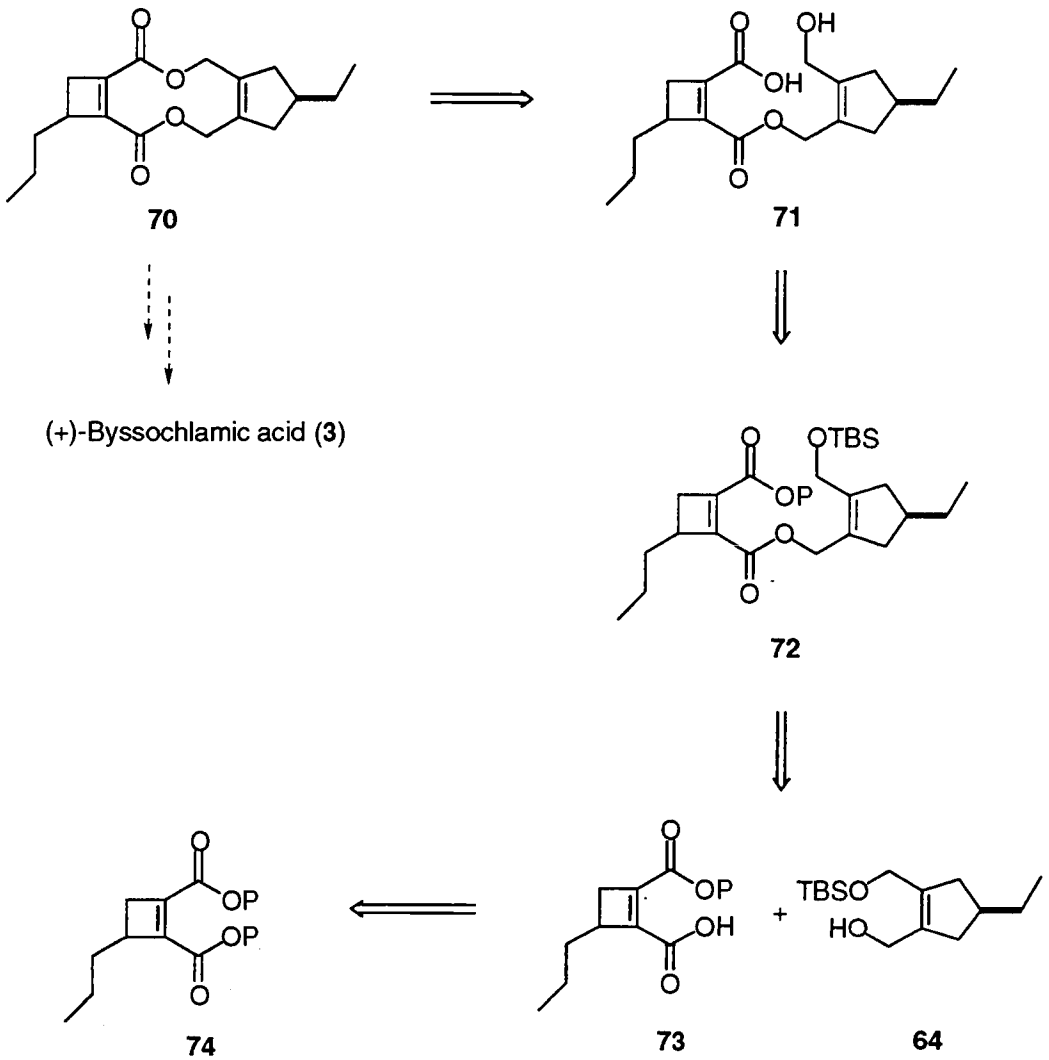
Scheme 17

Results and Discussion

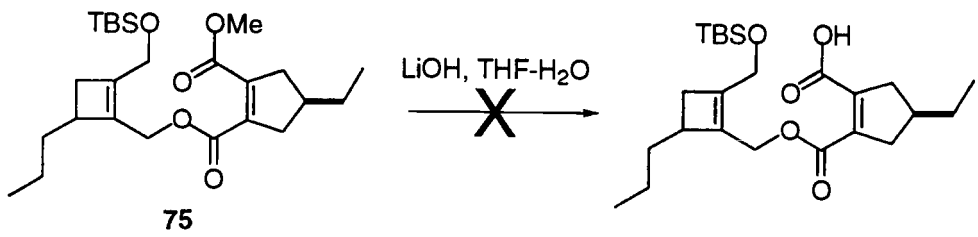
The conclusion reached from the previous research of Drapela was that decomposition of **68** under acidic conditions is a property inherent to this specific compound. However, in the racemic synthesis, coupling of diacid **45** with diol **49** to form diolide **50** under Keck-Steglich lactonization conditions is believed to proceed stepwise via an intermediate hydroxy acid. This successful coupling indicates the hydroxy acid **69** is not unstable. Therefore, if access to **69** can be gained by a route different from that shown in **Scheme 17**, a more favorable outcome may prevail leading to a diolide.

In continuing the earlier studies in these laboratories, our primary goal became the synthesis of diolide **70**, a key intermediate if an asymmetric synthesis of (+)-byssochlamic acid using the consecutive [2+2]-photoaddition and cycloreversion approach was to be realized (**Scheme 18**). With the knowledge already in hand that a *tert*-butyl ester was not a suitable means for protecting the carboxyl group of the cyclobutene component, we selected a different protecting group to circumvent the previous difficulties. Two major concerns needed to be addressed in choosing the correct protecting group. First, the protecting group from **72** must be removable under mild conditions which avoid strongly acidic or basic reagents. As previously observed with **68**, strongly acidic deprotection conditions would likely result in decomposition of the starting material. In addition, the selective hydrolysis of one of the esters in the presence of an adjacent ester that has a structurally similar environment would require a delicate

maneuver. These difficulties had already been encountered during attempts to deprotect the methyl ester **75** (**Scheme 19**).



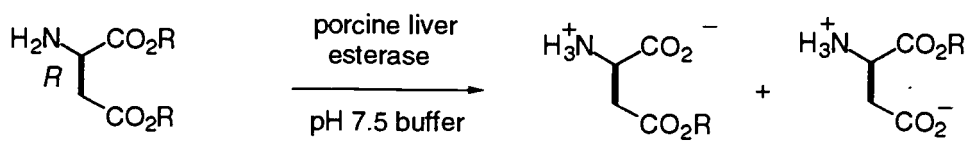
Scheme 18



75

Scheme 19

A second consideration was that the mono-protected acid **73** should be readily available from enzymatic hydrolysis of the corresponding diester. Toogood[32] reported the use of porcine liver esterase to differentiate the aspartate carboxylate functions by regioselective hydrolysis of the diesters **76** (**Scheme 20**). It was shown in these studies that the regioselectivity of this hydrolysis reaction was unaffected by the nature of the ester. Thus, our expectation was that porcine liver esterase hydrolysis of the diester **74** would parallel the esterase catalyzed reaction of dimethyl ester **44**.



76

R = Me
Et
^{t}Bu

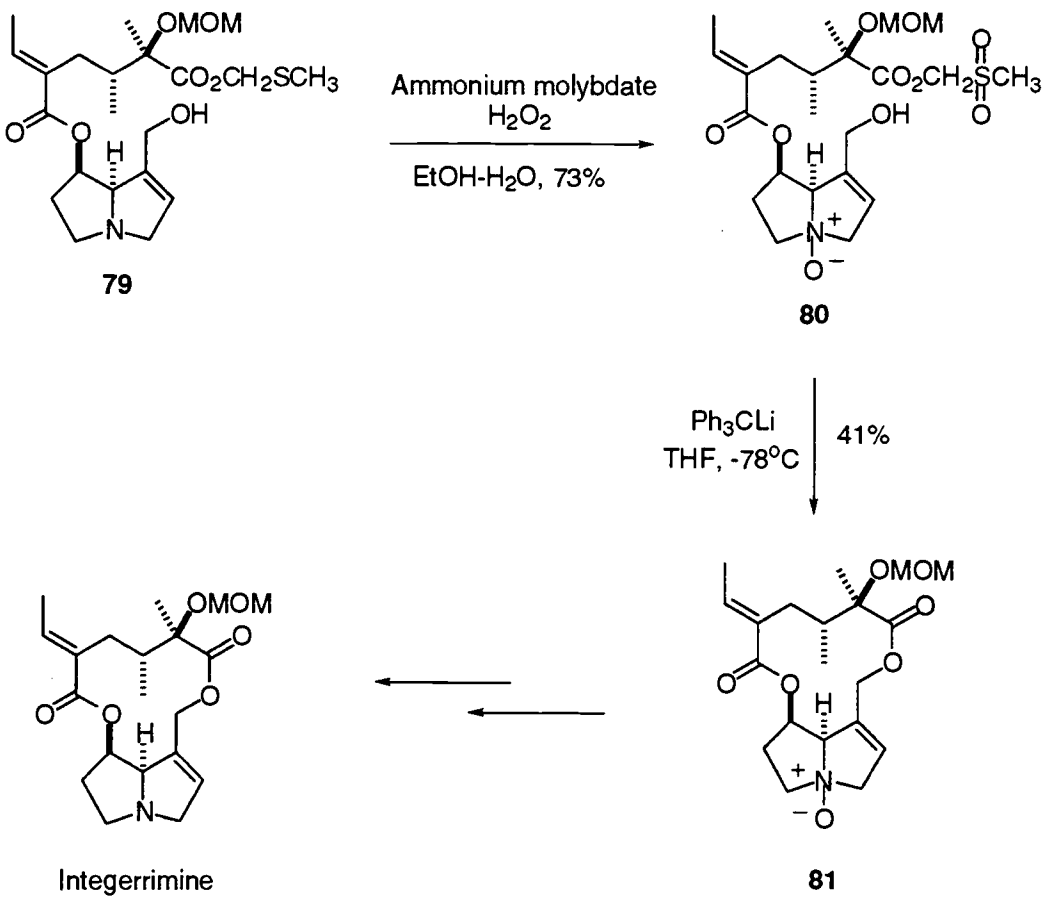
R = 92% (0.5 h)
96%
86%

77 + **78**

>98 : 2

Scheme 20

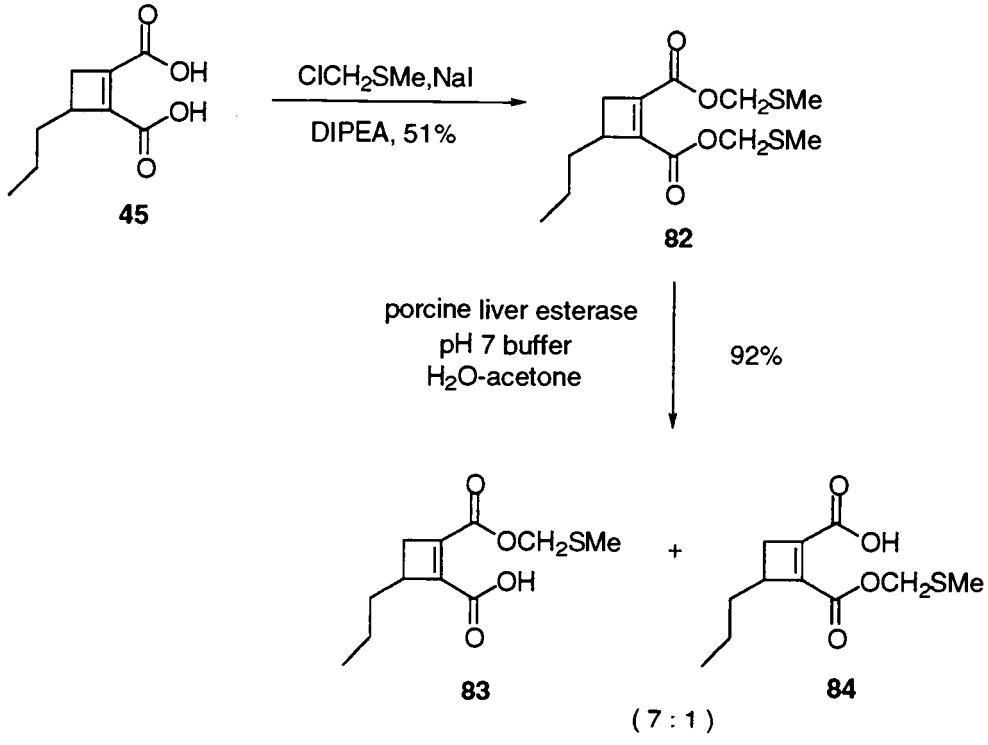
Consideration of these two issues led us to the methylthiomethyl (MTM) carboxylate as the protecting group in ester **72**. The methylthiomethyl group can be removed under essentially neutral conditions in the presence of heavy metal catalysts with a high affinity for sulfur such as mercury(II) or silver(I).[33] An additional advantage to the methylthiomethyl group as a protecting device is its usefulness in relay deprotection. Methylthiomethyl esters possess the stability of a typical unhindered ester towards base, but their lability can be greatly increased by oxidation to the corresponding methylsulfonylmethyl esters.[34] A striking example of the value of a methylthiomethyl ester in activating a carboxyl group towards nucleophilic attack can be found in the synthesis of the pyrrolizidine alkaloid integerrimine reported by Narasaka and co-workers (**Scheme 21**).[35] In this synthesis, activation of the carboxyl group in **79** was accomplished via oxidation of the methylthiomethyl ester to the corresponding methylsulfonylmethyl ester **80** with ammonium molybdate and hydrogen peroxide. Upon treatment with triphenylmethyllithium, **80** underwent macrolactonization to give the 12-membered bislactone **81**, which was advanced to integerrimine.



Scheme 21

Narasaka's chemistry offered an attractive means to avoid the complications arising from selective deprotection of **72**. Since a synthesis of alcohol **64** had already been developed in our laboratories, our effort was focused on the synthesis of the methylthiomethyl protected half acid **80** (**Scheme 22**). The previously synthesized diacid **45** was first treated with chloromethyl methyl sulfide to give bis-methylthiomethyl ester **82**. Enzymatic hydrolysis using buffered porcine liver esterase (pH 7) afforded a separable 7 : 1 mixture of half acids **83** and **84** in 92% yield. The major product from this hydrolysis reaction

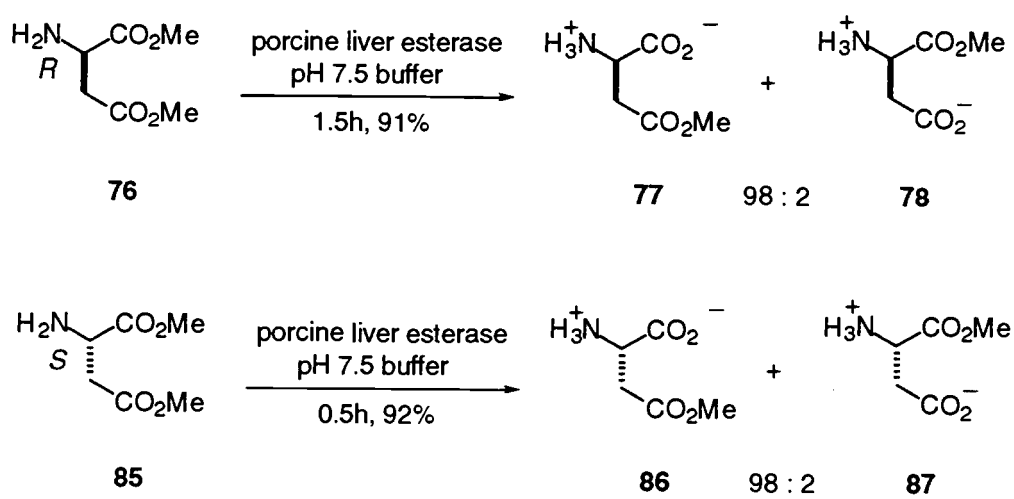
was assigned structure **83** by analogy with the esterase catalyzed reaction of dimethyl ester **44** (**Scheme 13**). The structural assignment to methyl ester **56**, in which the propyl group is placed adjacent to the carboxylic acid rather than the methyl ester moiety, had been based on a HMBC experiment which showed a weak coupling between the methylene protons of the cyclobutene ring and the ester carbonyl carbon.[28]



Scheme 22

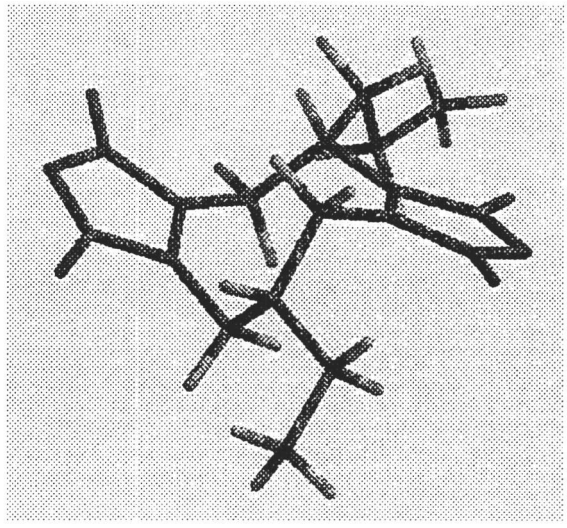
As previously mentioned, the quantitative yield of **56** and the 92% yield of mixture of **83** and **84** implied that the esterase had failed to distinguish enantiomers in the racemates **44** and **82** while effecting a nearly complete regioselective ester hydrolysis. Optical rotation values for **56** and **83** were zero,

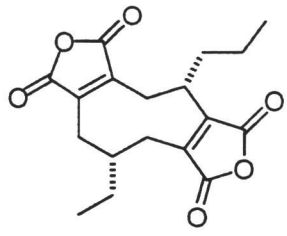
strongly suggesting that both compounds were indeed racemic. The failure of porcine liver esterase to distinguish stereoisomers of **44** and **82** while effecting highly regioselective hydrolysis of these diesters is presumably a reflection of the fact that the rate of hydrolysis for each enantiomer is essentially the same, thus precluding kinetic resolution. Although we must conclude that the esterase, while recognizing the location of the propyl substituent in relation to the two esters, makes no distinction between the orientations of the propyl group relative to the plane of the cyclobutene, this type of observation is not unique. Toogood[32] reported that hydrolysis of both (*R*)- and (*S*)-aspartate dimethyl esters **76** and **85** by porcine liver esterase resulted in selective hydrolysis of the α-ester to give the **77** and its enantiomer **86** (**Scheme 23**) within 0.5 hour and 1.5 hour, respectively. This result indicates that the three-fold rate difference for hydrolysis of the enantiomers **76** and **85** is insufficient for achieving clean kinetic resolution of racemic aspartate diesters.



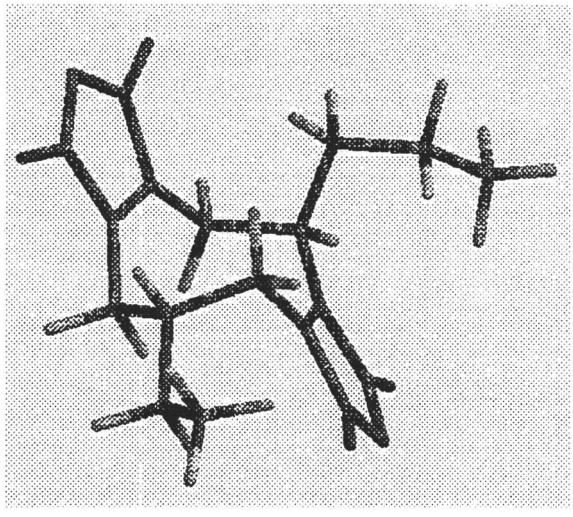
Scheme 23

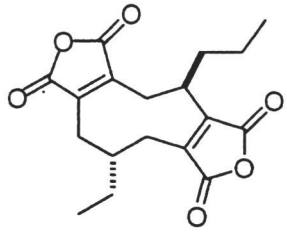
Fortunately, the racemic nature of **83** is of no consequence to the asymmetric synthesis of byssochlamic acid because it was already known from our previous work[21] that the propyl substituent can be epimerized in favor of the natural configuration at a late stage of the route to **3**. While continuing our progress toward **3**, the anticipated preference for the cis configuration of side chains was substantiated through a conformational analysis of byssochlamic acid in which energy minimization using a PM3 algorithm predicted a difference of ~2.6 kcal/mol between cis (**3c**) and trans (**3t**) isomers in favor of the former. The factor which destabilizes **3t** relative to **3c** is the pseudoaxial orientation of the propyl chain, which creates a transannular steric interaction with an endo hydrogen of the methylene adjacent to the ethyl substituent (**Figure. 1.4**). Interestingly, the nine-membered rings of both **3c** and **3t** adopt a chair-like conformation according to this computation and are therefore quite distinct from the 'U-shaped" conformation seen in the crystal structure of byssochlamic acid bis-*p*-bromophenylhydrazide **11**.[16] An important consequence of this conformational analysis of **3** is that, if the center bearing the propyl group is stereomutable, the absolute sense of an asymmetric synthesis of byssochlamic acid can be controlled through correct orientation of the remote ethyl substituent.





3c



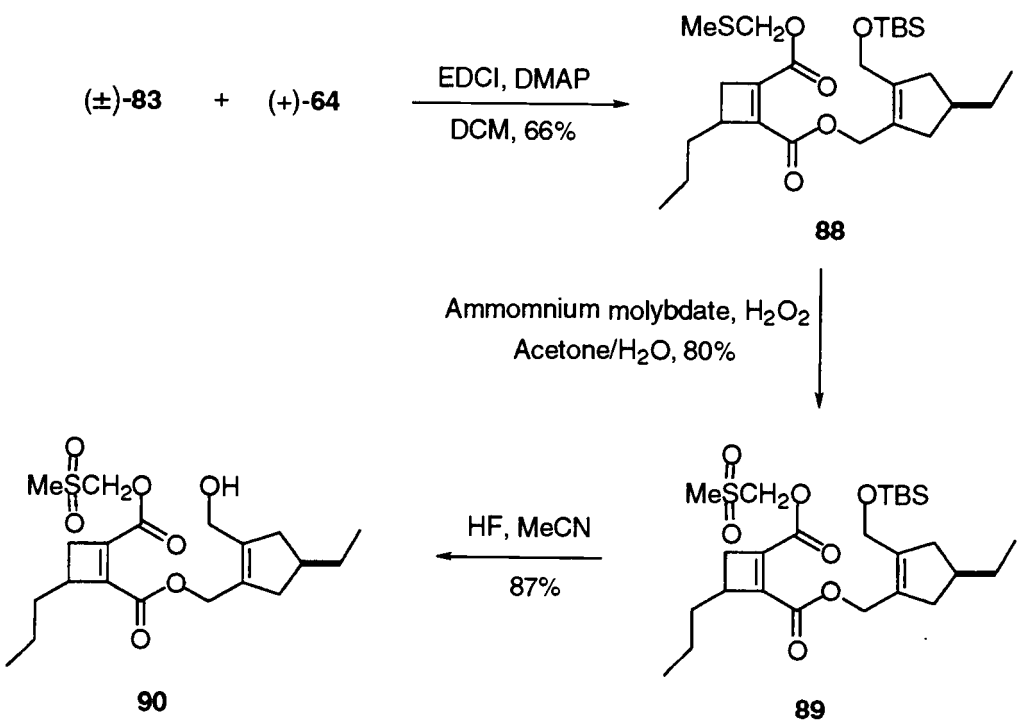


3t

Figure 1.4 Energy-minimized (PM3) conformations of byssochlamic acid (**3c**) and its trans isomer (**3t**).

This analysis allowed to the synthesis to proceed with the racemic form of the mono-methylthiomethyl ester **83** with the certainty that subsequent equilibration of the center bearing the propyl substituent would lead to the cis orientation of side chain characteristic of the natural product (**Scheme 24**). Racemic **83** and (+)-**64** were coupled using 1-(3-dimethylaminopropyl)-3-

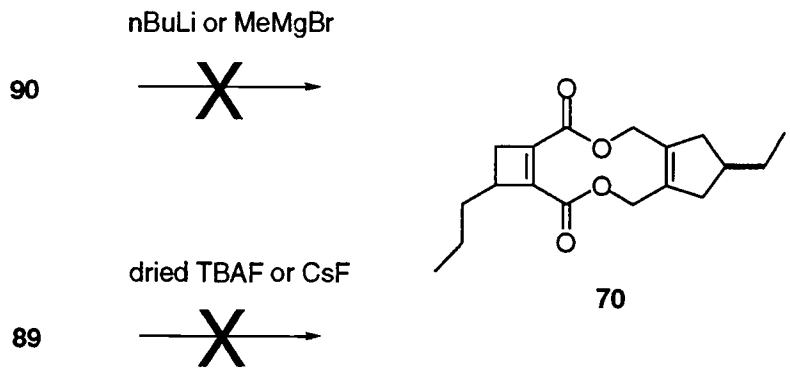
ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine to give an inseparable 1:1 mixture of stereoisomeric methylthiomethyl esters **88**. Oxidation of **8 8** with ammonium molybdate and hydrogen peroxide provided the corresponding methylsulfonylmethyl esters **89**, and the *tert*-butyldimethylsilyl group in **89** was removed to give alcohol **90**, again as a 1:1 mixture of inseparable stereoisomers.



Scheme 24

With **90** in hand, efforts were undertaken to promote the macrolactonization of this hydroxy diesters (**Scheme 25**), but all attempts using *n*-butyllithium or methylmagnesium bromide were unsuccessful. Under these conditions, only decomposition of the starting material was observed. Treatment

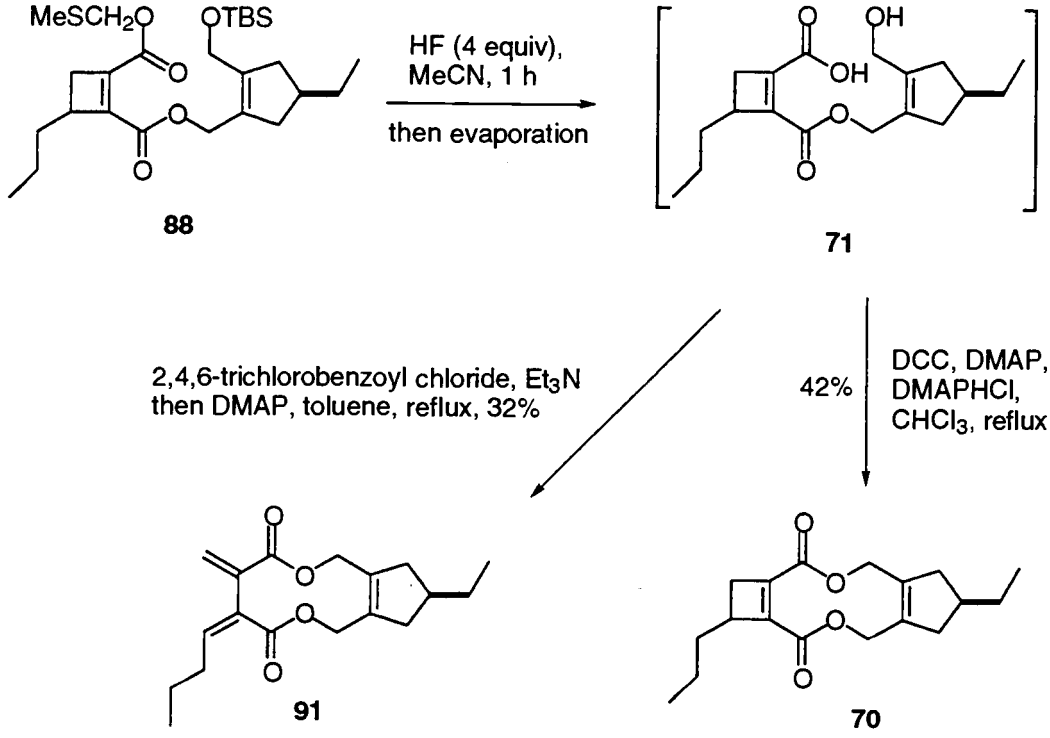
of **89** with various anhydrous fluoride sources such as dry tetrabutylammonium fluoride or cesium fluoride gave the same result.



Scheme 25

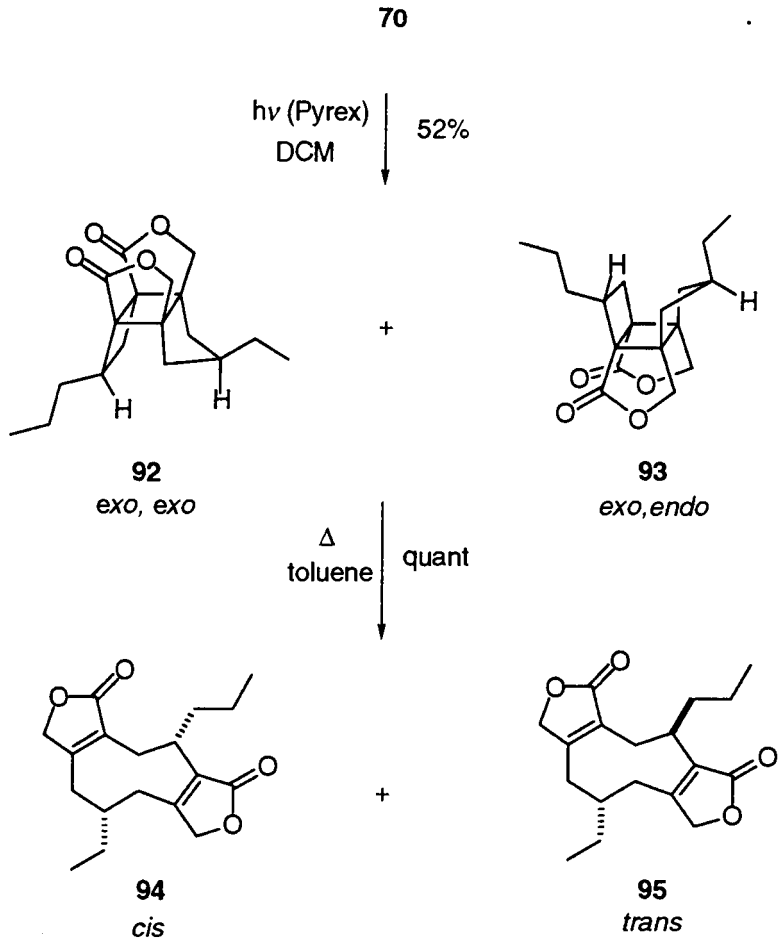
Although these negative results were discouraging, the simultaneous deprotection of both the methylthiomethyl group and the *tert*-butyldimethylsilyl group in **88** to form hydroxy acid **71** remained a possible escape route from this problem. Our goal was in situ synthesis of the diolide precursor, hydroxy acid **71**, in which the silyl ether and the cyclobutene ester would be cleaved in a single step that would not perturb the connecting ester linkage between cyclobutene and cyclopentene subunits. Thus, methylthiomethyl ester **88** was exposed to hydrogen fluoride which, as hoped, removed both the *tert*-butyldimethylsilyl and methylthiomethyl groups without compromising the cyclopentenylmethyl ester (**Scheme 26**). The hydroxy acid **71** generated in this reaction was not isolated but was subjected directly to Keck-Steglich lactonization conditions[27] to produce dilactone **70**. Interestingly, Yamaguchi lactonization conditions[31] produced

dilactone **91** in which the cyclobutene has undergone opening to a diene. This is probably due to the high temperature (refluxing toluene) at which lactonization carried out. Since the remote stereocenters in **88** provide no basis for stereoselection, diolide **70** was produced as a 1:1 mixture of stereoisomers at the center bearing the propyl substituent. The mixture proved to be inseparable under all chromatographic conditions.



Scheme 26

In contrast to **61**, diolide **70** exhibited significant absorption in its UV spectrum above 300 nm (ϵ ~16,000 at 313 nm), supporting the rationale based upon comparison of conformations of the two diolides, and suggesting a more productive outcome for the irradiation of **70**.

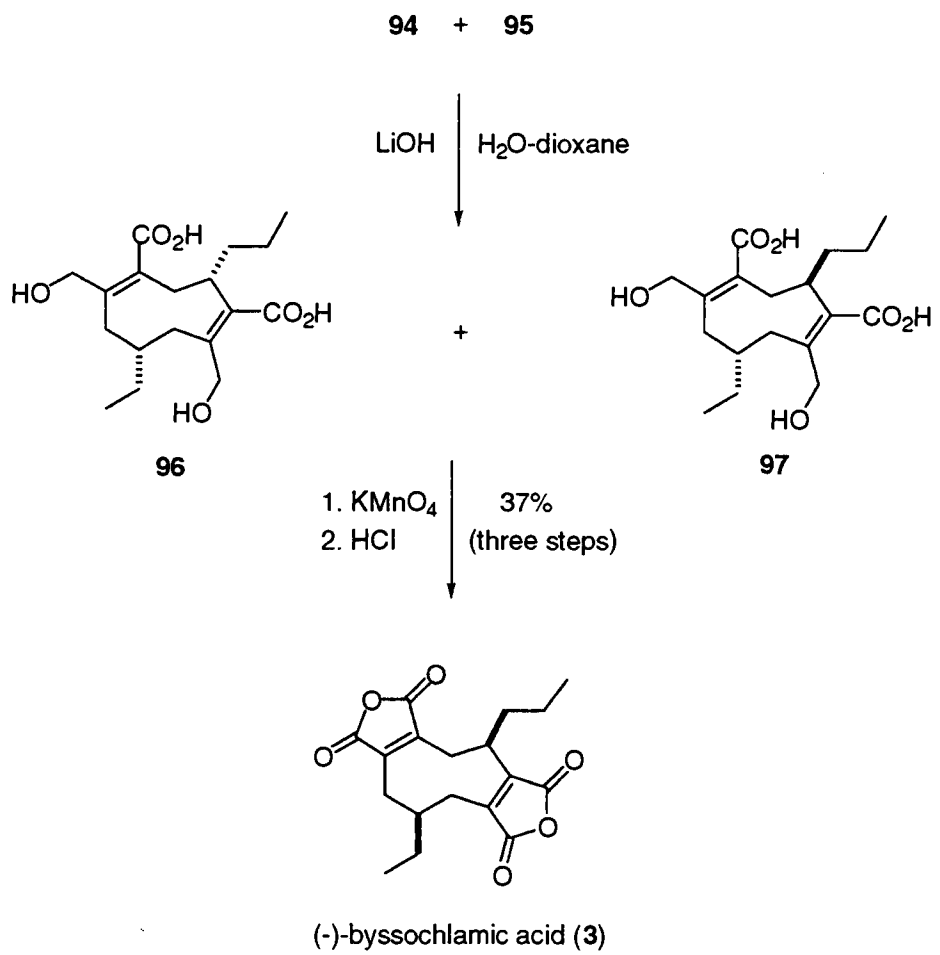


Scheme 27

In the event, irradiation of **70** (1:1 mixture) through Pyrex glass yielded two stereoisomeric photoproducts in approximately equal amount (**Scheme 27**). One of these products, resulting from the cis isomer of **70**, is assigned the exo,exo structure **92** in which both the ethyl and propyl substituents are directed away from the interior of the cage. The second photoproduct, derived from the trans isomer of **70**, is believed to be exo,endo adduct **93** in which the ethyl substituent rather than the propyl group occupies the interior space. Puckering of the cyclopentane ring of **93** moves the ethyl group away from the congested cage

interior, whereas the alternative photoadduct in which the propyl group is endo would create severe compression between the propyl substituent and a methylene group of the cyclopentane ring.

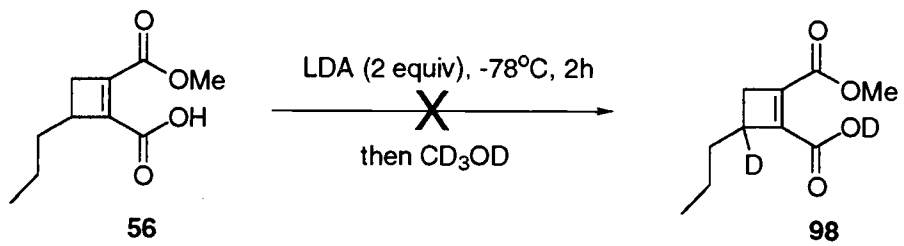
It was apparent during the photolysis of **70** that, even under the irradiation conditions, cycloreversion was taking place, and the facility of this fragmentation was confirmed when the mixture of **92** and **93** was heated in toluene. A quantitative yield of **94** and **95** resulted from this reaction, the former arising from **92** and the latter from **93** (**Scheme 27**).



Scheme 28

The steps from **94** and **95** to byssochlamic acid entailed hydrolysis of the pair of γ-lactones, oxidation of the resultant diol to tetracarboxylic acids **96** and **97**, and final treatment with hydrochloric acid to effect dehydration to give the bis anhydride (-)-**3**. As expected, the last step was also accompanied by epimerization of the propyl substituent in **97**, probably via a maleic-itaconic anhydride equilibrium, since only byssochlamic acid (**3**) and none of its trans isomer was produced in this sequence. However, to our suprise, synthetic **3** showed a negative value for its optical rotation measurement indicating that it is the enantiomer of natural byssochlamic acid (+)-**3**.

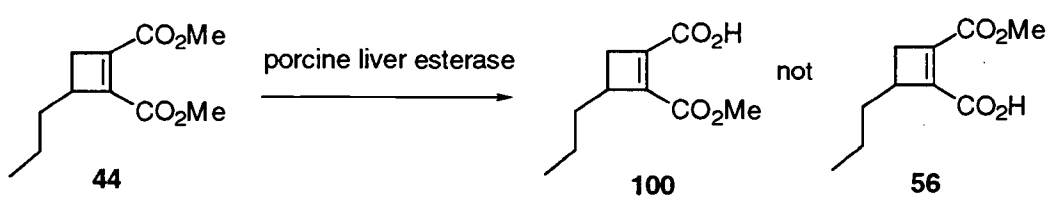
In order to rationalize this unexpected result, the entire synthetic sequence was carefully examined. It appeared that the only step which could be responsible for this outcome was the enzymatic hydrolysis of bis-methylthiomethyl ester **82**, in which the stereochemical assignment to the product **83** was based on perhaps misleading NMR studies conducted on the enzymatic hydrolysis product from dimethyl ester **44** (**Scheme 13**). In order to remove ambiguity in the assignments to the structures of mono-methylthiomethyl ester **83** and methyl ester **56**, a deuterium exchange experiment was devised (**Scheme 29**). In principle, a strong base should deprotonate the carboxylic acid and remove the γ-proton of the ester group in **56** to form a dianion. Subsequent quenching with d_4-methanol would give a deuteriated compound **98** in which NMR analysis of the protons in the cyclobutene ring would confirm the position of the propyl chain. Unfortunately, treatment of **56** with two equivalents of lithium diisopropylamide and d_4-methanol only resulted in the decomposition of the starting material.



56 98

Scheme 29

However, the cyclohexylamine salt of product of hydrolysis of **44** was crystalline, and X-ray crystallographic analysis of **99** established the structure of the hydrolysis product as **100** (**Figure 1.5**). Hence, the propyl side chain is adjacent to the ester group rather than to the carboxylic acid moiety as first thought. In retrospect, it is clear that too much weight was placed on a HMBC experiment which, at best, should have been regarded as inconclusive. The NMR evidence which led to the assignment of **56** as the esterase product from **44** could have been interpreted differently, particularly knowing that conclusions drawn from spin-spin couplings in small rings are notoriously unreliable.



44 100 56

Scheme 30

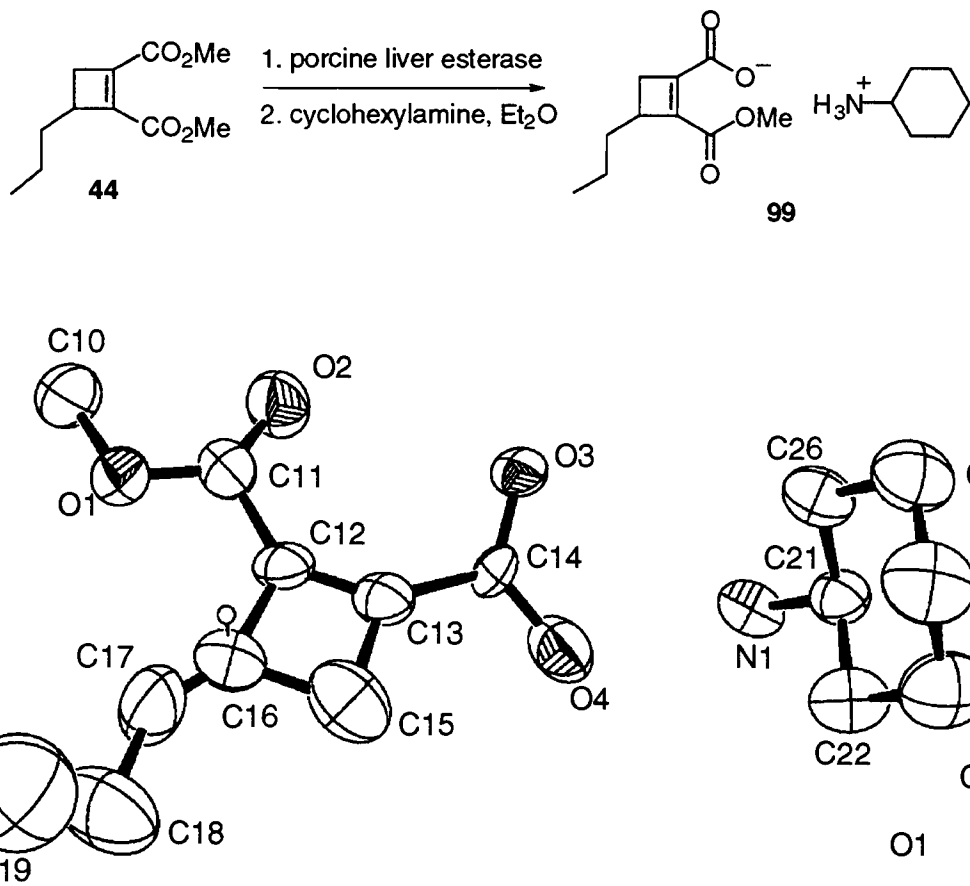
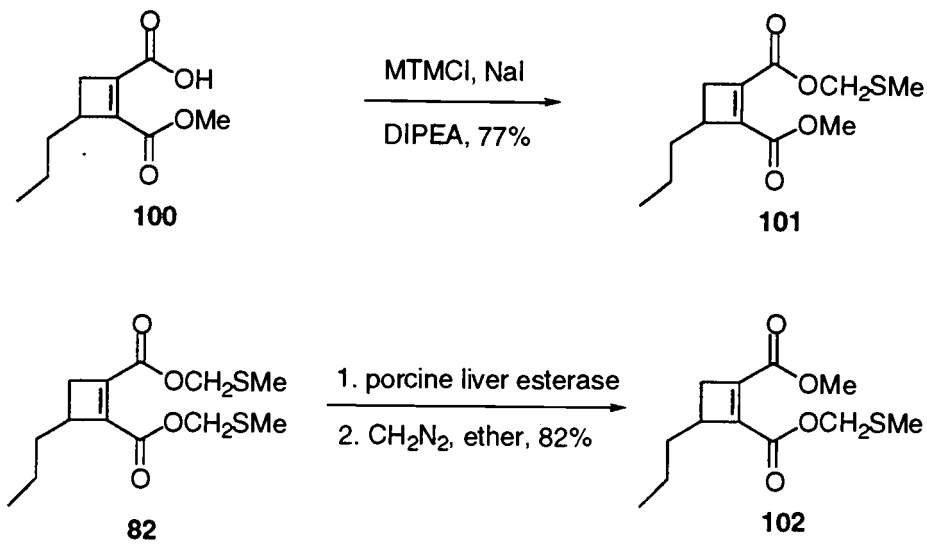


Figure 1.5 ORTEP representation from X-ray structure of **99**.

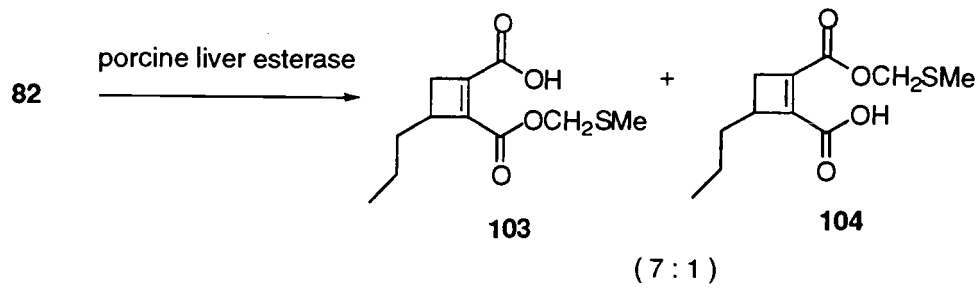
Correction of the structure of the product from porcine liver esterase hydrolysis of **44** as shown in **Scheme 30** raised another question regarding the structure of mono-methylthiomethyl ester **83**. We had hoped that porcine liver esterase hydrolysis of the bis-methylthiomethyl ester **82** would parallel the esterase catalyzed reaction of dimethyl ester **44** and our expectation was realized with comparison of spectroscopic data of **101** and **102** (**Scheme 31**). The carboxylic acid **100**, prepared from porcine liver esterase hydrolysis of dimethyl ester **44**, was converted into methylthiomethyl ester **101** and the

methylthiomethyl ester **102** was prepared from porcine liver esterase hydrolysis of bis-methylthiomethyl ester **82** followed by methylation of the resulting the half acid. If **44** and **82** result from the same regioselectivity in the hydrolysis reaction, **101** and **102** should be different compounds. Spectroscopic data revealed that these compounds are regioisomers, not identical, thereby proving that the enzymatic hydrolysis of **82** indeed parallel that of **44**.

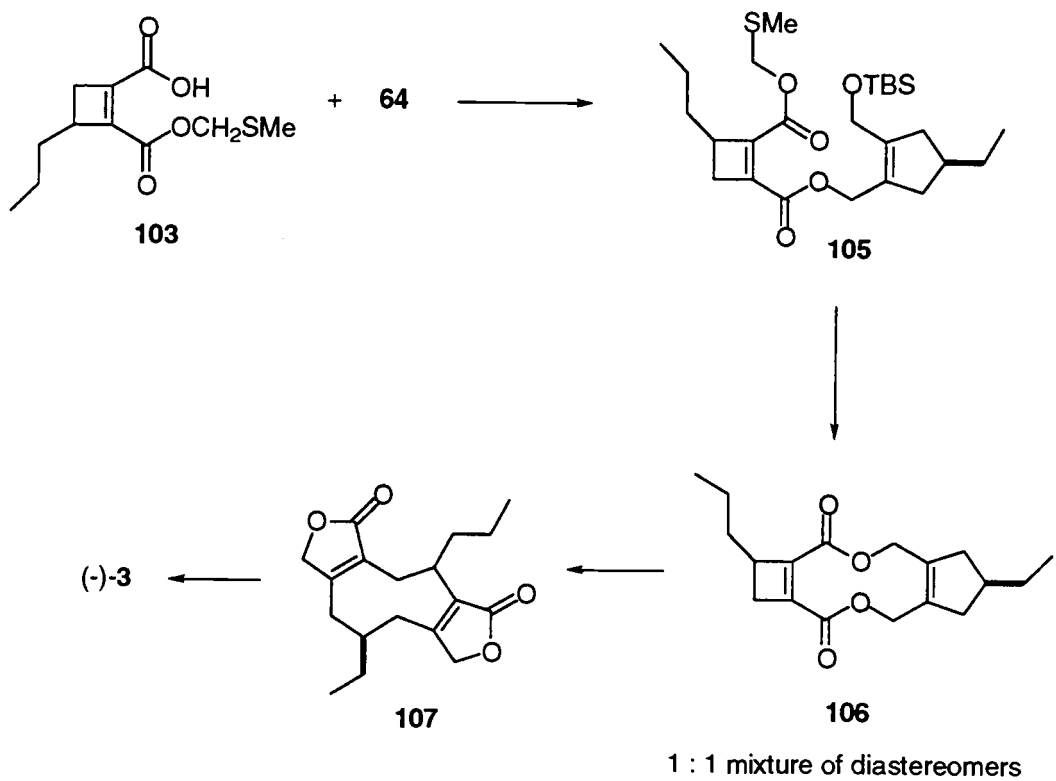


Scheme 31

The X-ray crystallographic analysis of the cyclohexylamine salt **99** together with the comparison of spectroscopic data of **101** and **102** established that the structure of the major methylthiomethyl ester from porcine liver esterase hydrolysis of **82** was not **83** but was in fact **103** as shown in **Scheme 32**.



Scheme 32



Scheme 33

With the structure of **103** now correct, the formation of (-)-**3** was easily explained by the sequence shown in **Scheme 33**. Coupling of **103** with **64** produced a 1 : 1 mixture of diastereomers **105** which gave diolide **106** after

deprotection followed by lactonization. Irradiation of diolide **106** and subsequent cycloreversion produced dilactone **107** as a cis/trans mixture which furnished (-)-**3** by oxidation and epimerization of the propyl chain.

With the recognition that the cis relationship of the ethyl and propyl substituents of **3** can be controlled through equilibration, the goal of an asymmetric synthesis of natural (+)-byssochlamic acid became a straightforward exercise. The enantiomeric relationship between diolide **106** which led to (-)-**3** and **70** which would afford (+)-**3** (**Figure 1.6**) reveals that the only difference lies in the configuration of the ethyl group (*S* in **106**, *R* in **70**). Thus, asymmetric synthesis of natural byssochlamic acid (+)-**3** can be achieved simply by reversing the configuration of the ethyl substituent of the cyclopentene.

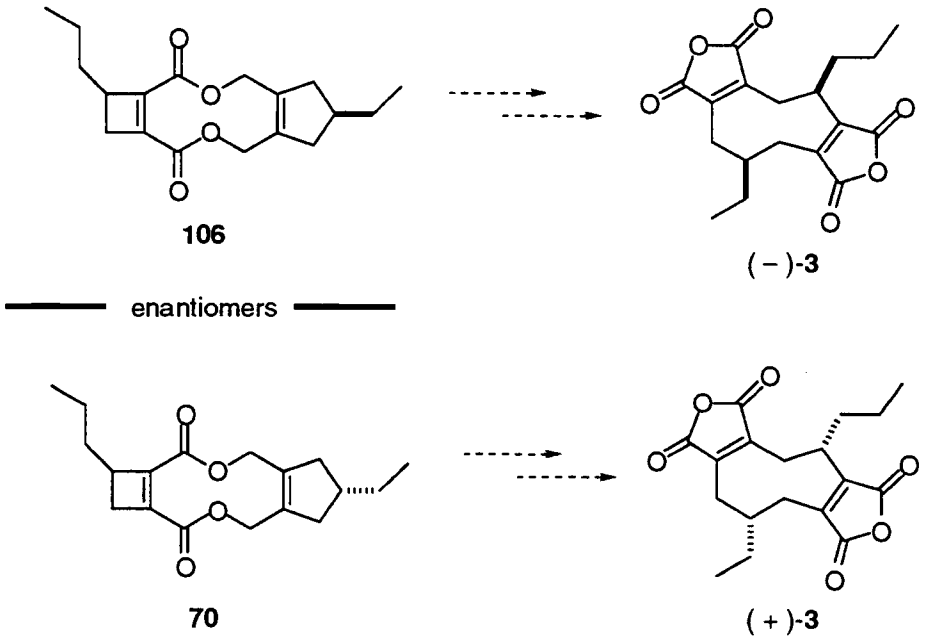
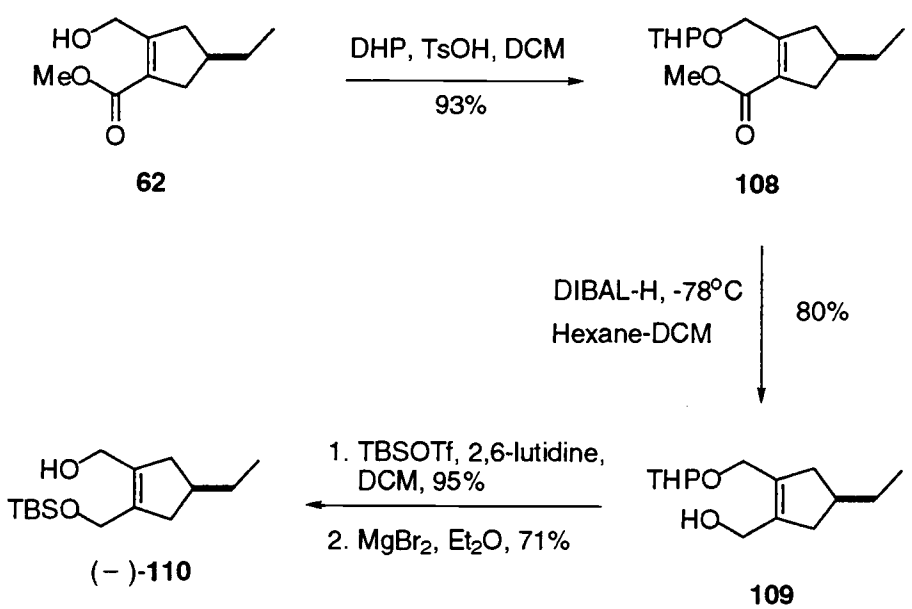


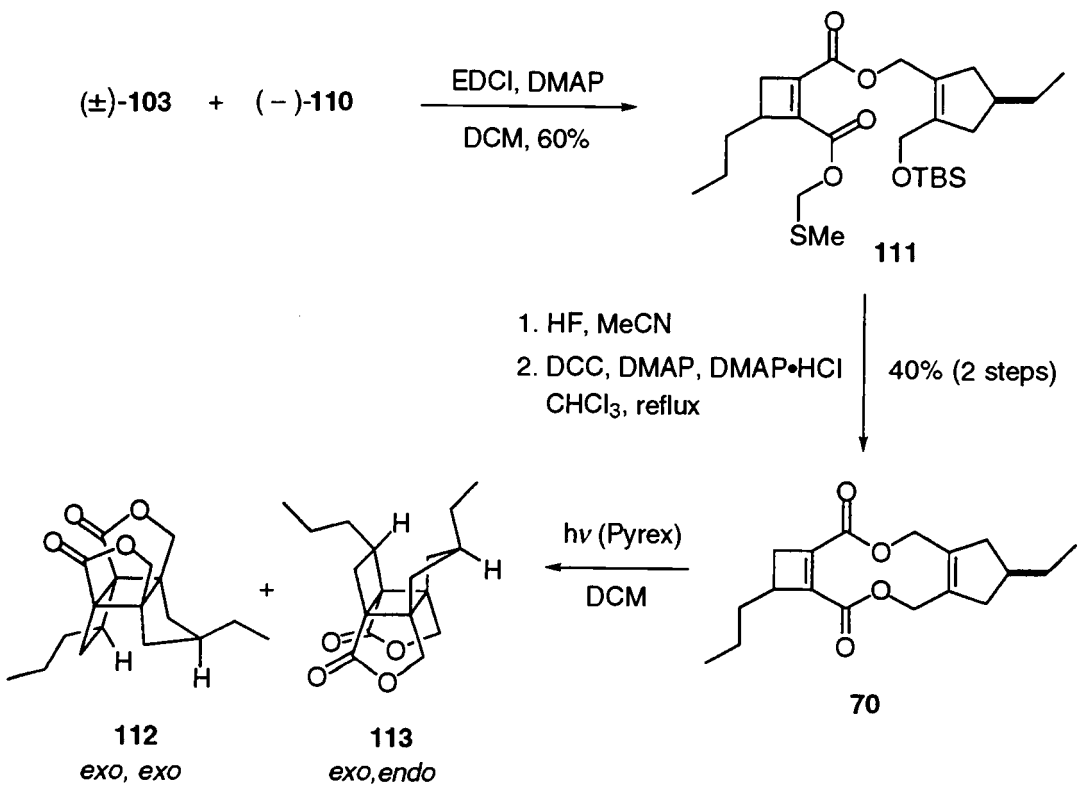
Figure 1.6 The enantiomeric relationship between **106** and **70**.

In principle, there are two options for accomplishing reversal of the ethyl configuration in **62**. A different esterase could perhaps be employed to effect desymmetrization of **48** in the opposite sense to **53** (**Scheme 12**).[36] Alternatively, **53** can be adapted to our goal by stepwise coupling with **103** in the reverse sequence. This approach only requires interchange of the primary alcohol and silyl ether substituents in **64**, a transformation which was easily achieved by protection of **62** with dihydropyran and reduction of the methyl ester in **108** to give alcohol **109**. Protection of this alcohol as its silyl ether was followed by selective removal of the tetrahydropyran protection with magnesium bromide in ether to give **110** (**Scheme 34**).[37] Optical rotation measurement confirmed that **110** was the enantiomer of **64**.



Scheme 34

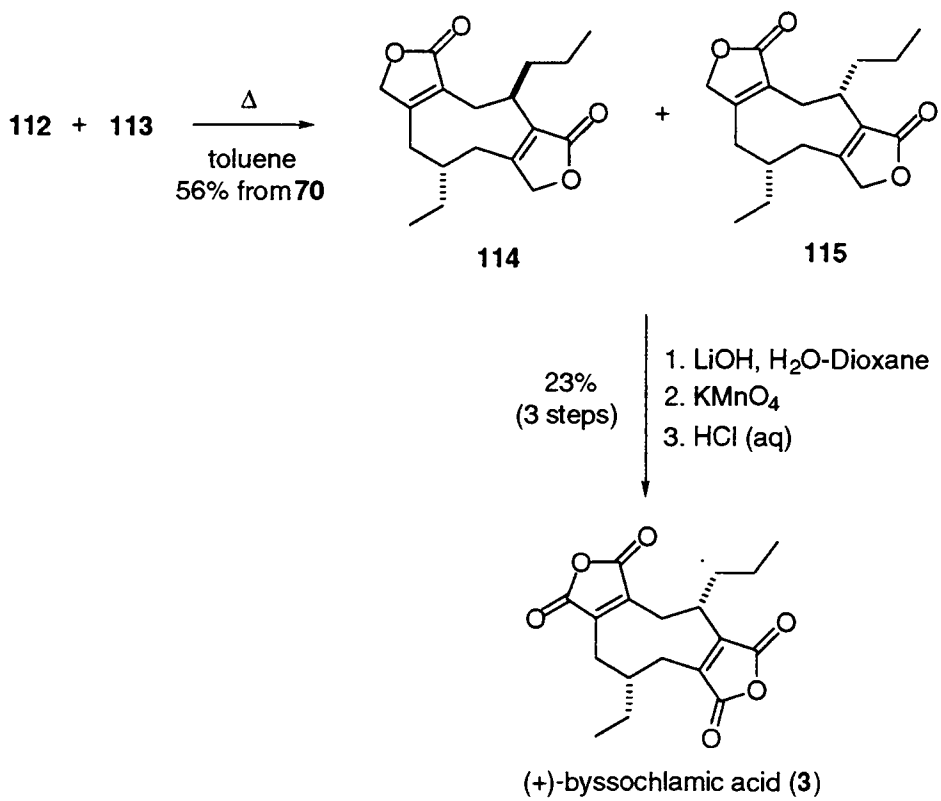
The alcohol **110** was used to esterify (±)-**103**, and the resultant diester **111** was deprotected and lactonized as before to give a 1:1 mixture of inseparable diolides **70** (**Scheme 35**). Irradiation of this stereoisomeric mixture gave exo,exo and exo,endo cage photoadducts **112** and **113** in equal quantity, the assumption again being made that in **113** the ethyl substituent rather than the propyl chain is more easily accommodated in an endo orientation.



Scheme 35

As with **92/93**, thermal cycloreversion of **112** and **113** was a quantitative reaction, resulting in a 1:1 mixture of dilactones **114** and **115**. The same

hydrolysis, oxidation, and acidification sequence used with **94** and **95** was applied to this mixture to give (+)-**3**, identical with a sample of natural byssochlamic acid supplied by the late Professor Sir Derek Barton.



Scheme 36

In conclusion, we have shown that a [2+2] photoaddition-cycloreversion pathway can be employed for asymmetric synthesis of both enantiomers of the nonadride byssochlamic acid (**3**). X-ray crystallographic analysis of the cyclohexylamine salt **99** showed that the structure of the monomethyl ester **100** from esterase hydrolysis of **44** was originally misassigned as **56** in Drapela's work. Recognition of the enantiomeric relationship of the two diolide **106** and **70**

allowed us to bypass this error and to synthesize both unnatural (-)-**3** from enantiopure alcohol (+)-**64**, and natural byssochlamic acid (+)-**3** from (-)-**110**, enantiomeric with (+)-**64**, respectively. The use of racemic (±)-**103** to reach both enantiomers of byssochlamic acid (**3**) demonstrated that the propyl group is indeed epimerizable and that the cis configuration of the two alkyl side chain is strongly preferred.

Experimental Section General

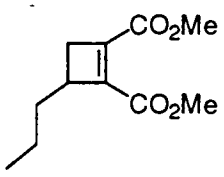
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, acetonitrile and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under stream of argon gas, and glass syringes were oven dried at 120 °C and cooled in a desicator over anhydrous calcium sulfate prior to use. Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure.

Analytical thin layer chromatography (TLC) was performed using precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in methanol or 1% solution of potassium permanganate in 2% 1 N sodium hydroxide in water. 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 Buchi melting point apparatus, and are uncorrected. Infrared (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 a 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 (Hz) and number of protons.

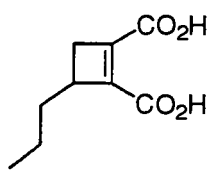
Chemical ionization (CI) high and low resolution mass spectroscopy (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained using a Varian MAT311 or a Finnegan 4000 spectrometer. X-ray crystallographic data were collected on a Siemens P4 spectrometer and these data were interpreted using the direct methods program contained in the SHELXTL (Silicon Graphics/Unix) software package.

Experimental Section



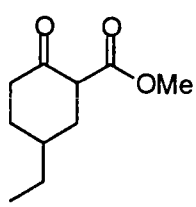
Dimethyl 3-*n*-Propylcyclobut-1-en-1,2-dicarboxylate (44). A photolysis apparatus, equipped with a Dry Ice condenser and an argon inlet, was charged with acetonitrile (250 mL), bromomaleic anhydride (8.00 g, 45.2 mmol), and benzophenone (1.6 g, 9 mmol). The solution was purged with argon for 1 h and 1-pentene (12.7 g, 181 mmol) was added. The mixture was irradiated with a 450-W Hanovia mercury lamp, using a Pyrex filter, for 3 h. The solvent was evaporated under reduced pressure, and the residue was taken up into Et_2O (100 mL) and stirred vigorously with 10% aqueous sodium carbonate (50 mL) for 1 h. The aqueous phase was separated and the process was repeated three times. The combined aqueous phases were acidified to pH 1 with 6N HCl and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was taken up in Et_2O (150 mL) and the solution was treated with ethereal diazomethane at 0 °C. The mixture was stirred for 1 h at 0 °C and concentrated under reduced pressure, and the residue was taken up into $CHCl_3$ (250 mL). To this solution was added DBU (16 mL, 107 mmol), and the mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was

diluted with $CHCl_3$ (100 mL), washed with water (50 mL) and brine (100 mL), and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 5.60 g (58%) of **44** as a colorless oil: IR (neat) 2955, 2925, 2867, 1738, 1717, 1641, 1443, 1299, 1209, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7 Hz), 1.35 (3H, m), 1.80 (1H, m), 2.21 (1H, dd, J = 2, 15 Hz), 2.75 (1H, dd, J = 4, 15 Hz), 2.93 (1H, m), 3.77 (3H, s), 3.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 33.5, 34.0, 40.5, 51.7, 51.8, 140.7, 146.4, 161.8, 161.9; MS(CI) *m/z* 213 (M^++H), 181, 170, 165, 151, 148, 137, 121, 93; HRMS (CI) *m/z* 213.1125 (calcd for $C_{11}H_{17}O_4$: 213.1127).



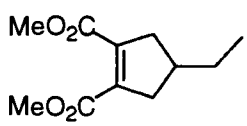
3-*n*-Propylcyclobut-1-en-1,2-dicarboxylic Acid (45). To a solution of **44** (0.226 g, 1.06 mmol) in THF (5 mL) and water (1.5 mL) was added lithium hydroxide monohydrate (0.10 g, 2.4 mmol). The mixture was stirred for 1 h at 0 °C, acidified to pH 1 with 1N HCl, and poured into a mixture of Et_2O (20 mL) and water (10 mL). The separated aqueous phase was extracted with Et_2O (2 x 20 mL), and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield 0.141

g (72%) of **45** as a colorless solid: mp 98-100 °C; IR (neat) 3400-2800 (br), 2964, 2935, 1723, 1621, 1445, 1284, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7 Hz), 1.4 (3H, m), 1.88 (1H, m), 2.36 (1H, dd, *J* = 1, 16 Hz), 2.88 (1H, dd, *J* = 4, 16 Hz), 3.06 (1H, m), 9.70-10.8 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.4, 33.4, 33.6, 40.7, 146.7, 151.0, 164.7, 164.8; MS(CI) *m/z* 167 (M^+-OH), 151, 140, 137, 125, 93; HRMS (CI) *m/z* 167.0709 (calcd for $C_9H_{11}O_3$: 167.0708).



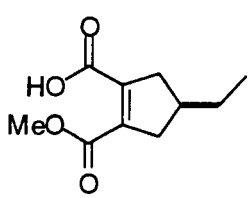
Methyl 5-ethyl-2-oxo-cyclohexancarboxylate (46). To a refluxing solution of dimethyl carbonate (28.7 mL, 340 mmol) and sodium hydride (6.8 g, 170 mmol, 60% in oil) in benzene (150 mL) was added a solution of 4-ethylcyclohexanone (7.16 g, 56.7 mmol) in benzene (50 mL) dropwise during 1 h. The mixture was refluxed for 1.5 h, then cooled to room temperature. Acetic acid (9.74 mL, 170 mmol) was added, and the mixture was washed with water. The aqueous phase was extracted with Et_2O (2 x 150 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 2% ethyl acetate in hexane as eluent, to give 9.70 g (93%) of **46** as a colorless oil: IR (neat) 2954, 2935, 2852, 1753, 1719, 1660, 1616, 1441, 1298, 1205 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7 Hz), 1.20-1.45 (4H, m), 1.68-1.85 (2H, m), 2.28-2.45 (3H, m), 3.73 (3H, s), 12.15 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 27.6, 28.4, 28.6, 29.0, 35.3, 51.3, 97.0, 172.1, 173.0; MS(CI) *m/z* 184 (M^+), 152, 128, 109, 95, 69; HRMS (CI) *m/z* 184.1101 (calcd for $C_{10}H_{16}O_3$: 184.1099).



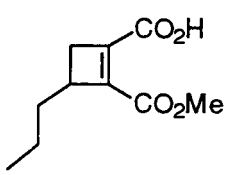
Dimethyl 4-ethylcyclopenten-1,2-dicarboxylate (48) To a solution of **46** (6.40 g, 34.7 mmol) in Et_2O (100 mL) was added Br_2 (3.70 mL, 72.9 mmol) dropwise at 0 °C during 40 min, and the mixture was stirred for 1.5 h at 0 °C. The solution was poured into a mixture of ice and saturated aqueous sodium bicarbonate (150 mL) at 0 °C, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was taken up into dry MeOH (100 mL), and this solution was added to a solution of NaOMe in MeOH [prepared by dissolving Na (3.19 g, 138.8 mmol) in MeOH (60 mL)] at 0 °C during 1 h. The mixture was allowed to warm to room temperature and was stirred for 30 min. The solution was poured into a mixture of ice and aqueous 1M $KHSO_4$ (120 mL) at 0 °C, and the resulting precipitate was filtered off by passage through a pad of Celite. The filtrate was extracted with Et_2O (3 x

100 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 2.90 g (39%) of **48** as a colorless oil: IR (neat) 2958, 2921, 2933, 2875, 2854, 1742, 1714, 1650, 1434, 1280, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7 Hz), 1.43 (2H, dq, J = 7, 7 Hz), 2.25-2.4 (3H, m), 2.85 (2H, m), 3.72 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 28.5, 38.5, 40.2, 51.9, 139.2, 166.0; MS(CI) *m/z* 212 (M^+), 181, 151, 137; HRMS (CI) *m/z* 212.1050 (calcd for $C_{11}H_{16}O_4$: 212.1049).



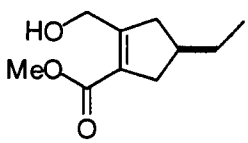
(*R*)-(+)-Methyl hydrogen 4-ethylcyclopenten-1,2-dicarboxylate (53). To a rapidly stirred mixture of **48** (1.70 g, 8.0 mmol) in acetone (20 mL) and pH 7 phosphate buffer (180 mL, sodium phosphate dibasic and potassium phosphate dibasic) at room temperature was added porcine liver esterase (200 mg, 4005 units). After stirring for 3 h at room temperature, the mixture was diluted with brine and ethyl acetate, and was acidified to pH 1 with 2N HCl at 0 °C. The resulting emulsion was filtered through a pad of Celite, and the filtrate was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were

washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield 1.55 g (98%) of **53**: $[\alpha]_D^{23}$ –7.8 (*c* 1.00, $CHCl_3$); IR (neat) 3400-2400 (br), 2952, 2921, 2664, 1735, 1730, 1650, 1458, 1350, 1293 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.9 (3H, t, *J* = 7 Hz), 1.42 (2H, dq, *J* = 7, 7 Hz), 2.18 (1H, m), 2.48-2.63 (2H, m), 2.95-3.12 (2H, m), 3.9 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 28.3, 36.2, 41.2, 42.3, 53.5, 137.8, 147.3, 163.8, 168.6; MS(CI) *m/z* 199 (M^++H), 181, 167, 151, 137; HRMS (CI) *m/z* 199.0969 (calcd for $C_{10}H_{15}O_4$: 199.0970).



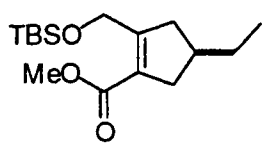
Methyl hydrogen 3-*n*-Propylcyclobut-1-en-1,2-dicarboxylate (56). To a rapidly stirred solution of **44** (0.10 g, 0.47 mmol) in acetone (3 mL) and pH 7 phosphate buffer (30 mL, sodium phosphate dibasic and potassium phosphate dibasic) at room temperature was added porcine liver esterase (9.4 mg, 188 units). The mixture was stirred for 3 h at room temperature, diluted with brine and ethyl acetate, and acidified to pH 1 with 2N HCl at 0 °C. The resulting emulsion was filtered through a pad of Celite and the filtrate was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced

pressure to yield 0.09 g (98%) of pure racemic **56**: IR (neat) 3400-2800 (br), 2959, 2930, 1746, 1681, 1640, 1445, 1338, 1294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7 Hz), 1.38 (3H, m), 1.88 (1H, m), 2.34 (1H, dd, *J* = 2, 16 Hz), 2.86 (1H, dd, *J* = 5, 16 Hz), 2.96 (1H, m), 3.92 (3H, s), 11.55-12.70 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 33.8, 34.0, 39.7, 53.2, 145.2, 149.7, 160.7, 165.3; MS(CI) *m/z* 199 (M^++H), 181, 167, 154, 137, 121, 111, 93; HRMS (CI) *m/z* 199.0971 (calcd for $C_{10}H_{15}O_4$: 199.0970).



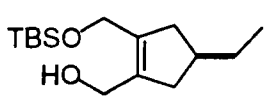
Methyl (4*R*)-4-Ethyl-2-hydroxymethylcyclopent-1-encarboxylate (62). To a solution of **53** (1.50 g, 7.57 mmol) and triethylamine (1.05 mL, 7.58 mmol) in THF (15 mL) at 0 °C was added a solution of ethyl chloroformate (0.72 mL, 7.58 mmol) in THF (5 mL) dropwise. The mixture was stirred at 0 °C for 30 min and filtered directly into a stirred solution of sodium borohydride (0.573 g, 15.15 mmol) in water (10 mL) at 0 °C. After stirring for 30 min, the mixture was acidified to pH 7 with 1N HCl and poured into a mixture of Et_2O (50 mL) and water (50 mL). The aqueous phase was separated and extracted with Et_2O (2 x 100 mL), and the combined organic extracts were washed with saturated aqueous sodium bicarbonate, water, and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl

acetate in hexane as eluent, to give 1.23 g (89%) of **62** as a colorless oil: $[\alpha]_D^{23}$ –5.7 (*c* 1.00, $CHCl_3$); IR (neat) 3422 (br), 2956, 2922, 2878, 1712, 1645, 1441, 1249, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, *J* = 7 Hz), 1.34 (2H, dq, *J* = 7, 7 Hz), 2.16 (1H, m), 2.28 (2H, m), 2.74 (2H, m), 3.74 (3H, s), 4.09 (1H, t, *J* = 6 Hz), 4.37 (1H, d, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 28.7, 37.6, 39.5, 42.6, 51.4, 60.3, 127.3, 159.4, 167.0; MS(CI) *m/z* 184 (M^+), 167, 155, 151, 123; HRMS (CI) *m/z* 184.1103 (calcd for $C_{10}H_{16}O_3$: 184.1099).



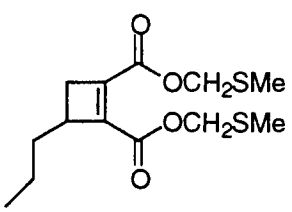
(R)-(+)-Methyl 4-Ethyl-2-(*tert*-butyldimethylsilyloxy)methylcyclopentene Carboxylate (63). To a stirred solution of **62** (13 mg, 0.070 mmol) and 2,6-lutidine (46 mg, 0.42 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added tert-butyldimethylsilyl trifluoromethanesulfonate (58 mg, 0.22 mmol) dropwise. The mixture was stirred at 0 °C for 1.5 h, MeOH (1 mL) was added dropwise, and the mixture was allowed to warm to room temperature and stirred for an additional 15 min. The mixture was poured into a mixture of CH_2Cl_2 (10 mL) and 3% aqueous copper sulfate (10 mL), and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure The residue was purified by chromatography on silica,

using 6% ethyl acetate in hexane as eluent, to yield 20 mg (95%) of **63**: $[\alpha]_D^{23}$ +1.6 (c 1.00, $CHCl_3$); IR (neat) 2954, 2929, 2855, 1713, 1644, 1464, 1435, 1361, 1233, 1191, 1122, 1086, 1034, 840 cm^{-1}; 1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (6H, s), 0.90 (3H, t, *J* = 6 Hz), 0.91 (9H, s), 1.41 (2H, dq, *J* = 6, 6 Hz), 2.19 (1H, m), 2.28 (2H, m), 2.81 (2H, m), 3.70 (3H, s), 4.70 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.5, 12.3, 18.2, 25.8, 28.8, 37.3, 39.4, 41.2, 50.9, 61.0, 125.3, 159.5, 166.0; MS(CI) *m/z* 299 (M^+), 283, 267, 251, 241, 167, 135, 115, 107, 89, 75; HRMS *m/z* 299.2041 (calcd for $C_{16}H_{31}O_3Si$: 299.2042).



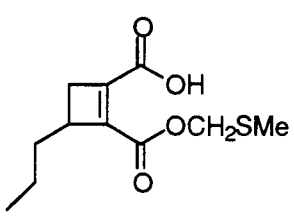
(*S*)-(+)-1-(*tert*-Butyldimethylsilyloxy)methyl-2-hydroxymethyl-4-ethylcyclopentene (64). To a stirred solution of diisobutylaluminum hydride (5.0 mL, 1.0M, 5.0 mmol) in hexanes at –78 °C was added a solution of **63** (500.0 mg, 1.675 mmol) in CH_2Cl_2 (4.0 mL) dropwise. The mixture was stirred at –78 °C for 3 h, MeOH (5 mL) was added, and the mixture was allowed to warm to room temperature. To this mixture was added CH_2Cl_2 (8 mL) followed by 20% aqueous Rochelle's Salt in water (8 mL), and the mixture was stirred until both layers were transparent. The phases were separated, and the aqueous portion was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated

under reduced pressure. The residue was purified by chromatography on silica, using 20% ethyl acetate in hexane as eluent, to afford 360 mg (80%) of **64**: $[\alpha]_D^{23}$ +1.0 (*c* 1.00, $CHCl_3$); IR (neat) 3349 (br), 2955, 2927, 2855, 1465, 1253, 1082, 1006, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (6H, s), 0.89 (3H, t, *J* = 7 Hz), 0.91 (9H, s), 1.40 (2H, dq, *J* = 7 Hz, 7 Hz), 2.09 (3H, m), 2.55 (2H, m), 4.16 (2H, s), 4.23 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.5, 12.4, 18.3, 25.8, 29.1, 37.8, 41.2, 41.4, 59.6, 60.5, 136.3, 136.3.



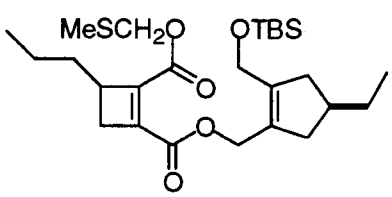
Bis-(Methylthio)methyl 3-*n*-Propylcyclobut-1-en-1,2-dicarboxylate (82). To a solution of chloromethyl methyl sulfide (1.50 mL, 17.9 mmol) in 1,2-dimethoxyethane (5 mL) was added sodium iodide (3.00 g, 20.2 mmol) in small portions. The mixture was stirred for 20 min at room temperature and a solution of **45** (0.61 g, 4.49 mmol) and *N,N*-diisopropylethylamine (3.1 mL, 17.9 mmol) in 1,2-dimethoxyethane (5 mL) was added dropwise. After 2 h at room temperature, the solution was heated at 70 °C for 2 h, then was cooled and cautiously diluted with water (25 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was

chromatographed on silica, using 8% ethyl acetate in hexane as eluent, to give 0.81 g (59%) of **82** as a colorless oil: IR (neat) 2954, 2922, 1720, 1634, 1430, 1262, 1195, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7 Hz), 1.38 (3H, m), 1.85 (1H, m), 2.26 (6H, s), 2.28 (1H, m), 2.78 (1H, dd, *J* = 4, 15 Hz), 2.95 (1H, m), 5.20 (1H, d, *J* = 13 Hz), 5.21 (2H, s), 5.27 (1H, d, *J* = 13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.4 (2), 20.4, 33.6, 34.0, 40.6, 68.6, 68.7, 141.0, 146.7, 160.7, 160.8; MS(CI) *m/z* 305 (M^++H), 275, 227, 195, 167; HRMS (CI) *m/z* 305.0878 (calcd for $C_{13}H_{21}O_4S_2$: 305.0881).



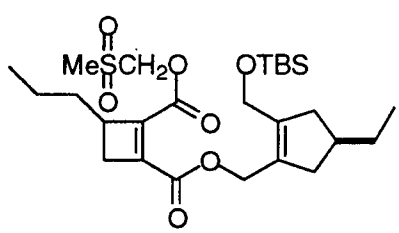
Methylthiomethyl hydrogen 3-*n*-Propylcyclobut-1-en-1,2-dicarboxylate (103). To a rapidly stirred mixture of **82** (0.155 g, 0.51 mmol) in acetone (2 mL) and pH 7 phosphate buffer (10 mL, sodium phosphate dibasic and potassium phosphate dibasic) at room temperature was added porcine liver esterase (5 mg, 100 units). After stirring for 3 h at room temperature, the mixture was diluted with brine (10 mL) and ethyl acetate (10 mL), and the resulting emulsion was filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (4 x 30 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield 0.11 g (90%) of a 7:1 mixture of **103** and **104** (determined by ^1H NMR analysis)

as racemates. Chromatography of the mixture on silica, using 50% ether in hexane as eluent, afforded 0.076 g of pure **103** as a colorless oil: IR (neat) 3300-2800 (br), 2959, 2930, 1738, 1673, 1631, 1421, 1349, 1266, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7 Hz), 1.43 (3H, m), 1.89 (1H, m), 2.31 (3H, s), 2.37 (1H, dd, *J* = 2, 16 Hz), 2.89 (1H, dd, *J* = 4, 16 Hz), 3.03 (1H, m), 5.36 (1H, d, *J* = 12 Hz), 5.39 (1H, d, *J* = 12 Hz), 12.03 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 15.7, 20.4, 33.7, 34.1, 39.7, 71.0, 144.9, 150.2, 160.3, 164.3; MS(CI) *m/z* 245 (M^++H), 195, 183, 167, 139, 123, 93; HRMS (CI) *m/z* 245.0846 (calcd for $C_{11}H_{17}O_4S$: 245.0848).



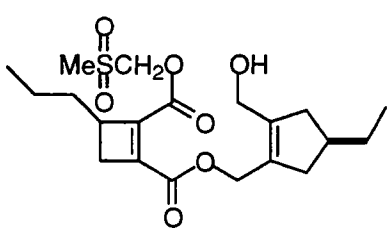
Methylthiomethyl ester 88.To a solution of **83** (0.048 g, 0.197 mmol) and **64** (0.053 g, 0.197 mmol) in dichloromethane (2 mL) was added sequentially solutions of 4-dimethylaminopyridine (0.048 g, 0.393 mmol) in dichloromethane (0.5 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.045 g, 0.236 mmol) in dichloromethane (0.5 mL) at room temperature. After stirring 4 h at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on silica, using 4% ethyl acetate in hexane as eluent, to give 0.06 g (66%) of **88** as a colorless oil: IR (neat) 2953, 2924, 1738, 1718, 1259, 1198, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88-

0.95 (m, 6H), 0.9 (s, 9H), 1.3-1.5 (m, 5H), 1.85 (m, 1H), 2.0-2.2 (m, 3H), 2.25 (dd, J = 2, 15 Hz, 1H), 2.27 (s, 3H), 2.59 (m, 2H), 2.78 (dd, J = 4, 15 Hz, 1H), 2.95 (m, 1H), 4.22 (d, J = 13 Hz, 1H), 4.28 (d, J = 13 Hz, 1H), 4.74 (d, J = 13 Hz, 1H), 4.8 (d, J = 13 Hz, 1H), 5.2 (d, J = 12 Hz, 1H), 5.27 (d, J = 12 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 12.5, 14.1, 15.4, 18.3, 20.4, 25.9, 29.2, 33.7, 34.0, 37.8, 40.5, 40.6, 40.9, 59.8, 61.0, 68.5, 130.4, 140.8, 141.7, 145.7, 160.9, 161.3; MS(CI) *m/z* 495 (M^+-H), 439, 435, 359, 343, 313, 253, 241, 195, 181; HRMS (CI) *m/z* 495.2601 (calcd for $C_{26}H_{43}O_5SiS$: 495.2601).



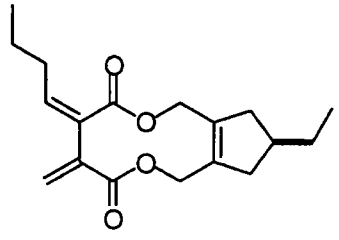
Methylsulfonylmethyl ester 89. A mixture of the **88** (0.02 g 0.04 mmol), 28% hydrogen peroxide (0.03 ml), 0.1 M aqueous ammonium molybdate (0.04 ml, 0.004 mmol), acetone (1.5 ml), and water (0.5 ml) was stirred for 3 h at room temperature. Water (2 ml) was added, and most of the acetone was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 X 10 ml) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 0.017 g (80%) of **89** as a colorless oil: IR (neat) 2957,

2931, 1729, 1457, 1339, 1257, 1211, 1113, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88-0.98 (m, 6H), 0.91 (s, 9H) 1.35-1.45 (m, 5H), 1.86 (m, 1H), 2.03-2.2 (m, 3H), 2.3 (dd, *J* = 1, 16 Hz, 1H), 2.5-2.62 (m, 2H), 2.84 (dd, *J* = 4, 16 Hz, 1H), 3.0 (m, 1H), 3.04 (s, 3H), 4.22 (d, *J* = 14 Hz, 1H), 4.24 (d, *J* = 15 Hz, 1H), 4.76 (d, *J* = 12 Hz, 1H), 4.8 (d, *J* = 12 Hz, 1H), 5.07 (d, *J* = 12 Hz, 1H), 5.15 (d, *J* = 12 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 12.4, 14.0, 18.3, 20.4, 25.9, 29.1, 33.8, 34.3, 37.8, 39.5, 40.5, 40.6, 40.9, 59.8, 61.2, 75.1, 130.1, 141.1, 143.4, 144.9, 158.6, 160.7; MS(CI) *m/z* 529 (M^++H), 513, 471, 441, 419, 375, 361, 253, 137; HRMS (CI) *m/z* 529.2641 (calcd for $C_{26}H_{45}O_7SiS$: 529.2655).



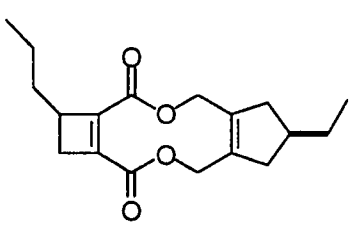
Alcohol 90. To a solution of **89** (0.072 g, 0.136 mmol) in acetonitrile (2 ml) at room temperature was added 4.8% hydrofluoric acid (0.23 ml, 0.55 mmol) dropwise. After stirring for 1 h at room temperature, the mixture was diluted with ether (20 ml), washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 0.049 g (87%) of **90** as a colorless oil: IR (neat) 3600-3200 (br), 2965, 2930, 1726, 1640, 1343, 1327, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88-0.96 (m, 6H), 1.3-1.5 (m, 5H), 1.84 (m, 1H), 2.03-2.2

(m, 3H), 2.25 (br s, 1H), 2.3 (dd, J = 1, 16 Hz, 1H), 2.5-2.65 (m, 2H), 2.81 (dd, J = 4, 16 Hz, 1H), 3.01 (m, 1H), 3.02 (s, 3H), 4.17 (d, J = 15 Hz, 1H), 4.21 (d, J = 15 Hz, 1H), 4.79 (d, J = 12 Hz, 1H), 4.8 (d, J = 12 Hz, 1H), 5.07 (d, J = 12 Hz, 1H), 5.15 (d, J = 12 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.0, 20.3, 29.1, 33.8, 34.2, 37.9, 39.5, 40.5, 40.7, 41.0, 59.0, 61.2, 75.1, 131.4, 141.5, 143.6, 144.7, 158.6, 161.0; MS(CI) *m/z* 413 (M^+-H), 397, 350, 331, 259, 167, 138, 120; HRMS (CI) *m/z* 413.1637 (calcd for $C_{20}H_{29}O_7S$: 413.1634).



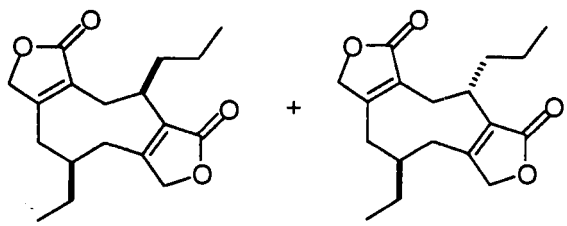
Dilactone 91. To a solution of **88** (0.02 g, 0.04 mmol) in acetonitrile (4 ml) at room temperature was added 4.8% hydrofluoric acid (0.067 ml, 0.16 mmol) dropwise. After stirring for 1 h at room temperature, the solvent was removed under reduced pressure and the residue was left under vacum (1 mmHg) for 6 h. The residue was taken up into tetrahydrofuran (0.5 ml) and added to a solution of 2,4,6-trichlorobenzoyl chloride (9.8 mg, 0.04 mmol) and triethylamine (4.6 mg, 0.046 mmol) in tetrahydrofuran (0.5 ml) at room temperature The mixture was allowed to stir at room temperature overnight and filtered through glass wool into dry toluene (5 ml). The resulting solution was added via syringe pump over 18 h to a refluxing solution of 4-dimethylaminopyridine (24 mg, 0.2 mmol) in toluene (35 ml). After addition was completed, the reaction mixture was cooled to room

temperature. The reaction mixture was filtered through a pad of silica, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica, using 5% ethyl acetate in hexane as eluent, to give 3.8 mg (32%) of **91** as a colorless oil:); IR (neat) 2959, 2930, 1732, 1288, 1196, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 0.98 (t, *J* = 7 Hz, 3H), 1.39(m, 2H), 1.54 (m, 2H), 2.03-2.2 (m, 3H), 2.47 (m, 2H), 2.6 (d, *J* = 8 Hz, 1H), 2.65 (d, *J* = 7 Hz, 1H), 4.7-4.9 (m, 4H), 5.79 (s, 1H), 6.2 (s, 1H), 6.49 (t, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 13.8, 22.3, 28.7, 31.4, 37.4, 42.9, 43.1, 61.6, 62.4, 124.6, 129.8, 131.6, 131.7, 140.0, 146.8, 165.7, 166.5; MS(CI) *m/z* 304 (M^+), 287, 274, 258, 231, 167, 138, 121; HRMS (CI) *m/z* 304.1673 (calcd for $C_{18}H_{24}O_4$: 304.1675).

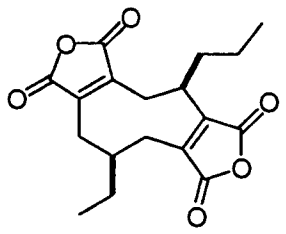


Diolide 106. To a solution of **88** (0.10 g, 0.20 mmol) in acetonitrile (4 mL) at room temperature was added 48% hydrofluoric acid (0.016 mL, 0.804 mmol) dropwise. After stirring the solution for 1 h at room temperature, the solvent was removed under reduced pressure and the residue was dried under vacuum (1 mm Hg) for 5 h. The resulting crude hydroxy acid was taken up into $CHCl_3$ (15 mL) and the solution was added to a refluxing solution of *N,N'*-dicyclohexylcarbodiimide (0.167 g, 0.804 mmol), 4-(dimethylamino)pyridine

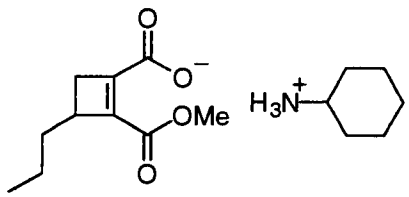
(0.123 g, 1.00 mmol), and 4-(dimethylamino)pyridine hydrochloride (0.154 g, 1.00 mmol) in $CHCl_3$ (100 mL) *via* syringe pump during 18 h. After addition was complete, the mixture was cooled to room temperature and methanol (1 mL) followed by acetic acid (0.05 g) were added. Stirring was continued for 1 h and the mixture was concentrated to a volume of 5 mL, diluted with Et_2O (20 mL), filtered, and concentrated. The residue was chromatographed on silica, using 5% ethyl acetate in hexane as eluent, to give 30 mg (49%) of **106** as a colorless oil: IR (neat) 2954, 2925, 1719, 1293, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (6H, m), 1.35-1.56 (5H, m), 1.75 (1H, m), 2.05-2.20 (3H, m), 2.37 (1H, dd, J = 1, 15 Hz), 2.46-2.60 (m, 2H), 2.87 (1H, dd, J = 4, 15 Hz), 3.12 (1H, m), 4.60-4.91 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 14.0, 20.7, 28.8, 33.6, 34.4, 37.2, 41.3, 43.1, 43.2, 62.2, 62.4, 132.1 (2), 143.4, 149.3, 162.4, 162.6; MS(CI) *m/z* 305 (M^++H), 286, 257, 229, 193, 153, 149, 121; HRMS (CI) *m/z* 305.1749 (calcd for $C_{18}H_{25}O_4$: 305.1753).



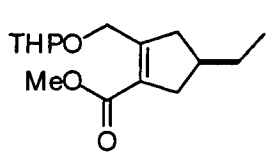
Dilactone 94 and 95. A photolysis apparatus, equipped with a Dry Ice condenser and an argon inlet, was charged with a solution of **70** (7.0 mg, 0.023 mmol) in CH_2Cl_2 (20 mL). The solution was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Pyrex filter for 3.5 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica, using 5% ethyl acetate in hexane and then 60% ethyl acetate in hexane as eluent, to give 1 mg of a mixture of **70** and 4.2 mg of a mixture of **92**, **93**, **94**, and **95**. The mixture was taken up into toluene (2 mL) and heated to reflux for 7 h. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give 3.5 mg (50%, 58% based on recovered **70**) of **94** and **95** as a colorless oil: IR (neat) 2949, 2911, 1754, 1667, 1458, 1067, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, m), 1.03 (3H, m), 1.11-1.40 (2H, m), 1.41-1.72 (4H, m), 1.75-2.02 (1H, m), 2.24-2.55 (5H, m), 2.72 (1H, m), 2.96-3.30 (1H, m), 4.43-4.78 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 12.3, 13.9, 14.0, 20.7, 21.1, 27.7, 27.8, 29.0, 29.7, 30.1, 31.1, 32.0, 33.1, 34.5, 35.3, 41.8, 42.3, 70.8, 71.5, 71.8, 72.3, 127.6, 128.3, 130.4, 131.8, 158.6, 159.0, 159.7, 160.0, 174.3, 174.7, 174.9; MS(CI) *m/z* 305 (M^++H), 286, 257, 193, 153; HRMS (CI) *m/z* 305.1753 (calcd for $C_{18}H_{25}O_4$: 305.1753).



(–)-Byssochalmic Acid. To a solution of **94** and **95** (2.0 mg, 0.0065 mmol) in dioxane (1 mL) and water (1 mL) was added lithium hydroxide monohydrate (2.8 mg, 0.065 mmol), and the mixture was stirred for 2.5 h at 100 °C. The mixture was cooled to room temperature and $KMnO_4$ (4.2 mg, 0.026 mmol) was added. After 2 h at room temperature, the mixture was cooled to 0 °C, acidified to pH 1 with 2N HCl, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.5 mg (22%) of (-)-**3**: $[\alpha]_D^{23}$ –83 (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7 Hz, 3H), 1.12 (t, *J* = 7 Hz, 3H), 1.28-1.50 (m, 2H), 1.50-1.72 (m, 4H), 1.90 (m, 1H), 2.25-2.43 (m, 2H), 2.65 (m, 1H), 2.72 (dd, *J* = 2, 14 Hz, 1H), 2.75-2.98 (m, 2H), 3.41 (m, 1H).

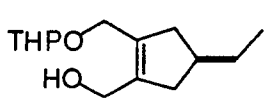


Cyclohexylammonium Carboxylate 99. To a solution of **100** (0.05 g, 0.252 mmol) in Et_2O (2 mL) was added cyclohexylamine (0.029 mL, 0.252 mmol) and the mixture was stirred for 10 min. After removal of the solvent, the residual solid was washed with Et_2O and crystallized by vapor diffusion from $CHCl_3$ to give **99**: IR (neat) 2925, 2857, 1724, 1633, 1543, 1384, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7 Hz), 1.05-1.40 (8H, m), 1.60 (1H, d, *J* = 12 Hz), 1.72 (2H, d, *J* = 13 Hz), 1.8 (1H, m), 1.99 (2H, d, *J* = 10 Hz), 2.19 (1H, dd, *J* = 1, 15 Hz), 2.73 (1H, dd, *J* = 4, 15 Hz), 2.83 (1H, m), 2.95 (1H, m), 3.72 (3H, s), 5.80-7.20 (3H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.5, 24.6, 24.9, 31.4, 34.6, 34.6, 39.1, 50.2, 51.3, 136.5, 152.9, 162.8, 168.9; MS(CI) *m/z* 298 (M^++H), 280, 254, 199, 181, 167, 154, 137, 93; HRMS *m/z* 298.2019 (calcd for $C_{16}H_{28}NO_4$: 298.2018).



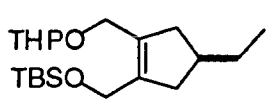
Methyl (4*R*)-4-Ethyl-2-(2-tetrahydropyranyloxy)methylcyclopent-1-encarboxlate (108). To a solution of **62** (0.09 g, 0.50 mmol) and dihydropyran

(0.11 mL, 1.24 mmol) in CH_2Cl_2 (2 mL) at room temperature was added *p*-toluenesulfonic acid monohydrate (0.001 g, 0.005 mmol). After stirring for 1 h, the mixture was diluted with ether (20 mL), washed with aqueous sodium bicarbonate and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 5% ethyl acetate in hexane as eluent, to give 0.12 g (93%) of **108** as a colorless oil: IR (neat) 2935, 2876, 2852, 1712, 1650, 1445, 1352, 1228, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H, t, *J* = 7 Hz), 1.31 (2H, dq, *J* = 7, 7 Hz), 1.38-1.80 (6H, m), 2.04 (1H, m), 2.21 (2H, m), 2.61-2.81 (2H, m), 3.40 (1H, m), 3.62 (3H, s), 3.75 (1H, m), 4.52 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 19.4, 25.3, 28.8, 30.5, 37.4, 37.5, 39.3, 41.5, 41.6, 50.9, 62.0, 64.6, 98.4, 98.4, 127.3, 155.5, 155.6, 165.7; MS(CI) *m/z* 269 (M^++H), 236, 207, 199, 184, 167, 155, 107; HRMS (CI) *m/z* 269.1753 (calcd for $C_{15}H_{25}O_4$: 269.1753).



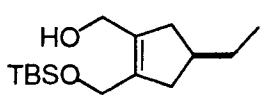
(4*S*)-4-Ethyl-2-(2-tetrahydropyranyloxy)methylcyclopent-1-enmethanol (109). To a solution of diisobutylaluminium hydride (1.73 mL, 1M in hexane, 1.73 mmol) at 0 °C was added a solution of **43** (0.155 g, 0.587 mmol) in CH_2Cl_2 (3 mL) dropwise. The mixture was stirred for 1 h at -78 °C, allowed to warm to room temperature, and diluted with CH_2Cl_2 (20 mL). A saturated solution of Rochelle's salt (20 mL) was added and, after stirring for 20 min, the mixture was

extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.126 g (91%) of **44** as a colorless oil: IR (neat) 3448 (br), 2925, 2881, 2852, 1130, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7 Hz), 1.38 (2H, dq, *J* = 7, 7 Hz), 1.43-1.85 (6H, m), 2.00-2.21 (3H, m), 2.45-2.77 (3H, m), 3.51 (1H, m), 3.82 (1H, m), 4.02-4.23 (4H, m), 4.6 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 19.0, 25.3, 29.2, 30.3, 38.0, 38.0, 41.2, 41.2, 41.4, 41.5, 58.9, 61.8, 62.8, 96.7, 96.7, 134.0, 139.8; MS(CI) *m/z* 222 (M^+-H_2O), 205, 155, 138, 122, 109, 85; HRMS (CI) *m/z* 222.1622 (calcd for $C_{14}H_{22}O_2$: 222.1620).



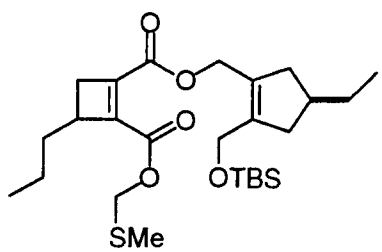
(4R)-1-(*Tert*-butyldimethylsilyloxy)methyl-4-ethyl-2-(2-tetrahydropyranyloxy)methyl-cyclopent-1-ene. To a solution **109** (0.113 g, 0.47 mmol) and 2,6-lutidine (0.11 mL, 0.94 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.16 mL, 0.7 mmol) dropwise. After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature, diluted with CH_2Cl_2 (20 mL), washed with brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 7% ethyl acetate in hexane as eluent, to give

0.158 g (95%) of (4R)-1-(*Tert*-butyldimethylsilyloxy)methyl-4-ethyl-2-(2-tetrahydropyranyloxy)methyl-cyclopent-1-ene. as a colorless oil: IR (neat) 2955, 2928, 2862, 1474, 1259, 1078, 1022, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (12H, m), 1.39 (1H, m), 1.45-1.61 (4H, m), 1.67 (1H, m), 1.81 (1H, m), 2.10 (3H, m), 2.58 (2H, m), 3.48 (1H, m), 3.85 (1H, m), 4.05-4.3 (4H, m), 4.55 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 12.5, 18.3, 19.4, 25.5, 25.9, 29.2, 30.6, 37.8, 40.5, 40.6, 41.2, 41.3, 59.6, 62.0, 62.9, 97.6, 133.1, 139.0; MS(CI) *m/z* 353 (M^+-H), 297, 252, 159, 85; HRMS (CI) *m/z* 353.2512 (calcd for $C_{20}H_{37}O_3Si$: 353.2512).



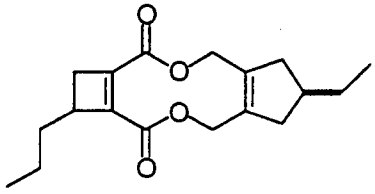
(4*S*)-4-Ethyl-2-(*tert*-butyldimethylsilyloxy)methylcyclopent-1-enmethanol (110). To a solution of (4R)-1-(*Tert*-butyldimethylsilyloxy)methyl-4-ethyl-2-(2-tetrahydropyranyloxy)methyl-cyclopent-1-ene (0.125 g, 0.353 mmol) in Et_2O (4 mL) at room temperature was added magnesium bromide (0.228 g, 0.883 mmol). After stirring for 5 h at room temperature, the mixture was diluted with Et_2O (20 mL), washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 0.068 g (71%) of **110** as a colorless oil: $[\alpha]_D^{23}$ –1.0 (*c* 2.7, $CHCl_3$); IR (neat) 3389 (br), 2955, 2926, 2854, 1465, 1260, 1082, 1006, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.89 (t, *J* = 7 Hz, 3H),

0.91 (s, 9H), 1.40 (dq, J = 7, 7 Hz, 2H), 2.09 (m, 3H), 2.55 (m, 3H), 4.16 (s, 2H), 4.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 12.5, 18.3, 25.8, 29.1, 37.8, 41.3, 41.4, 59.5, 60.5, 136.4, 136.5; MS(CI) *m/z* 269 (M^+-H), 253, 213, 195, 121; HRMS (CI) *m/z* 269.1933 (calcd for $C_{15}H_{29}O_2Si$: 269.1937).



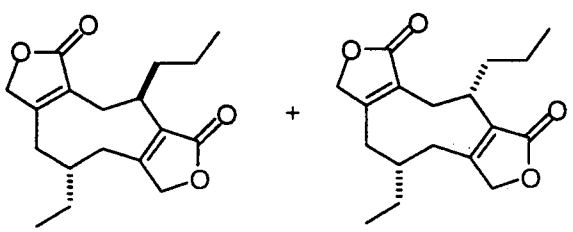
Diester 111. To a solution of **103** (0.12 g, 0.49 mmol) and **110** (0.13 g, 0.49 mmol) in CH_2Cl_2 (3 mL) was added sequentially solutions of 4-(dimethylamino)pyridine (0.12 g, 0.98 mmol) in CH_2Cl_2 (1 mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14 g, 0.74 mmol) in CH_2Cl_2 (1 mL) at room temperature. The mixture was stirred for 4 h at room temperature, the solvent was removed under reduced pressure, and the residue was chromatographed on silica, using 3% ethyl acetate in hexane as eluent, to give 0.145 g (60%) of **111** as a colorless oil: IR (neat) 2953, 2923, 1731, 1462, 1253, 1198, 1081, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.88-0.95 (6H, m), 0.89 (9H, s), 1.31-1.48 (5H, m), 1.85 (1H, m), 2.01-2.20 (3H, m), 2.25 (1H, dd, J = 2, 15 Hz), 2.27 (3H, s), 2.59 (2H, m), 2.78 (1H, dd, J = 4, 15 Hz), 2.95 (1H, m), 4.22 (1H, d, J = 13 Hz), 4.28 (1H, d, J = 13 Hz), 4.74 (1H, d, J = 13 Hz), 4.80 (1H, d, J = 13 Hz), 5.20 (1H, d, J = 12 Hz), 5.27 (1H, d, J = 12

Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 12.5, 14.1, 15.4, 18.3, 20.4, 25.9, 29.2, 33.7, 34.0, 37.8, 40.5, 40.6, 40.9, 59.8, 61.0, 68.5, 130.4, 140.8, 141.7, 145.7, 160.9, 161.3; MS(CI) *m/z* 495 (M^+-H), 439, 435, 359, 343, 301, 252, 241, 195, 181, 133; HRMS (CI) *m/z* 495.2601 (calcd for $C_{26}H_{43}O_5SiS$: 495.2601).



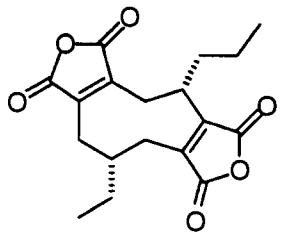
Diolide 70. To a solution of **111** (0.096 g, 0.194 mmol) in acetonitrile (2 mL) at room temperature was added 48% hydrofluoric acid (0.015 mL, 0.77 mmol) dropwise. The solution was stirred for 1.5 h at room temperature, the solvent was removed under reduced pressure, and the residue was dried under vacuum (1 mm Hg) for 6 h. The resulting crude hydroxy acid was taken up into $CHCl_3$ (10 mL) and the solution was added to a refluxing solution of *N,N'*-dicyclohexylcarbodiimide (0.16 g, 0.77 mmol), 4-(dimethylamino)pyridine (0.12 g, 0.98 mmol), and 4-(dimethylamino)pyridine hydrochloride (0.15 g, 0.98 mmol) in $CHCl_3$ (50 mL) *via* syringe pump over 20 h. After addition was complete, the reaction mixture was cooled to room temperature, and methanol (1 mL) followed by acetic acid (0.05 g) were added. Stirring was continued for 30 min, and the mixture was concentrated to a volume of 5 mL, diluted with Et_2O (20 mL), filtered, and concentrated. The residue was chromatographed on silica, using 5% ethyl acetate in hexane as eluent, to give 23.6 mg (40%) of **70** as a colorless oil:

IR (neat) 2957, 2928, 1722, 1299, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (6H, m), 1.35-1.56 (m, 5H), 1.75 (m, 1H), 2.05-2.20 (m, 3H), 2.37 (dd, *J* = 1, 15 Hz, 1H), 2.46-2.60 (m, 2H), 2.87 (dd, *J* = 4, 15 Hz, 1H), 3.12 (m, 1H), 4.60-4.91 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 14.0, 20.7, 28.8, 33.6, 34.4, 37.2, 41.3, 43.1, 43.2, 62.2, 62.4, 132.1 (2), 143.4, 149.3, 162.4, 162.6; MS(CI) *m/z* 304 (M^+), 286, 258, 224, 206, 191, 177, 168, 163, 137, 120; HRMS (CI) *m/z* 304.1674 (calcd for $C_{18}H_{24}O_4$: 304.1675).



Dilactone 114 and 115. A photolysis apparatus, equipped with a Dry Ice condenser and an argon inlet, was charged with a solution of **70** (0.040 mg, 0.13 mmol) in CH_2Cl_2 (100 mL). The solution was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Pyrex filter for 6 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica, using 5% ethyl acetate in hexane and 70% ethyl acetate in hexane as eluent, to give 7 mg of **70** and 19 mg of a mixture of **112**, **113**, **114**, and **115**. The mixture was taken up into toluene (3 mL) and heated to reflux for 7 h. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give

17.5 mg (44%, 56% based on recovered **70**) of **114** and **115** as a colorless oil: IR (neat) 2958, 2930, 1750, 1653, 1457, 1060, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.03 (m, 3H), 1.10-1.40 (m, 2H), 1.41-1.72 (m, 4H), 1.72-2.00 (m, 1H), 2.25-2.58 (m, 5H), 2.70 (m, 1H), 2.96-3.28 (m, 1H), 4.43-4.75 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.3, 13.9, 14.0, 20.7, 21.1, 27.7, 27.8, 29.0, 29.8, 30.3, 31.2, 32.1, 33.2, 34.5, 35.3, 41.6, 42.2, 70.8, 71.5, 71.8, 72.3, 127.4, 128.1, 130.1, 131.6, 158.2, 158.8, 159.2, 159.8, 173.9, 174.3, 174.8, 174.9; MS(CI) *m/z* 304 (M^+), 286, 257, 224, 193, 167, 153, 143, 119, 99; HRMS (CI) *m/z* 304.1681 (calcd for $C_{18}H_{24}O_4$: 304.1675).



(+)-Byssochlamic Acid. To a solution of **114** and **115** (11 mg, 0.036 mmol) in dioxane (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (15 mg, 0.36 mmol) and the mixture was stirred for 1.5 h at 50 °C. The mixture was cooled to 0 °C and $KMnO_4$ (40 mg, 0.252 mmol) was added. After 1 h at room temperature, the solution was heated at 40 °C for 1 h, then was cooled to 0 °C and acidified to pH 1 with 2N HCl. The mixture was extracted with CH_2Cl_2 (5 x 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue

was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 2.8 mg (23%) of (+)-**3**: mp 164-165 °C; $[\alpha]_D^{23}$ +101 (*c* 0.24, $CHCl_3$); IR (neat) 2966, 2934, 1829, 1766, 1260, 927 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7 Hz), 1.12 (3H, t, *J* = 7 Hz), 1.28-1.50 (2H, m), 1.50-1.75 (4H, m), 1.90 (1H, m), 2.25-2.43 (2H, m), 2.65 (1H, m), 2.72 (1H, dd, J = 2, 14 Hz), 2.77-2.98 (2H, m), 3.41 (1H, m); 13C NMR (75 MHz, CDCl3) (11.6, 13.7, 20.6, 28.1, 29.2, 29.7, 30.0, 34.7, 36.0, 40.4, 143.2, 143.4, 144.1, 144.7, 164.9, 165.4 (2), 165.7; MS(CI) m/z 332 (M+), 260, 208, 166, 125; HRMS (CI) m/z 332.1263 (calcd for C18H20O6: 332.1259).

References

1. Sutherland, J. K. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 131.

2. Wijkman, N. *Just. Lieb. Ann. Chim.* **1931**, *485*, 61.

3. Raistrick, H.; Smith, G. *Biochem. J.* **1933**, *27*, 1814.

4. a) Wilson, B. J.; Wilson, C.H. *J. Bacteriol.* **1962**, *83*, 693. (b) Büchi, G.; Snader, K. M.; White, J. D.; Gougoutas, J. Z.; Singh, S. *J. Am. Chem. Soc.* **1970**, *92*, 6638.

5. Overeem, J. C.; Mackor, A. *Recl. Trav. Chim. Pays-Bos* **1973**, *92*, 349.

6. Crane, R. I.; Hedden, P.; MacMillan, J.; Turner, W. B. *J. Chem. Soc. Perkin Trans 1* **1973**, 194.

7. Arai, K.; Shimizu, S.; Miyajima, H.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2870.

8. Dabrah, T. T.; Kaneko, T.; Massefski, Jr., W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

9. Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.

10. (a) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737. (b) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157. (c) Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552. (d) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1877, 1880. (e) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015. (f) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784. (g) Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 12721. (h) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890.

11. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1699. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H-S. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1676.

12. Olliver, Smith, J. Bot. 1933 71, 196.

13. Baldwin, J. E.; Barton, D. H. R.; Bloomer, J. L.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *Experientia* **1962**, *18*, 345.

14. (a) Sutter, H.; Wijkman, N. *Just. Lieb. Ann. Chim.* **1933**, *505*, 248. (b) Sutter, H.; Wijkman, N. *Just. Lieb. Ann. Chim.* **1935**, *519*, 97. (c) Sutter, H.; Rottmayr, F.; Porsch H. *Just. Lieb. Ann. Chim.* **1936**, *521*, 189.

15. (a) Kraft, K.; Porsch, H. *Just. Lieb. Ann. Chim.* **1937**, *527*, 168. (b) Kraft, K. *Just. Lieb. Ann. Chim.* **1937**, *530*, 20.

16. Hamor, T. A.; Paul, I. C.; Monteath Robertson, J.; Sim. G. A. *Experientia* **1962**, *18*, 352.

17. Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787.

18. Moss, M. O. In *Microbial Toxins*; Ciegler, A., Ed.; Academic Press: New York & London, **1971**, *6*, 381.

19. (a) Asano, M.; Kanematsu, T. *Chem. Ber.* **1932**, 65. (b) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, *28*, 828

20. Stork, G.; Tabak, J. M.; Blount, J. F. *J. Am. Chem. Soc.* **1972**, *94*, 4735.

21. White, J. D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673.

22. Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 225.

23. (a) Lange, G. L.; Huggins, M.-A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409. (b) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749.

24. (a) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267. (b) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (c) Wender, P. A.; Letendre, L. J. *J. Org. Chem.* **1980**, *45*, 367.

25. (a) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (b) Williams, J. R.; Callahan, J. F. *J. Chem. Soc. Chem. Commun.* **1979**, 405. (c) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4475, 4479. (d) Randall, M. L.; Lo, P. C-K.; Bonitatebus Jr., P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534 and reference 5 cited.

26. Cf.: Schorno, K. S.; Adolphen, G. H.; Eisenbraun, E. J. *J. Org. Chem.* **1969**, *34*, 2801.

27. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

28. Drapela, N. E. Synthetic Studies of nonadrides. **1998**, 139.

29. Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc. Chem. Commun.* **1984**, 236.

30. Soai, K.; Yokoyama, S.; Mochida, Y. *Synthesis* **1987**, 647.

31. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

32. Stein, K. A.; Toogood, P. L. *J. Org. Chem.* **1995**, *60*, 8110.

33. Corey, E. J.; Bock, M. *Tetrahedron Lett.* **1975**, 3269.

34. Gerdes, J. M.; Wade, L. G. *Tetrahedron Lett.* **1979**, 689.

35. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

36. (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. Am. Chem. Soc. 1984, 106, 3695. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc. Chem. Commun.* **1986**, 1248.

37. Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439

PART II. AN APPROACH TO THE NOOTROPIC AGENT HUPERZINE A.

Chapter III. AN APPROACH TO THE NOOTROPIC AGENT HUPREZINE A

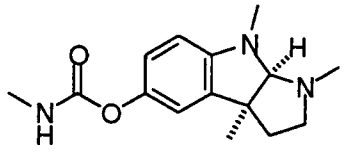
History and Background

Alzheimer's disease is a common neurodegenerative disorder that accompanies aging and afflicts an estimated 4,000,000 people in the U.S. alone. The disease leads to progressive loss in cognitive abilities, performance of routine tasks, time and space orientation, communication skills, abstract thinking, and personality. Since incidence of Alzheimer's disease increases with age (approximately 40% of individuals over 85 have Alzheimer's disease), more people will be at risk in coming years.[1]

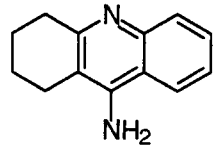
While the etiology of Alzheimer's disease is not fully understood, many of those involved in research in this field believe that the deposition of senile plaque, formed through aggregation of insoluble β-amyloid, a protein of unknown function, is closely related to the degree of cognitive function impairment. Senile plaque may be linked to a deficiency which develops in the cholinergic system of Alzheimer's patients. The primary neurotransmitter in the cholinergic system, acetylcholine, is produced at lower levels in these individuals due to a decrease in the level of choline acetyltransferase, the enzyme that mediates acetylcholine synthesis. The amount of choline acetyltransferase is known to be reduced by 50-95% in Alzheimer's patients compared with age matched controls.[2]

Accordingly, enhancement of the central cholinergic function has been regarded as one of the most promising approaches for treating Alzheimer's disease patients. This is mainly achieved by means of acetylcholinesterase inhibitors. Acetylcholinesterase hydrolyzes the neurotransmitter acetylcholine into

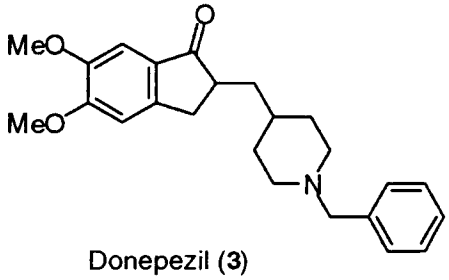
acetate anion and choline. Through inhibition of this enzyme, the concentration of acetylcholine is increased resulting in improved cognitive functions. Among the several known acetylcholinesterase inhibitors are physostigmine (**1**), the recently marketed tacrine (**2**),[3] donepezil (**3**),[4] and rivastigmine (**4**)[5] (**Figure 2.1**). Unfortunately, the use of physostigmine has limits due to its short duration of action, and tacrine, although now approved for use in the U. S., is a liver toxin.[6]



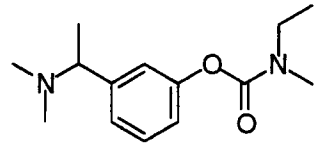
Physostigmine (**1**)



Tacrine (**2**)



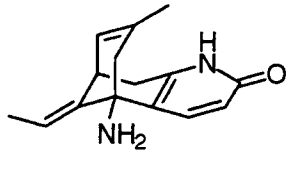
Donepezil (**3**)



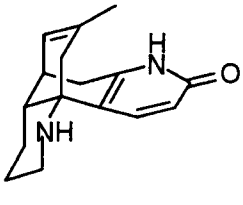
Rivastigmine (**4**)

Figure 2.1 Structures of some known acetylcholinesterase inhibitors.

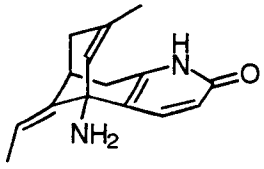
Huperzine A (**5**) is an alkaloid from the clubmoss *Huperzia serrata* (Thunb.) Trev. = *Lycopodium serratum* Thunb., which is used in the treatment of Alzheimer's disease.[7] In fact, *H. serrata* has been used in Chinese traditional medicine under the name Chien Tseng Ta to treat several illnesses.[8] In pharmacological studies carried out during the late 1980s, huperzine A proved to be a very potent inhibitor of the acetylcholinesterase. Recently, purified natural huperzine A has undergone clinical trials in China in patients suffering from various memory disorders including Alzheimer's disease.[9]



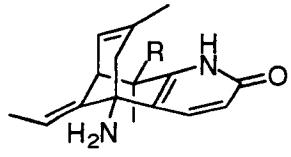
Huperzine A (**5**)



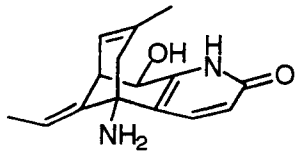
Huperzine B (**6**)



Selagine (**7**)



R = H (**8**)
R =Me (**9**)



6β-Hydroxyhuperzine A (**10**)

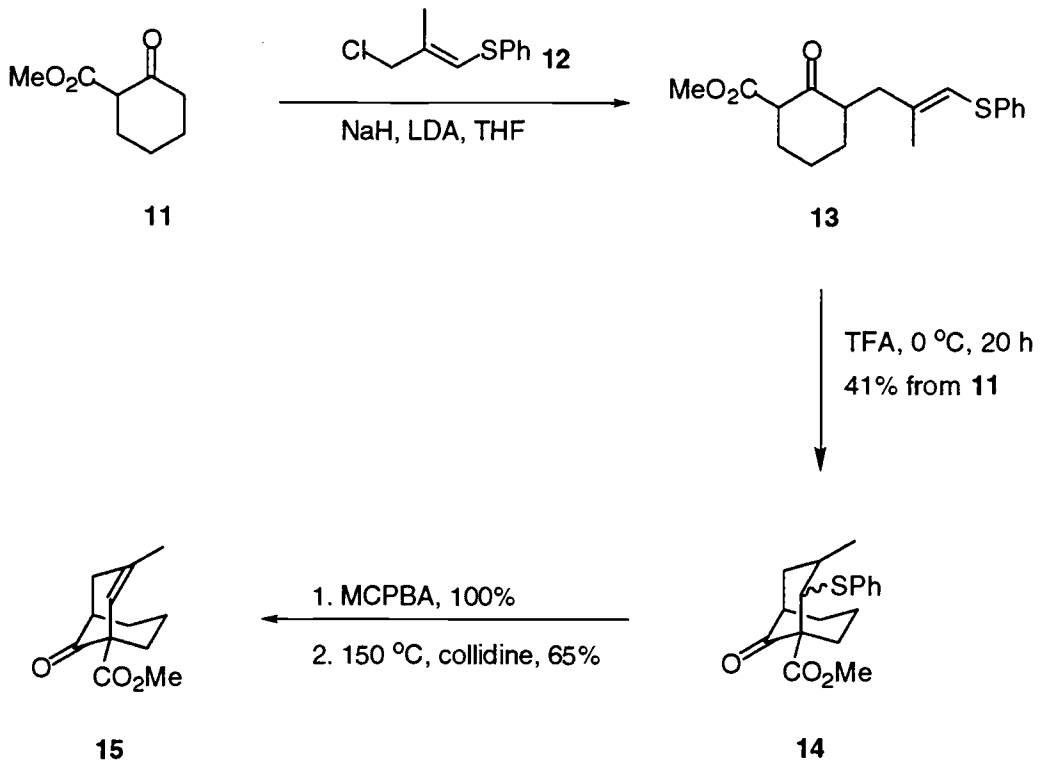
Figure 2.2 Huperzine A and analogs.

Huperzine A (**5**) has been shown to improve memory 1-4 h after injection in individuals suffering from serious Alzheimer's dementia and other memory impairments.[10] Several huperzine A derivatives (**8** and **9**, **Figure 2.2**) more potent than the natural product were also developed by modeling the interaction of huperzine A with acetylcholinesterase.[11]

Huperzine A (**5**) was first isolated in 1960 by Wiesner and coworkers from the plant *Lycopodium selago*, but was assigned an incorrect structure **7**.[12] A later comparison of the alkaloid selagine and huperzine A by Liu and coworkers showed that they were identical and that Wiesner's structural assignment (**7**) to huperzine A was incorrect.[13] In addition to huperzine A (**5**) and B (**6**), only one other alkaloid, 6β-hydroxyhuperzine A (**10**), has been found to possess the huperzine ring system (**Figure 2.2**).

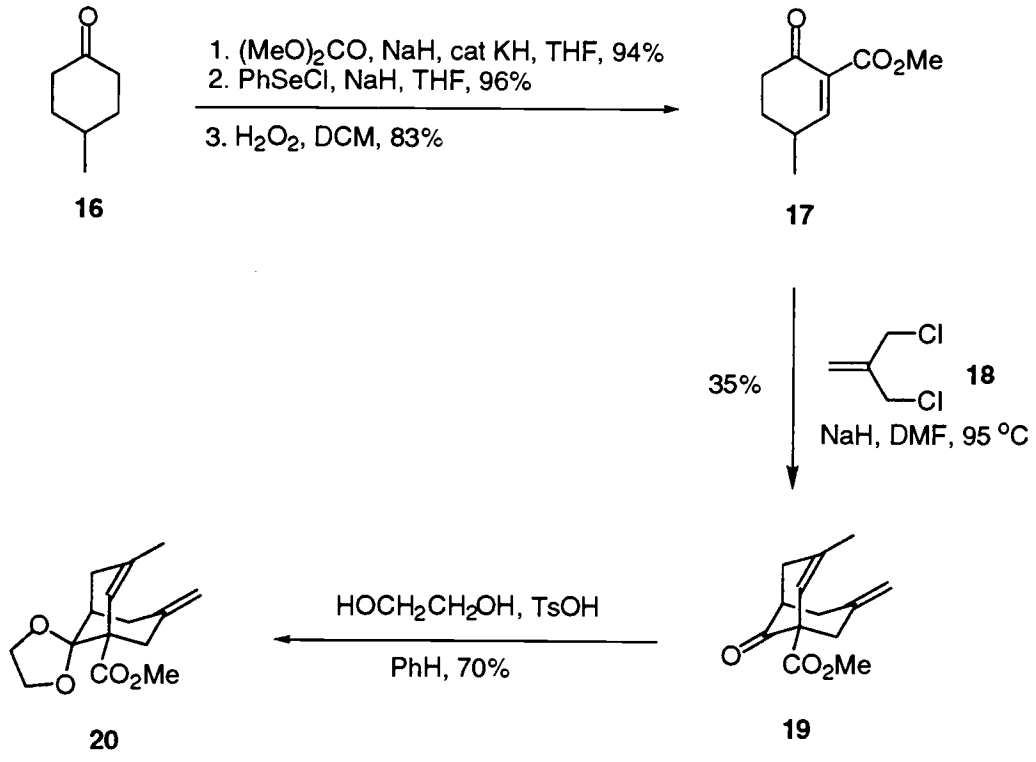
In spite of huperzine A's interesting structure and its important biological activity, relatively few research groups have investigated its synthesis and only two have achieved a total synthesis. However, prior to the discovery that the huperzine A/selagine structure was misassigned, several studies were initiated towards the synthesis of these supposed natural products.

One of the first investigations into the synthesis of selagine (**7**) was published by Kende and coworkers who prepared keto ester **15**, possessing the tricyclic framework assigned to selagine (**7**) (**Scheme 1**).[14] The synthesis of **15** began with 2-carbomethoxycyclohexanone (**11**), which was alkylated with allylic chloride **12** using Weiler's method to afford the sulfide **13**. After acid catalyzed cyclization, the thiophenyl group was oxidized and the resulting sulfoxide underwent elimination to give the bicyclic compound **15**.



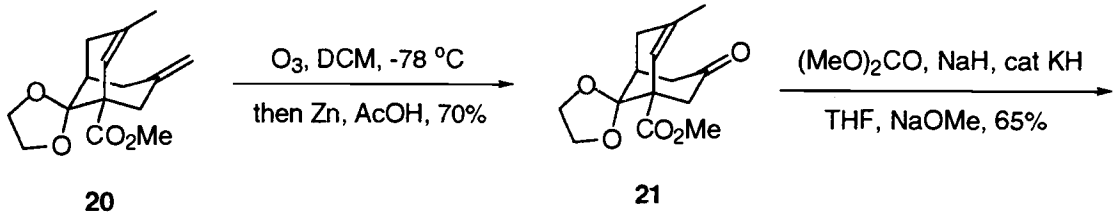
Scheme 1

Similar methodology was developed by Gravel[15] who used selenium in place of sulfur to allow for a more gentle oxidation-elimination to the olefin **19**. Gravel and coworkers' approach to the bicyclic framework proposed for selagine started with 4-methylcyclohexanone (**16**) which was advanced in three steps to the enone **17** (**Scheme 2**).[16] Dual alkylation with the dichloride **18** afforded the bicyclo[3.3.1]nonane **19** which was converted to its ethylene ketal **20**.

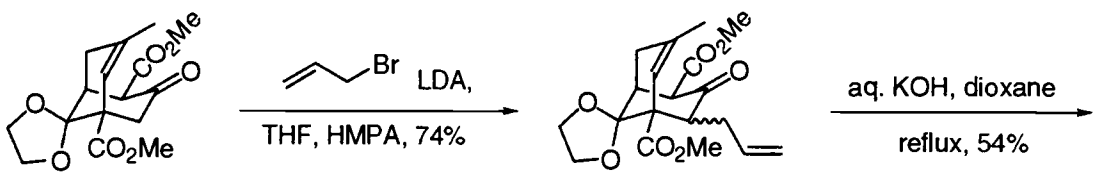


Scheme 2

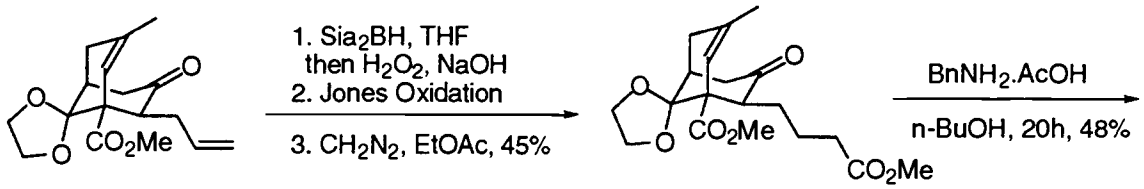
The pyridone annulation began with selective ozonolysis of the disubstituted double bond of **20**, and the resulting ketone **21** was taken to the β-keto ester **22** with dimethyl carbonate and sodium hydride (**Scheme 3**). Alkylation of the dianion of **22** with allyl bromide using Weiler's method afforded **23** as a mixture of diastereomers. The mixture was equilibrated and the carbomethoxy group was removed with aqueous potassium hydroxide to give **24** in which the allyl group occupied the equatorial orientation. Hydroboration of the terminal vinyl group was followed by oxidation of the resulting alcohol to a carboxylic acid, and the latter was esterified with diazomethane to yield the keto ester **25**. Pyridone formation was achieved with benzylamine to give **26**, and the



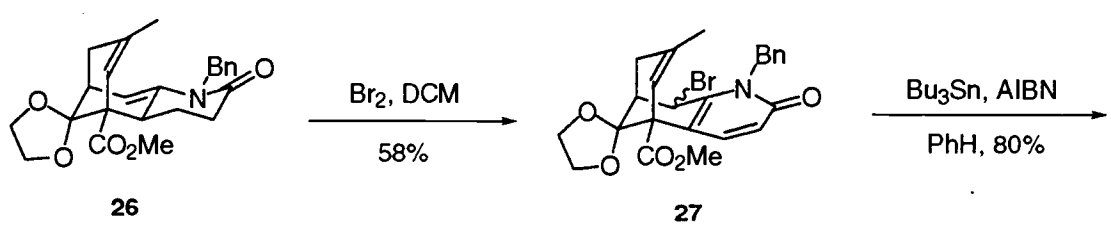
20 **21**



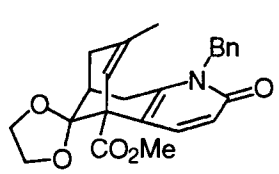
22 **23**



24 **25**



26 **27**

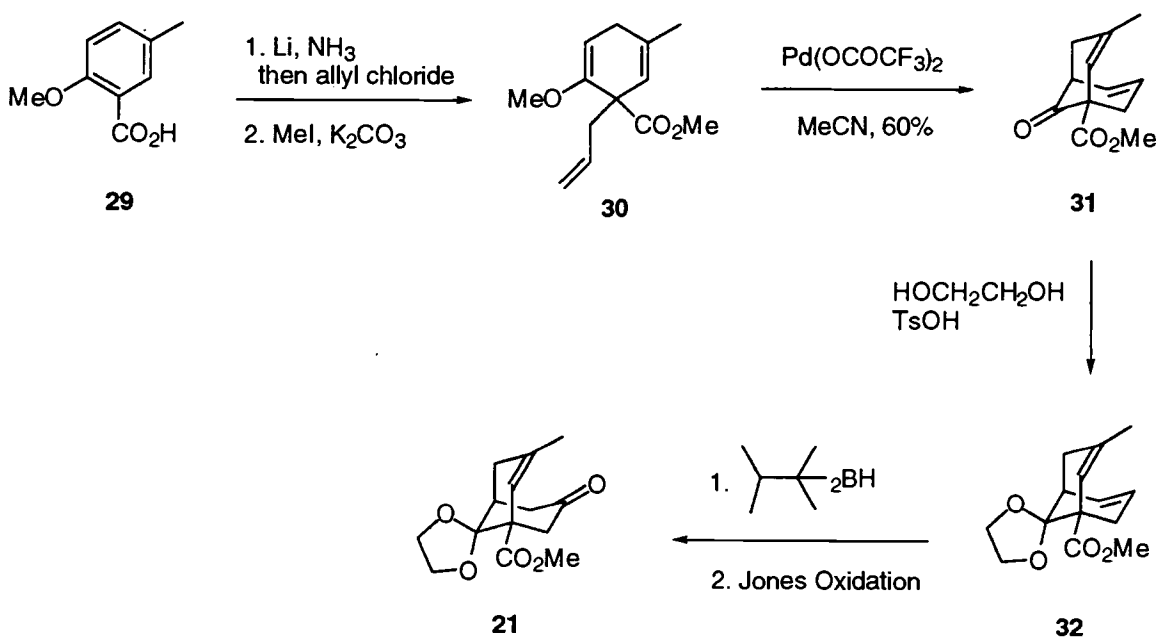


28

Scheme 3

enamine double bond was isomerized into the ring fusion with bromine, followed by further oxidation to the bromopyridone **27**. The bromine was removed under reducing conditions to give **28** possessing the tricyclic framework of selagine (**7**).

A second route to the selagine bicyclic framework was published by Kende.[17] This approach began with Birch reductive alkylation of 2-methoxy-5-methylbenzoic acid (**29**) with allyl chloride to afford the triene **30** which, upon treatment with palladium(II) trifluoroacetate in acetonitrile, gave the bicyclo[3.3.1]nonane **31**. The ketone functional group was protected as its ketal, the disubstituted olefin was hydroborated regioselectively, and the resulting alcohol was oxidized to afford the ketone **21** (**Scheme 4**).



29 **30** **31**

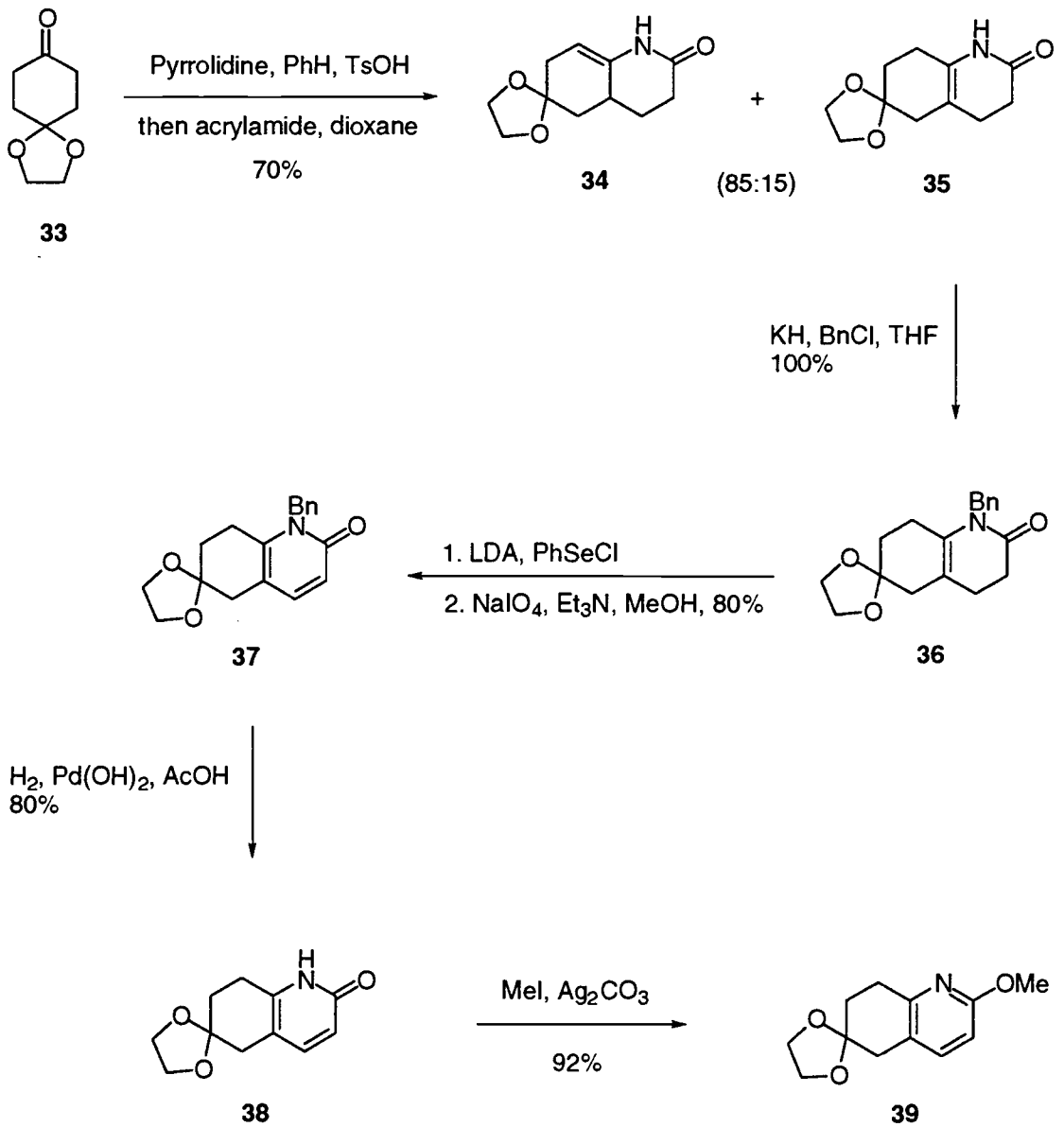
21 **32**

Scheme 4

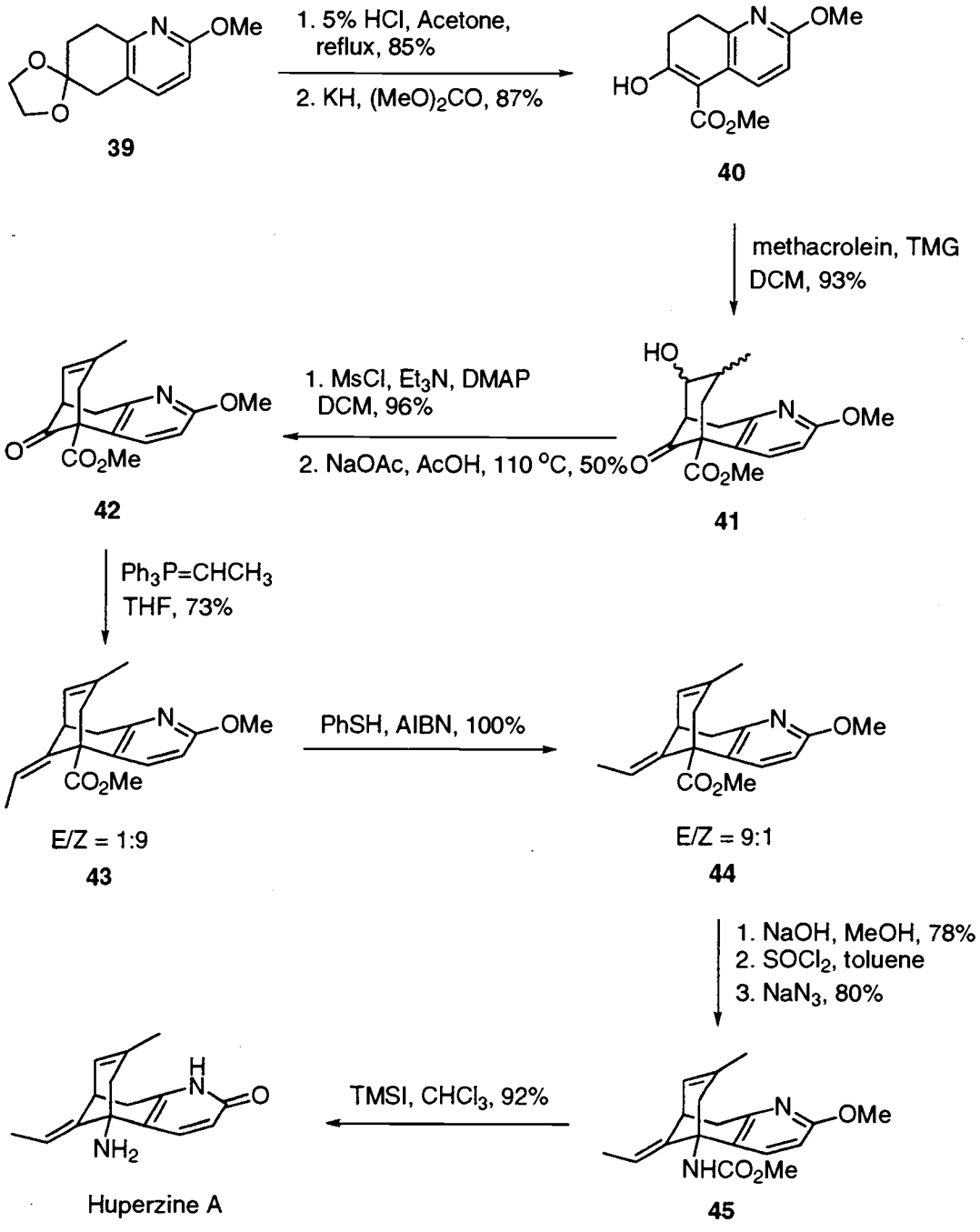
The first completed total synthesis of huperzine A was not reported until 1989 when Kozikowski and coworkers described a route that has now been

revised several times.[18] In Kozikowski's initial publication,[19] the synthesis of **38** was accomplished by reacting the enamine of **33** with acrylamide in aqueous dioxane (**Scheme 5**). This returned a 85:15 mixture of **34** and **35**, from which the minor isomer **35** was separated, N-benzylated, and dehydrogenated to afford the pyridone **37**. Due to its instability, **37** was converted to the methoxypyridine **39** through debenzylation and treatment of **38** with methyl iodide and silver(I) carbonate.

Following ketal hydrolysis of **39**, carbomethoxylation with methyl carbonate and potassium hydride gave **40** and set the stage for insertion of the three-carbon bridge to form the bicyclo[3.3.1]nonane system (**Scheme 6**). The 1,1,3,3-tetramethylguanidine (TMG) catalyzed Michael-aldol reaction of **40** with methacrolein proceeded in good yield to give **41** as a mixture of diastereomers. The ketol mixture **41** was dehydrated to the alkene **42** by reaction of its derived mesylates with sodium acetate and acetic acid. Wittig reaction with ethylidenetriphenylphosphorane took place to provide a 9:1 mixture of the (*Z*)- and (*E*)-alkenes **43**. The *Z/E* mixture was isomerized to a mixture **44** comprised predominantly of the (*E*)-olefin by heating with thiophenol and azobisisobutyronitrile. The methyl ester was saponified, and the resulting acid was employed in a Curtius rearrangement which afforded the urethane **45**. Lastly, trimethylsilyl iodide was employed to effect both N- and O-deprotection (**Scheme 6**).

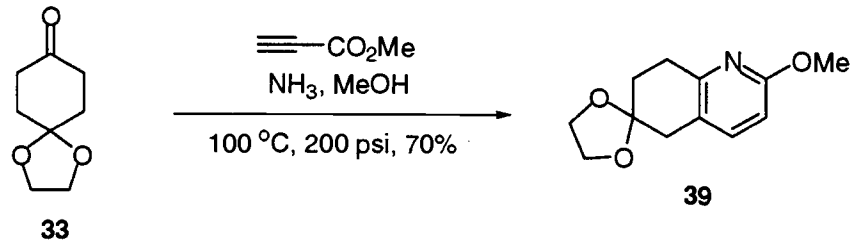

Pyrrolidine, PhH, TsOH
then acrylamide, dioxane
70%
33
34
(85:15)
35
KH, BnCl, THF
100%
36
1. LDA, PhSeCl
2. NaIO4, Et3N, MeOH, 80%
37
H2, Pd(OH)2, AcOH
80%
38
MeI, Ag2CO3
92%
39

Scheme 5



Scheme 6

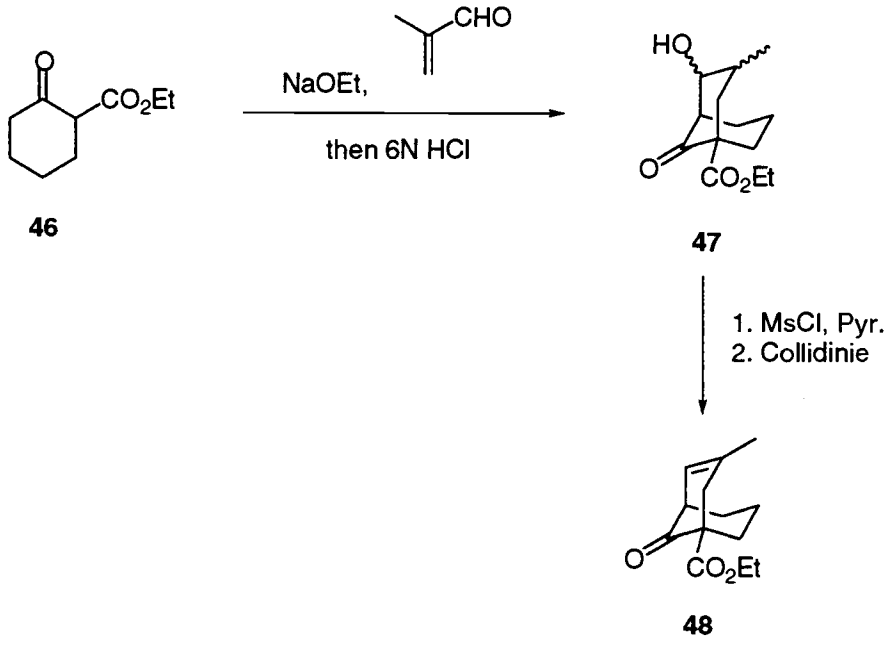
In Kozikowski's improved route to huperzine A, **33** was converted to **39** in one pot with propiolate and ammonia under high pressure (**Scheme 7**).[20]



33 39

Scheme 7

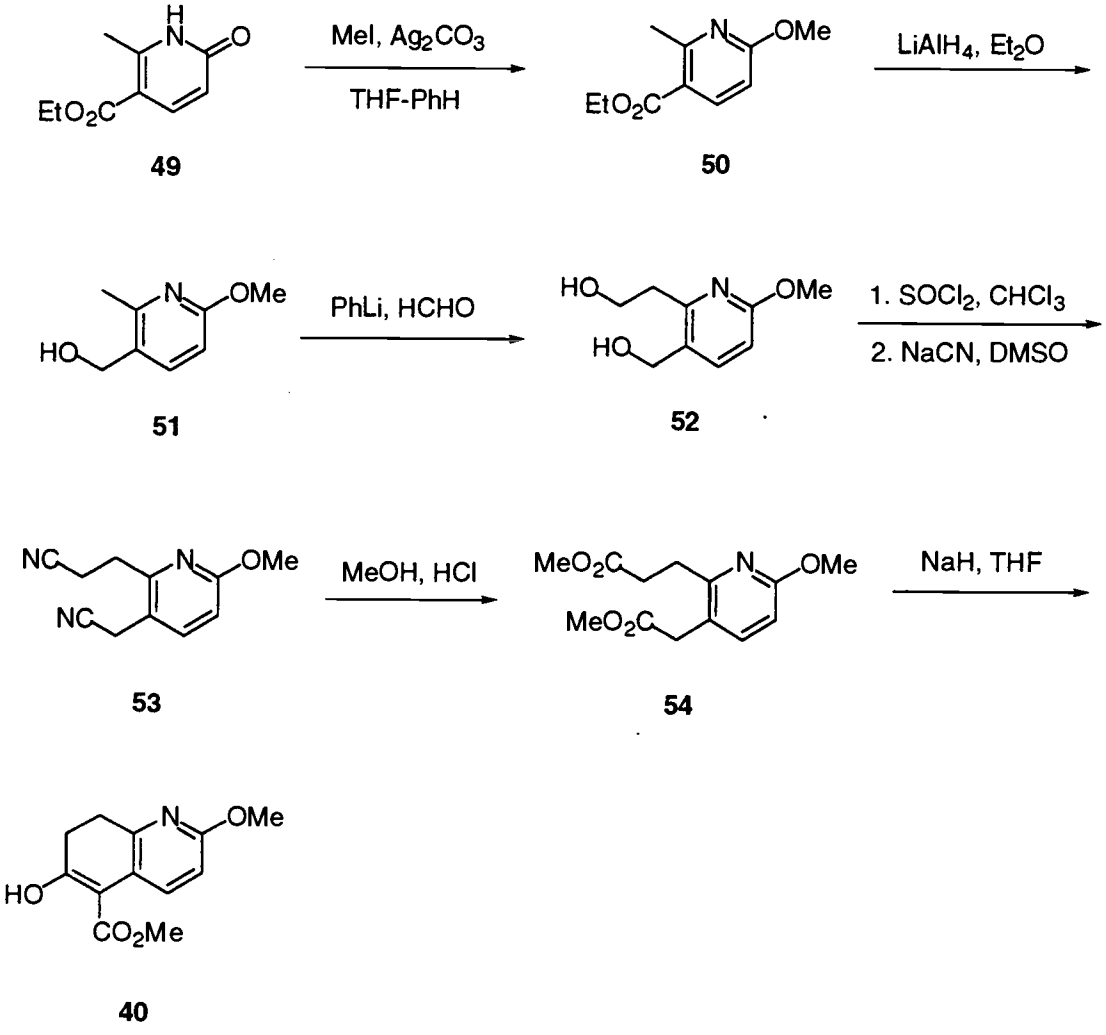
It should be noted that the Michael-aldol methodology used by Kozikowski is not original, but was developed by Raphael[21] and coworkers in 1966 and was subsequently exploited by Horii[22] and coworkers in 1968. Horii assembled the bicyclo[3.3.1]nonane ring system **48** using this approach in his studies directed at the synthesis of lycopodium alkaloids (**Scheme 8**).



46 47 48

Scheme 8

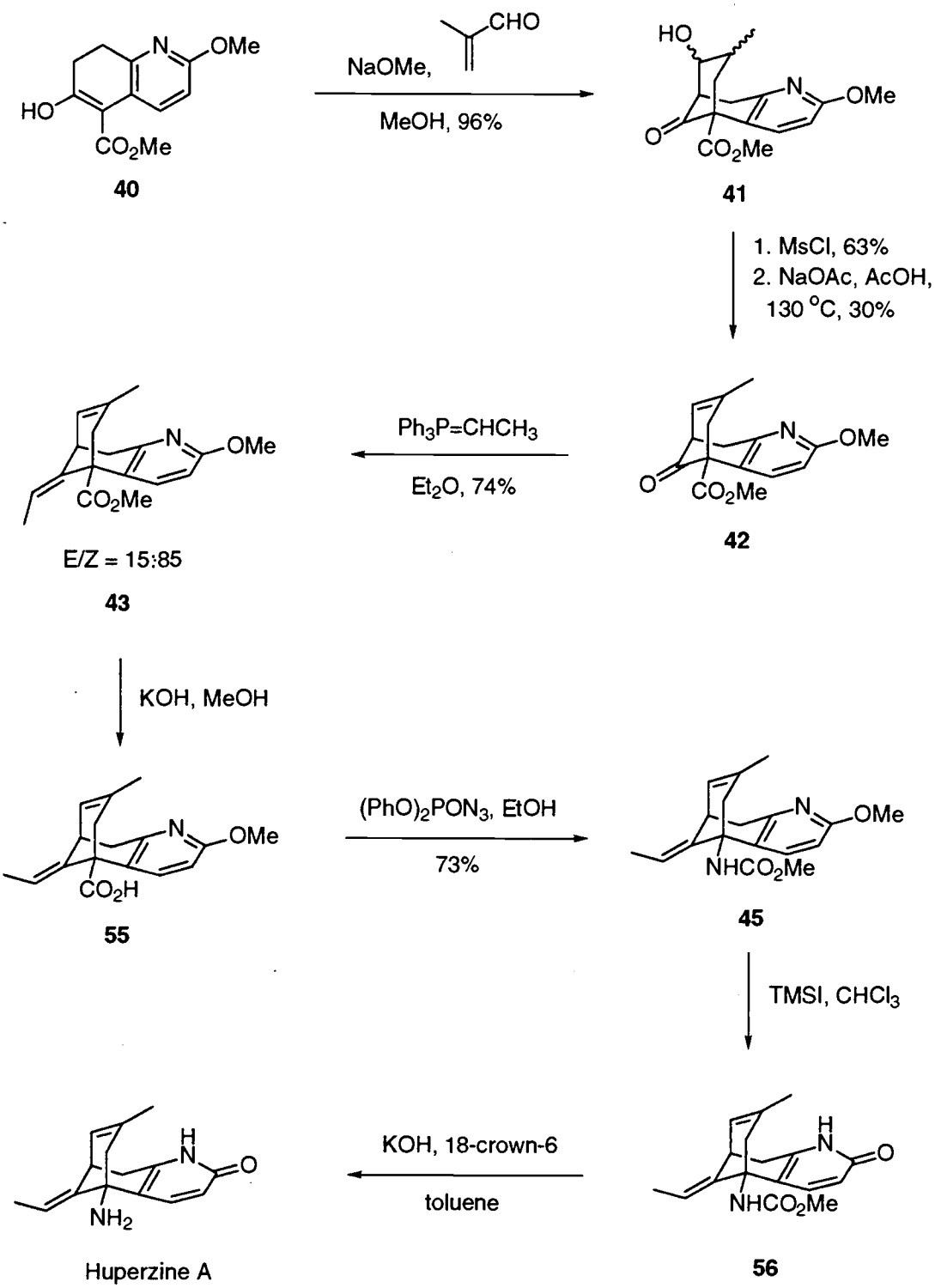
Shortly after Kozikowski published his first synthesis of huperzine A, a second almost identical synthesis was published by Ji and Qian.[23] The only significant difference in Ji's synthesis is the method used to prepare key intermediate **40**, which was obtained from 5-methoxycarbonyl-6-methyl-2-pyridone (**49**) (**Scheme 9**).



Scheme 9

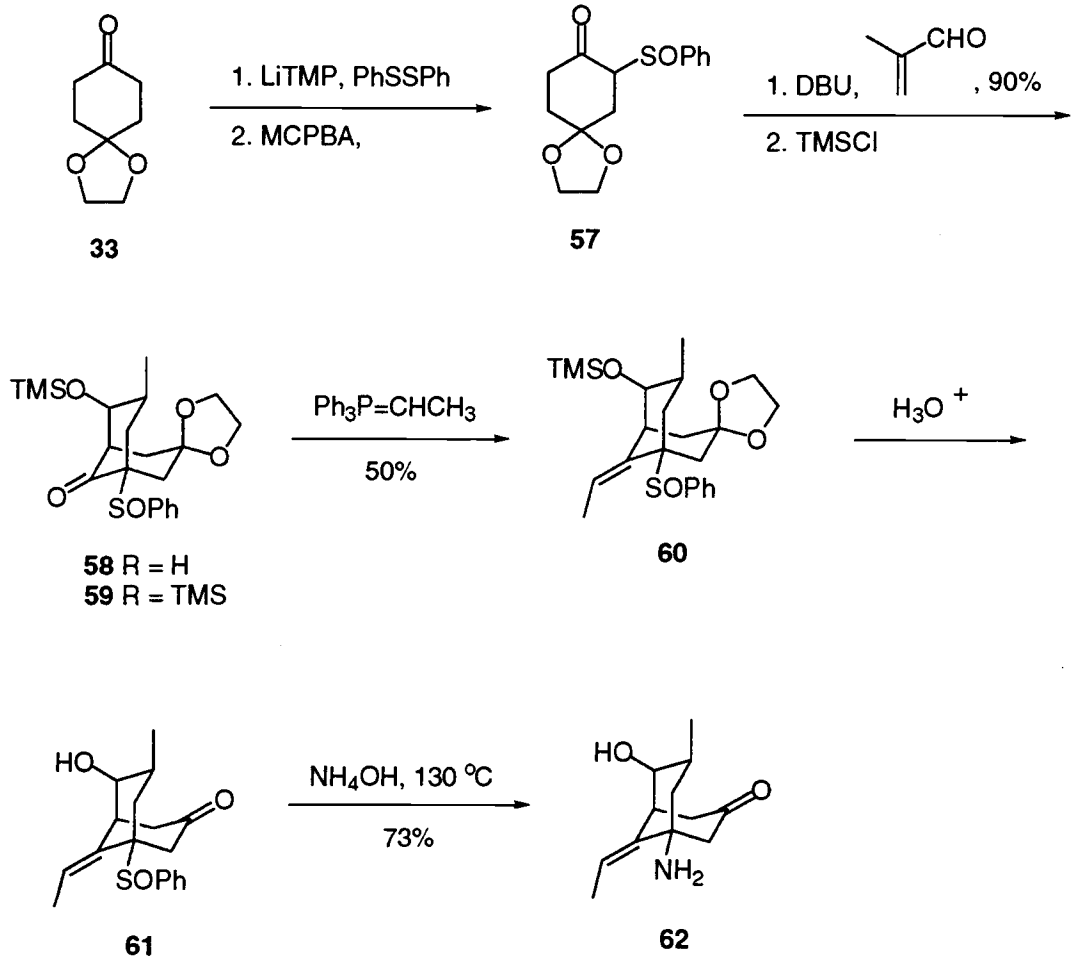
Conversion of **49** to the methoxypyridine **50** was followed by reduction of the ester to afford **51**. The methyl substituent at C6 was metallated and the anion was condensed with formaldehyde to give the diol **52** which was converted to the bis-nitrile **53** via the corresponding dichloride. The bisnitrile **53** was solvolyzed with methanol to yield the diester **54**, which upon Dieckmam condensation with sodium hydride returned the methoxypyridine **40**.

From this point forward, Ji's synthesis of huperzine A is remarkably similar to Kozikowski's (**Scheme 10**). The keto ester **40** was used as a substrate for a Michael-aldol reaction with methacrolein to furnish the alcohol **41** as a mixture of diastereomers at both the hydroxyl and methyl bearing stereocenters. The hydroxyl group of **41** was mesylated, and the stereoisomeric mixture was exposed to hot acetic acid and sodium acetate to afford the olefin **42** in modest yield. Ji's synthesis was completed with a Wittig olefination which installed the exocyclic ethylidene function of **43** and gave an 85:15 mixture of *Z* and *E* isomers, respectively. The mixture was treated with aqueous potassium hydroxide which resulted in the selective saponification of the *E* isomer. The carboxylic acid **55** was treated with diphenylphosphoryl azide and ethanol to effect a Curtius rearrangement, and the intermediate isocyanate was trapped with ethanol to yield the urethane **45**. The final steps involved deprotection of the pyridone with trimethylsilyl iodide and decomposition of the urethane in aqueous base to afford huperzine A.


HO
N
OMe
CO2Me
40
NaOMe,
CHO
MeOH, 96%
HO
N
OMe
O
CO2Me
41
1. MsCl, 63%
2. NaOAc, AcOH,
130 °C, 30%
N
OMe
O
CO2Me
42
Ph3P=CHCH3
Et2O, 74%
N
OMe
CO2Me
E/Z = 15:85
43
KOH, MeOH
N
OMe
CO2H
55
(PhO)2PON3, EtOH
73%
N
OMe
NHCO2Me
45
TMSI, CHCl3
H
N
O
NHCO2Me
56
KOH, 18-crown-6
toluene
H
N
O
NH2
Huperzine A

Scheme 10

Kraus and coworkers[24] have published a preliminary investigation into the synthesis of huperzine A in which the monoprotected diketone **33** was the starting material for their approach (**Scheme 11**).



33 **57**

58 R = H
59 R = TMS

60

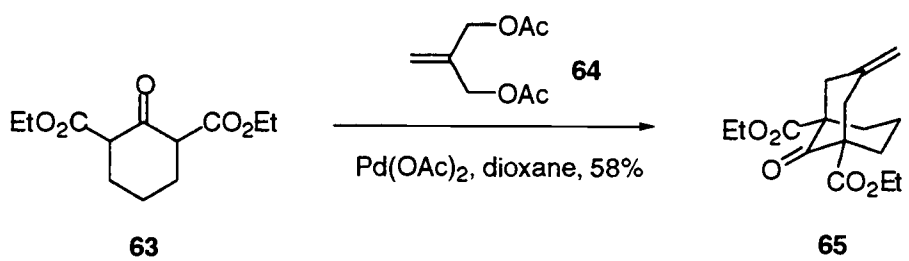
61 **62**

Scheme 11

This substance **33** was converted to the keto sulfoxide **57** in two steps Once again, methacrolein was used in a Michael-aldol reaction with **57** to afford the bicyclic[3.3.1]nonane **58** with cis stereochemistry. The hydroxyl group was protected, and a Wittig olefination returned the *Z* olefin **60** which is hydrolyzed to

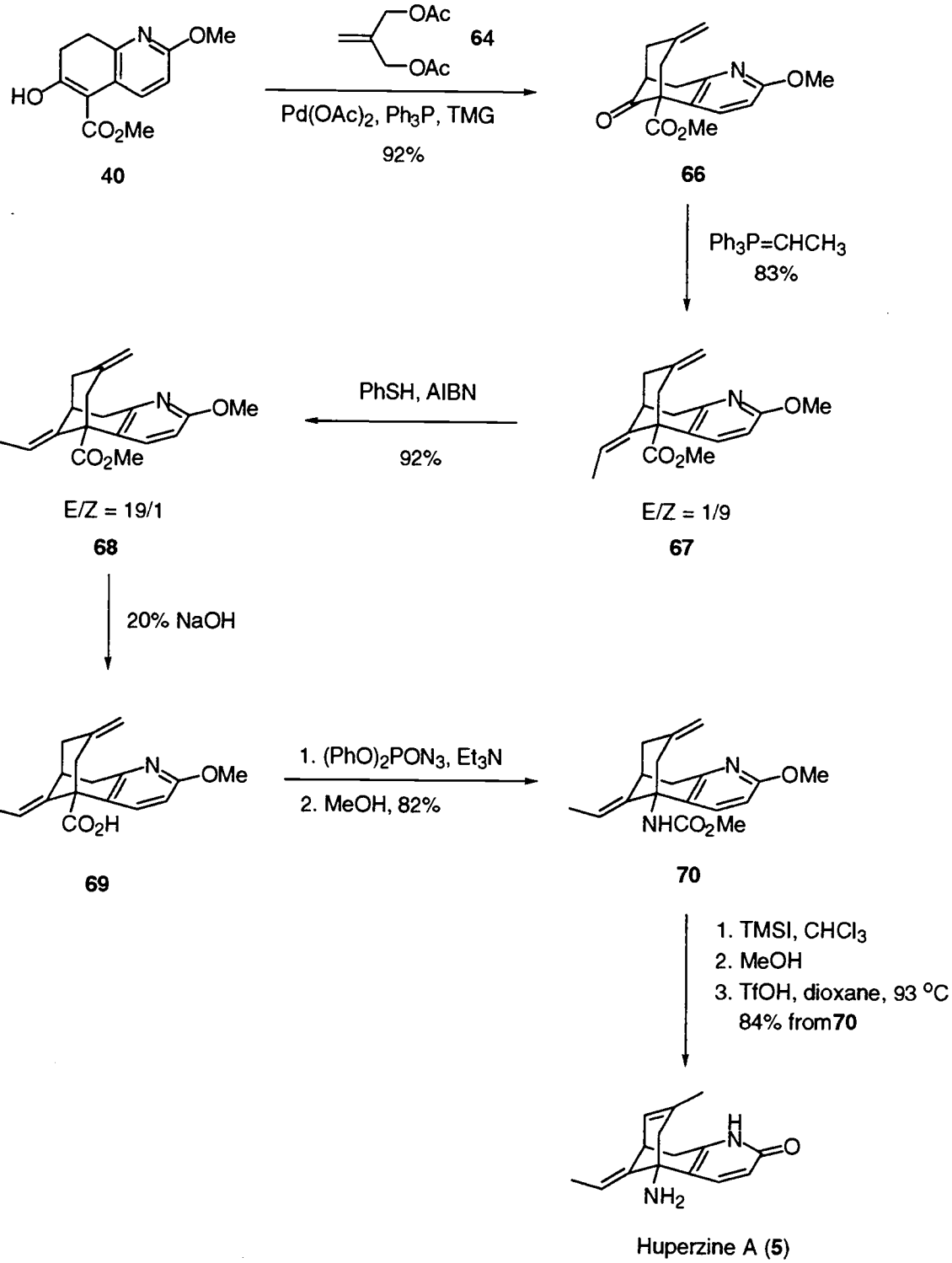
the ketone **61**. The novel aspect of this approach was the incorporation of the bridgehead amine. Thermal elimination of the sulfoxide presumably results in the formation of a transient bridgehead olefin which was trapped by ammonia to give **62**.

A substantial improvement on the Michael-aldol strategy was reported by Kozikowski using a palladium-catalyzed bicycloannulation reaction originally developed by Huang and Lu.[25] These investigators reported the reaction of bifunctional allylic alkylating agent **64** with 1,3-bis-nucleophile **63** under palladium catalysis to form bicyclic ketoester **65** (**Scheme 12**)



Scheme 12

In Kozikowski's second route to huperzine A (**Scheme 13**), the palladium-catalyzed bicycloannulation of β-keto eater **40** with 2-methylene-1,3-propanediol diacetate **64** in the presence of palladium catalyst afforded the methylene-bridged structure **66** in good yield.[26] To complete the synthesis, the ketone **66** was condensed with ethylidenetriphenylphosphorane to give a 9:1 mixture of *Z* and *E* alkenes **67** which isomerized with thiophenol and α,α-azoisobutyronitrile

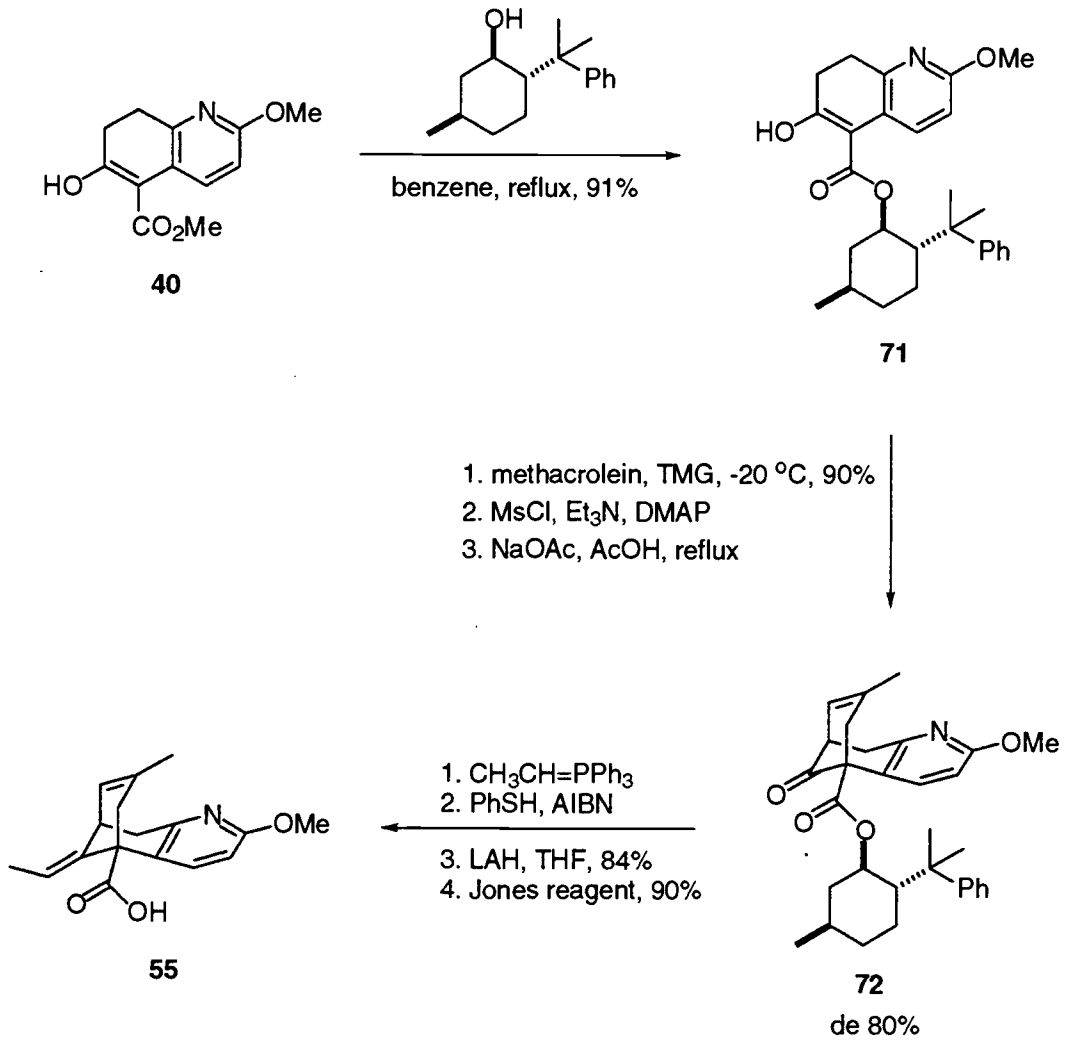

OAc
OAc
64
HO
N
OMe
CO2Me
40
Pd(OAc)2, Ph3P, TMG
92%
O
66
Ph3P=CHCH3
83%
PhSH, AIBN
92%
E/Z = 19/1
68
E/Z = 1/9
67
20% NaOH
CO2H
69
1. (PhO)2PON3, Et3N
2. MeOH, 82%
NHCO2Me
70
1. TMSI, CHCl3
2. MeOH
3. TfOH, dioxane, 93 °C
84% from 70
H
NH2
Huperzine A (5)

Scheme 13

(AIBN) to a 19:1 mixture of *E* and *Z* alkenes **68**, respectively. The methyl ester was saponified and the resulting acid **69** was employed in a Curtius rearrangement which afforded the urethane **70**. Lastly, the pyridone ring and amine were liberated via treatment with trimethylsilyl iodide, and the exocyclic double bond was isomerized with trifluoromethanesulfonic acid to afford **5**.

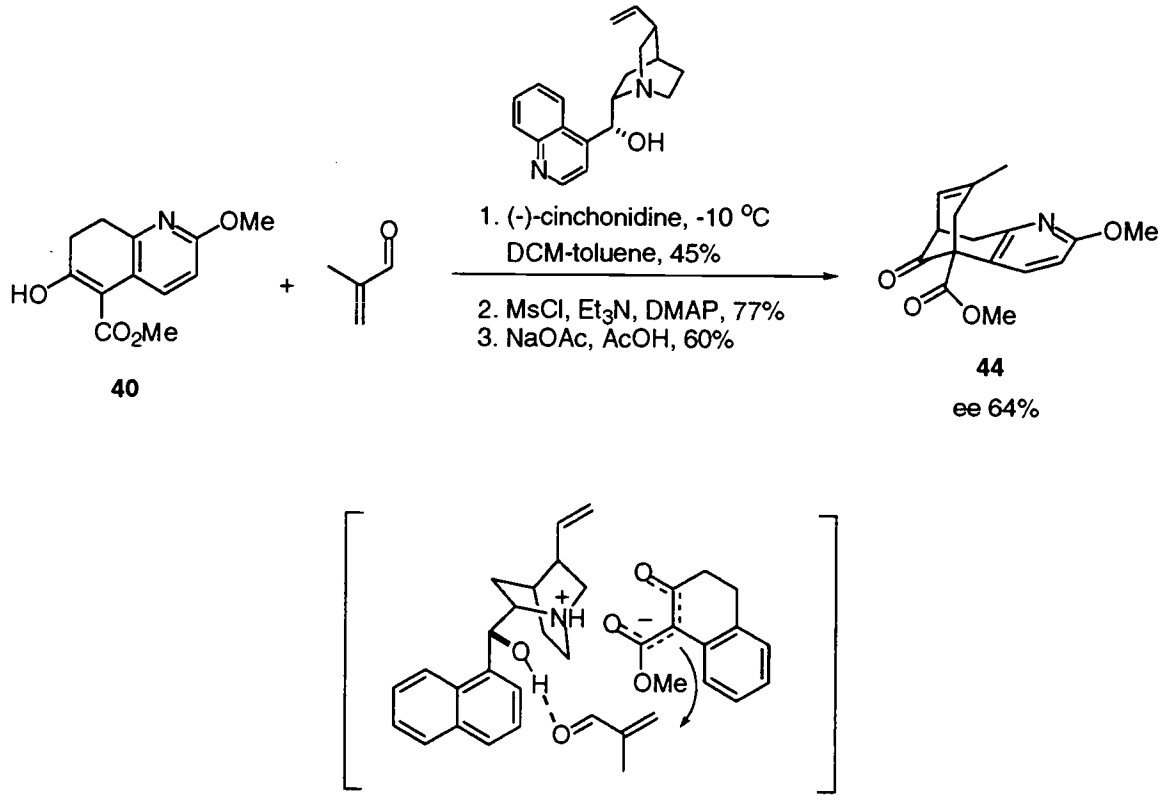
Following the route established to (±)-huperzine A, several groups have reported asymmetric syntheses of (-)- and (+)-huperzine A using, either the Michael-aldol strategy or the palladium-catalyzed bicycloannulation to construct the bicyclo[3.3.1]nonane framework of huperzine A.

The first synthesis of (-)-huperzine A was described by Kozikowski[27] using the Michael-aldol route with a (-)-8-phenylmenthol derived chiral auxiliary (**Scheme 14**). Transesterification of **40** with (-)-8-phenylmenthol, Michael-aldol reaction at -20 °C, and dehydration yield a separable 9 : 1 mixture of the diastereoisomers **72**. For the major isomer, further steps in its transformation to huperzine **A** were similar to those reported previously. After Wittig reaction and isomerization of the *E/Z* mixture, the bulky phenylmenthol group in **72** was reduced to give the corresponding primary alcohol which was reoxidized to the enantiomerically pure acid **55**.



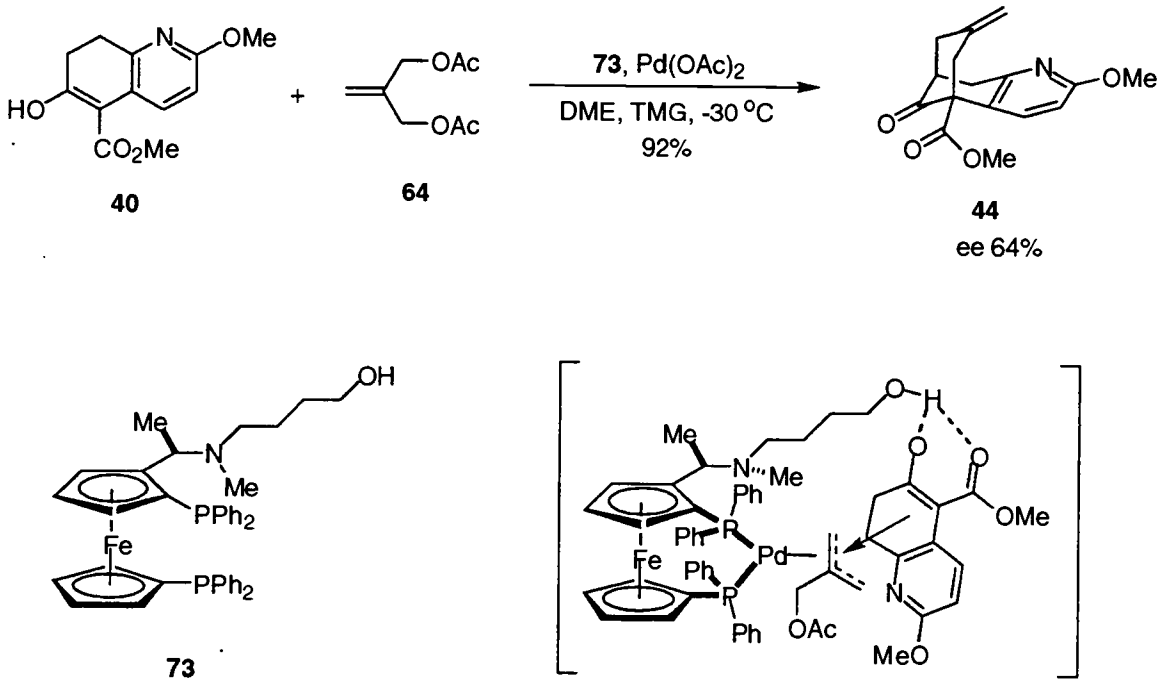
Scheme 14

A more recent asymmetric approach using a chiral base was reported by Terashima.[28] In this work, various commercially available *Cinchona* alkaloids were used as Michael-aldol catalysts, the best result was observed with one equivalent of (-)-cinchonidine. This afforded **44** with an enantiomeric excess of 64% (**Scheme 15**). To explain the observed ee and the absolute configuration of **44**, a plausible transition state model based on an ion-pairing mechanism[29] was postulated for the asymmetric Michael addition promoted by (-)-cinchonidine.



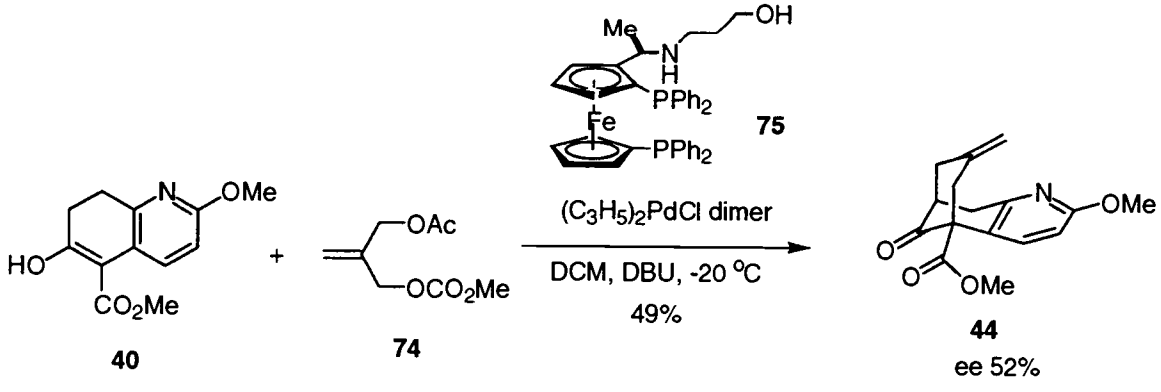
Scheme 15

The same group also developed an asymmetric bicycloannulation of **40** with 2-methylene-1,3-propandiol diacetate **64** catalyzed by a palladium catalyst carrying ferrocenylphosphine ligands.[28] Use of a modified chiral ferrocenyl ligand **73** previously developed by Hayashi afforded **44** with an enantiomeric excess of 64% (**Scheme 16**). The enantioselectivity observed for this bicycloannulation may be explained by a secondary ligand-substrate interaction[30] involving hydrogen bonding between the terminal hydroxyl group of the pendant chain and the attacking nucleophile as postulated in **Scheme 16**.



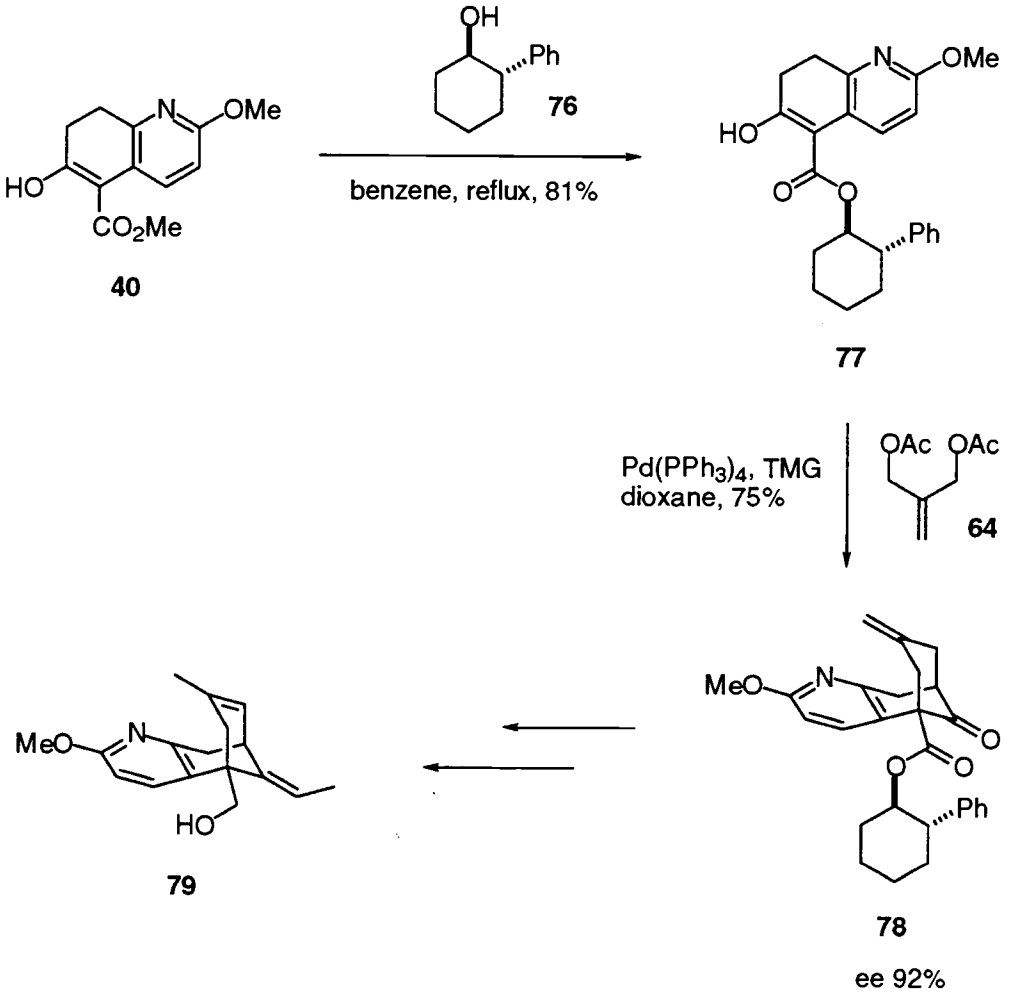
Scheme 16

A similar result was obtained by He and Bai[31] who prepared compound **44** in 52% ee with another modified Hayashi catalyst **75** (**Scheme 17**).



Scheme 17

In 1999, Langlois and coworkers reported a new formal enantioselective synthesis of (+)-huperzine A using palladium mediated annulation of β-keto ester **77** derived from **64** and (1*R*,2*S*)-2-phenylcyclohexanol (**76**).[32] A diastereomeric excess of 92% was obtained in this reaction (**Scheme 18**).



Scheme 18

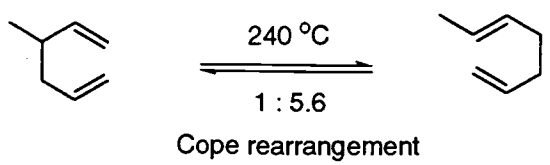
In summary, it is noteworthy that only two general methods have been developed for assembling the bicyclo[3.3.1]nonane framework of huperzine A. These are: (a) a Michael-aldol strategy, utilized initially by Horri and subsequently

by Kozikowski, Ji and Kraus, and (b) a palladium-catalyzed bicycloannulation originally developed by Huang and Lu and later applied to huperzine A by Kozikowski and Gravel.

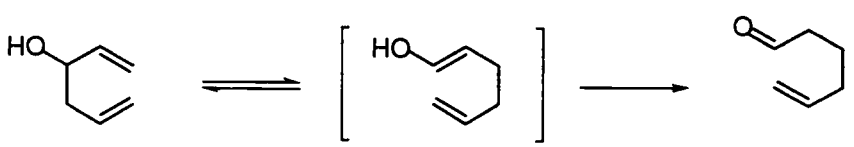
All asymmetric approaches of (-)- and (+)-huperzine A are based on these two methods. Thus, Kozikowski reported a Michael-aldol annulation using (-)-8-phenylmenthol as a chiral auxiliary. *Cinchona* alkaloids such as (-)-cinchonidine have been used as Michael-aldol bases by Terashima who also developed an asymmetric palladium-catalyzed bicycloannulation using Hayashi's chiral ferrocenylphosphine ligands. The latter were used by He and Bai in their approach as well. Langlois reported an enantioselective synthesis of (+)-huperzine A via palladium mediated annulation using (1*R*,2*S*)-2-phenylcyclohexanol as chiral auxiliary.

Results and Discussion

The Cope rearrangements[33] has played a pivotal role in many synthetic efforts directed at natural products.[34] It is important to recognize that the rearrangement is reversible; the starting and product 1,5-dienes exist in equilibrium at the rearrangement temperature through a cyclic transition state. Also, the rearrangement usually require high temperature, generally ~200 °C (**Scheme 19**).

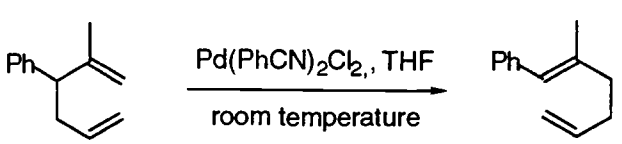


Cope rearrangement



80 **81** **82**

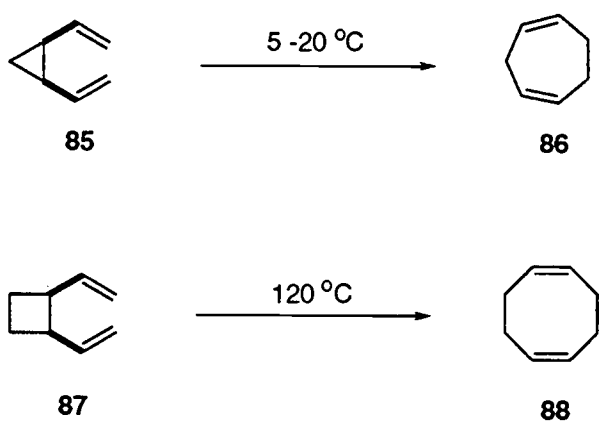
oxy-Cope rearrangement



83 **84**

Scheme 19

Two approaches have been studied which effectively lower the temperature at which Cope rearrangement occurs. First, the rearrangement is accelerated by placing an electron-donating substituent such as a hydroxyl group at carbons C3 or C4 of the 1,5-diene. This results, after rearrangement, in an enol **81** whose tautomerization leads irreversibly to an unsaturated carbonyl compound **82**.[35] A second approach employs catalysis to accelerate the reaction.[36] For example, 2-methyl-3-phenylhexa-1,5-diene (**83**) rearranged at room temperature in the presence of a palladium(II) catalyst to (*E*)-2-methyl-1-phenylhexa-1,5-diene (**84**).



85 **86**

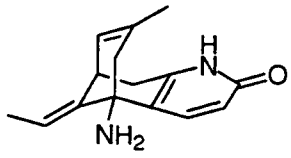
87 **88**

Scheme 20

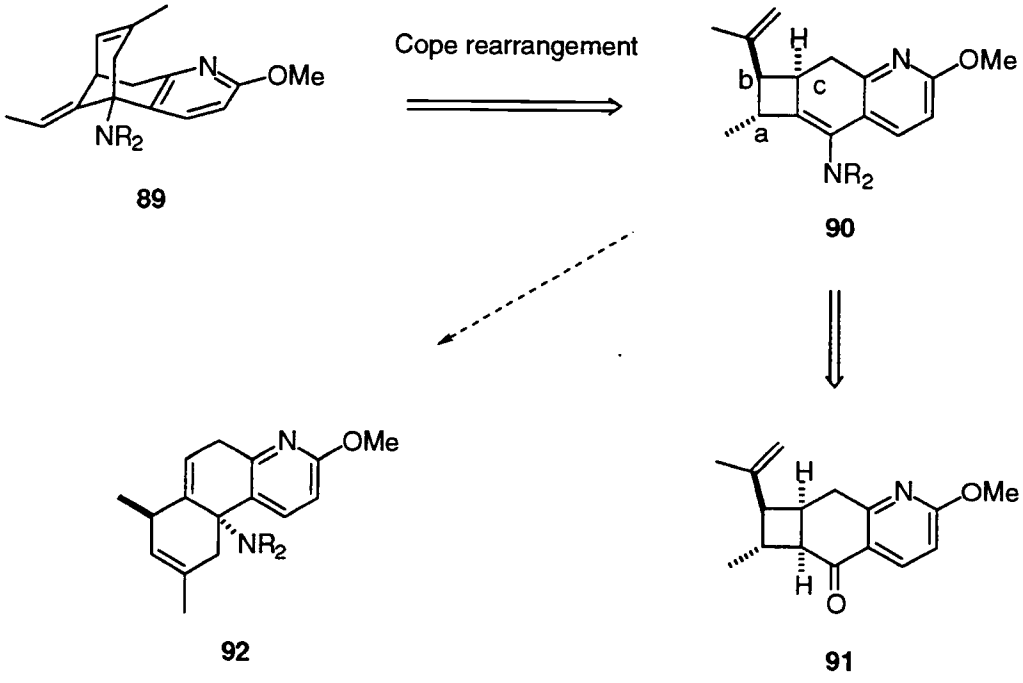
The position of equilibrium in Cope rearrangement is determined by several factors, including the substitution pattern, conjugation, ring strain, or the irreversible conversion of one diene to a more stable product. Thus, cis-1,2-divinylcyclopropanes and cis-divinylcyclobutanes are known to undergo facile Cope rearrangement to less-strained seven- and eight-membered ring dienes, respectively, as shown in **Scheme 20**. For example, cis-1,2-divinylcyclopropane

(**85**) undergoes spontaneous Cope rearrangement below room temperature[37] to produce 1,4-cycloheptadiene (**86**), and cis-1,2-divinylcyclobutane (**87**) rearranges easily[38] to afford 1,5-cyclooctadiene (**88**).

Our approach to the synthesis of huperzine A (**5**) is based on a strategy that employs Cope rearrangement of enamine **90** to assemble the complete framework of the target structure in a single step (**Scheme 21**). This enamine is envisioned to arise from ketone **91**.

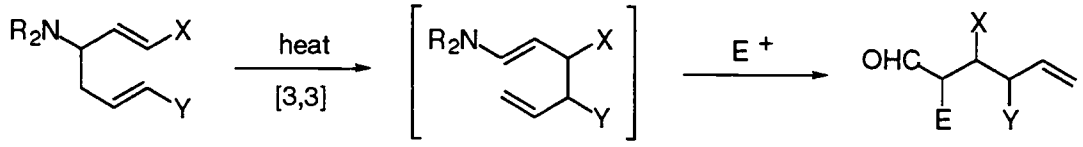


Huperzine A (**5**)



Scheme 21

There is no known precedent for this type of enamine-Cope rearrangement in which a 3-amino-1,5-diene is produced. However, the reverse reaction in which thermally induced [3,3]-sigmatropic rearrangement of a 3-amino-1,5-diene occurs to give the corresponding enamine has been reported.[39] In that case, the enamine was derivatized by alkylation (**Scheme 22**).[36] Another question underlying our approach is whether the Cope rearrangement of enamine **90** could also proceed via cleavage of Cb-Cc bond to yield the unwanted product **92** (**Scheme 21**).

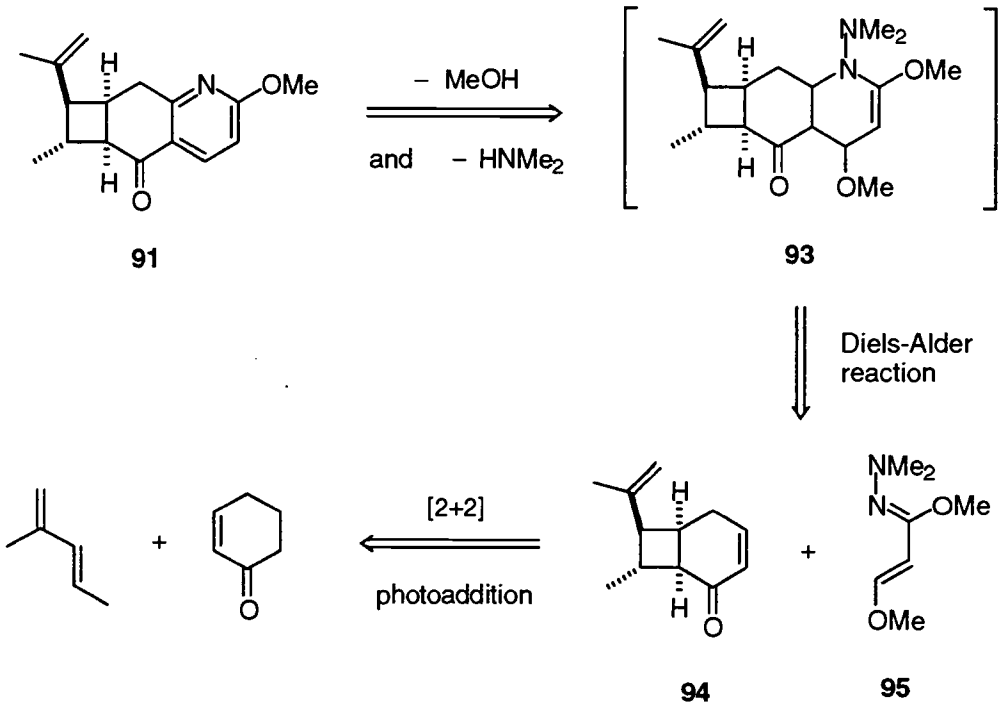


Scheme 22

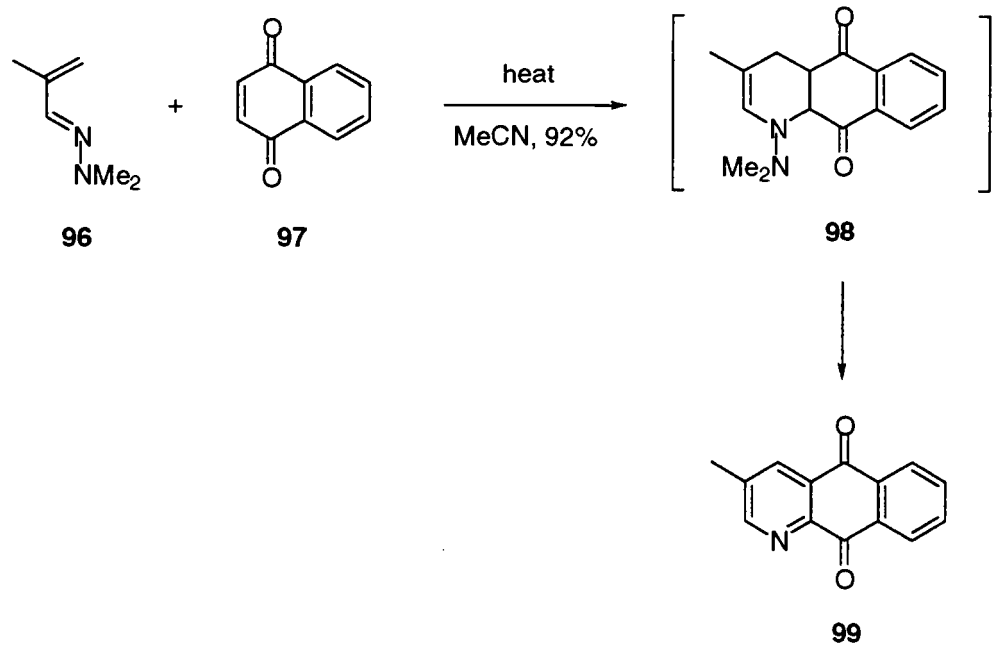
Although fully aware of the potential difficulties involved in this enamine-Cope rearrangement strategy for synthesis to huperzine A, we were nevertheless optimistic that the presence of the strained cyclobutane in **90** would be sufficient to drive the equilibrium toward target structure **89**. Clearly, the bicyclic structure of **89** can not revert to the enamine **90**.

The structure of the key intermediate **91** is unique in that it has a cyclobutane ring bearing an *exo*-methyl group on one side and a methoxypyridine ring on the other. Our initial intention was to synthesize enone **94** in the expectation that upon treatment with a 1-aza-1,3-diene such as **95** it would undergo regioselective Diels-Alder addition to produce the corresponding

[4+2] adduct **93** (**Scheme 23**). Subsequent loss of methanol and dimethylamine from **93** would yield the a methoxypyridine **91** in a single operation. Precedent for a hetero-Diels-Alder reaction using this type of azadiene was reported by Ghosez and coworkers[40] who demonstrated that treatment of the N-dimethylhydrazone **96** with naphthoquinone in acetonitrile produces the aromatized adduct **99** via the cycloadduct **98** (**Scheme 24**). Cyclobutane rings are frequently prepared by enone-olefin [2+2] photoaddition,[41] and we planned to synthesize the 4-membered ring of **91** by means of a photo-cycloaddition between cyclohexenone and 2-methyl-1,3-pentadiene (**Scheme 23**).

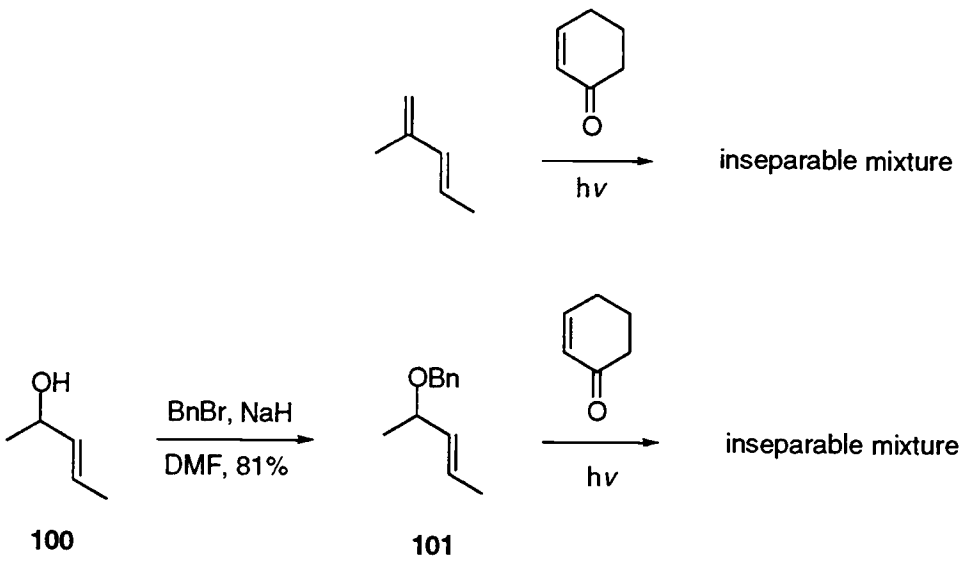


Scheme 23



Scheme 24

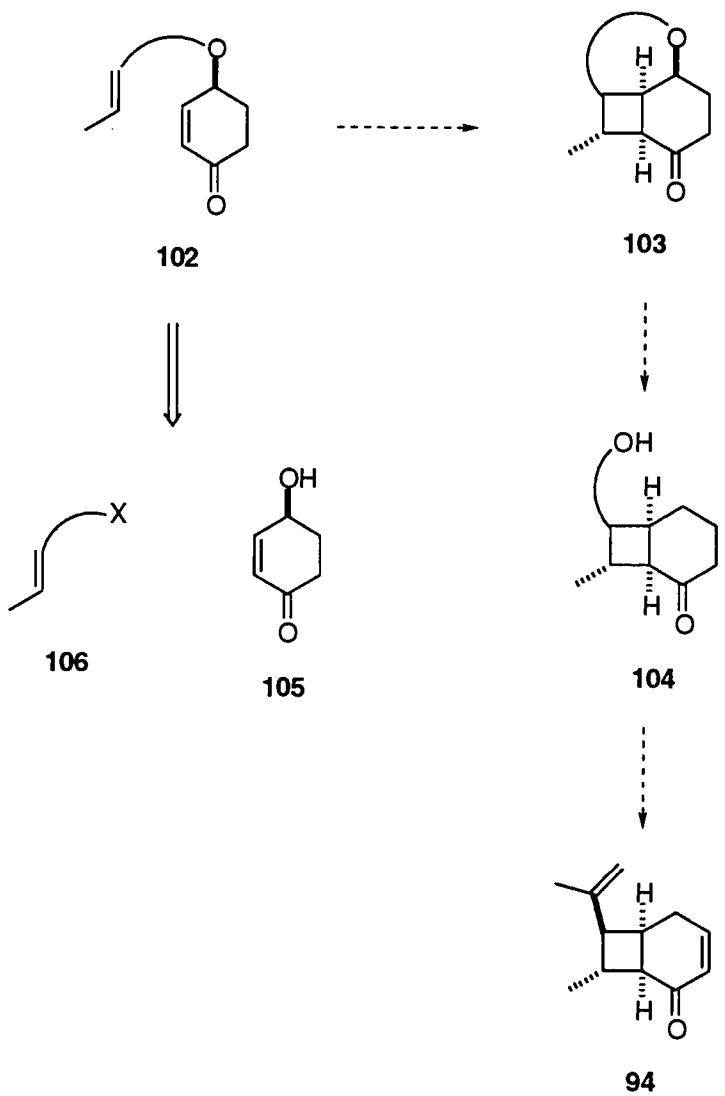
Initial studies of the intermolecular photo-cycloaddition of 2-cyclohexenone with both 2-methyl-1,3-pentadiene and olefin **101**, prepared from 3-pentene-2-ol **100**, were abandoned because inseparable isomeric cycloadducts were obtained. Furthermore, a large amount of olefin was necessary to avoid dimerization of the enones, a requirement that was not practical for a multistep synthesis. Various solvents and the presence of sensitizers were not helpful in solving this problem (**Scheme 25**).



Scheme 25

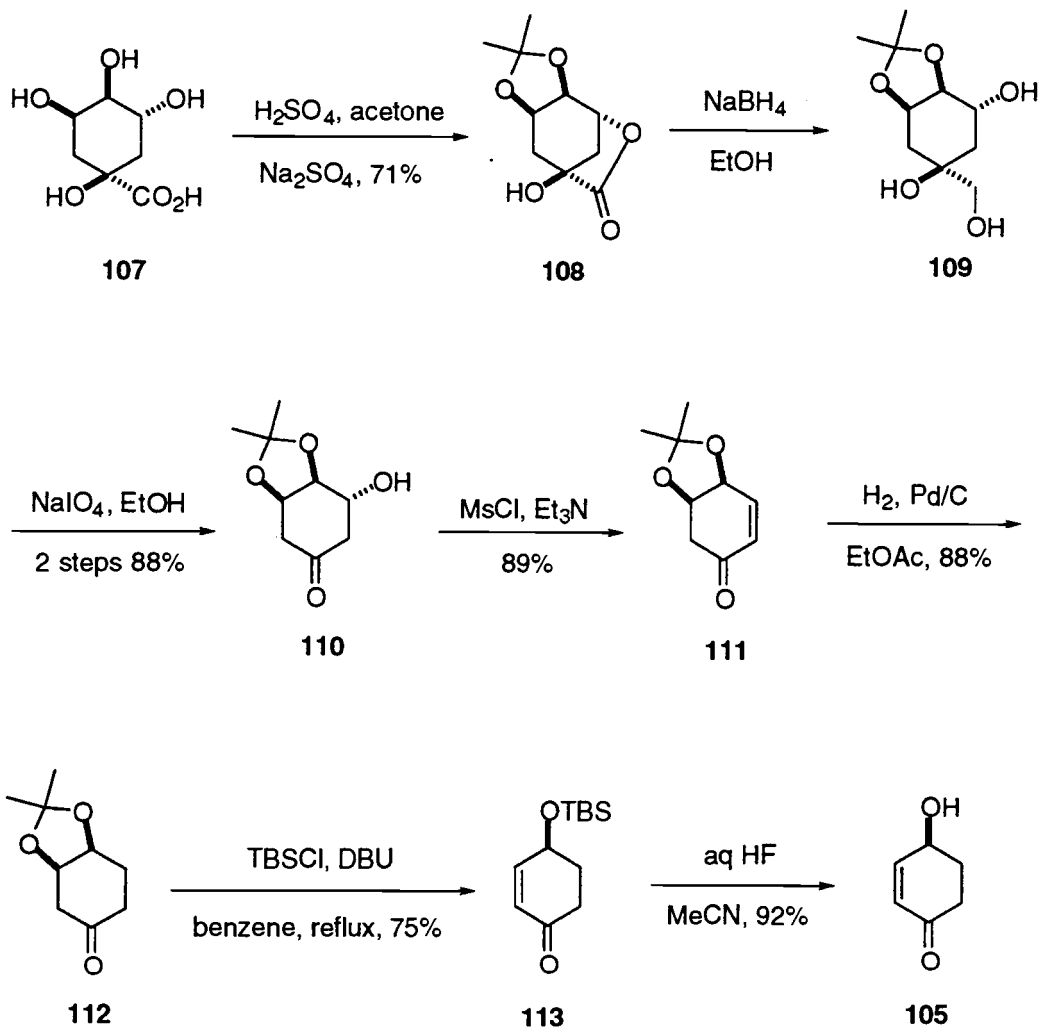
Given the difficulties encountered with the intermolecular photoaddition, a more practical method for assembling the required bicyclo[4.2.0]octane system was clearly needed. For this reason it was decided to investigate an intramolecular photoaddition route.[42] A synthetic plan employing an intramolecular [2+2] photoaddition for the synthesis of huperzine A is shown in **Scheme 26**. This scheme requires additional steps to cleave the C-O bond in cycloadduct **103** and to convert the side chain in **104** to the isopropylene group needed for the Cope rearrangement. However, we envisioned that the intramolecular [2+2] photoaddition of enone **102** would be highly regioselective and diastereoselective. In particular, the methyl group in the cycloadduct **103** should occupy the desired *exo* position in order to avoid steric congestion. The photoaddition substrate **102** would be obtained from 4-hydroxy-2-cyclohexene-1-one (**105**) and a coupling partner **106**.

The eventual goal of our approach to huperzine A (**5**) was to develop an enantioselective synthesis, and the plan outlined in **Scheme 26** can be easily adapted to this purpose, since the required (*S*)-4-hydroxy-2-cyclohexene-1-one (**105**) is available in optically pure form via a known procedure.[43]



Scheme 26

Our synthesis of (*S*)-4-hydroxy-2-cyclohexene-1-one (**105**) which utilized (-)-quinic acid (**107**) as the starting material was carried out according to a literature procedure,but with some modifications (**Scheme 27**).[44]

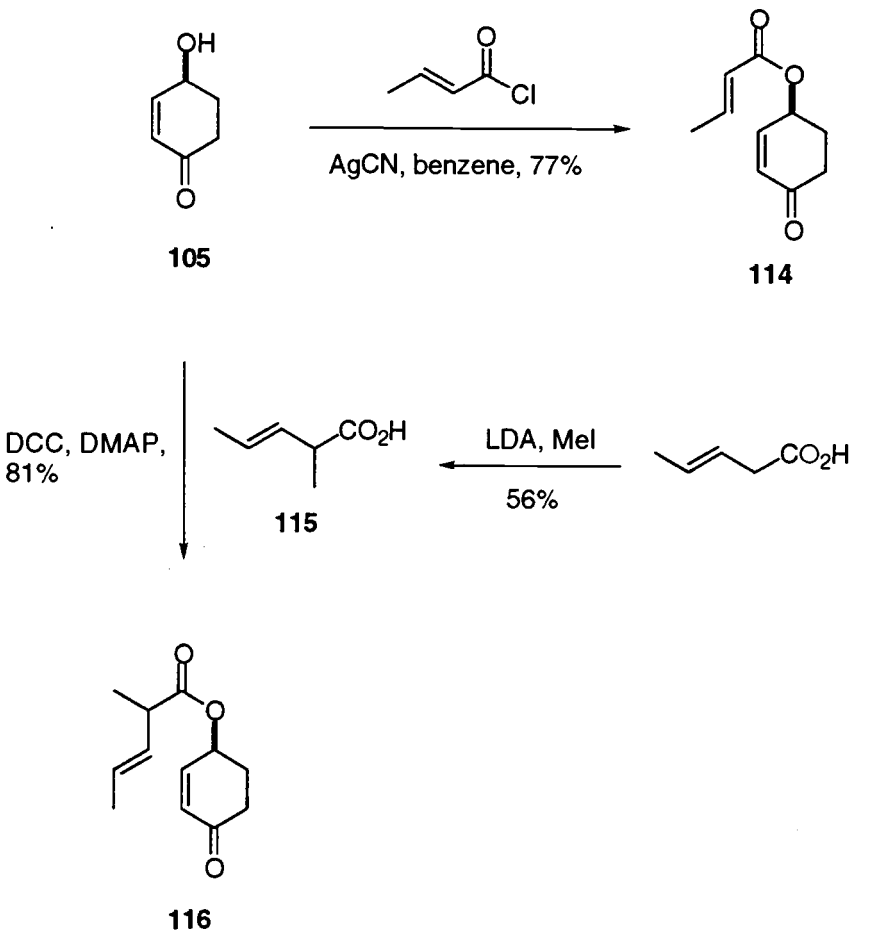


Scheme 27

(-)-Quinic acid (**107**) was first converted into its isopropylidene derivative **108** in acidic acetone. Since the triol **109** from lithium aluminum hydride (LAH) reduction of lactone **108** was difficult to purify, we instead reduced **108** with sodium borohydride ($NaBH_4$) and carried out subsequent oxidative cleavage of

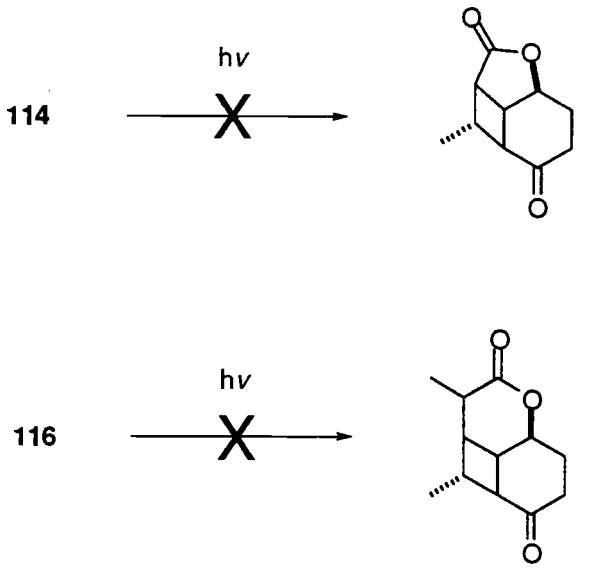
the crude triol with sodium periodate to afford hydroxy ketone **110** in high yield. The hydroxyl group was removed from **110** by a sequence involving elimination and hydrogenation of the derived enone **111** to give ketone **112**. Treatment of **112** with *tert*-butyldimethylsilyl chloride and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) afforded **113** which was treated with aqueous hydrogen fluoride to give (*S*)- 4-hydroxy-2-cyclohexene-1-one (**105**).

According to the "Rule of Five", as termed by Hammond and Srinivasan,[45] five membered rings are highly favored during intramolecular [2+2] photoaddition. This led us to choose **114** as the substrate for photoaddition (**Scheme 28**). Since **105** is highly sensitive to both acid and base, a mild reaction was required to acylate the hydroxyl group of this cyclohexenone with crotonyl chloride. After considerable experimentation, the ester **114** was obtained by acylation of **105** with crotonyl chloride in the presence of silver cyanide. A second photoaddition substrate **116**, containing an additional carbon in the acyl appendage, was prepared by treating **105** with 1,3-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and 2-methyl-3-pentenoic acid **115**. The latter was obtained by methylation of the dianion of 3-pentenoic acid. Our expectation was that, after cleavage of the C-O bond of the cycloadduct, the methyl bearing side chain on the cyclobutane ring could be easily transformed into the isopropylene group necessary for the Cope rearrangement.



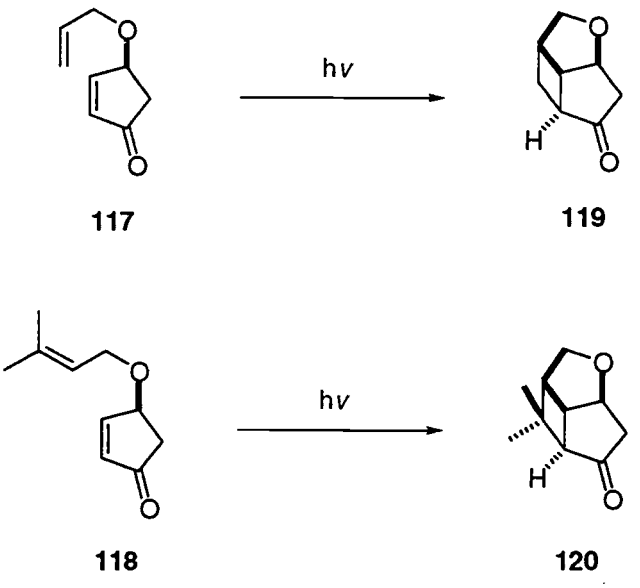
Scheme 28

Unfortunately, irradiation of **114** or **116** under various conditions did not yield any cycloadducts, but instead provided a complex mixture of products which could not be identified (**Scheme 29**). The presence of olefinic protons in the ^{1}H NMR spectrum of the crude mixture indicated that neither **114** nor **116** had undergone photoaddition.



Scheme 29

A possible solution to this problem was recognized in the work of Gariboldi who photocyclized a series of 4-(allyloxy)cyclopentenones, all of which gave the expected [2+2] adducts (**Scheme 30**).[46]. The 4-(allyloxy)cyclopentenones **117** and **118** were shown to produce the cyclobutanes **119** and **120**, respectively. The implication from this work was that an ether tether rather than an ester was needed for successful photoaddition.

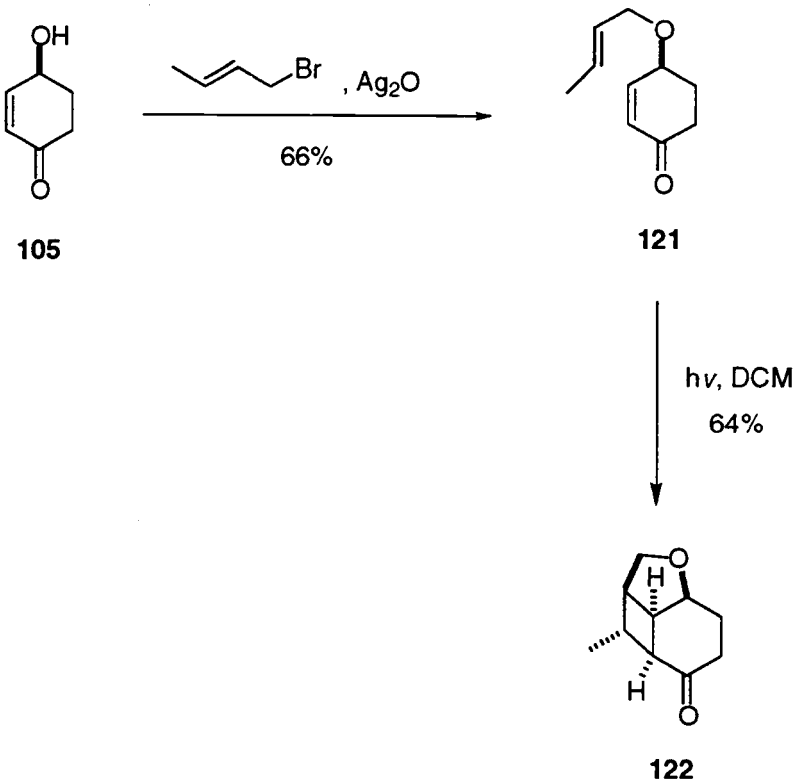


117 **119**

118 **120**

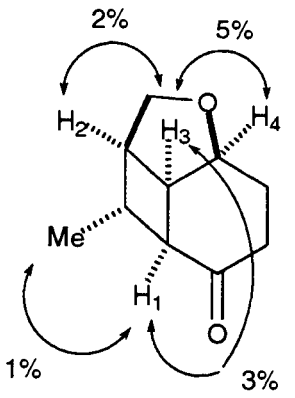
Scheme 30

With this idea in mind, we next attempted to synthesize ether **121**. Formation of **121** was not as straightforward as the synthesis of esters **114** and **116**, but, after considerable experimentation, hydroxy enone **105** was found to give the etherified product **121** using crotyl bromide in large excess in the presence of silver(I) oxide (**Scheme 31**).[47] With enone **121** in hand, its intramolecular [2+2] photo reaction was investigated. The best results were obtained from irradiation of **121** in dichloromethane at 0 °C in the absence of a sensitizer. In this reaction, the cycloadduct **122** was formed in 64% yield along with small amounts of unidentified cycloadducts.



Scheme 31

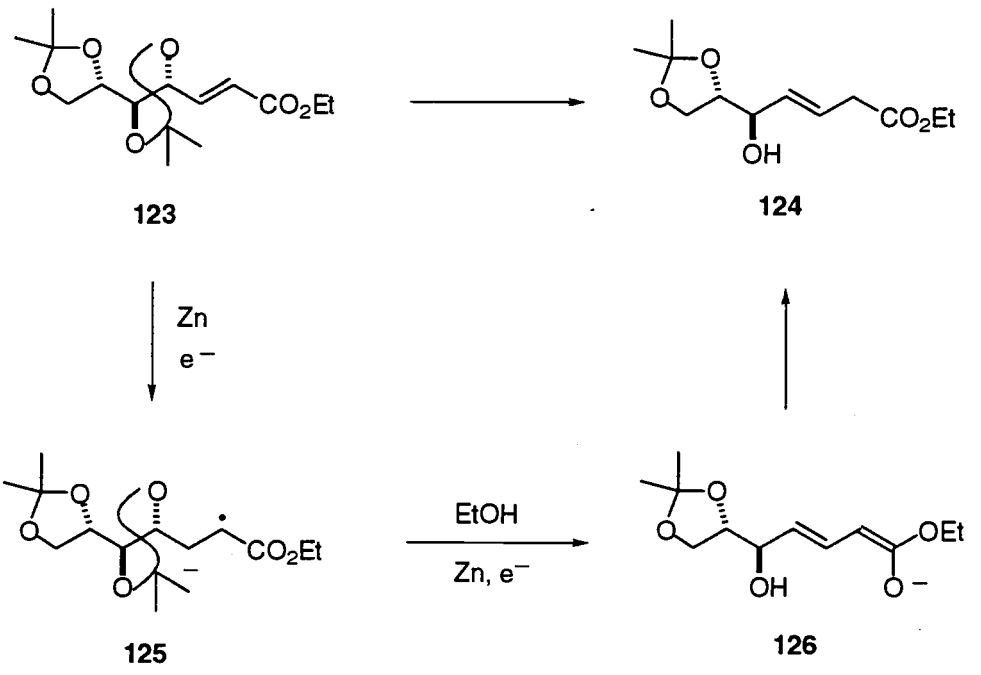
The stereochemistry of cycloadduct **122** was confirmed by ^{1}H NMR and NOE experiments as shown in **Figure 2.3**. The two protons H_1 and H_3 on the ring junction displayed a 3% signal enhancement in a NOE experiment which indicates a cis relationship between the cyclohexanone and the cyclobutane rings. The *exo* orientation of the methyl group on the cyclobutane ring was assigned from its 1% signal enhancement when ring junction proton H_1 was irradiated. Finally, 2% and 5% signal enhancements of protons H_3 with H_2 and H_4 confirmed that the tricyclic cycloadduct **122** has a rigid cage-like structure.



122

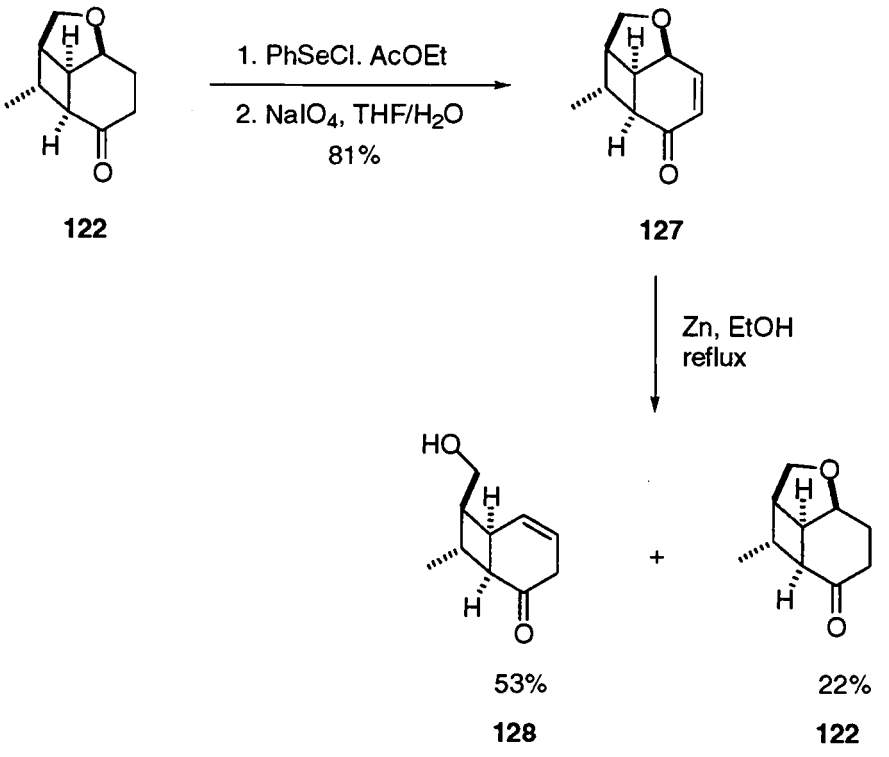
Figure 2.3 NOE data for cycloadduct **122**.

The cycloadduct **125** presented us with, our next task, which was to cleave the bond between the γ-carbon and oxygen as intended previously. A survey of the literature showed that there are many methods to remove an oxygen on the γ-carbon of an α,β-unsaturated carbonyl compound. For example, Yadav reported reductive deoxygenation of α,β -unsaturated ester **123** with zinc to obtain β,γ-unsaturated ester **124** (**Scheme 32**).[48] A plausible mechanism for this reaction involves the supply of an electron from zinc to generate radical anion **125** which then undergoes reductive elimination of the γ-oxygen with accompanying olefin migration. Other electron transfer reagents such as samarium diiodide,[49] magnesium,[50] lithium in ammonia, and sodium amalgam[51] have been used.



Scheme 32

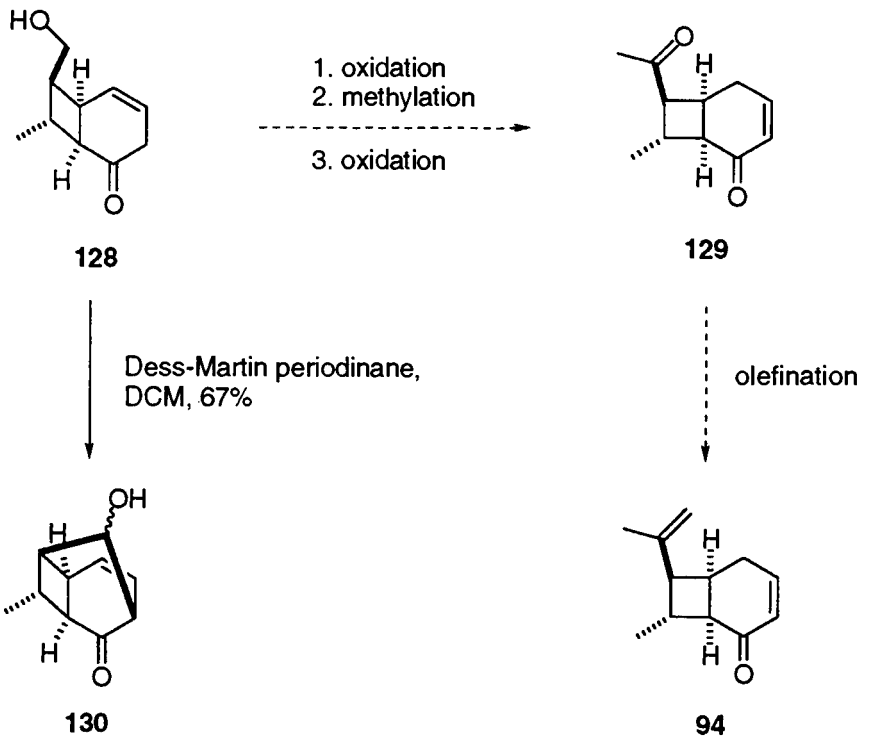
Anticipating that one of these methods would successfully effect reductive elimination, the cycloadduct **122** was converted into enone **127** by treatment with phenylselenyl chloride followed by oxidation with sodium periodate (**Scheme 33**). The enone **127** was subjected to the reducing agents described above, but reductive cleavage of the C-O bond could only be achieved by refluxing the enone **127** in ethanol in the presence of activated zinc. This produced primary alcohol **128** and the cyclohexanone **122** in 53% and 22% yield, respectively. The formation of **122** was not unexpected because the intermediate anion can abstract a proton from ethanol. Treatment of enone **127** with samarium diiodide, magnesium, or sodium amalgam did not give **128** but only caused decomposition of the starting material.



122 **127** **128** **122**

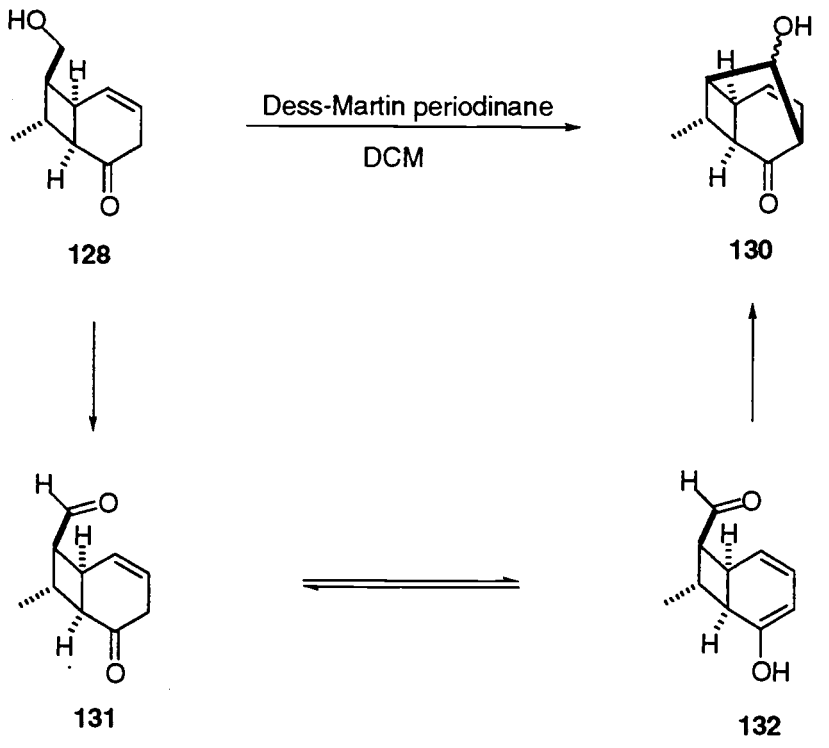
Scheme 33

At this point, we decided to attempt the conversion of the primary alcohol group in **128** into the isopropylene unit that would be needed for eventual Cope rearrangement. Our plan was to use an oxidation-methylation-oxidation sequence to form a diketone **129** which could be transformed into the isopropylene **94** by a selective carbonyl olefination (**Scheme 34**). However, when the alcohol **128** was treated with Dess-Martin periodinane, the isolated product was not the expected aldehyde but the hydroxy ketone **130** resulting from an intramolecular aldol condensation.



Scheme 34

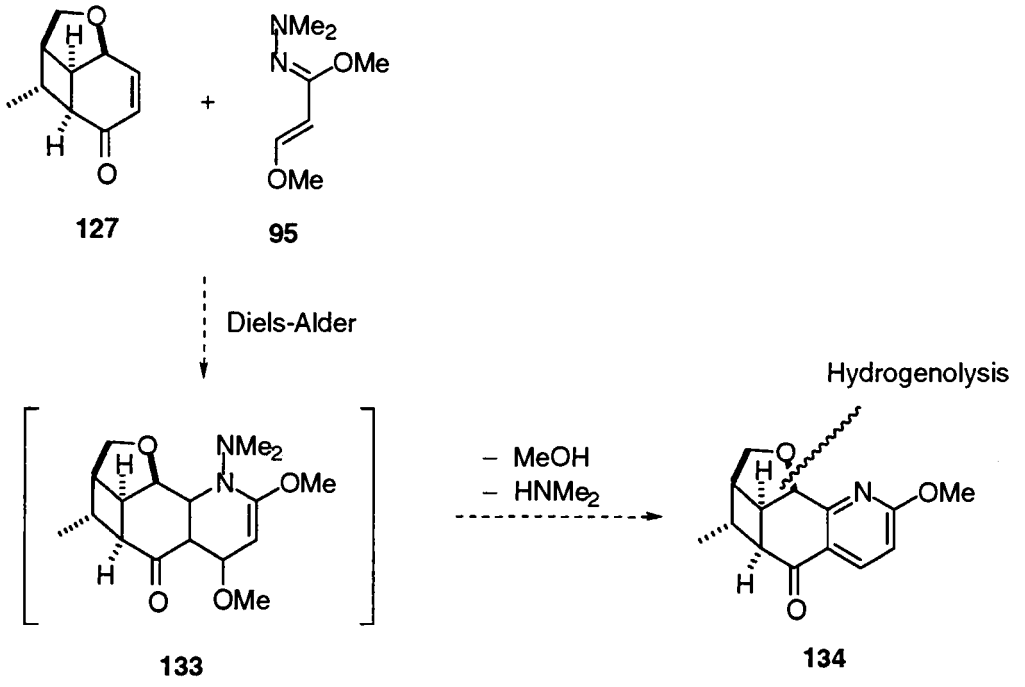
Before chromatography of the crude reaction mixture, a characteristic aldehyde peak at δ 9.85 was clearly visible in the ^{1}H NMR spectrum. This suggested that the aldehyde **131** was generated but was converted into **130** during the chromatographic purification. A plausible mechanism for the transformation of **128** into **130** is shown in **Scheme 35**. Enolization of the initially formed aldehyde **131** would give dienol **132**, and subsequent intramolecular aldol reaction between the enol and the aldehyde moiety would produce the secondary alcohol **130**.



Scheme 35

At this point, we realized that we could not reproduce the zinc-mediated reductive deoxygenation of the enone **127** (see **Scheme 33**). Since it is known that the results of many reactions using zinc metal are highly dependent on the activated state of zinc,[52] it seems reasonable to assign the lack of reproducibility of deoxygenation of **127** to the zinc used. Thus, several different activation methods[53] were employed to obtain active zinc metal. However, all attempts to effect the deoxygenation with newly activated zinc resulted in uniformly no reaction. Changing the solvent also showed no reaction. These results indicated that this is not a function of the activity of zinc or solvent. Further analysis, however, revealed that this result is probably due to the acidity of the reaction medium. When **127** was heated with zinc in the presence of acids such as acetic

acid, hydrogen chloride, of hydrogen iodide, the enone **127** slowly decomposed, and no separable spot was detected in thin layer chromatographic analysis. Since the initial successful conversion of **127** to **128** was carried out without such acids, the lack of reproducibility of deoxygenation of **127** is presumably due to trace amount of impurities contaminated in enone **127**. The acidic contaminants were likely introduced in to the **127** during its formation which employs a acidic condition (**Scheme 33**).



Scheme 36

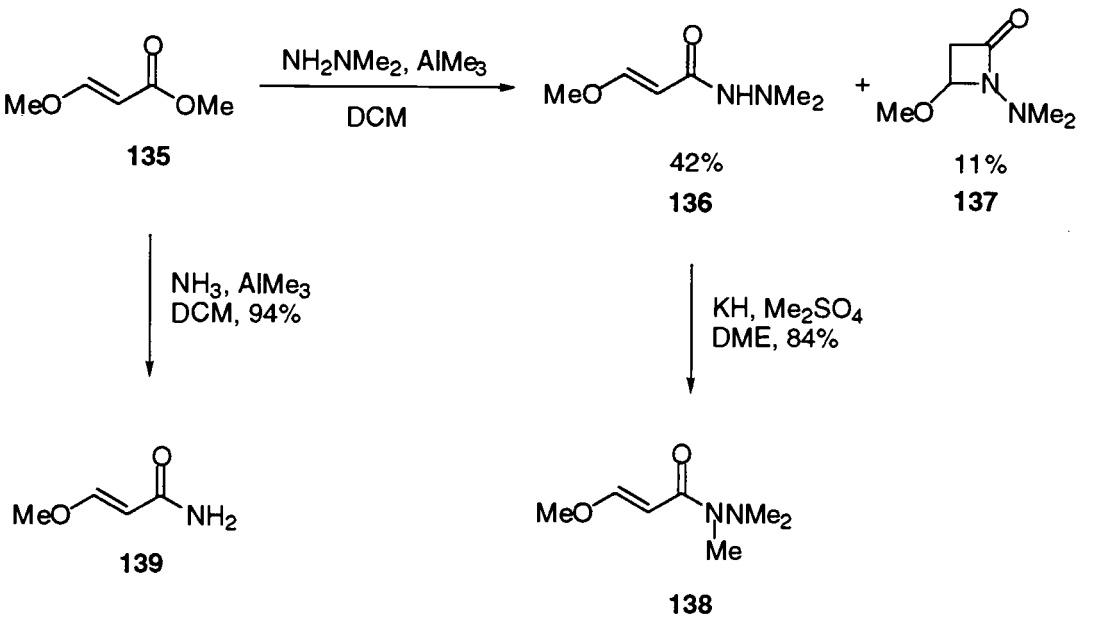
Since it had not been possible to find reliable reaction conditions for the cleavage of the γ-carbon-oxygen bond in enone **127**, it was decided to delay this step and instead pursue the annulation required to install the pyridine ring of huperzine A. For this, a hetero-Diels-Alder reaction of **127** with an azadiene was

envisioned. In this approach, we anticipated that the Diels-Alder adduct **133** from **127** and **95** would undergo spontaneous aromatization to give methoxypyridine **134**. In this scenario, cleavage of the C-O bond in **134** could be achieved using hydrogenolysis[54] since the oxygen substituent is now attached to a benzylic carbon (**Scheme 36**).

Studies published by Ghosez (see **Scheme 24**),[40] indicate that the presence of the dimethylamino group on the nitrogen of an azadiene results in both increased Diels-Alder reactivity of the azadiene with respect to an electrophilic dienophile, and in a reversal of its polarity. The latter results from an increase in the coefficient at C4 of the highest occupied molecular orbital of the azadiene. However, we believed that the presence of the two methoxy groups in the azadiene would override this polarity reversal and would ensure the desired regiochemical outcome from the Diels-Alder reaction.

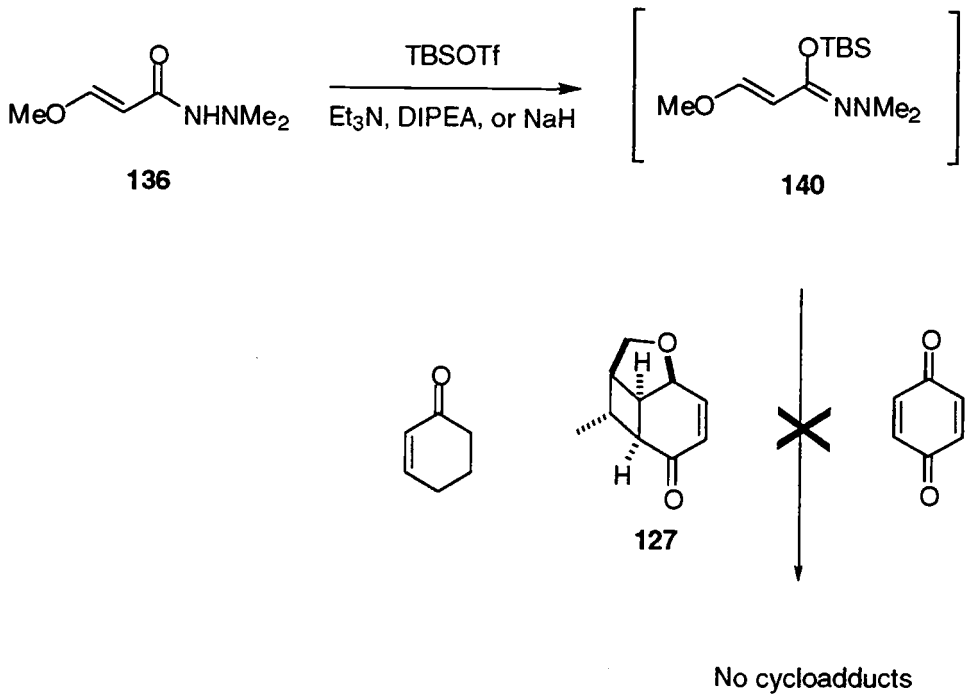
Based on this premise, we attempted to prepare a suitable diene for cycloaddition to **127** (**Scheme 37**). Methyl trans-3-methoxyacrylate (**135**) was treated with 1,1-dimethyl hydrazine and trimethylaluminum[55] to give the amide **136** along with a small amount of the β-lactam **137** resulting from intramolecular Michael addition of **136**. Similarly, the amide **139** was prepared using trimethylaluminum and ammonia. Unfortunately, O-methylation of the amides **136** and **139** was unsuccessful and the requisite azadiene **95** was not formed under any of the reaction conditions that were attempted. For example, in the case of **136**, treatment with dimethyl sulfate and potassium hydride as the base, the only product was the N-methylated amide **138**. The use of triethyloxonium

tetrafluoroborate (Et_3OBF_4) with **136** and **139** caused decomposition of these amides.



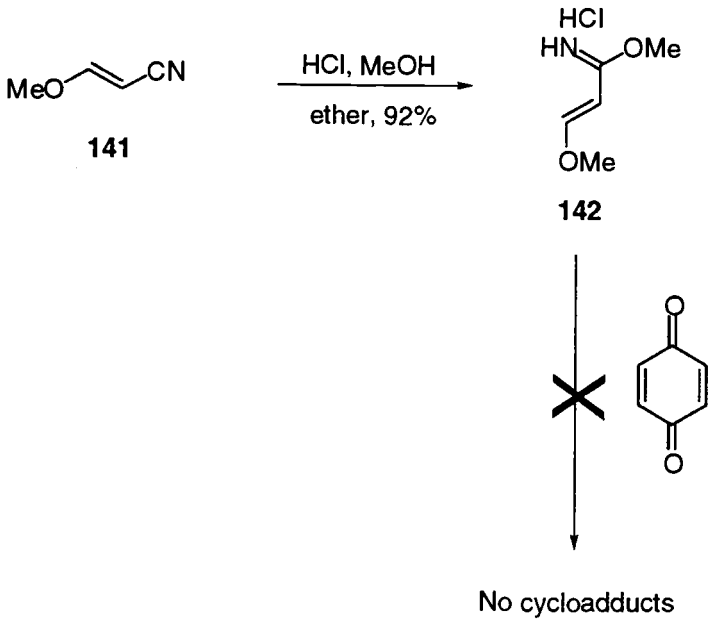
Scheme 37

Since the preparation of azadiene **95** from the amide **136** was unsuccessful, our next endeavor was focussed on an in situ Diels-Alder reaction using a transient azadiene **140** (**Scheme 38**). However, treatment of **136** with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of bases such as triethylamine, diisopropylethylamine, or sodium hydride, and subsequent addition of dienophiles such as cyclohexenone or the enone **127** resulted in decomposition. Most of the dienophiles were recovered intact. Even a very reactive dienophile such as benzoquinone did not form a cycloadduct.



Scheme 38

These negative results can be explained in two ways. First, the azadiene **140** was, in fact prepared, but it was unreactive toward dienophiles. Alternatively, the azadiene was not formed from the treatment of the amide **136** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and bases. To make sure that an azadiene was indeed present in the reaction, we synthesized the known diene **142** from 3-methoxyacrylonitrile (**141**) (**Scheme 39**).[56] The fact that **142** did not undergo the a Diels-Alder reaction benzoquinone implies that methoxy substituents at C2 and C4 of the azadiene are not sufficient to overcome an intrinsically unreactive Diels-Alder partner.

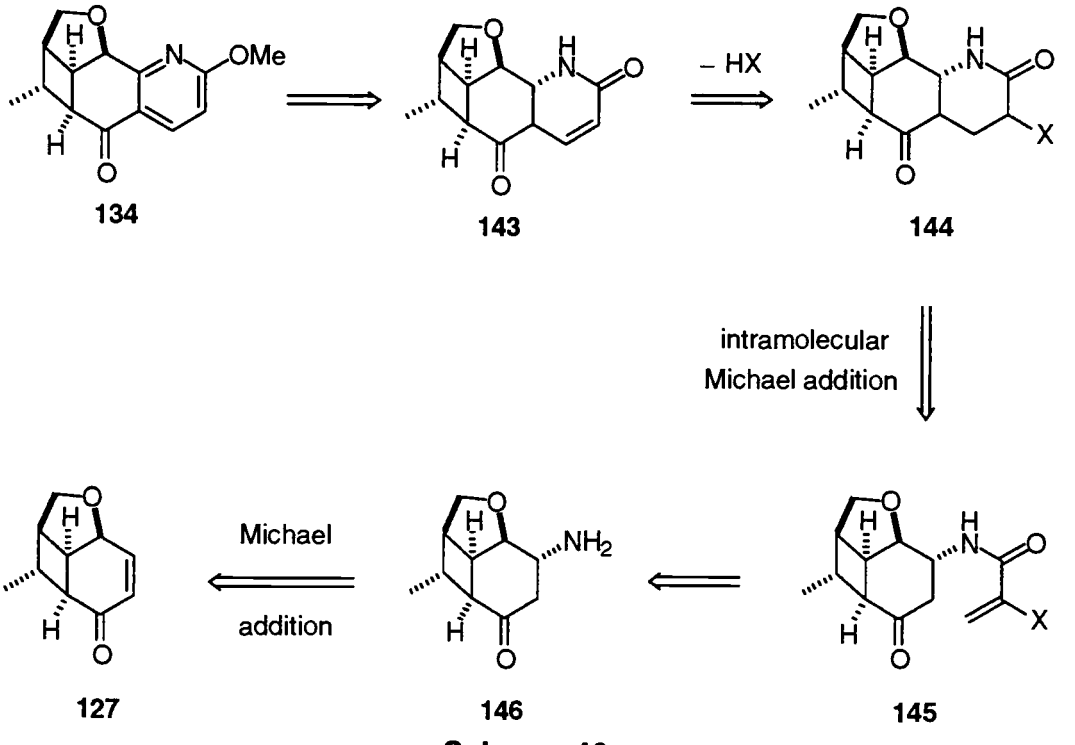


Scheme 39

Since most of the azadienes which were reported to undergo the Diels-Alder reaction have a methyl substituent at C3 or C4,[57] it is clear that the substitution pattern on the azadiene is a crucial factor for successful cycloaddition. It is also known[58] that the presence of a substituent at the C2 position decreases the reactivity of the diene due to steric interactions in the transition state of the Diels-Alder reaction. These factors led us to conclude that azadiene **142** is not a suitable partner for the Diels-Alder reaction.

The failure to append the methoxypyridine needed for huperzine A via a hetero-Diels-Alder reaction with enone **127** prompted a search for a stepwise route to this goal. Our second approach was based on an intramolecular Michael addition strategy and is shown in **Scheme 40**. It was surmised that dehydrogenation of the α,β-unsaturated δ-lactam **143**, derived from **144** by elimination of HX, would lead to the methoxypyridine **134**. In principle, **144** could

be obtained by intramolecular Michael reaction of **145**, which could be synthesized from the enone **127** by Michael reaction of ammonia to give **146**

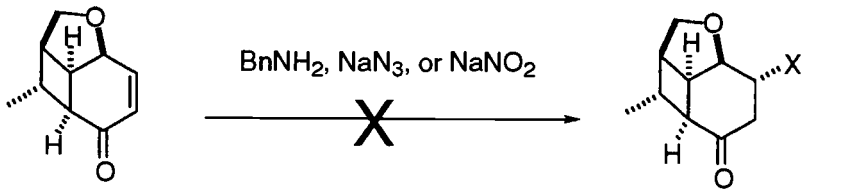


134 **143** **144**

127 **146** **145**

Scheme 40

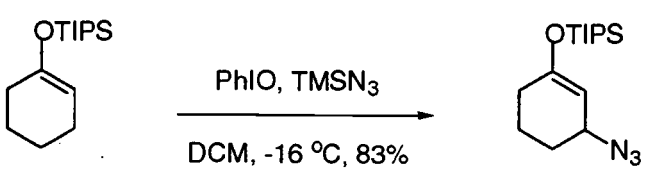
Our initial attempts to incorporate a nitrogen functionality at the β-position of the enone **127** using a Michael addition were foiled by incomplete reaction and the inseparability of the reaction products (**Scheme 41**). Several Michael donors such as benzylamine, sodium azide, and sodium nitrite were investigated, but none gave the a Michael adduct.



127

Scheme 41

A possible solution to this problem was recognized in the work of Magnus, who reported the transformation of a triisopropylsilyl enol ether to a β-azido triisopropylsilyl enol ether (**Scheme 42**).[59] Specifically, Magnus showed that treatment of **147** with iodosobenzene and trimethylsilyl azide ($TMSN_3$) at a temperature between -16 and -19 °C produced β-azido triisopropylsilyl enol ether **148**.

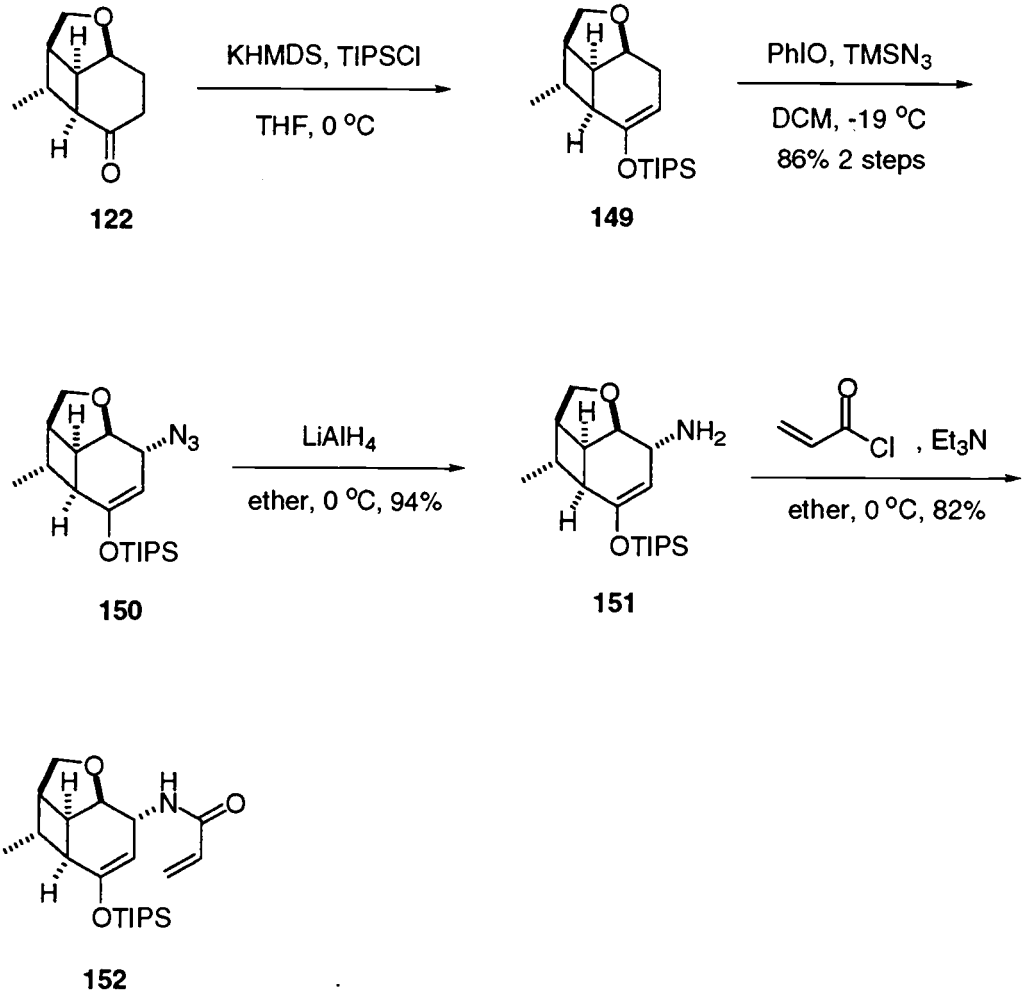


147 **148**

Scheme 42

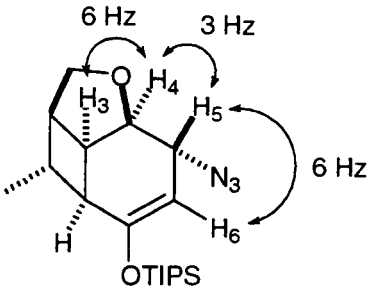
Implementation of this plan began by silylating the ketone **122** with triisopropylsilyl chloride to afford the triisopropylsilyl enol ether **149** (**Scheme 43**). Treatment of the silyl enol ether **149** with iodosobenzene and trimethylsilyl azide at -19 °C cleanly furnished the azide **150** as a single stereoisomer. The stereochemistry of the azide **150** was assigned by vicinal coupling constants of

protons in ^{1}H NMR spectrum (**Figure 2.4**). The β-proton H_5 showed a clean *dd* pattern. The coupling constants were 6 Hz with vinyl proton H_6 and 3 Hz with H_4, and this assignment was later confirmed by X-ray crystallographic analysis of **157** (**Figure 2.5**). Reduction of **150** with lithium aluminum hydride gave the primary amine **151** which was acylated with acryloyl chloride to give the amide **152** (**Scheme 43**).



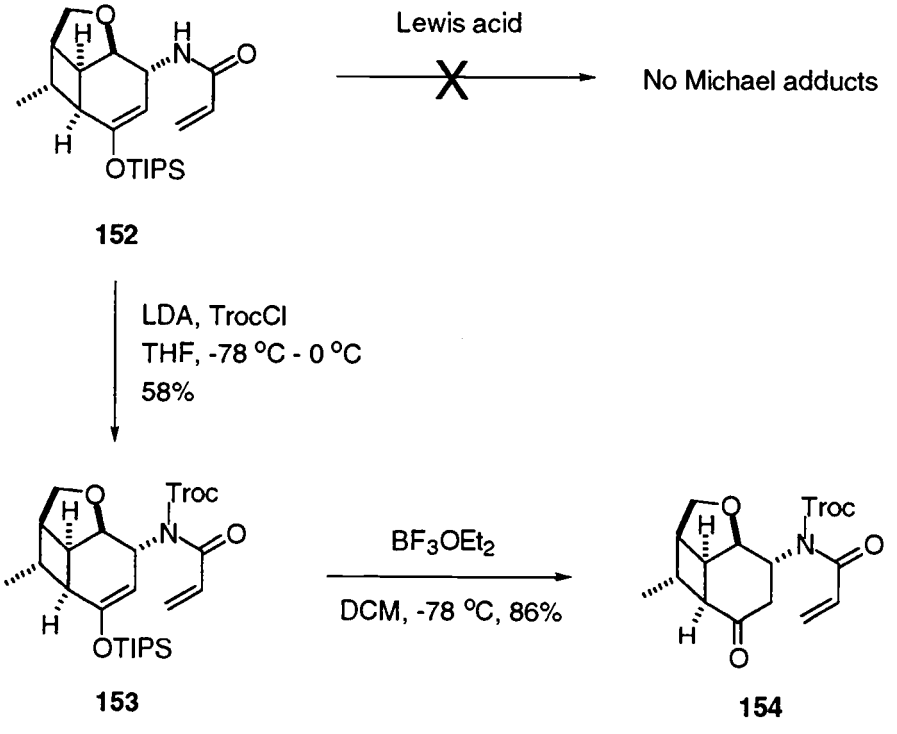
122 **149** **150** **151** **152**

Scheme 43



150

Figure 2.4 Coupling pattern of protons in **150**.

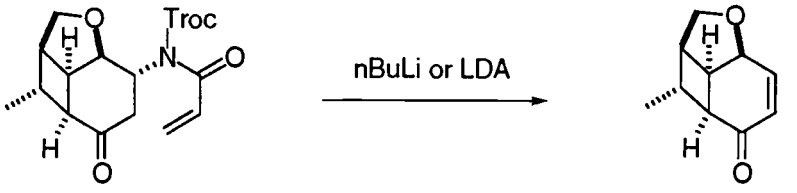


Scheme 44

With **152** in hand, efforts were undertaken to promote the intramolecular Michael reaction of this acrylamide (**Scheme 44**). Disappointingly, all attempts to effect cyclization using various Lewis acids such as titanium(IV) chloride, boron

trifluoride diethyl etherate, trimethylaluminum, and *tert*-butyldimethylsilyl trifluoromethanesulfonate were unsuccessful. Under acidic conditions, decomposition of the starting amide was the predominant outcome. Compound **153**, prepared by treatment of **152** with 2,2,2-trichloroethoxycarbonyl chloride, was exposed to boron trifluoride diethyl etherate, but this produced only the ketone **154**.

Attempts to employ base-promoted Michael reactions of **154** were also unsuccessful. In the presence of strongly basic reagents such as butyllithium or lithium diisopropylamide (LDA), the amide moiety was eliminated to leave the enone **127** (**Scheme 45**).

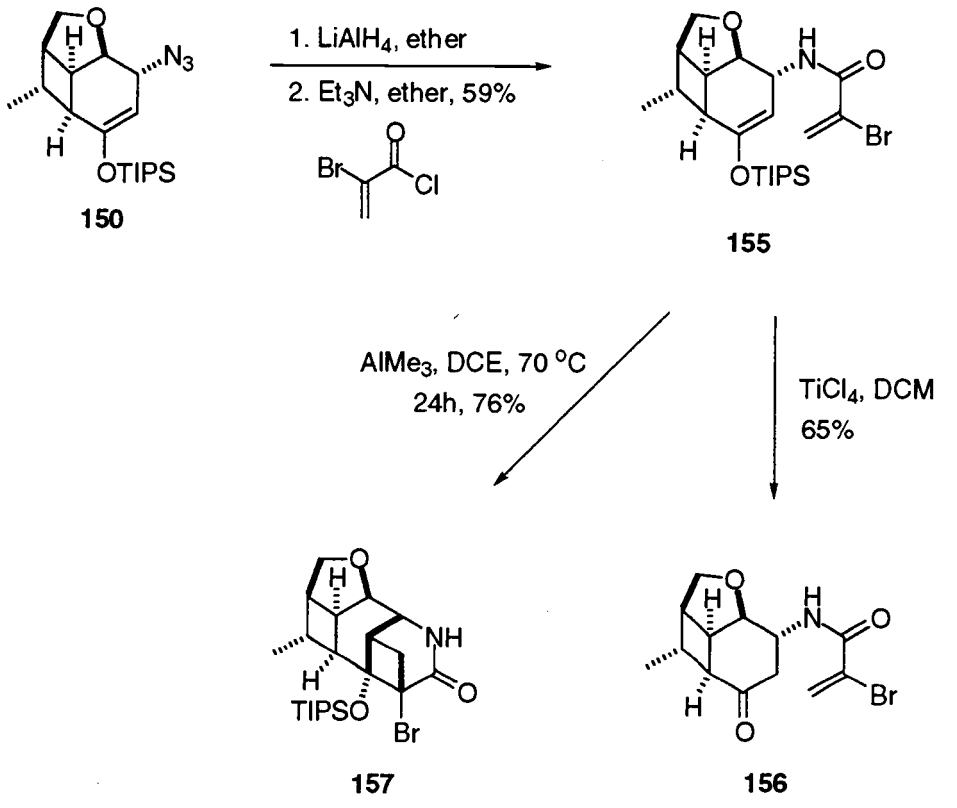


154 **127**

Scheme 45

In light of these results, a search was initiated to find a more reactive Michael acceptor than the acrylamide of **152**, in the hope that milder reaction conditions could avoid desilylation and/or decomposition of the Michael reaction substrate. α-Bromo-acrylamide **155** appeared to satisfy this requirement and was synthesized from azide **150** using reduction with lithium aluminum hydride followed by acylation with α-bromoacryloyl acid (**Scheme 46**). Although initial

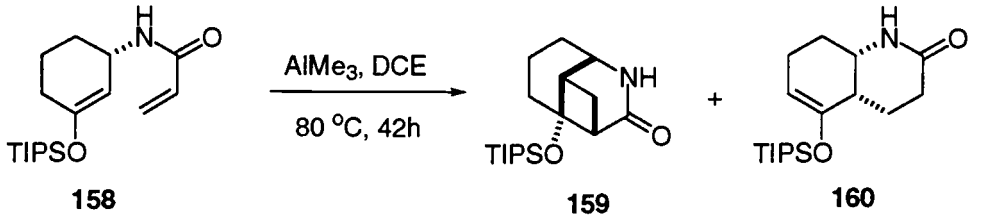
attempts to effect a the Michael reaction with **155** gave similar results to those previously seen with **152** (for example, treatment with titanium(IV) chloride caused desilylation and gave the corresponding ketone **156**), further experimentation was found to produce a new compound **157** in modest yield when **155** was heated in dichloroethane in the presence of trimethylaluminum, (**Scheme 46**).



Scheme 46

This unexpected result was found to have precedent when it was discovered that Magnus and coworkers had published a similar observation

during their studies on the intramolecular [2+2] cyclization of β-amino triisopropylsilyl enol ethers.[60] Thus, when the triisopropylsilyl enol ether **158** was treated with trimethylaluminum, the lactam **159** and cyclobutane **160** were produced in yields of 9% and 43%, respectively (**Scheme 47**).

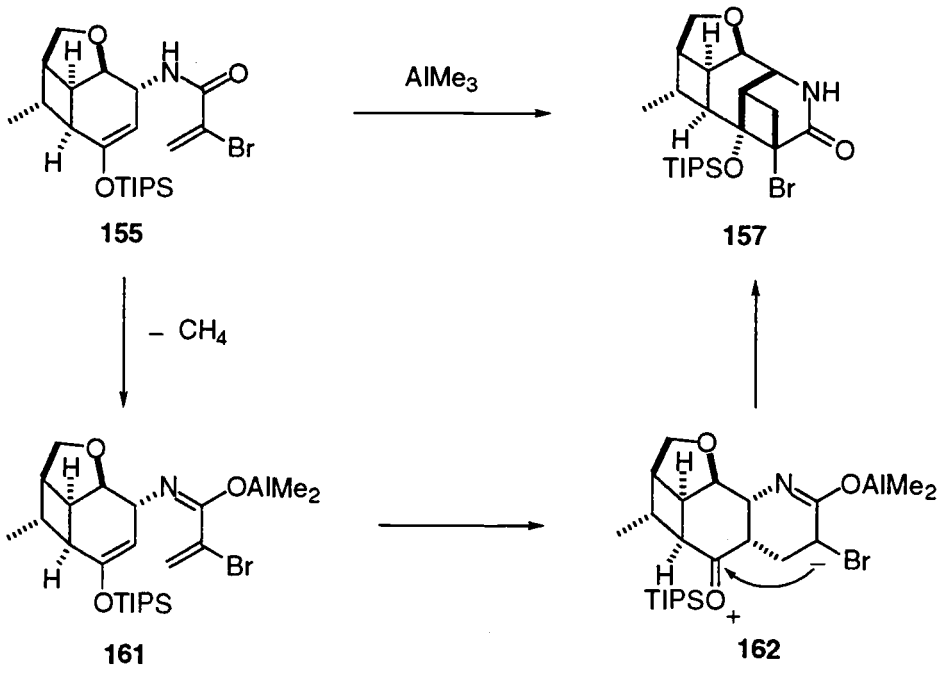


158 **159** **160**

Scheme 47

The formation of the cyclobutane containing structure **157** can be explained by the mechanism shown in **Scheme 48**. Initial reaction of amide **155** and trimethylaluminum would form the imidate **161** which undergoes intramolecular Michael reaction to generate the zwitterion **162**. Subsequent attack of the anion in **162** at the α-face of the carbonyl carbon would form the cyclobutane **157**.

The identity of the structure **157** was independently verified by X-ray crystallography (**Figure 2.5**). The crystal structure of **157** reveals interesting configurational details of this molecule, including the fact that the photoaddition of enone **121** indeed formed the desired cyclobutane ring with the correct stereochemistry at both the ring junction and the methyl group.



Scheme 48

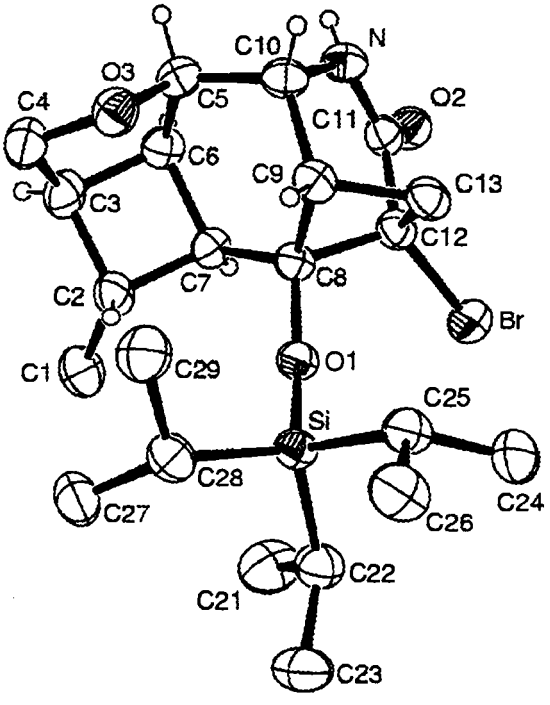
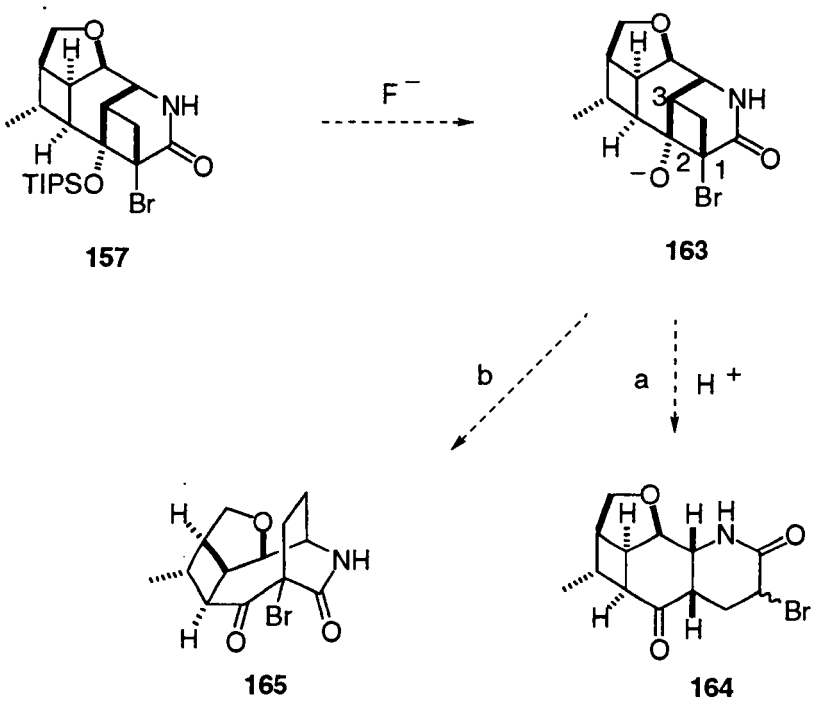


Figure 2.5 ORTEP Representation from X-ray structure of **157**.

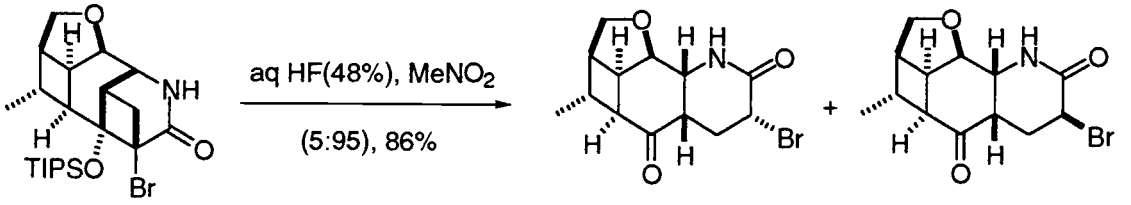
Even though the Michael reaction of **155** did not furnish the desired lactam, it was reasonable to suppose that desilylation of **157** would produce **164**. This would occur via intermediate **163** which should undergo concomitant cleavage of the C1-C2 bond to yield **164** rather than fracture of the C2-C3 bond to form the bridged structure **165** (**Scheme 49**). The reason we believed pathway a should be favored over b is that the anion generated from cleavage of the C1-C2 bond can be stabilized by both the carbonyl group and the bromine substituent.



Scheme 49

As expected, when **157** was treated with aqueous hydrogen fluoride in nitromethane, stereoisomeric lactams **166** and **167** were produced. These were

was obtained as a separable 3:1 mixture in favor of **166** (**Scheme 50**). It should be mentioned that this reaction was found to be highly sensitive to the solvent used, and only nitromethane gave the **166/167** mixture. Most other solvents such as acetonitrile, tetrahydrofuran, and methanol caused decomposition of **157**.

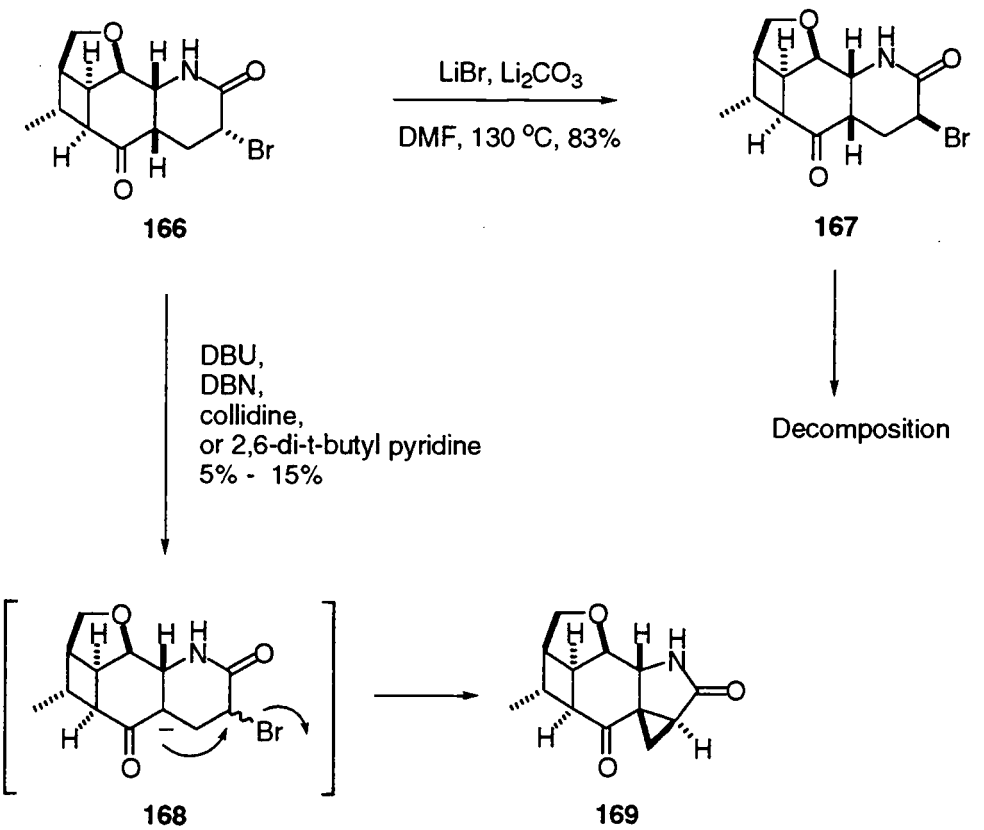


157 **166** **167**

Scheme 50

With **166** and **167** in hand, our next goal was elimination of hydrogen bromide. Introduction of the double bond by this means would facilitate aromatization of the δ-lactam to form an α-pyridone. The results of attempted dehydrobromination are shown in **Scheme 51**. Treatment of the major isomer **166** with lithium carbonate in the presence of lithium bromide produced only the minor isomer **167** by epimerization. Longer reaction time failed to complete the reaction and resulted in slow decomposition of **166** and **167**. Interestingly, treatment of **166** with organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), collidine, or 2,6-di-*tert*-butylpyridine gave cyclopropane **169**. The latter is formed probably via anion **168**, which displaces bromide in a manner similar to that seen in a Favorski reaction. The structure of **169** was assigned through the use of ^{1}H, ^{13}C, and

HSQC-COSY NMR analyses. The HSQC-COSY experiment revealed a proton-proton spin system linking the methylene protons and methine proton on the cyclopropane. The coupling pattern in the ^{1}H NMR of **169** is also in agreement with this structural assignment.

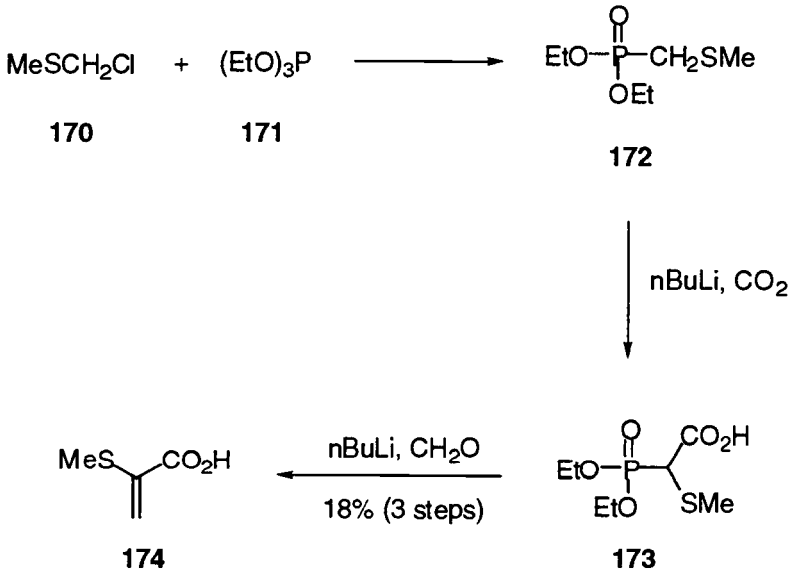


Scheme 51

These findings indicated that dehydrobromination of substrates **166** or **167** is not a feasible way to form the desired α,β-unsaturated lactam. It was therefore decided to prepare a substrate for intramolecular Michael reaction bearing a methylthio or phenylseleno group in place of the problematic bromine, in the

belief that the corresponding sulfoxide or selenoxide would undergo facile synelimination to produce a conjugated double bond.[61]

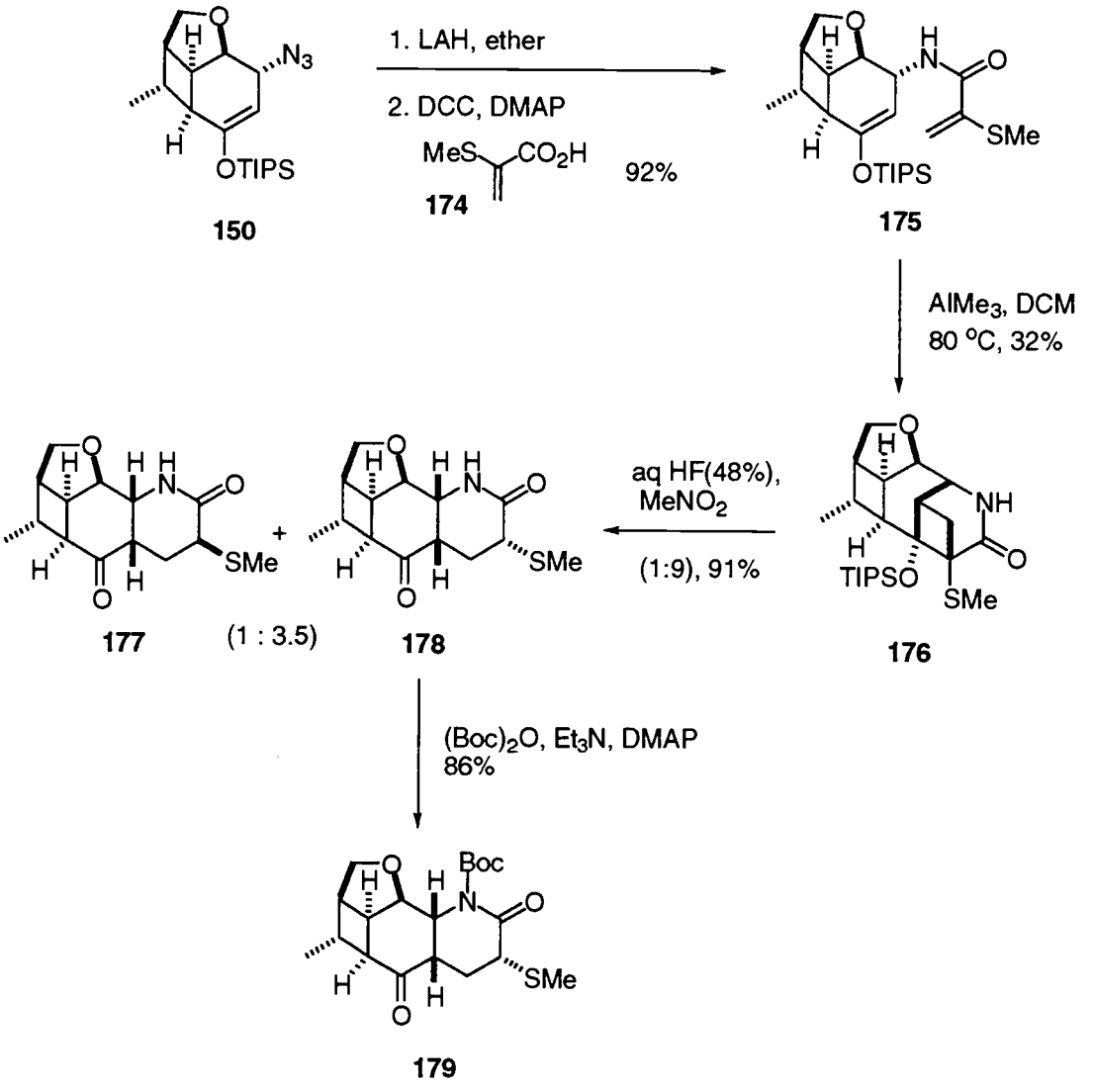
α-Methylthioacrylic acid was synthesized according to the literature procedure (**Scheme 52**).[62] A mixture of methylthiomethyl chloride (**170**) and triethyl phosphite (**171**) was heated to form diethylphosphorylmethyl methyl sulfide (**172**) which was treated with butyllithium and carbon dioxide to give the carboxylic acid **173**. A Horner reaction of the phosphonate **173** with formaldehyde furnished α-methylthioacrylic acid **174** in an overall 18% yield for the three steps.



Scheme 52

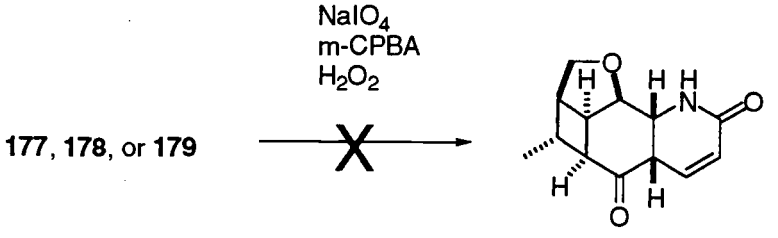
Acylation of the primary amine, obtained from reduction of azide **150**, with **174** using 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine afforded amine **175** in a good yield. The Michael reaction of **175** in the presence of

trimethylaluminum again led to a the cyclobutane **176**, and subsequent treatment of **176** with aqueous hydrogen fluoride in nitromethane produced a 1:3.5 mixture of diastereomeric lactams **177** and **178**, as expected. The major isomer **178** was next protected as its *tert*-butoxycarbonyl derivative **179** (**Scheme 53**).



Scheme 53

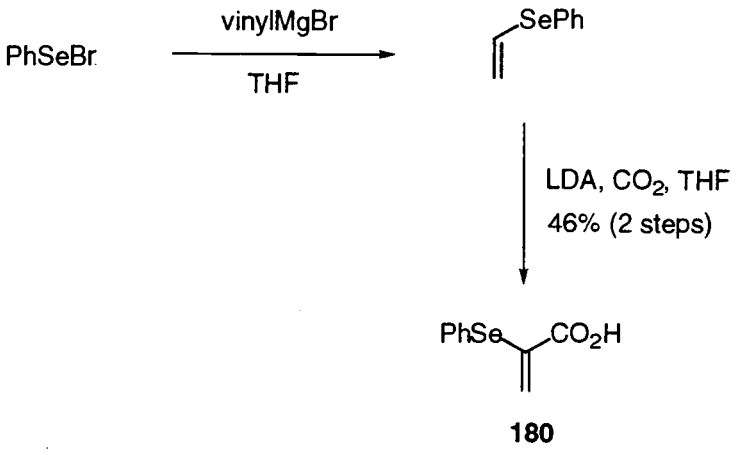
Disappointingly, all attempts to bring about oxidative elimination of the methylthio group via its sulfoxide in **177**, **178**, and **179** met with failure (**Scheme 54**). When these compounds were treated with oxidants such as sodium periodate, 3-chloroperoxybenzoic acid, or hydrogen peroxide, they gave inseparable mixtures of unidentified products. The crude NMR of the reaction mixture in each case showed complex resonances in the vinylic region which could not be assigned to specific structures.



Scheme 54

This unfavorable outcome led us to explore the use of the acrylic acid analogous to **174** in which a phenylselenyl group replaces the methythio substituent. In general, the elimination of selenoxides takes place at temperatures between 0 °C and 25 °C, contrasting with the more stable sulfoxides, which generally require temperatures around 60 °C -120 °C in order for elimination to occur. Our hope was that a lower reaction temperature for elimination would allow us to isolate the desired but perhaps thermally unstable α,β-unsaturated lactams.

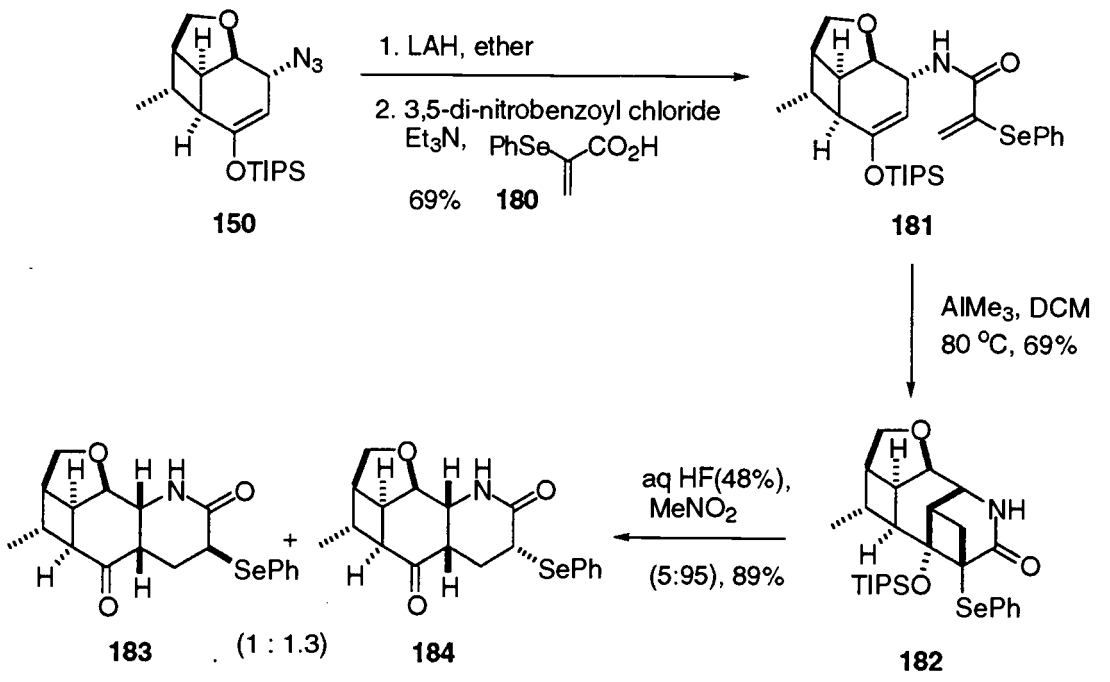
α-Phenylselenoacrylic acid **180** was synthesized according to a procedure reported by Reich (**Scheme 55**).[63] Phenylselenyl bromide was treated with vinylmagnesium bromide to give phenylvinylselenide. The anion generated by deprotonation of the phenylvinylselenide with lithium diisopropylamide was treated with carbon dioxide to give α-phenylselenoacrylic acid **180**.



180

Scheme 55

The previous sequence of reactions using α-methylthioacrylic acid **174** was now applied to the derivative **180**. Acylation of the primary amine, obtained by reduction of azide **150**, with **180** in the presence of 3,5-dinitrobenzoyl chloride afforded amide **181** (**Scheme 56**). The Michael reaction of **181** in the presence of trimethylaluminum again gave a cyclobutane **182**, and subsequent treatment of **182** with aqueous hydrogen fluoride in nitromethane produced a 1:1.3 mixture of diastereomeric lactams **183** and **184**.



Scheme 56

It was interesting to find that the β-selenide **183** when treated with sodium periodate showed vinylic protons in the ^{1}H NMR of the product mixture, whereas α-selenide **184** did not. A careful conformational analysis was undertaken to understand these results. It is known that selenoxide elimination requires a syn relationship between the oxygen on the selenium and the hydrogen which is lost (**Figure 2.6**),[64] and it is clear that selenoxide **186** generated from α-selenide **184** would suffer an unfavorable steric interaction between the phenyl group on selenium and cyclohexanone ring. In case of the β-selenoxide **185**, a syn alignment for elimination can be easily achieved by orienting the phenyl group away from the rest of the molecule.

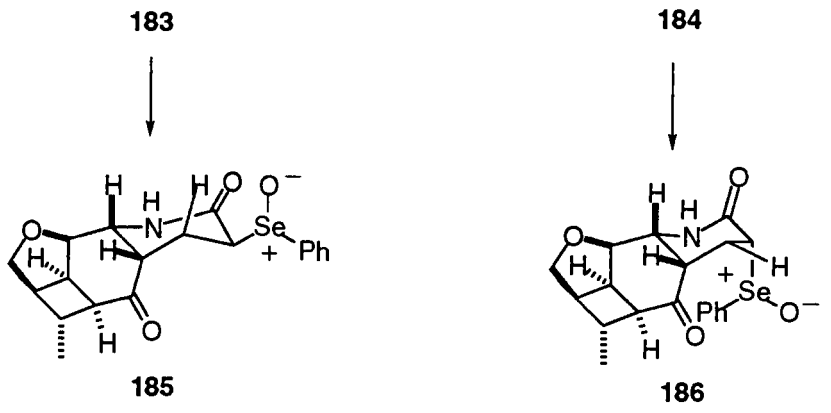
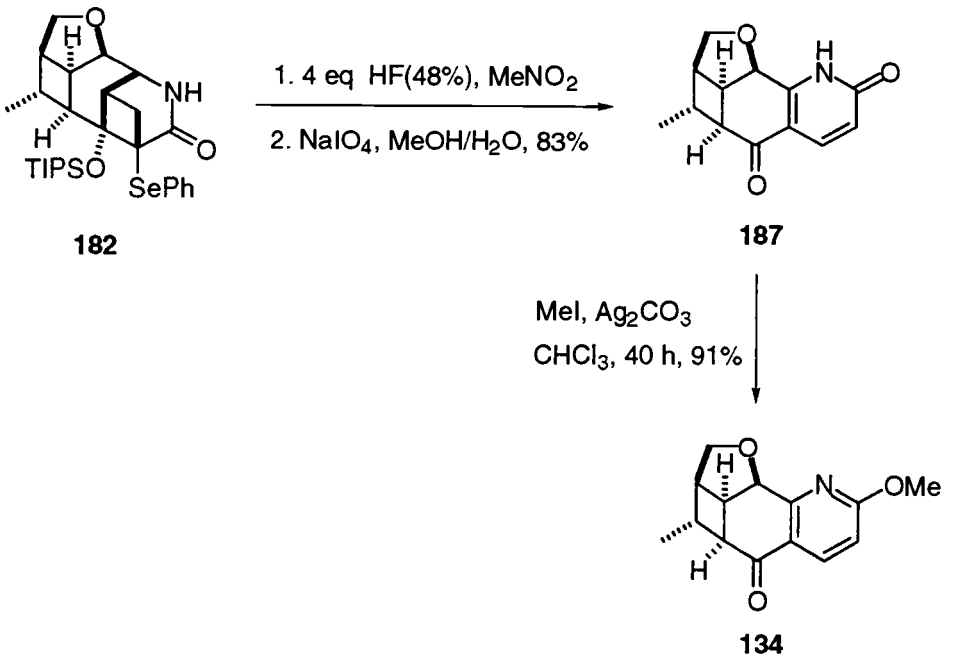


Figure 2.6 Conformation of selenoxides **185** and **186**.

This analysis led us to examine the possibility of equilibrating **183** and **184** in the hope that β-selenoxide **183** would predominant. It was found that with five equivalents of hydrogen fluoride complete desilylation of **182** was accomplished and that the equilibrium was forced toward the β-selenide **183** in up to a 10:1 ratio. Having reliable access to the selenide **183**, we once again began to investigate the elimination step. After much experimentation, It was found that the desired pyridone **187** could prepared from silyl ether **182** by treatment with four equivalent hydrogen fluoride in nitromethane, and subsequent exposure of the mixture of selenides to sodium periodate. Under these conditions, the pyridone **187** was obtained in 83% yield from **182** (**Scheme 57**). The pyridone was converted uneventfully into the methoxypyridine **134** by reaction with iodomethane in the presence of silver carbonate.

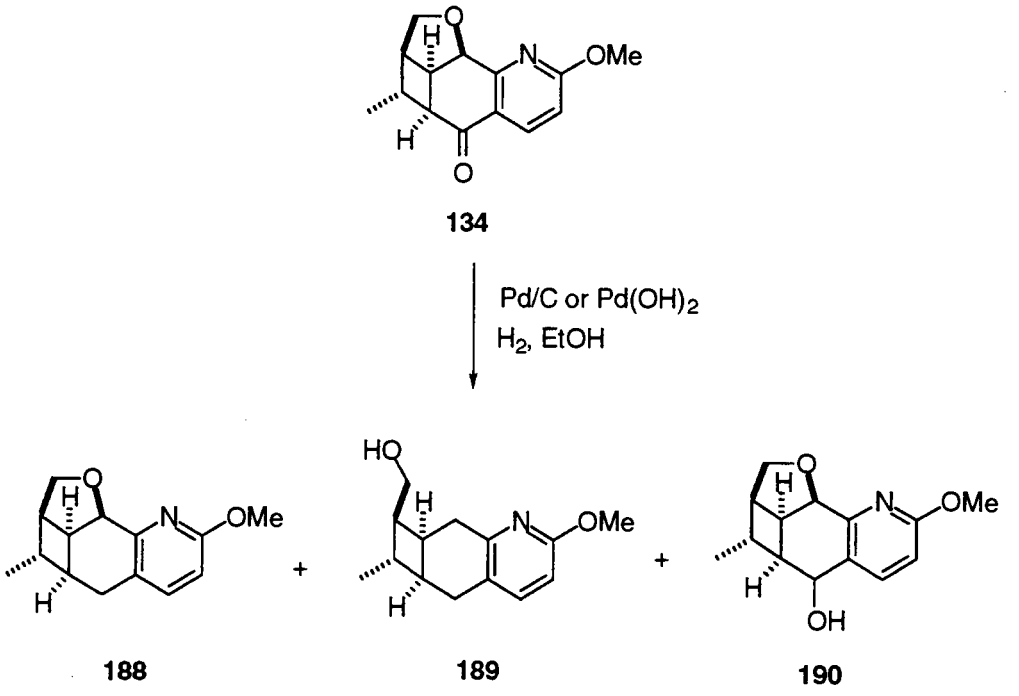


182 187 134

Scheme 57

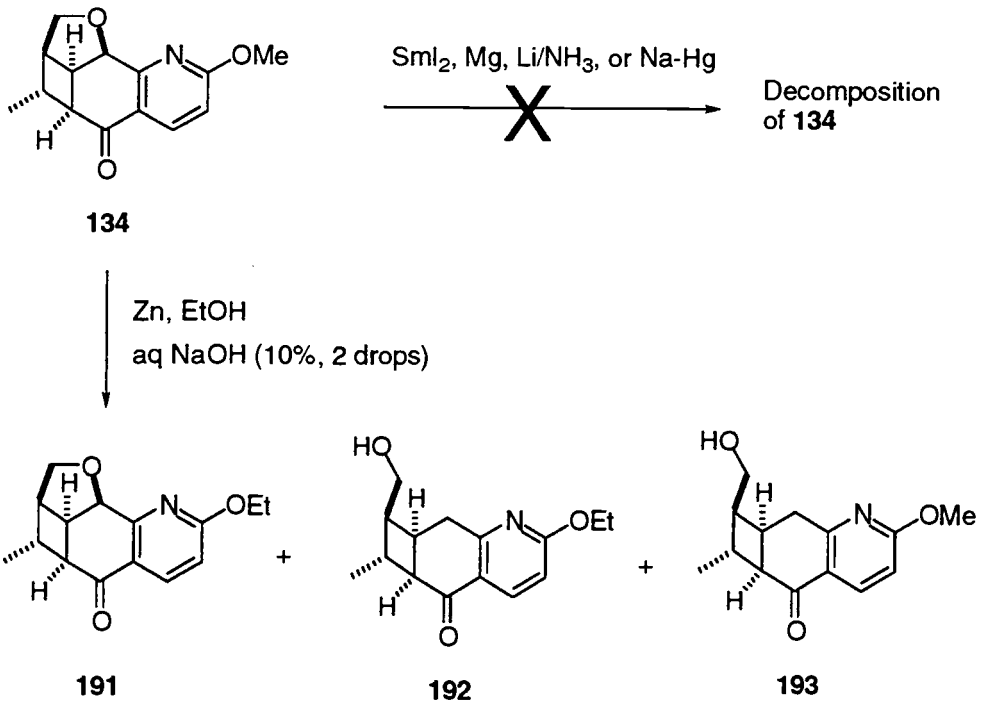
With **134** in hand, our next endeavor was directed towards cleavage of the C-O bond. This was envisioned by means of hydrogenolysis, the expectation being that activation of the benzylic ether by the pyridine moiety would assist this cleavage. Treatment of **134** with palladium-on-carbon (10%) in ethanol under an atmosphere of hydrogen gas gave a mixture of three products identified as **188**, **189**, and **190** (**Scheme 58**). It was clear from the absence of a carbonyl group in these products that the ketone was reduced under the hydrogenolysis conditions. The use of palladium hydroxide on carbon as catalyst gave similar results. Careful monitoring of the reaction revealed that reduction of the carbonyl group in **134** is appreciably faster than hydrogenolysis of the C-O bond. Other reducing conditions were also problematic. For example, a catalyst system consisting of palladium-on-carbon in methanol and acetic acid resulted only in decomposition

of the starting ketone **134**, and no reduction product at all was seen with palladium-on-alumina or with Pd-black as catalyst. At this point, our hopes returned to an electron transfer process as a potential solution to this problem.



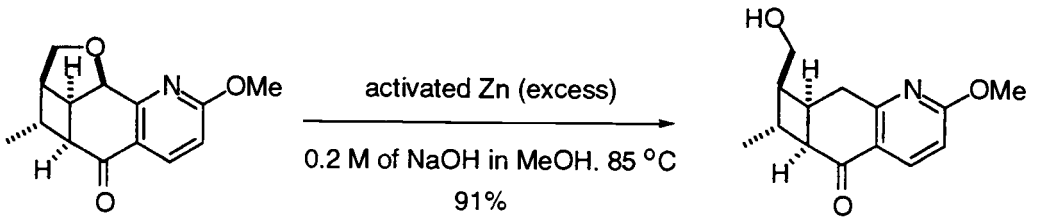
Scheme 58

Once again, many reagents were examined. All attempts using samarium diiodide, magnesium, lithium in ammonia, and sodium amalgam resulted in extensive decomposition of the starting material. However, it was pleasing to discover that heating **134** with activated zinc in ethanol containing two drops of 10% aqueous sodium hydroxide produced a mixture of three products **191**, **192**, and **193** in which no carbonyl reduction had occurred (**Scheme 59**). The desired product was **193** whereas **191** and **192** were derived from exchange of the methoxy substituent on the pyridine with ethanol used as the solvent.



Scheme 59

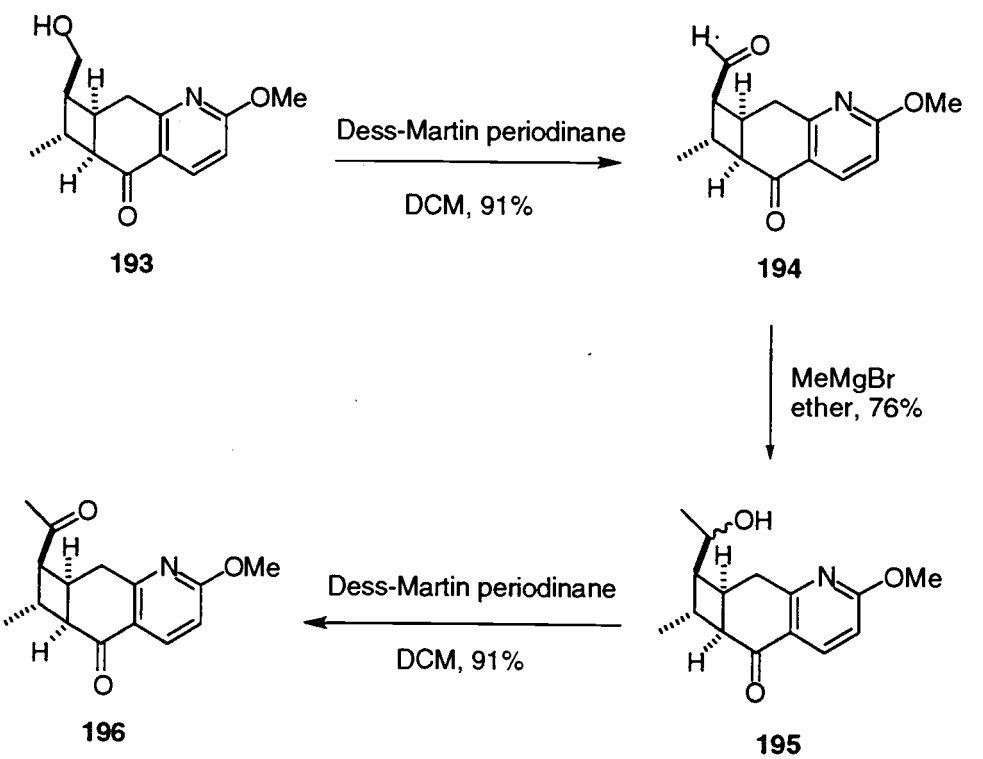
Clearly, the use of methanol as solvent instead of ethanol would result in this transformation being a practical means for the preparation of **193**. After further experimentation, **134** was found to give primary alcohol **193** in excellent yield when a 0.2 M solution of sodium hydroxide in methanol containing **134** was refluxed in the presence of freshly activated zinc (**Scheme 60**). The zinc used in this experiment was activated by Newman's method.[53] Zinc dust (12 g) was stirred with 2% hydrogen chloride (30 mL) for 30 min, and was washed with a portion of 2% hydrogen chloride (30 mL), three portions of water (20 mL), two portions of ethanol (20 mL), and finally with a portion of absolute diethyl ether (30 mL). Then, the zinc was dried under reduced pressure (1 mmHg) for two hours before use.



134 **193**

Scheme 60

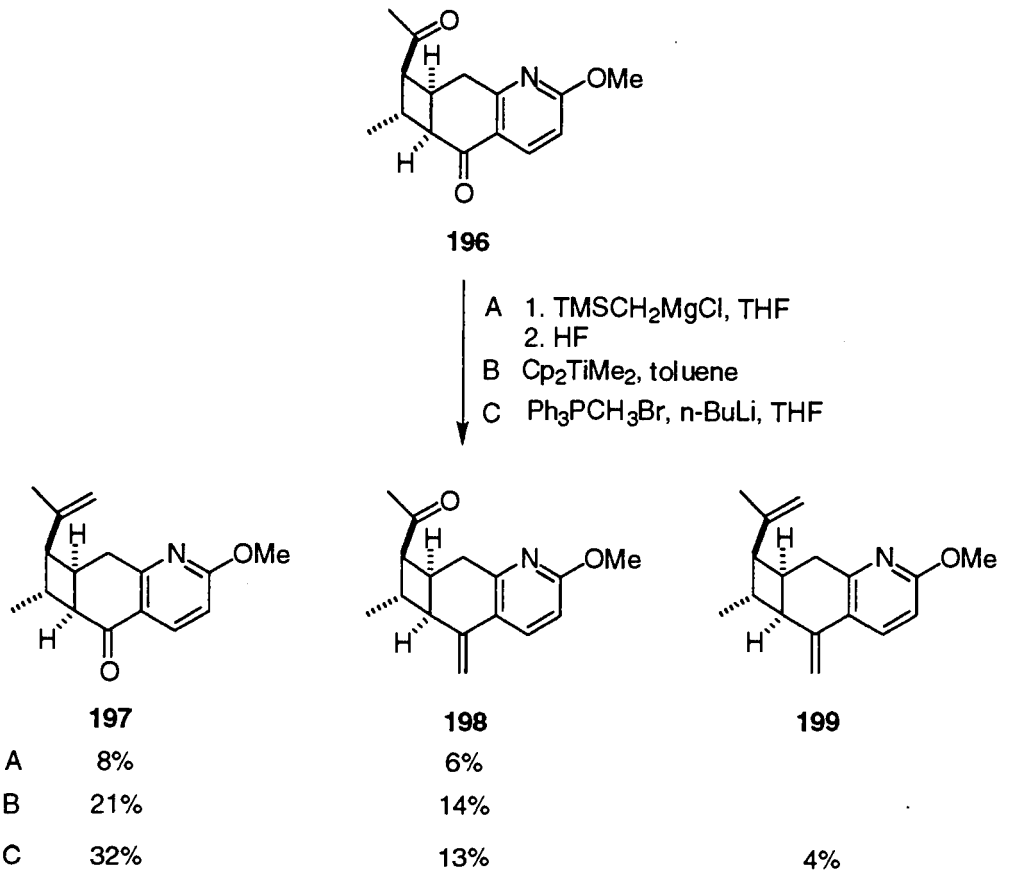
The acquisition of **193** enabled us to proceed to our next goal which was to convert the primary alcohol moiety to an isopropylene group. The latter is a prerequisite for the Cope rearrangement at the center of our plan as shown in **Scheme 21**.



193 **194** **195** **196**

Scheme 61

The alcohol **193** was first oxidized with Dess-Martin periodinane to aldehyde **194** which afforded a diastereomeric mixture of secondary alcohols **195** upon treatment with methylmagnesium bromide. Treatment of this mixture with Dess-Martin periodinane gave diketone **196** (**Scheme 61**).



Scheme 62

Diketone **196** now presented the problem of selective olefination of the methyl ketone while leaving the cyclohexanone intact (**Scheme 62**). Peterson olefination[65] (A) of **196** produced the desired olefin **197** and its regioisomer **198** in only 8% and 6% yield, respectively, and it was assumed that the highly acidic

reaction medium which prevails during the elimination of the intermediate hydroxy silane was the reason for the poor yields. In an attempt to improve the yield and selectivity of methylenation, **196** was treated with Petasis' reagent[66] (B). Although, the yields of **197** and **198** were slightly higher, the ratio of products from this and the Peterson olefination suggested that the two ketones have similar reactivity towards nucleophiles. Nevertheless, an acceptable result was achieved using a Wittig reaction (C) which furnished a 2.5:1 mixture of **197** and **198** along with a small amount of the bismethylenated product **199**. The structure **197** was confirmed by an X-ray crystallographic analysis (**Figure 2.7**).

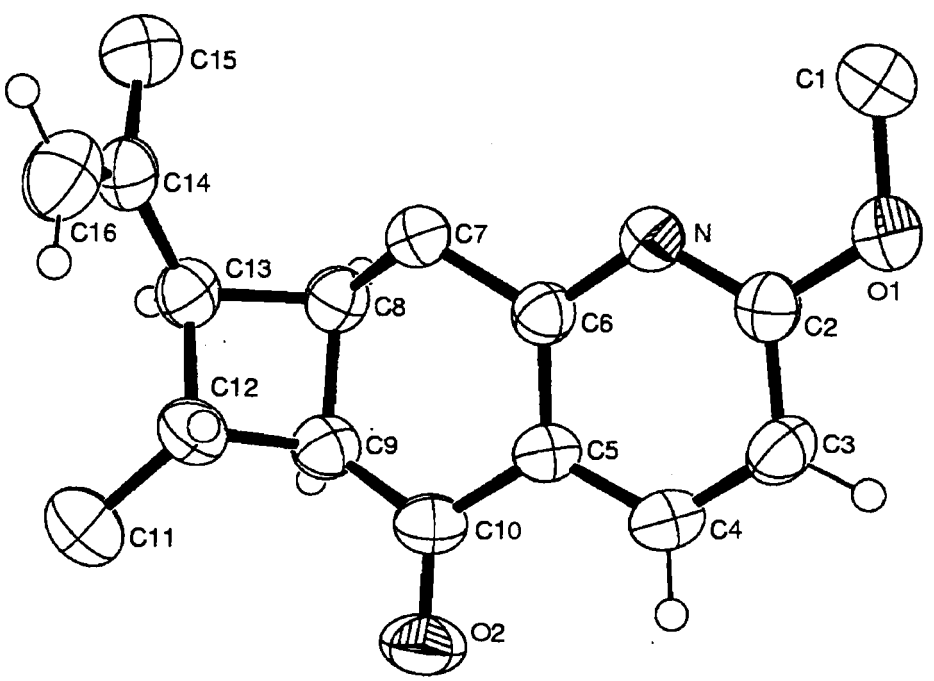
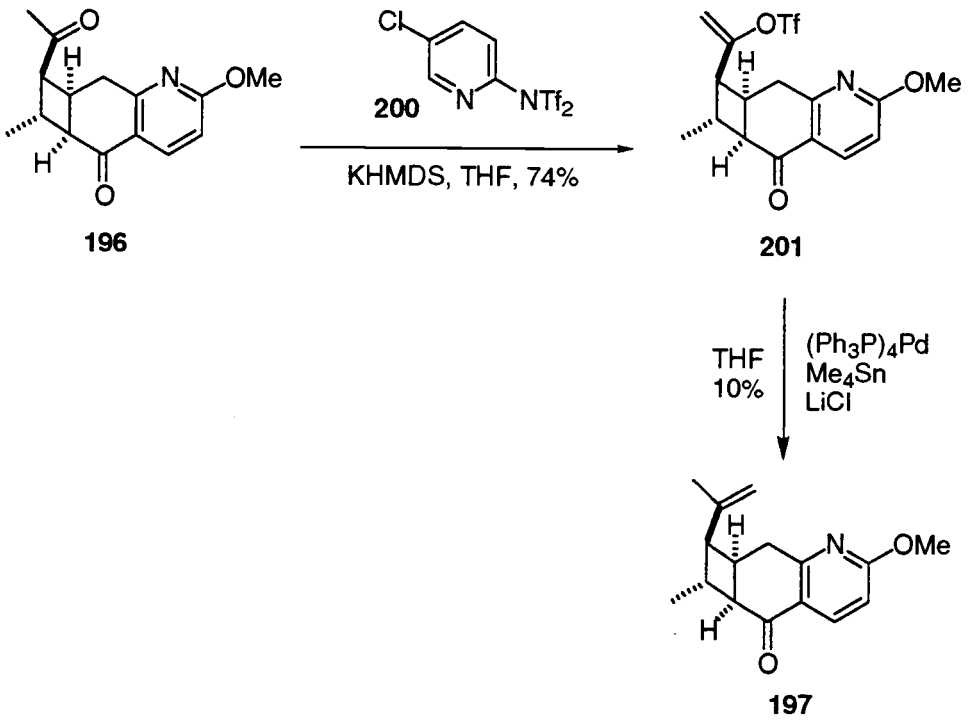


Figure 2.7 ORTEP Representation from X-ray structure of **197**

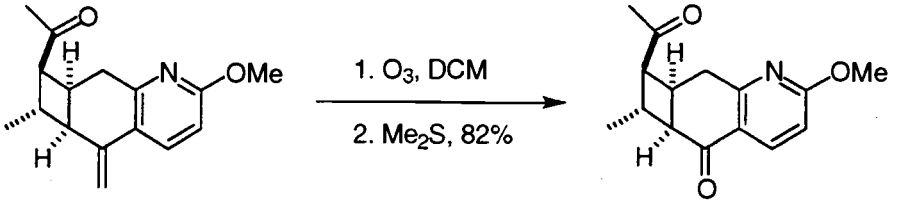
With only modest results from the Wittig reaction of **196**, we decided to search for a more selective method for converting this diketone to **197**. A Stille coupling of the enoltriflate[67] derived from **196** appeared to offer better prospect for selective methylenation of the methyl ketone. Even though diketone **196** has acidic protons at three different positions, we believed that highly regioselective enolate formation would be possible by deprotonation of the methyl group by treatment with a sterically hindered base. The basis for this assumption is that the other two centers at which deprotonation could occur are on the cyclobutane ring and those enolates would suffer from a degree of ring strain which is absent in the enolate from deprotonation of the methyl group.



Scheme 63

In order to test this postulate, **196** was treated with Comins' reagent (**200**)[68] in the presence of potassium bis(trimethylsilyl)amide (KHMDS). As expected, the sole product was an enoltriflate **201** (**Scheme 63**). Unfortunately, the Stille coupling of **201** with tetramethyltin in the presence of palladium catalysts gave only a poor yield of **197**.

With the disappointing outcome from our efforts with the Stille coupling, our attention returned to the Wittig reaction of **196** for the synthesis of the **197**. A small consolation from that approach was that it proved possible to convert the isomer **198** back to the diketone **196** by ozonolysis, so that unwanted material could be recycled (**Scheme 64**).

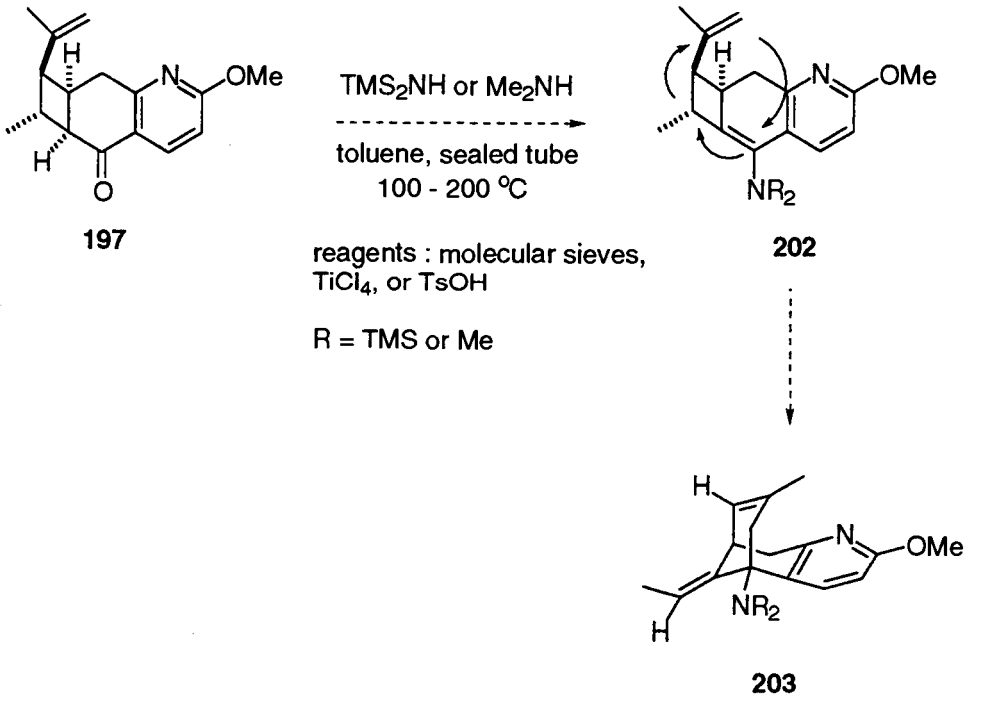


198 **196**

Scheme 64

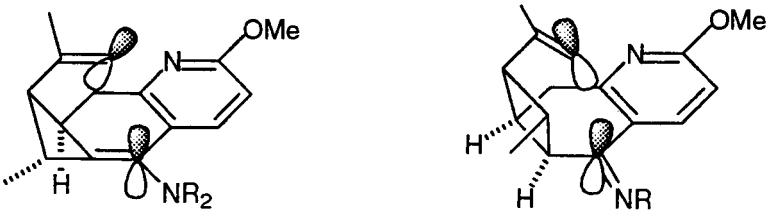
With **197** in hand, it was time to examine the proposed enamine-Cope rearrangement that is pivotal reaction in our route to huperzine A. Since the natural product is a primary amine, conventional enamine formation with **197** would require removal of the substituent on the nitrogen atom after rearrangement. We first decided to explore 1,1,1,3,3,3-hexamethyldisilazane and dimethylamine as secondary amines for the enamine formation, recognizing that the trimethylsilyl group could be removed by treatment with fluoride and the N-

methyl substituent could be cleaved by an oxidative method. However, all attempts to prepare an enamine of **197** with these amines met with failure (**Scheme 65**). For example, no indication of the presence of **202** or **203** was evident in the mixture obtained by heating **197** with these amines in the presence of drying agents such as molecular sieves or titanium(IV) chloride. The use of an acid catalyst, *p*-toluenesulfonic acid, also gave negative results. Thin layer chromatographic analysis of the reaction mixture showed mainly the starting material with a trace of unidentifiable products. NMR analysis of the crude mixture showed no peaks in the region 5.3 - 5.5 ppm where vinyl protons of **203** would be expected to resonate. To our suprise, the cyclobutane ring of ketone **197** was quite stable at temperatures as high as 160 °C; at higher temperatures (>180 °C) decomposition of **197** was observed.



Scheme 65

The foregoing difficulties led us to reevaluate the feasibility of the Cope rearrangement of enamine **202**. Mechanistically, the Cope rearrangement occurs through a six-membered chair- or boat-like transition state in which two π-orbitals can overlap. However, modeling of the enamine structure **202** revealed that the π-orbitals in **202** adopt a perpendicular position to each other due to the rigid cyclobutane ring interposed between the reacting termini (**Figure 2.8**). This could be one of the reasons for the failure of Cope rearrangement, although, another possibility was that the enamine **202** was not formed under the reaction conditions.

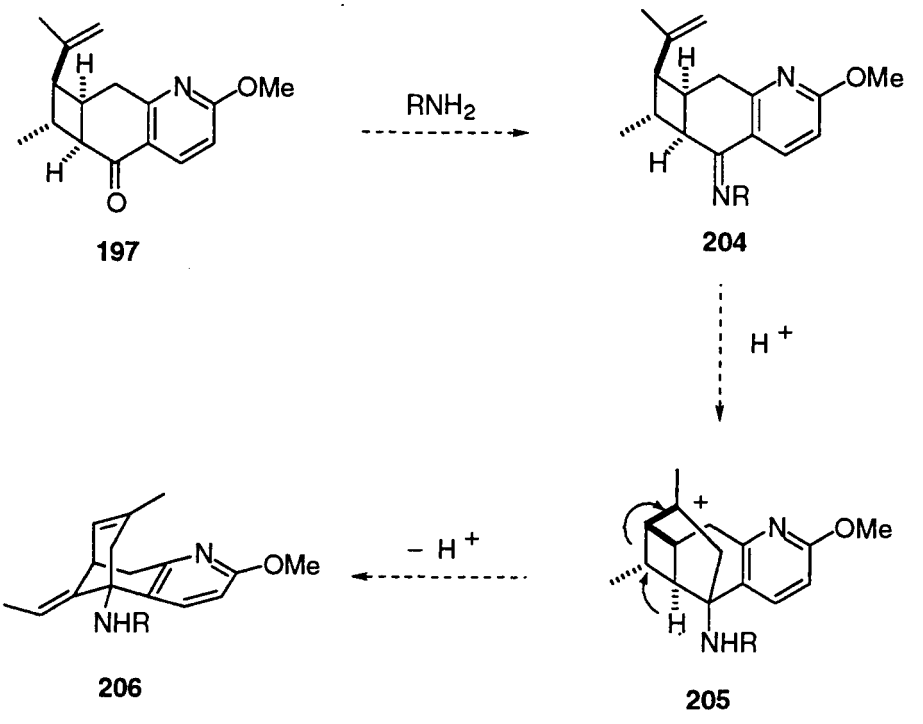


enamine **202** imine **204**

Figure 2.8 Conformation of enamine **202** and imine **204**

A potential solution to the difficulties experienced with preparation of the enamine of **197** is cyclization of the corresponding imine of **197**, a process that can be envisioned under acid catalysts. The attraction of this approach was that the formation of imine **204** from **197** would provide a straightforward way to incorporate the bridgehead amine of huperzine A. In principle, cyclization of imine **204** should be easier than Cope rearrangement of enamine **202** due to better alignment of the two π-orbitals (**Figure 2.8**). A stepwise acid-catalyzed cyclization would proceed via cyclobutyl carbinyl cation **205** (**Scheme 66**).

Opening of the cyclobutane in **205** and loss of a proton would lead directly to the desired bicyclic structure **206**.

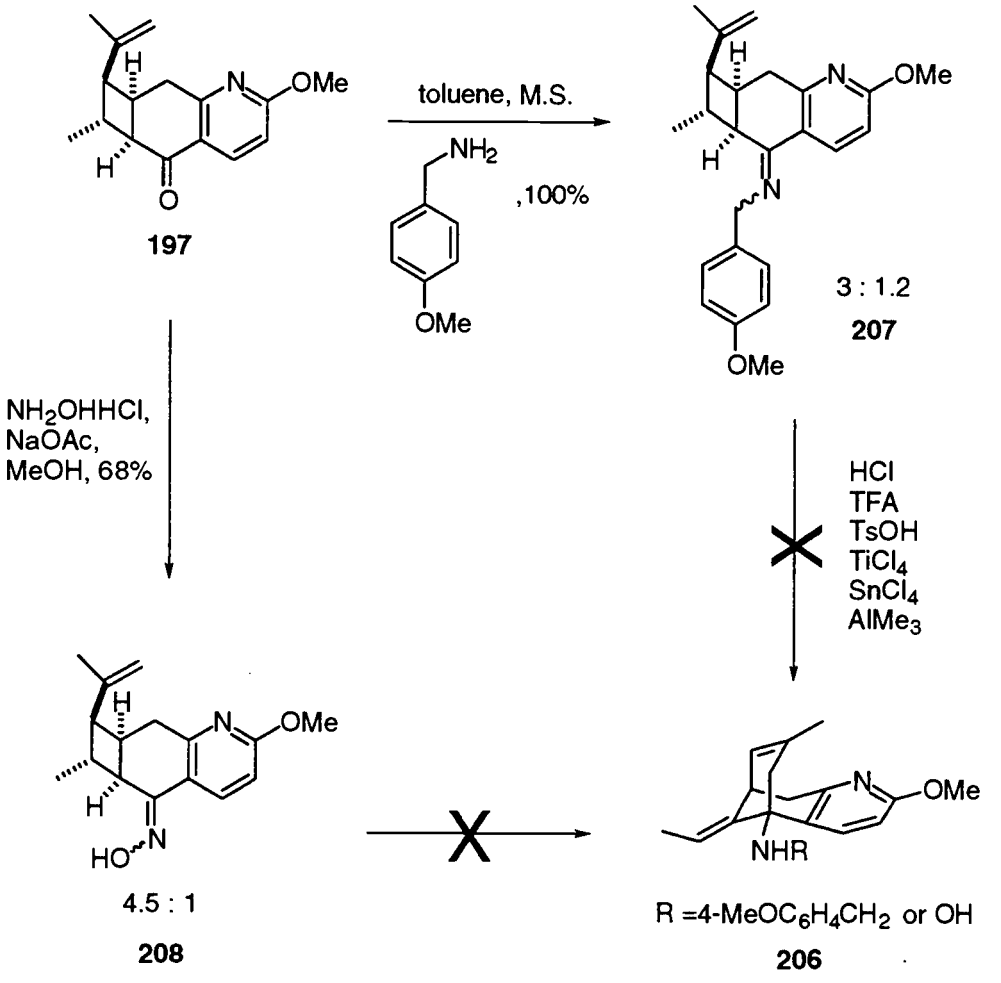


197 **204** **205** **206**

Scheme 66

When ketone **197** was heated with *p*-methoxybenzylamine in toluene in the presence of molecular sieves, a 3:1.2 mixture of syn and anti imines **207** was produced (**Scheme 67**). The oxime derivative **208** was also prepared from **197** using hydroxylamine hydrochloride and sodium acetate in methanol. However, neither **207** nor **208** yielded any cyclization products when reacted with acids such as hydrogen chloride, trifluoroacetic acid, *p*-toluenesulfonic acid, titanium(IV) chloride, tin(IV) chloride, or trimethylaluminum. In most cases, the

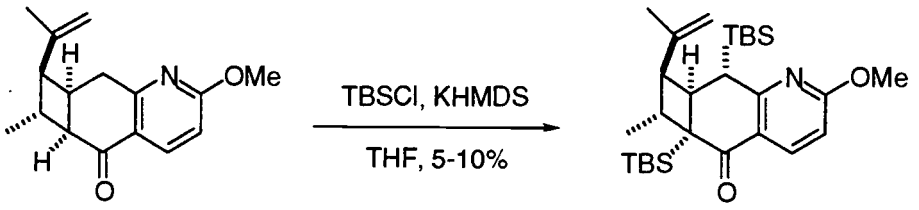
only isolated product was the ketone **197**; heating the reaction mixture above 180 °C caused complete destruction of the starting material.



Scheme 67

Since cyclization of imine **207** was unsuccessful, revisitation of the Cope rearrangement appeared to be the final option. Specifically, we proposed to use the silyl enol ether of ketone **197** as an alternative substrate to enamine **202** to gain access to huperzine A. Although we could not establish that enamine **202** was formed, we believed it likely that the silyl enol ether of **197** could be isolated

and would be available to serve as a Cope rearrangement substrate. In this approach, the rearrangement product would be a silyl ether which would need to be converted to an amine by additional steps. However, all attempts to prepare the silyl enol ether of ketone **197** met with failure. A variety of bases including lithium diisopropylamide, lithium bis(trimethylsilyl)amide (LiHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), potassium hydride, and sodium hydride were used, but all resulted in decomposition of **197**. When **197** was treated with potassium bis(trimethylsilyl)amide (KHMDS) and *tert*-butyldimethylsilyl chloride, the bis C-silylated product **209** was isolated (**Scheme 68**)



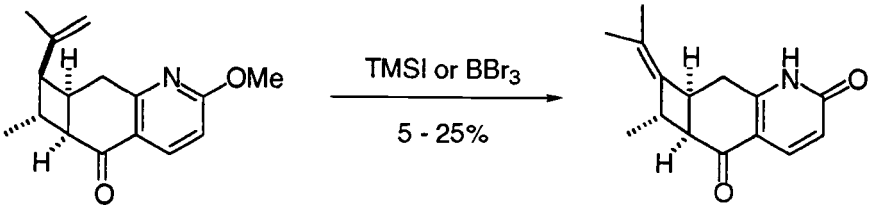
197 **209**

Scheme 68

The structure of **209** was deduced from its IR spectrum and from ^{1}H, ^{13}C, COSY, and HMBC NMR experiments. The proton NMR clearly indicated the presence of two *tert*-butyldimethylsilyl groups in this structure, which ^{13}C and COSY analysis confirmed that the cyclobutane ring and the carbonyl group are still present. HMBC data showed that one of the *tert*-butyldimethylsilyl groups is at the benzylic carbon whereas the other is attached to the carbon α to the ketone in **209**. Silylation at carbon in ketone **197** rather than O-silylation lends

support to the view that formation of the strained enamine **202** is likely to be very difficult.

It was considered possible that the problems associated with approaches to huperzine A from the pyridine **197** could be due to a lack of reactivity of the keto group resulting from conjugation with the methoxy substituent. This led us to modify **197** by replacing the methoxy group of the pyridine moiety by an electron withdrawing functionality which would be expected to increase the electrophilic reactivity of the ketone. Thus, ketone **197** was subjected to demethylation using trimethylsilyl iodide in chloroform in anticipation that an α-pyridone would result (**Scheme 69**). However, the product from this reaction in low yield was **210** in which the isopropylene substituent had isomerized to give a tetrasubstituted double bond. Exposure of **197** to borontribromide gave the same result. This series of failure directed towards conversion of **197** and its derivatives into an immediate precursor of huperzine A effectively terminated our approach along the lines of [3,3] sigmatropic and related processes.

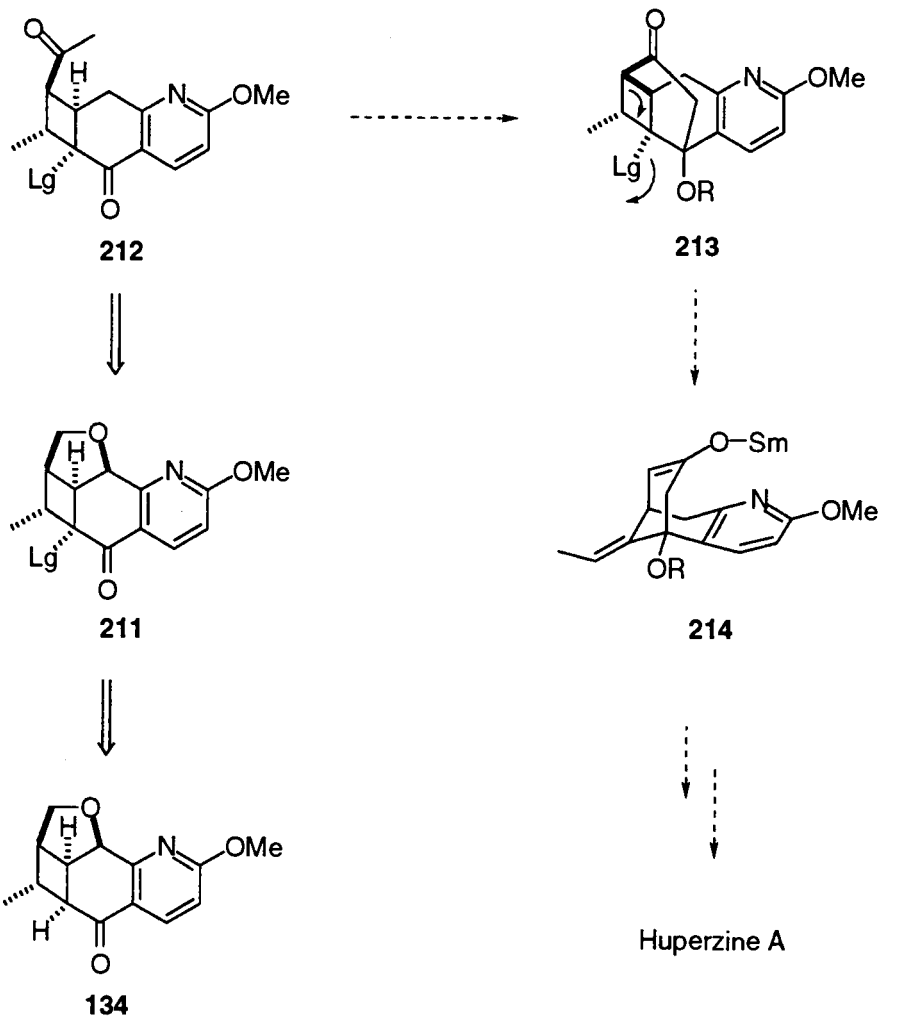


197 **210**

Scheme 69

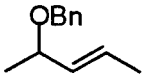
On a more positive note, we were able to develop direct access to the cyclobutane **122** with desired stereochemistry via an intramolecular [2+2] photoaddition of the enantiopure enone **121**. Although our azadiene Diels-Alder approach to the methoxypyridine system was unsuccessful, this objective was achieved by intramolecular Michael addition followed by selenoxide elimination. Unfortunately, the key transformation of ketone **197** into a precursor of huperzine A by means of an sigmatropic rearrangement was thwarted by difficulties which were not anticipated. Although, a negative result has to be viewed with caution, we must conclude that the Cope rearrangement approach is not a practical route to huperzine A.

In light of the difficulties that were encountered with bond formation between the carbonyl carbon and the terminal carbon of the isopropylene group in **197**, it might be fruitful to consider an alternative intramolecular aldol reaction of diketone **212** as a future approach (**Scheme 70**). The diketone **212** bearing a leaving group (Lg) would be synthesized from **134** using chemistry already developed in the course of our research. Intramolecular aldol reaction of **212** would lead to the tricyclic structure **213** which could perhaps undergo reductive cleavage with an electron transfer reagent such as samarium diiodide. This would produce enolate species **214** which in principle would establish a route to huperzine A.

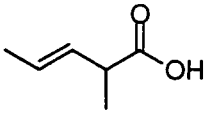


Scheme 70

Experimental Section

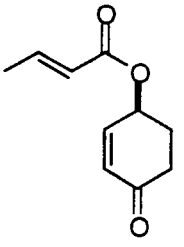


2-Benzyloxy-3-pentene (101). To a solution of the 3-pentene-2-ol (0.084 g, 0.98 mmol) in DMF (1.5 mL) at was added NaH (0.035 g, 1.47 mmol) and benzyl bromide (0.17 mL, 1.47 mmol) at 0 °C. After stirring for 2 h at room temperature, the mixture was diluted with ether (10 mL), washed with brine (5 mL). The phases were separated, and aqueous portion was extracted with ether (10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, using 5% ethyl acetate in hexane as eluent, to give 0.13 g (81%) of **101** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, J = 6 Hz, 3H), 1.74 (dd, J = 2, 6 Hz, 3H), 3.89 (dq, J = 6, 8 Hz, 1H), 4.37 (d, J = 12 Hz, 1H), 4.54 (d, J = 12 Hz, 1H), 5.40 (ddq, J = 2, 8, 15 Hz, 1H), 5.61 (dq, J = 6, 15 Hz, 1H), 7.20-7.42 (m, 5H).



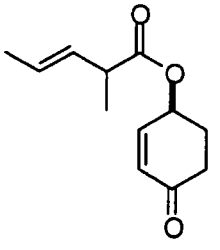
2-Methyl-3-pentenoic acid (115). To a solution of diisopropylamine (0.58 mL, 4.15 mmol) in THF (7 mL) was added n-butyllithium (0.57 M, 2.6 mL, 4.15 mmol)

dropwise at -78 °C, and the mixture was stirred for 20 min at 0 °C. 2-pentenoic acid (0.2 mL, 1.98 mmol) was added, and the mixture was stirred for 30 min at 0 °C. A solution of iodomethane (0.14 mL, 2.18 mmol) in THF (3 mL) was added at -78 °C, and the mixture was allowed to warm to room temperature. After stirring for 30 min, the reaction was quenched with 5% aqueous NaOH (2 mL). After evaporation of THF, the aqueous solution was washed with ether (2 x 5 mL). The aqueous phase was acidified to pH 2 with concentrated hydrochloric acid at 0 °C. The aqueous phase was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the resulting oil was distilled to yield 0.13 g (97%, 1.5 mmHg, 55-59 °C) of 2-methyl-3-pentenoic acid (**115**) as a colorless oil: IR (neat) 3200 (br), 2974, 1710, 1465, 1285 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 7 Hz, 3H), 1.68 (dd, J = 1, 7 Hz, 3H), 3.5 (m, 1H), 5.45 (m, 1H), 5.59 (m, 1H), 11.3-11.5 (bs, 1H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 17.5, 37.5, 126.5, 128.8, 181.5.



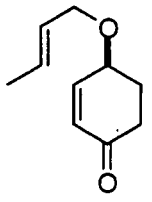
Ester 114. To a solution of AgCN (35 mg, 0.27 mmol) and 4-hydroxy-2-cyclohexen-1-one (30 mg, 0.27 mmol) in benzene (2 mL) at room temperature

was added crotonyl chloride (31 mg, 0.29 mmol). After stirring for 2 h at room temperature, the mixture was heated for 6 h at 80 °C. After cooling to room temperature, the mixture was diluted with ether (20 mL), washed with 10% aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 10% ethyl acetate in hexane as eluent, to give 37 mg (77%) of **114** as a colorless oil: $[\alpha]_D^{23}$ -172.2° (*c* 1.48, $CHCl_3$); IR (neat) 2961, 1718, 1687, 1257, 1175, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.9 (dd, *J* = 1.7, 7.1 Hz, 3H), 2.0-2.2 (m, 1H), 2.3-2.5 (m, 2H), 2.6 (m, 1H), 5.6, (m, 1H), 5.8-5.9 (dq, *J* = 1.7, 15.4 Hz, 1H), 6.0-6.1 (m, 1H), 6.8-6.9 (ddd, *J* = 1.6, 2.7, 10.5 Hz, 1H), 6.9-7.1 (dq, *J* = 7.1, 15.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 28.7, 34.9, 67.3, 122.0, 130.7, 146.0, 147.8, 165.5, 197.9.



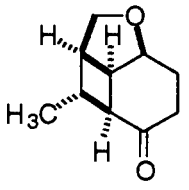
Ester 116. To a solution of 2-methyl-3-pentenoic acid (0.1 g, 0.93 mmol) and 4-hydroxy-2-cyclohexen-1-one (0.1 g, 0.85 mmol) in ether (2 mL) was added sequentially solutions of *N,N'*-dicyclohexylcarbodiimide (0.19 g, 0.93 mmol) and 4-dimethylaminopyridine (0.01 g, 0.09 mmol) at room temperature. After stirring 4 h at room temperature, the *N, N*-dicyclohexyl urea was filtered off and the filtrate was washed with water (3 X 1 mL), aqueous 5% acetic acid (3 x 1 mL) and with water (3 x 1 mL), dried over anhydrous $MgSO_4$. After removal of the solvent, the

residue was chromatographed on silica, using 25% ethyl acetate in hexane as eluent, to give 0.143 g (81%) of **116** as a mixture of two diastereomers: IR (neat) 2934, 1735, 1692, 1246, 1165, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 7 Hz, 3H), 1.69 (dd, *J* = 2, 7 Hz, 3H), 2.09 (m, 1H), 2.35 (m, 1H), 2.47 (m, 1H), 2.60 (m, 2H), 3.48 (m, 1H), 5.40 (m, 1H), 5.58 (m, 2H), 6.05 (m, 1H), 6.83 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 17.5, 28.4, 28.5, 34.8, 37.7, 67.4, 67.5, 126.5, 128.9, 130.7, 130.8, 147.4, 147.5, 174.2, 197.8.

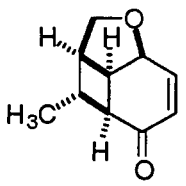


Ether 121. To a solution of 4-hydroxy-2-cyclohexen-1-one (0.33 g, 2.94 mmol) in crotyl bromide (2.5 mL) at 0 °C was added silver(I) oxide (1.7 g, 7.36 mmol) in portions. After stirring for 6 h at room temperature, the excess silver(I) oxide was filtered off. After removal of the excess crotyl bromide under reduced pressure, the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.81 g (59%) of **121** as a colorless oil: $[\alpha]_D^{23}$ -122° (*c* 1.51, $CHCl_3$); IR (neat) 2946, 2851, 1686, 1251, 1094, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (dd, *J* = 1, 6 Hz, 3H), 1.91-2.05 (m, 1H), 2.28-2.40 (m, 2H), 2.53-2.65 (m, 1H), 3.98 (m, 2H), 4.20 (m, 1H), 5.53-5.65 (dtq, *J* = 1, 6, 15 Hz, 1H), 5.67-5.85 (dtq, *J* = 1, 6, 15 Hz, 1H), 5.98 (m, 1H), 6.97(ddd, *J* = 2, 3, 10 Hz, 1H), 5.21 (s, 2H), 5.27 (d, *J* = 13 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 29.1,

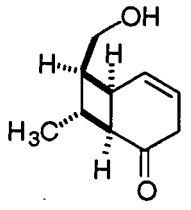
35.2, 69.7, 72.0, 127.0, 129.5, 130.2, 150.7, 198.7; MS(CI) *m/z* 167 (M^++H), 149, 141, 123, 113; HRMS (CI) *m/z* 167.1072 (calcd for $C_{10}H_{15}O_2$: 167.1072).



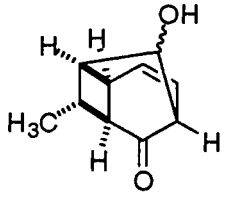
Cycloadduct 122. A photolysis apparatus was charged with dichloromethane (300 mL) and **121** (0.91 g, 5.48 mmol). After bubbling with argon for 2 h, the mixture was irradiated by using Hanovia mercury lamp with a Pyrex filter for 2 h at 0 °C. The solvent was evaporated under reduced pressure the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.52 g (58%) of cycloadduct **122** and 0.16 g of mixture of cycloadducts: $[\alpha]_D^{23}$ +238° (*c* 2.3, $CHCl_3$); IR (neat) 2954, 2925, 2861, 1697, 1175, 1057, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 7 Hz, 3H), 1.91 (dddd, *J* = 2, 4, 14, 14 Hz, 1H), 2.08-2.28 (m, 2H), 2.39-2.50 (m, 2H), 2.58 (m, 1H), 2.85-2.95 (ddd, *J* = 8, 14, 15 Hz, 1H), 3.02 (q, *J* = 8 Hz, 1H), 3.57 (dd, *J* = 4, 9 Hz, 1H), 3.85 (d, *J* = 9 Hz, 1H), 3.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 27.4, 32.7, 37.8, 39.2, 45.4, 47.8, 72.5, 74.0, 211.7; MS(CI) *m/z* 167 (M^++H), 157, 149, 141, 137, 123, 113, 95; HRMS (CI) *m/z* 166.0994(calcd for $C_{10}H_{15}O_2$: 167.0994).



Enone 127. To a solution of **122** (0.02 g, 0.12 mmol) in ethyl acetate (4 mL) was added phenylselenyl chloride (0.035 g, 0.18 mmol). After stirring for 1 h at room temperature, the mixture was washed with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous NaCl (1 mL). After removal of the solvent, the residue dissolved in tetrahydrofuran (4 mL) and water (2 mL) was treated with $NaIO_4$ (77 mg, 0.36 mmol). After stirring for 3 h at room temperature, the mixture was poured into ether (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.016 g (81%) of **127** as a colorless oil: $[\alpha]_D^{23}$ +175° (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2924, 2862, 1668, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 7 Hz, 3H), 2.31 (m, 1H), 2.58 (dd, *J* = 8, 8 Hz, 1H), 2.70 (m, 1H), 3.17 (ddd, *J* = 8, 8, 8 Hz, 1H), 3.59 (dd, *J* = 4, 9 Hz, 1H), 3.80 (d, *J* = 9 Hz, 1H), 4.38 (dd, *J* = 5, 8 Hz, 1H), 6.15 (d, *J* = 10 Hz, 1H) 7.08 (dd, *J* = 5, 10 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 37.4, 39.4, 44.2, 46.0, 70.4, 71.1, 131.6, 144.7, 198.0; MS(CI) *m/z* 165 (M^++H), 147, 139, 135, 111, 95; HRMS (CI) *m/z* 165.0915(calcd for $C_{10}H_{13}O_2$: 167.0916).

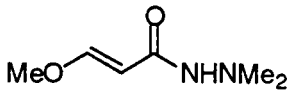


Alcohol 128. To a solution of Zn-Cu dust (0.098 g) in dry ethanol (3 mL) was added a solution of **127** (0.049 g) in dry ethanol (1 mL) under argon atmosphere. The mixture was refluxed for 10 h at 85 °C. The solution was then cooled to room temperature and filtered. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.026 g (52%) of **128** as a colorless oil and 0.011 g (22%) of saturated ketone **122**: IR (neat) 3419(br), 2920, 2862, 1699, 1257, 1020.cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 6.7 Hz, 3H), 2.20-2.43 (m, 2H), 2.64 (m, 1H), 2.81-2.90 (m, 1H), 3.00-3.14 (m, 1H), 3.29-3.38 (m, 1H), 3.65-3.71 (m, 2H), 5.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 36.9, 37.0, 37.4, 47.6, 49.7, 62.8, 124.6, 125.9, 208.2.



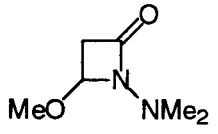
Hydroxy ketone 130. To a solution of **128** (0.014 g, 0.082 mmol) in DCM (3 mL) was added Dess-Martine periodinane(0.052 g, 0.123 mmol). The solution was

stirred for 1.5 h at room temperature. The solution was diluted with ether (5 mL) and aqueous 10% $Na_2S_2O_3$(2 mL) and strred for 20 mim. Then the solution washed with brine (5 mL) and aqueous solution was extracted with ether (2 x 20 mL). The combined organic solution was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.009 g (67%) of **130** as a colorless oil: IR (neat) 3409(br), 2959, 1719, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 7 Hz, 3H), 2.42 (m, 2H), 2.57 (m, 1H), 3.25 (m, 1H), 3.62 (ddd, J = 2, 6, 11 Hz, 1H), 4.04 (m, 1H), 6.19 (m, 1H), 6.32(ddd, J = 2, 6, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 33.8, 38.3, 41.9, 51.3, 58.5, 73.8, 131.6, 132.6, 209.9.

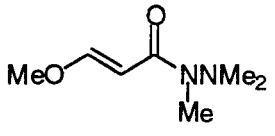


Amide 136. To a solution of dimethylhydrazine (0.3 mL, 4.05 mmol) in dichloromethane (10 mL) at 0 °C was added Me_3Al (2.03 mL, 2 M in hexane, 4.05 mmol) dropwise. After the mixture was stirred for 20 min at room temperature, methyl trans-3-methoxyacrylate (0.2 mL, 1.84 mmol) was added dropwise. The solution was heated at 40 °C for 15 h, cooled, and cautiously quenched with aqueous 0.1 N HCl. The aqueous phase was extracted with dichloromethane (5 x 20 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 10% ethyl acetate in hexane as eluent, to give

0.11 g (42%) of **136** as a colorless oil and 0.027 g (11%) of **137**: IR (neat) 3500 (br), 3194, 2952, 1670, 1616, 1205, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 6H), 2.70 (br s, 1H), 3.68 (s, 1H), 6.04 (d, *J* = 13 Hz, 1H), 7.65 (d, *J* = 13 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.5 (2C), 57.3, 94.0, 162.5, 169.4; MS(CI) *m/z* 145 (M^++H), 113, 102, 85; HRMS (CI) *m/z* 145.0977 (calcd for $C_6H_{13}N_2O_2$: 145.0977).

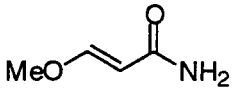


137; IR (neat) 2994, 2950, 1739, 1621, 1435, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 6H), 3.26 (d, *J* = 7 Hz, 2H), 3.68 (s, 3H), 6.59 (dd, *J* = 7, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ38.2, 42.8 (2C), 51.7, 128.8, 171.3



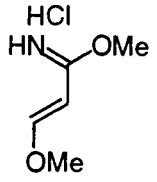
Amide 138. To a solution of KH (0.033 g, 0.82 mmol) in DME (2 mL) at 0 °C was added a solution of **136** (0.059 g, 0.41 mmol) in DME (2 mL). After the mixture was stirred for 30 min at 0 °C, a solution of Me_2SO_4 (0.078 mL, 0.82 mmol) in HMPA (1 mL) was added dropwise. After stirring 30 min at 0 °C, the solution was quenched with water. The aqueous phase was extracted with 1:1 mixture of ether

and hexane (5 x 20 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give 0.049 g (84%) of **138** as a colorless oil: IR (neat) 2941, 1653, 1601, 1229, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 6H), 2.92 (s, 3H), 3.70 (s, 3H), 6.28 (d, *J* = 16 Hz, 1H), 7.59 (d, *J* = 16 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9 (2C), 57.3, 77.1, 95.2, 161.6, 168.9, 169.4; MS(CI) *m/z* 159 (M^++H), 145, 127, 116; HRMS (CI) *m/z* 159.1133 (calcd for $C_7H_{15}N_2O_2$: 159.1133).

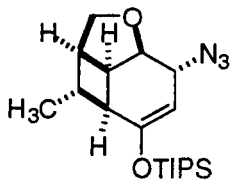


trans-3-Methylacrylamide (139). To a solution NH_3 (0.14 g, 8.23 mmol) in dichloromethane (8 mL) at 0 °C was added Me_3Al (4.12 mL, 2 M in hexane, 8.23 mmol) dropwise. After the mixture was stirred for 20 min at room temperature, methyl trans-3-methoxyacrylate (0.36 mL, 3.29 mmol) was added dropwise. The solution was heated at 40 °C for 20 h, cooled, and cautiously quenched with aqueous 0.1 N HCl. The aqueous phase was extracted with dichloromethane (10 x 10 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 10% ethyl acetate in hexane as eluent, to give 0.31 g (93%) of trans-3-Methylacrylamide (**139**). as a colorless oil:

IR (neat) 3007, 3140, 1664, 1587, 1411, 1222, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 5.14 (d, *J* = 12 Hz, 1H), 5.21-5.48 (br s, 2H), 7.68 (d, *J* = 12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.5, 97.0, 161.8, 168.6; MS(CI) *m/z* 102 (M^++H), 85, 72; HRMS (CI) *m/z* 102.0555 (calcd for $C_4H_8NO_2$: 102.0555).

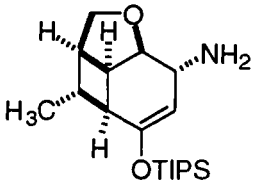


Azadiene 142. To the mixture of the 3-methoxy acrylonitrile (2 mL, 23.9 mmol) and MeOH (0.97 mL, 23.9 mmol) was added dry HCl gas (0.87 g, 23.9 mmol) at 0 °C. The mixture was stoppered and placed in refrigerater for 2 days. The solid was filtered and washed with hexane to give 2.4 g (67%) of **142**: IR (neat) 2864, 1633, 1360, 1252, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.29 (s, 3H), 6.00 (d, *J* = 13 Hz, 1H), 7.88 (d, *J* = 13 Hz, 1H), 10.90 (br s, 1H), 11.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.6, 59.4, 92.2, 167.1, 171.8; MS(CI) *m/z* 116 (M^+-Cl), 102, 85; HRMS (CI) *m/z* 116.0711 (calcd for $C_5H_{10}NO_2$: 116.0712).

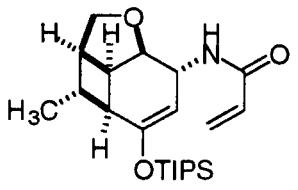


Azide 150. To a solution of **122** (0.2 g, 1.2 mmol) and TIPSCl (0.31 mL, 1.44 mmol) in THF (5 mL) was added slowly KHMDS (2.9 mL, 0.5 mol solution in toluene, 1.44 mmol) at 0 °C and the solution was stirred for 30 min at room temperature. The mixture was diluted with ether (20 mL) and washed with water and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 2% ethyl acetate in hexane as eluent, to give crude silyl enol ether **149**. The silyl enol ether **149** was dissolved in DCM (10 mL) and iodosobenzene (0.32 g, 1.44 mmol) was added to the solution. The mixture was cooled to -19 °C. To a suspension of the mixture was added trimethylsilyl azide (0.38 mL, 2.89 mmol). After stirring 45 min at -19 °C, the suspension became a white solution and allowed to warm to room temperature. The solvent was removed in vacuo, and the resulting residue was filtered and washed with 1:1 mixture of ether (30 mL) and hexane (30 mL). After removal of the solvent, the residue was chromatographed on silica, using 4% ethyl acetate in hexane as eluent, to give 0.32 g (73%) of **150** as a colorless oil: $[\alpha]_D^{23}$ -110.0° (*c* 1.2, $CHCl_3$); IR (neat) 2946, 2866, 2099, 1649, 1377, 1228, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (dd, *J* = 2, 7 Hz, 18H), 1.12-1.28 (m, 3H), 1.22 (d, *J* = 7 Hz, 3H), 1.90 (m, 1H), 2.29 (dd, *J* = 6, 8 Hz, 1H), 2.49 (ddd, *J* = 5, 5, 8 Hz, 1H), 3.08 (ddd, *J* = 6, 8, 8 Hz, 1H), 3.51 (dd, *J* = 5, 9 Hz, 1H), 3.75 (d, *J* = 9 Hz, 1H), 3.79 (dd, *J* = 3, 6 Hz, 1H), 4.20 (dd, *J* = 2, 6 Hz, 1H), 4.83 (d, *J* = 6 Hz, 1H); ^{13}C NMR

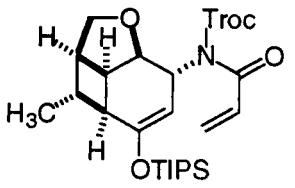
(75 MHz, $CDCl_3$) δ 12.5 (3C), 17.9 (7C), 21.8, 34.5, 38.6, 40.0, 44.4, 58.7, 72.6, 93.9, 157.8; MS(CI) *m/z* 364 (M^++H), 321, 266, 165, 157, 131; HRMS (CI) *m/z* 364.2419 (calcd for $C_{19}H_{34}N_3O_2Si$: 364.2402).



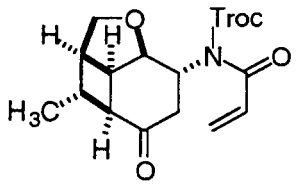
Amine 151. To a solution of **150** (0.1 g, 0.275 mmol) in ether (4 mL) was added LAH (0.015 g, 0.41 mmol) at 0 °C and the solution was stirred for 1 h. The mixture was diluted with ether and quenched with aqueous 15% NaOH (0.027 mL), stirred with $MgSO_4$ (3 g) for 2 h. The mixture was filtered and washed with ethyl acetate. After removal of the solvent, the residue was chromatographed on silica, using 7% methanol in dichloromethane as eluent, to give 0.085 g (89%) of **151** as a colorless oil: $[\alpha]_D^{23}$ +2.1° (*c* 1.9, $CHCl_3$); IR (neat) 3353 (br), 3281 (br), 2943, 2864, 1659, 1462, 1371, 1221, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (dd, *J* = 2, 7 Hz, 18H), 1.10-1.25 (m, 3H), 1.20 (d, *J* = 7 Hz, 3H), 1.65 (br s, 2H), 1.90 (m, 1H), 2.19 (dd, *J* = 6, 9 Hz, 1H), 2.45 (ddd, *J* = 5, 5, 8 Hz, 1H), 3.08 (m, 1H), 3.50 (dd, *J* = 5, 9 Hz, 1H), 3.67 (dd, *J* = 2, 6 Hz, 1H), 3.76 (m, 2H), 4.89 (d, *J* = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 18.0 (6C), 21.9, 33.7, 38.4, 40.0, 44.3, 48.7, 72.6, 80.7, 101.8, 153.3.



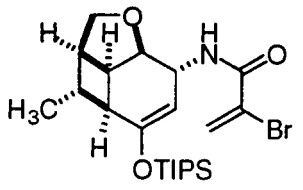
Amide 152. To a solution of a silyl enol ether **150** (0.263 g, 0.742 mmol) in ether (6 mL) at 0 °C was added LAH (0.041 g, 1.09 mmol) and the solution was stirred for 1 h. The mixture was diluted with ether and quenched with 15% aqueous NaOH (0.078 mL), stirred with $MgSO_4$ (2.63 g) for 2 h. The mixture was filtered and washed with ethyl acetate. Evaporation of solvent gave crude amine **151** (0.24 g). To a solution of crude amine and triethyl amine (0.12 mL, 0.87 mmol) in ether (6 mL) at 0 °C was added acrylol chloride (0.076 mL, 0.94 mmol) and the solution was stirred for 1 h. The mixture was diluted with ether (30 mL), washed with 0.1 N HCl and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 5% methanol in dichloromethane as eluent, to give 0.24 g (84%) of **152** as a colorless oil: IR (neat) 3273 (br), 2944, 2865, 1655, 1532, 1223, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (dd, J = 3, 7 Hz, 18H), 1.10-1.23 (m, 3H), 1.20 (d, J = 7 Hz, 3H), 1.92 (m, 1H), 2.20 (dd, J = 6, 9 Hz, 1H), 2.43 (m, 1H), 2.96 (m, 1H), 3.48 (dd, J = 5, 9 Hz, 1H), 3.78 (d, J = 9 Hz, 1H), 3.82 (dd, J = 2, 6 Hz, 1H), 4.79 (d, J = 6 Hz, 1H), 4.90 (m, 1H), 5.15 (m, 1H), 5.62 (dd, J = 1, 10 Hz, 1H), 6.01 (dd, J = 10, 17 Hz, 1H), 6.25 (dd, J = 1, 17 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 17.9 (6C), 21.9, 33.9, 38.2, 39.9, 44.4, 47.2, 72.6, 76.3, 97.3, 126.4, 130.8, 155.7, 164.3; MS(CI) *m/z* 184 (M^+), 167, 155, 151, 123; MS(CI) *m/z* 392 (M^++H), 390, 376, 348, 321, 319, 308, 276, 184; HRMS (CI) *m/z* 392.2622 (calcd for $C_{22}H_{38}NO_3Si$: 392.2621).



Amide 153. LDA was formed by addition of nBuLi (0.022 mL, 0.035 mmol) to a solution of $^{i}Pr_2NH$ (0.005 mL, 0.035 mmol) in THF (1 mL) at -78 °C, and the solution was stirred at -78 °C temperature for 20 min. To a solution of a **152** (0.0115 g, 0.029 mmol) in THF (1 mL) was added LDA solution at -78 °C and the solution was stirred for 15 min, and added TrocCl (0.006 mL, 0.044 mmol). The mixture was diluted with ether (10 mL), washed with water and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 0.0095 g (58%) of **153** as a colorless oil: IR (neat) 2944, 2923, 2864, 1740, 1693, 1666, 1403, 1381, 1276, 1197, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (dd, *J* = 7, 10 Hz, 18H), 1.08-1.18 (m, 3H), 1.20 (d, *J* = 7 Hz, 3H), 1.92 (ddd, *J* = 7, 7, 7 Hz, 1H), 2.35 (dd, *J* = 7, 7 Hz, 1H), 2.43 (m, 1H), 3.25 (ddd, *J* = 8, 8, 8 Hz, 1H), 3.47 (dd, *J* = 5, 9 Hz, 1H), 3.71 (d, *J* = 9 Hz, 1H), 3.82 (d, *J* = 7 Hz, 1H), 4.49 (d, *J* = 6 Hz, 1H), 4.79 (d, *J* = 8 Hz, 1H), 4.87 (d, *J* = 8 Hz, 1H), 5.43 (d, *J* = 6 Hz, 1H), 5.70 (dd, *J* = 1, 10 Hz, 1H), 6.30 (dd, *J* = 1, 17 Hz, 1H), 6.68 (dd, *J* = 10, 17 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 17.9 (6C), 21.8, 36.2, 38.6, 40.4, 45.0, 55.7, 71.9, 75.6, 78.1, 93.8, 94.3, 128.7, 131.7, 152.8, 158.2, 167.8; MS(CI) *m/z* 564 (M^++H), 524, 493, 452, 450, 398, 358, 321; HRMS (CI) *m/z* 564.1508 (calcd for $C_{25}H_{37}Cl_3NO_5Si$: 564.1507).

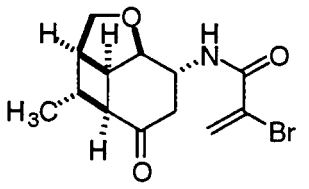


Ketone 154. To a solution of **153** (0.008 g, 0.014 mmol) in DCM (2 mL) was added $BF_3 \bullet OEt_2$ (0.0034 mL, 0.028 mmol) at -78 °C. After stirring for 1 h at -78 °C, the mixture was allowed to warm to room temperature, diluted with ether (10 mL), washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 40% ethyl acetate in hexane as eluent, to give 0.005 g (86%) of **154** as a colorless oil: IR (neat) 2956, 2921, 2862, 1741, 1693, 1402, 1316, 1296, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7 Hz, 3H), 2.15 (ddd, *J* = 7, 7, 7 Hz, 1H), 2.43-2.60 (m, 2H), 2.69 (dd, *J* = 8, 8 Hz, 1H), 2.90 (dd, *J* = 8, 17 Hz, 1H), 3.23 (ddd, *J* = 8, 8, 8 Hz, 1H), 3.50 (dd, *J* = 4, 9 Hz, 1H), 3.80 (d, *J* = 9 Hz, 1H), 3.88 (dd, *J* = 1, 6 Hz, 1H), 4.83 (d, *J* = 12 Hz, 1H), 4.89 (d, *J* = 12 Hz, 1H), 5.28 (ddd, *J* = 2, 4, 8 Hz, 1H), 5.77 (dd, *J* = 1, 10 Hz, 1H), 6.34 (dd, *J* = 1, 17 Hz, 1H), 6.68 (dd, *J* = 10, 17 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 37.2, 37.6, 39.1, 45.1, 46.7, 56.5, 71.9, 75.8, 94.0, 130.0, 131.0, 152.5, 168.5, 207.6; MS(CI) *m/z* 410 (M^++H), 376, 356, 320, 246, 165; HRMS (CI) *m/z* 410.0330 (calcd for $C_{25}H_{37}Cl_3NO_5Si$: 410.0329).

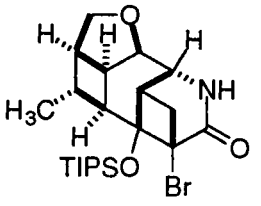


Acrylamide 155. To a solution of azide **150** (0.263 g, 0.742 mmol) in ether (7 mL) at 0 °C was added LAH (0.041 g, 1.09 mmol) and the solution was stirred for 1 h. The mixture was diluted with ether and quenched with 15% aqueous NaOH (0.078 mL), stirred with $MgSO_4$ (2.63 g) for 2 h. The mixture was filtered and washed with ethyl acetate. Evaporation of solvent gave crude amine (0.24 g). The solution of 2-bromoacrylic acid (0.44 g, 2.9 mmol), oxalyl chloride (0.76 mL, 8.69 mmol) and catalytic amounts of DMF in dichloromethane (5 mL) was stirred at room temperature for 12 h .After evaporation of solvent, the acid chloride was added to the solution of crude amine and triethyl amine (0.3 mL, 2.17 mmol) in ether (8 mL) at 0 °C, and the solution was stirred for 1 h. The mixture was diluted with ether (30 mL), washed with aqueous 0.1 N HCl and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 13% ethyl acetate in hexane as eluent, to give 0.2 g (59%) of **155** as a colorless oil: IR (neat) 3325 (br), 2943, 2864, 1657, 1495, 1223, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (dd, J = 3, 7 Hz, 18H), 1.12-1.21 (m, 3H), 1.20 (d, J = 7 Hz, 3H), 1.92 (m, 1H), 2.23 (dd, J = 6, 9 Hz, 1H), 2.47 (ddd, J = 5, 5, 8 Hz, 1H), 2.99 (m, 1H), 3.49 (dd, J = 5, 9 Hz, 1H), 3.78 (d, J = 9 Hz, 1H), 3.82 (dd, J = 2, 6 Hz, 1H), 4.81 (m, 2H), 6.00 (d, J = 1 Hz, 1H), 6.22(br d, J = 6 Hz, 1H), 7.00 (d, J = 1Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (3C), 17.9 (6C), 21.9, 33.9, 38.2, 40.0, 44.4, 48.3, 72.7, 75.9, 97.0, 122.7, 127.5, 156.3, 159.8; MS(CI) *m/z*

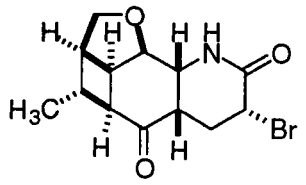
470 (M^++H), 428, 400, 392, 321, 193, 165, 157; HRMS (CI) *m/z* 470.1728 (calcd for $C_{22}H_{37}BrNO_3Si$: 470.1726).



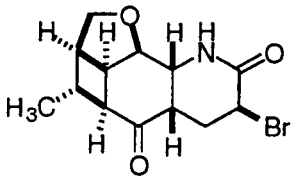
Ketone 156. To a solution of **155** (0.0022 g, 0.0047 mmol) in dichloromethane (2 mL) was added $TiCl_4$ (0.0012 mL, 1 M in dichloromethane, 0.012 mmol) at -78 °C and the solution was stirred for 1 h at -78 °C. The mixture was diluted with ether (10 mL), washed with brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 40% ethyl acetate in hexane as eluent, to give 0.001 g (68%) of **156** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 7 Hz, 3H), 2.23 (m, 1H), 2.40 (m, 1H), 2.59 (m, 1H), 2.68 (m, 1H), 3.13 (m, 1H), 3.20 (dd, *J* = 5, 16 Hz, 1H), 3.62 (dd, *J* = 4, 10 Hz, 1H), 3.93 (d, *J* = 9 Hz, 1H), 4.04 (dd, *J* = 3, 6 Hz, 1H), 4.79 (m, 1H), 6.03 (d, *J* = 2 Hz, 1H), 6.40 (m, 1H), 7.00 (d, *J* = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 37.0, 37.8, 38.3, 44.6, 47.0, 51.0, 72.9, 75.0, 121.9, 128.3, 160.2, 225.8.



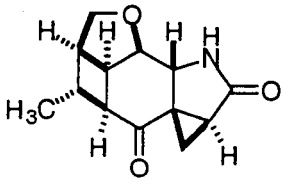
Triisopropylsilyl ether 157. To a solution of **155** (0.01 g. 0.021mmol) in dichloroethane (2 mL) was added Me_3Al (0.027 mL, 2 M in hexane, 0.027 mmol) at room temperature and the solution was stirred at 70 °C for 24 h. The mixture was diluted with ethyl acetate (10 mL), washed with aqueous $NaHCO_3$ (0.5 mL) and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give 0.0076 g (76%) of **157** as a yellow solid: IR (neat) 3296 (br), 2944, 2925, 2866, 1689, 1459, 1195, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.23 (m, 21H), 1.12 (d, *J* = 7 Hz, 3H), 1.79 (dd, *J* = 6, 9 Hz, 1H), 2.19 (m, 1H), 2.20 (ddd, *J* = 5, 5, 8 Hz, 1H), 2.29 (d, *J* = 9 Hz, 1H), 2.85 (m, 1H), 3.00 (dd, *J* = 7, 9 Hz, 1H), 3.10 (ddd, *J* = 1, 5, 7 Hz, 1H), 3.69 (dd, *J* = 5, 9 Hz, 1H), 3.90 (dd, *J* = 6, 6 Hz, 1H), 3.92 (d, *J* = 9 Hz, 1H), 4.09 (m, 1H), 6.11 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (3C), 18.5 (Si-^{i}Pr), 18.6 (Si-^{i}Pr), 22.4, 33.9, 36.2, 36.9, 37.9, 38.4, 41.2, 50.9, 69.0, 75.9, 77.9, 81.4, 172.6; MS(CI) *m/z* 470 (M^++H), 428, 406, 390, 362, 321, 250, 232; HRMS (CI) *m/z* 469.1638 (calcd for $C_{22}H_{36}BrNO_3Si$: 469.1648).



Lactam 166. To a solution of **157** (0.195 g, 0.415 mmol) in $MeNO_2$ (20 mL) was added aqueous HF(48%, 1 mL) at room temperature and the solution was stirred for 2 h. The mixture was diluted with ethyl acetate (50 mL), washed with aqueous $NaHCO_3$ (10 mL) and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 90% ethyl acetate in hexane and 1% methanol in ethyl acetate as eluent, to give 0.083 g (64%) of **166** as a colorless oil and 0.029 g (22%) of **167** as a colorless oil: IR (neat) 3193 (br), 3062 (br), 2950, 2916, 2862, 1676, 942 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, *J* = 7 Hz, 3H), 2.20 (m, 1H), 2.48-2.60 (m, 2H), 2.71 (dd, *J* = 6, 9 Hz, 1H), 2.95 (m, 1H), 3.09 (ddd, *J* = 4, 4, 15 Hz, 1H), 3.38 (m, 1H), 3.66 (dd, *J* = 5, 9 Hz, 1H), 3.87 (dd, *J* = 4, 6 Hz, 1H), 3.95 (d, *J* = 9 Hz, 1H), 4.38 (dd, *J* = 4, 5 Hz, 1H), 4.48 (dd, *J* = 4, 6 Hz, 1H), 6.43 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 31.2, 36.9, 38.6, 39.6, 41.1, 44.2, 45.4, 54.2, 73.8, 76.1, 169.3, 210.6; MS(CI) *m/z* 314 (M^++H), 276, 264, 236, 166; HRMS (CI) *m/z* 314.0392 (calcd for $C_{13}H_{17}BrNO_3$: 314.0392).

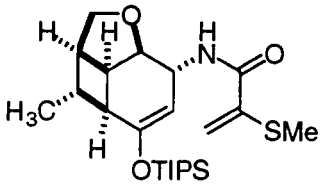


Lactam 167. IR (neat) 3210 (br), 3085 (br), 2953, 2923, 2863, 1681, 1270, 1179, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 7 Hz, 3H), 2.10-2.30 (m, 2H), 2.55 (dd, *J* = 8, 8 Hz, 1H), 2.68(m, 1H), 3.18 (m, 3H), 3.62 (dd, *J* = 4, 10 Hz, 1H), 3.90 (d, *J* = 10 Hz, 1H), 3.91 (m, 1H), 4.47 (dd, *J* = 3, 3 Hz, 1H), 4.53 (dd, *J* = 7, 10 Hz, 1H), 6.53 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 32.6, 37.1, 37.7, 40.8, 41.1, 44.6, 46.7, 56.8 72.7, 75.8, 168.9, 208.5; MS(CI) *m/z* 314 (M^++H), 276, 264, 250, 236, 166; HRMS (CI) *m/z* 314.0390 (calcd for $C_{13}H_{17}BrNO_3$: 314.0392).



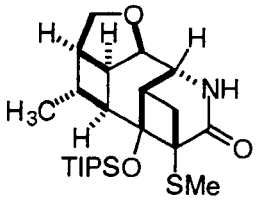
Cyclopropane 169. To a solution of the **166** (0.003 g, 0.01 mmol) in toluene (4 mL) was added DBU (0.0043 mL, 0.029 mmol) at room temperature and the solution was refluxed for 4 h. The mixture was diluted with ether (10 mL), washed with brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 80% ethyl acetate in hexane and 1% methanol in ethyl acetate as eluent, to give 0.001 g (43%) of **169** as a colorless oil: IR

(neat) 2920, 2847, 1699, 1459, 1406, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (dd, *J* = 5, 5 Hz, 1H), 1.25 (d, *J* = 7 Hz, 3H), 1.91 (dd, *J* = 4, 9 Hz, 1H), 2.19 (dd, *J* = 5, 9 Hz, 1H), 2.30 (m, 1H), 2.51 (dd, *J* = 6, 9 Hz, 1H), 3.59 (ddd, *J* = 5, 5, 7 Hz, 1H), 3.48 (m, 1H), 3.57 (dd, *J* = 5, 9 Hz, 1H), 3.78 (d, *J* = 5 Hz, 1H), 3.90 (d, *J* = 9 Hz, 1H), 4.29, (s, 1H), 5.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 21.8, 30.0, 35.5, 36.7, 38.4, 44.9, 45.4, 58.9, 73.3, 77.6, 174.5, 206.1; MS(CI) *m/z* 234 (M^++H), 180, 164; HRMS (CI) *m/z* 234.1125 (calcd for $C_{13}H_{16}NO_3$: 234.1130).



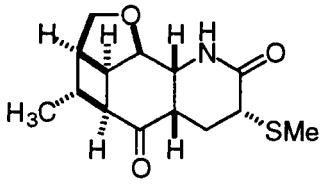
Acrylamide 175. To a solution of **155** (0.119 g, 0.326 mmol) in ether (3 mL) at 0 °C was added LAH (0.019 g, 0.48 mmol) and the solution was stirred for 1 h. The mixture was diluted with ether and quenched with 15% aqueous NaOH (0.070 mL), stirred with $MgSO_4$ (2.63 g) for 2 h. The mixture was filtered and washed with ethyl acetate. Evaporation of solvent gave crude amine (0.11 g). To a solution of the crude amine and 4-dimethylaminopyridine (0.012 g, 0.098 mmol) in dichloromethane (5 mL) was added sequentially solutions of DCC (0.138 g, 0.67 mmol) in dichloromethane (1 mL) and α-methylthioacrylic acid (0.007 g, o.65 mmol) in dichloromethane (1 mL) at room temperature. After stirring 3 h at room temperature, the solvent was removed under reduced pressure and the

residue was filtered and washed with cold ether (20 mL). The filterate was washed with H_2O (5 mL), and the aqueous phase was extracted with ether (4 x 15 mL). The combined organic layers was washed with brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 20% ethyl acetate in hexane as eluent, to give 0.131 g (92%) of **175** as a colorless oil: IR (neat) 3312 (br), 2945, 2923, 2864, 1653, 1489, 1381, 1223, 1196; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (m, 18H), 1.10-1.20 (m, 3H), 1.20 (d, *J* = 7 Hz, 3H), 1.92 (m, 1H), 2.22 (m, 1H), 2 27 (s, 3H), 2.43 (ddd, *J* = 5, 5, 8 Hz, 1H), 2.99 (m, 1H), 3.49 (dd, *J* = 5, 9 Hz, 1H), 3.75 (d, *J* = 9 Hz, 1H), 3.82 (dd, *J* = 2, 6 Hz, 1H), 4.80 (d, *J* = 7 Hz, 1H), 4.87 (ddd, *J* = 3, 7, 7 Hz, 1H), 5.40 (s, 1H), 6.10(br d, *J* = 7 Hz, 1H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (3C), 16.2, 17.9 (6C), 21.9, 33.9, 38.2, 40.0, 44.4, 47.6, 72.6, 76.2, 97.3, 119.5, 140.1, 155.9, 163.1; MS(CI) *m/z* 438 (M^++H), 422, 408, 384, 368, 338, 321, 131; HRMS (CI) *m/z* 438.2479 (calcd for $C_{23}H_{40}NO_3SSi$: 438.2498).



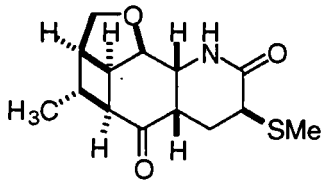
Triisopropylsilyl ether 176. To a solution of **175** (0.38 g. 0.87mmol) in dichloromethane (20 mL) was added Me_3Al (1.3 mL, 2 M in hexane, 2.6 mmol) at room temperature and the solution was stirred at 80 °C for 9 h. The mixture was diluted with ethyl acetate (50 mL), washed with aqueous $NaHCO_3$ (10 mL) and

brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give 0.1 g (32%) of **176** as a yellow solid: IR (neat) 3262 (br), 2946, 2923, 2865, 1676, 1655, 1465, 1192, 1146, 1126. cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* = 7 Hz, 3H), 1.13-1.23 (m, 21H), 1.89 (dd, *J* = 6, 9 Hz, 1H), 2.01 (d, *J* = 9 Hz, 1H), 2.05-2.20 (m, 2H), 2.11 (s, 3H), 2.67 (dd, *J* = 7, 9 Hz, 1H), 2.90 (m, 1H), 2.99 (m, 1H), 3.69 (dd, *J* = 5, 9 Hz, 1H), 3.85 (dd, *J* = 6, 6 Hz, 1H), 3.92 (d, *J* = 9 Hz, 1H), 4.07 (m, 1H), 5.17 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 14.4 (3C), 18.5 (Si-^{i}Pr), 18.6 (Si-^{i}Pr), 22.6, 32.8, 34.3, 36.7, 36.9, 40.0, 41.2, 51.3, 63.6, 75.9, 77.8, 81.0, 175.3; MS(CI) *m/z* 437 (M^+), 422, 394, 368, 321; HRMS (CI) *m/z* 437.2413 (calcd for $C_{23}H_{39}NO_3SSi$: 437.2420).

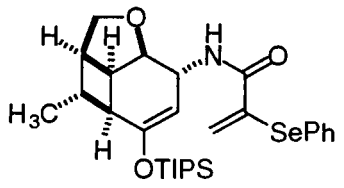


Lactam 178. To a solution of **176** (0.1 g, 0.23 mmol) in $MeNO_2$ (2.7 mL) was added aqueous HF(48%, 0.3 mL) at room temperature and the solution was stirred for 2 h. The mixture was diluted with ethyl acetate (50 mL), washed with aqueous $NaHCO_3$ (10 mL) and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 3% methanol in ethyl acetate as eluent, to give 0.0046 g (71%) of **178** as a colorless oil and 0.013 g (20%) of **177** as a colorless oil: IR (neat) 3164 (br), 3070 (br), 2961, 2901, 2872,

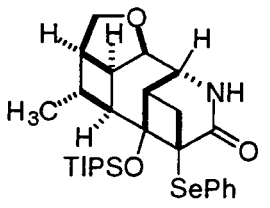
1697, 1693, 1672, 1390, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J* = 7 Hz, 3H), 2.15 (m, 1H), 2.20 (s, 3H), 2.25 (m, 1H), 2.54 (ddd, *J* = 5, 5, 7 Hz, 1H), 2.70 (dd, *J* = 7, 9 Hz, 1H), 2.77 (ddd, *J* = 4, 4, 14 Hz, 1H), 2.89 (m, 1H), 3.30 (m, 1H), 3.32 (dd, *J* = 4, 7 Hz, 1H), 3.62 (dd, *J* = 5, 9 Hz, 1H), 3.89 (dd, *J* = 4, 6 Hz, 1H), 3.90 (d, *J* = 9 Hz, 1H), 4.30 (dd, *J* = 4, 4 Hz, 1H), 6.60 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 21.7, 26.7, 36.7, 38.8, 39.4, 43.8, 44.2, 45.3, 54.3, 73.6, 76.3, 172.1, 210.8; MS(CI) *m/z* 282 (M^++H), 264, 252, 236; HRMS (CI) *m/z* 282.1162 (calcd for $C_{14}H_{20}NO_3S$: 282.1164).



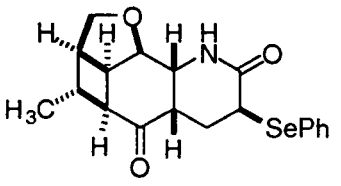
Lactam 177. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7 Hz, 3H), 1.65 (ddd, *J* = 5, 10, 14 Hz, 1H), 2.20 (m, 1H), 2.25 (s, 3H), 2.54 (dd, *J* = 8, 8 Hz, 1H), 2.670 (m, 1H), 2.72 (ddd, *J* = 4, 8, 14 Hz, 1H), 3.17 (m, 2H), 3.40 (dd, *J* = 8, 10 Hz, 1H), 3.62 (dd, *J* = 4, 9 Hz, 1H), 3.83 (dd, *J* = 3, 7 Hz, 1H), 3.90 (d, *J* = 10 Hz, 1H), 4.39 (dd, *J* = 3, 3 Hz, 1H), 6.62 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 21.0, 27.7, 37.1, 37.8, 39.9, 41.9, 44.5, 46.7, 56.3, 72.8, 76.1, 172.0, 196.4.



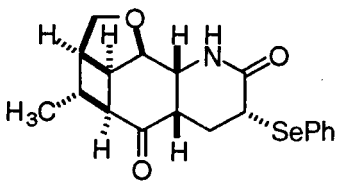
Amide 181. To a solution of **150** (0.029 g, 0.078 mmol) in ether (1 mL) at 0 °C was added LAH (0.005 g, 0.117 mmol) and the solution was stirred for 1 h. The mixture was diluted with ether and quenched with 15% aqueous NaOH (0.017 mL), stirred with $MgSO_4$ (0.5 g) for 2 h. To a solution of the 3,5-dinitrobenzoyl chloride(0.037 g, 0.163 mmol) and Et_3N (0.045 mL, 0.325 mmol) in dichloromethane (1 mL) at room temperature was added a solution of α-phenylselenoacrylic acid (0.037 g, 0.163 mmol) in dichloromethane (1 mL). After stirring 1 h at room temperature, the solution of crude amine and DMAP (0.001 g, 0.008 mmol) in dichloromethane (0.5 mL) was added, and the mixture was stirred for 1 h. After removal of the solvent, the residue was chromatographed on silica, using 15% ethyl acetate in hexane as eluent, to give 0.03 g (69%) of **181** as a colorless oil: $[\alpha]_D^{23}$ -0.47° (*c* 1.5, $CHCl_3$); IR (neat) 3395 (br), 2944, 2864, 1655, 1649, 1491, 1477, 1223, 1196; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.15 (m, 21H), 1.17 (d, *J* = 7 Hz, 3H), 1.85 (m, 1H), 2.02 (dd, *J* = 6, 8 Hz, 1H), 2 29-2.40 (m, 2H), 3.40 (dd, *J* = 4, 9 Hz, 1H), 3.58 (dd, *J* = 2, 6 Hz, 1H), 3.70 (d, *J* = 9 Hz, 1H), 4.67 (d, *J* = 7 Hz, 1H), 4.73 (ddd, *J* = 3, 7, 7 Hz, 1H), 6.10 (s, 1H), 6.40 (br d, *J* = 7 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 18.0 (6C), 22.0, 33.6, 38.2, 39.9, 44.3, 48.0, 72.6, 75.9, 97.3, 127.5, 129.5, 131.1, 131.3, 133.1, 133.2, 156.0, 162.8; MS(CI) *m/z* 547 (M^+), 478, 432, 392, 350, 321, 236, 159; HRMS (CI) *m/z* 547.2023 (calcd for $C_{28}H_{41}NO_3Si^{78}Se$: 547.2021).



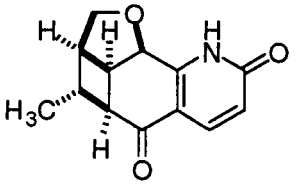
Triisopropylsilyl ether 182. To a solution of **181** (0.15 g. 0.275 mmol) in dichloromethane (10 mL) was added Me_3Al (0.42 mL, 2 M in hexane, 0.824 mmol) at room temperature and the solution was stirred at 80 °C for 38 h. The mixture was diluted with dichloromethane (30 mL) and saturated aqueous K-F tartrate (30 mL) and the mixture was vigously stirred for 15 min. The aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic solution was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 90% ethyl acetate in hexane as eluent, to give 0.104 g (69%) of **182** as a white solid: $[\alpha]_D^{23}$ -8.3° (*c* 1.8, $CHCl_3$); IR (neat) 3237 (br), 3067 (br), 2955, 2862, 1677, 1470, 1201, 1147, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, *J* = 7 Hz, 3H), 1.13-1.31 (m, 21H), 1.79 (dd, *J* = 7, 9 Hz, 1H), 2.02-2.20 (m, 3H), 2.84 (m, 1H), 3.02 (m, 1H), 3.69 (dd, *J* = 5, 9 Hz, 1H), 3.84 (dd, *J* = 5, 5 Hz, 1H), 3.94 (d, *J* = 9 Hz, 1H), 4.02 (dd, *J* = 4, 4 Hz, 1H), 5.80 (br s, 1H), 7.18 (m, 3H), 7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (3C), 18.7 (Si-^{i}Pr), 18.8 (Si-^{i}Pr), 22.5, 34.1, 35.2, 36.7, 38.1, 39.6, 41.2, 51.4, 64.9, 76.0, 78.1, 82.5, 127.3, 127.9, 128.4, 135.4, 175.4; MS(CI) *m/z* 547 (M^+), 478, 432, 390, 322, 276, 251; HRMS (CI) *m/z* 547.2025 (calcd for $C_{28}H_{41}NO_3Si^{80}Se$: 547.2021).



Ketone 183. To a solution of **182** (0.014 g, 0.026 mmol) in $MeNO_2$ (1.9 mL) was added aqueous HF (48%, 0.1 mL) at room temperature and the solution was stirred for 2 h. The mixture was diluted with ethyl acetate (20 mL), washed with aqueous $NaHCO_3$ (5 mL) and brine, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 90% ethyl acetate in hexane as eluent, to give 0.004 g (40%) of **183** as a colorless oil and 0.005 g (50%) of **184** as a colorless oil: IR (neat) 3184 (br), 3070 (br), 2951, 2934, 2859, 1693, 1660, 1475, 1395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7 Hz, 3H), 1.80 (ddd, *J* = 5, 11, 14 Hz, 1H), 2.19 (m, 1H), 2.50 (dd, *J* = 8, 8 Hz, 1H), 2.62 (ddd, *J* = 4, 6, 7 Hz, 1H), 2.83 (ddd, *J* = 3, 8, 14 Hz, 1H), 3.01 (dd, *J* = 4, 7 Hz, 1H), 3.10 (ddd, *J* = 7, 7, 8 Hz, 1H), 3.58 (dd, *J* = 4, 10 Hz, 1H), 3.82 (dd, *J* = 3, 7 Hz, 1H), 3.84 (d, *J* = 10 Hz, 1H), 4.01 (dd, *J* = 8, 11 Hz, 1H), 4.08 (dd, *J* = 3, 3 Hz, 1H), 7.02 (s, 1H), 7.32 (m, 3H), 7.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 28.8, 37.1, 37.7, 37.8, 40.3, 44.6, 46.9, 56.6, 72.8, 76.0, 127.6, 128.4, 129.1, 135.4, 172.1, 209.0; MS(CI) *m/z* 390 (M^++H), 310, 264, 236, 217, 159; HRMS (CI) *m/z* 390.0766 (calcd for $C_{19}H_{22}NO_3{}^{78}Se$: 390.0773).

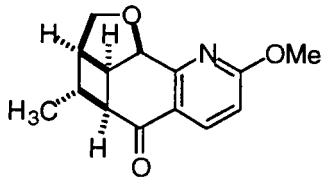


Ketone 183. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24(d, *J* = 7 Hz, 3H), 2.12-2.30 (m, 2H), 2.57 (m, 1H), 2.68 (dd, *J* = 8, 8 Hz, 1H), 2.79 (ddd, *J* = 5, 5, 15 Hz, 1H), 2.94 (ddd, *J* = 5, 5, 5 Hz, 1H), 3.30 (ddd, *J* = 7, 7, 7 Hz, 1H), 3.60 (dd, *J* = 5, 9 Hz, 1H), 3.84 (dd, *J* = 4, 6 Hz, 1H), 3.89 (d, *J* = 9 Hz, 1H), 3.99 (dd, *J* = 5, 7 Hz, 1H), 4.30 (dd, *J* = 4, 4 Hz, 1H), 6.78 (br s, 1H), 7.29 (m, 3H), 7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 28.2, 37.2, 39.0, 39.6, 40.1, 44.5, 45.6, 55.0, 73.5, 76.4, 128.1, 129.0, 129.9, 134.9, 172.9, 210.9.



Pyridone 187. To a solution of **182** (0.02 g, 0.037 mmol) in $MeNO_2$ (10 mL) at room temperature was added aqueous HF (4.8%, 0.06 mL, 0.15 mmol) dropwise. After stirring for 1.5 h at room temperature, the solvent was removed under reduced pressure. To a solution of the residue in MeOH (5 mL) and H_2O (1,3 mL) was added $NaIO_4$ (0.0235 g, 0.11 mmol) in H_2O (0.2 mL). After stirring 15 h at room temperature, the solvent was removed under reduced pressure and the residue was diluted with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (2

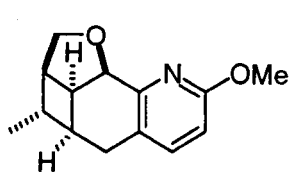
ml) and brine(5 mL). The combined aqueous layers was extracted with $CHCl_3$ (4 x 20 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 2% methanol in ethyl acetate as eluent, to give 0.007 g (83%) of **187** as white solid: mp 197-199 °C; $[\alpha]_D^{23}$ -114.8° (*c* 1.0, $CHCl_3$); IR (neat) 2958, 1655, 1638, 1408, 1285, 1248; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7 Hz, 3H), 1.35 (m, 1H), 2.75 (dd, *J* = 8, 8 Hz, 1H), 2.80 (m, 1H), 3.37 (ddd, *J* = 8, 8, 8 Hz, 1H), 3.57(dd, *J* = 4, 9 Hz, 1H), 3.89 (d, *J* = 9 Hz, 1H), 4.77 (d, *J* = 8 Hz, 1H), 6.60 (d, *J* = 10 Hz, 1H), 8.05 (d, *J* = 10 Hz, 1H), 12.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 37.5, 39.3, 43.3, 46.0, 72.1, 72.2, 114.2, 120.9, 138.6, 151.2, 165.2, 193.1; MS(CI) *m/z* 232 (M^++H), 223, 203, 189, 174, 149, 131, 121; HRMS (CI) *m/z* 232.0974 (calcd for $C_{13}H_{14}NO_3$: 232.0974).



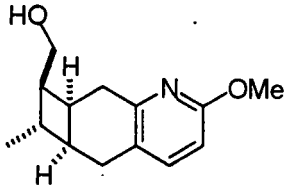
Methoxypyridine 134. To a solution of the **187** (0.029 g, 0.126 mmol) in $CHCl_3$ (2 mL) at room temperature was added Ag_2CO_3 (0.173 g, 0.628 mmol) and methyliodide (0.47 mL, 7.53 mmol) and the mixture was stirred for 40 h at room temperature. The mixture was filtered through a pad of Celite and washed with ether (10 ml). The solvent was removed under reduced pressure and the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.028 g (91%) of **134** as a white solid: mp 100-102 °C; $[\alpha]_D^{23}$ -3.8° (*c* 2.0,

$CHCl_3$); IR (neat) 2949, 2920, 2857, 1671, 1594, 1484, 1324, 1269 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, d, *J* = 7 Hz), 2.34 (1H, m), 2.73 (1H, dd, *J* = 8, 8 Hz), 2.78 (1H, ddd, *J* = 4, 6, 7 Hz), 3.32 (1H, dd, *J* = 8, 8, 8 Hz), 3.68 (1H, dd, *J* = 4, 9 Hz), 3.85 (1H, d, *J* = 9 Hz), 4.05 (3H, s), 4.79 (1H, d, *J* = 7 Hz), 6.80 (1H, d, *J* = 9 Hz), 8.20 (1H, d, *J* = 9 Hz); 13C NMR (75 MHz, CDCl3) δ 21.5, 37.2, 39.0, 43.9, 46.1, 54.2, 71.9, 77.1, 112.4, 122.8, 137.9, 159.0, 166.6, 196.7; MS(CI) *m/z* 246 (M^++H), 216, 192, 175; HRMS (CI) *m/z* 246.11273 (calcd for $C_{14}H_{16}NO_3$: 246.11320).

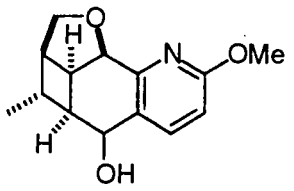
Hydrogenolysis of 134. To a solution of the**134** (0.020 g, 0.082 mmol) in EtOH (2 mL) at room temperature was added 10% palladium-on-charcoal (0.020 g), and the suspension was stirred under hydrogen at one atmosphere for 8 h. The mixture was filtered through a pad of Celite, and washed with ether (20 mL). The solvent was removed under reduced pressure and the residue was chromatographed on silica, using 8% ethyl acetate in hexane as eluent, to give 0.006 g of **134**, 0.003 g (16%, 23% based of recovered aa) of **188**, 0.004g (21%, 30% based of recovered aa) of **189**, and 0.003 g (15%, 21% based on recovered aa) of **190**.



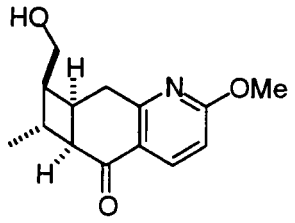
188: IR (neat) 2944, 2915, 1606, 1484, 1313, 1259, 1035 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, d, *J* = 7 Hz), 1.88 (1H, m), 2.10 (1H, m), 2.59 (1H, m), 2.65 (1H, dd, *J* = 5, 16 Hz), 2.90 (1H, dd, *J* = 9, 16 Hz), 3.03 (1H, ddd, *J* = 7, 7, 7 Hz), 3.75 (1H, dd, *J* = 5, 9 Hz), 3.90 (1H, d, *J* = 9 Hz), 3.97 (3H, s), 4.77 (1H, d, *J* = 6 Hz), 6.63 (1H, d, *J* = 8 Hz), 7.30 (1H, d, *J* = 8 Hz); MS(CI) *m/z* 232 (M^++H), 214, 202, 159, 130; HRMS (CI) *m/z* 232.13362 (calcd for $C_{14}H_{18}NO_2$: 232.13375).



189: IR (neat) 3350 (br), 2936, 2915, 1595, 1583, 1473, 1422, 1301, 1031 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 7 Hz), 1.40 (1H, m), 2.20 (1H, ddd, *J* = 7, 9, 17 Hz), 2.35 (1H, m), 2.49 (1H, dd, *J* = 3, 15 Hz), 2.70 (2H, m), 2.86 (1H, dd, *J* = 3, 3 Hz), 2.90 (1H, dd, *J* = 3, 3 Hz), 3.39 (1H, dd, *J* = 7, 11 Hz), 3.50 (1H, dd, *J* = 9, 9 Hz), 3.94 (3H, s), 6.53 (1H, d, *J* = 8 Hz), 7.26 (1H, d, *J* = 8 Hz); MS(CI) *m/z* 234 (M^++H), 216, 202, 161, 146, 128; HRMS(CI) *m/z* 234.14927 (calcd for $C_{14}H_{20}NO_2$: 234.14940).

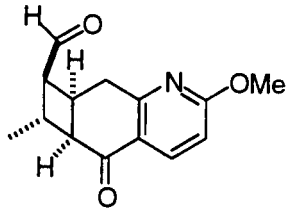


190: IR (neat) 3409 (br), 2940, 2916, 2847, 1606, 1489, 1332, 1313, 1259, 1029 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, d, *J* = 7 Hz), 2.30 (1H, m), 2.55 (2H, m), 2.86 (1H, m), 3.20 (1H, ddd, *J* = 7, 7, 9 Hz), 3.80 (1H, dd, *J* = 5, 9 Hz), 3.98 (3H, s), 4.06 (1H, d, *J* = 9 Hz), 4.69 (1H, d, *J* = 6 Hz), 4.76 (1H, dd, *J* = 8, 11 Hz), 6.73 (1H, d, *J* = 8 Hz), 7.64 (1H, d, *J* = 8 Hz); MS(CI) *m/z* 248 (M^++H), 230, 216, 202, 186, 176, 159, 130; HRMS(CI) *m/z* 248.12893 (calcd for $C_{14}H_{18}NO_3$: 248.12867).



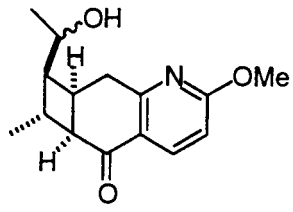
Alcohol 193. To a solution of the **134** (0.020 g, 0.082 mmol) in MeOH (20 mL, 0.2 M solution of NaOH) at room temperature was added activated Zn (0.54 g, 8.2 mmol) and the suspension was stirred 2 h at 90 °C. Additional 0.54 g of activated Zn was added to the mixture. After stirring 4 h at 90 °C, the mixture was cooled down to the room temperature and neuturalrized with 1N HCl in MeOH (4 mL) and dried over $MgSO_4$. After filteration through a pad of Celite, the solvent was removed under reduced pressure and the residue was chromatographed on silica, using 40% ethyl acetate in hexane as eluent, to give 0.019 g (94%) of **193** as a white solid: mp 107-110 °C; IR (neat) 3394 (br), 2916, 2853, 1668, 1625, 1589, 1328 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6 Hz), 2.35 (2H,

m), 2.75 (1H, dd, J = 8, 8 Hz), 3.10 (3H, m), 3.67 (1H, dd, J = 6, 11 Hz), 3.73 (1H, dd, J = 8, 11 Hz), 4.00 (3H, s), 6.74 (1H, d, J = 9 Hz), 8.07 (1H, d, J = 9 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 21, 29, 38(2C), 45, 47, 54, 62, 110, 123, 138, 162, 166, 198; MS(CI) *m/z* 248 (M^++H), 230, 204, 190; HRMS(CI) *m/z* 248.12842 (calcd for $C_{14}H_{18}NO_3$: 248.12867).



Aldehyde 194. To a solution of the **193** (0.013 g, 0.053 mmol) in CH_2Cl_2 (3 mL) at room temperature was added Dess-Martin periodinane (0.038 g, 0.11 mmol). After stirring 1 h at room temperature, the mixture was diluted with ether (5 mL) and 10% aqueous $Na_2S_2O_3$ (2 mL) and stirred for 20 min. The aqueous phase was separated and extracted with ether (10 mL), and the combined organic solvents was diluted with saturated aqueous $NaHCO_3$ (5 mL), and stirred for 20 min. The organic layer was wahed with water (3 mL) and brine (3 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.012 g (93%) of **194** as a colorless oil: IR (neat) 2955, 2925, 1710, 1666, 1590, 1572, 1409, 1321, 1262 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 6 Hz), 2.80 (1H, dd, J = 8, 8 Hz), 3.02 (4H, m), 3.45 (1H, m), 3.98 (3H, s), 6.67 (1H, d, J = 9 Hz), 8.09 (1H, d, J = 9 Hz), 9.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21,

30, 31, 35, 46, 54(2C), 110, 123, 138, 161, 166, 197, 202; MS(CI) *m/z* 246 (M^++H), 217, 202, 160; HRMS(CI) *m/z* 246.11260 (calcd for $C_{14}H_{16}NO_3$: 246.11302).

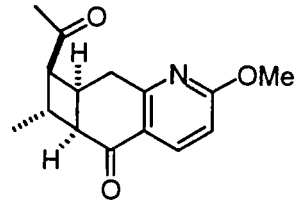


Alcohol 195. To a solution of the **194** (0.025 g, 0.10 mmol) in CH_2Cl_2 (4 mL) at –78 °C was added MeMgI (0.1 mL, 0.15 mmol) dropwise. After stirring 1 h at –78 °C, the reaction was quenched with water, and the mixture was allowed to warm to room temperature. The mixture was diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), and brine (3 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.009 g (40%) of **195** and 0.008 g (36%) of diastereomer of **195** as colorless oil.

195: IR (neat) 3408, 2959, 2891, 1650, 1586, 1322, 1269, 1020 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6 Hz), 1.10 (3H, d, *J* = 7 Hz), 1.60 (1H, s), 2.05 (1H, dd, *J* = 9, 18 Hz), 2.25 (1H, m), 2.70 (1H, dd, *J* = 9, 9 Hz), 3.10 (2H, m), 3.25 (1H, dd, *J* = 11, 20 Hz), 3.87 (1H, m), 3.99 (3H, s), 6.68 (1H, d, *J* = 9 Hz), 8.07 (1H, d, *J* = 9 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 20.9, 21.8, 29.5(2C), 37.6, 46.2, 51.1, 53.9, 67.6, 109.7, 123.0, 130.9, 137.5, 163.0, 166.3, 198.0;

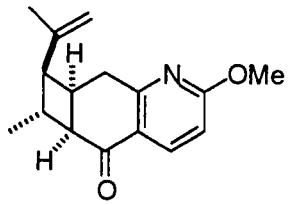
MS(CI) *m/z* 262 (M^++H), 244, 228, 175, 146; HRMS(CI) *m/z* 262.14438 (calcd for $C_{15}H_{20}NO_3$: 262.14432).

diastereomer of 195: IR (neat) 3457 (br), 2954, 2920 ,1669, 1591, 1484, 1415, 1318, 1269 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 6 Hz), 1.39 (3H, d, *J* = 7 Hz), 1.59 (1H, s), 2.03 (1H, m), 2.65 (2H, m), 2.95 (2H, m), 3.13 (1H, dd, *J* = 11, 20 Hz), 4.00 (1H, m), 4.01 (3H, s), 6.64 (1H, d, *J* = 8 Hz), 8.06 (1H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 21.6, 22.8, 29.6, 30.1, 38.9, 46.4, 51.0, 53.9, 68.6, 109.8, 124.3, 137.5, 164.7, 166.7, 197.7; MS(CI) *m/z* 262 (M^++H), 244, 228, 204, 175, 146; HRMS(CI) *m/z* 262.14389 (calcd for $C_{15}H_{20}NO_3$: 262.14432).



Diketone 196. To a solution of the **195** (0.024 g, 0.092 mmol) in CH_2Cl_2 (3 mL) at room temperature was added Dess-Martin periodinane (0.067 g, 0.184 mmol). After stirring 2 h at room temperature, the mixture was diluted with ether (30 mL) and 10% aqueous $Na_2S_2O_3$ (5 mL) and stirred for 10 min. The aqueous phase was separated and extracted with ether (10 mL), and the combined organic solvents was diluted with saturated aqueous $NaHCO_3$ (5 mL), and stirred for 10 min. The organic layer was washed with water (5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was

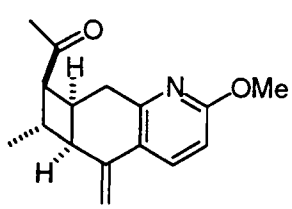
chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 0.022 g (92%) of **196** as a colorless oil: IR (neat) 2944, 2925, 1704, 1674, 1630, 1591, 1567, 1415, 1327, 1264 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, d, *J* = 6 Hz), 2.15 (3H, s), 2.70 (1H, dd, *J* = 8, 8 Hz), 2.90 (1H, dd, *J* = 10, 17 Hz), 3.01 (3H, m), 3.31 (1H, m), 3.97 (3H, s), 6.65 (1H, d, *J* = 9 Hz), 8.07 (1H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 20.3, 29.1, 30.1, 32.0, 35.0, 45.1, 53.9, 54.8, 110.1, 122.8, 137.4, 161.8, 166.3, 196.7, 207.1; MS(CI) *m/z* 260 (M^++H), 216, 204, 175, 146, ; HRMS(CI) *m/z* 260.12872 (calcd for $C_{15}H_{18}NO_3$: 260.12867).



Ketone 197. To a suspension of dry (120 °C, 1 mmHg, 18 h) methyltriphenylphosphonium bromide (0.521 g, 1.46 mmol) in THF (10 mL) under argon atmosphere at 0 °C was added nBuLi (0.567 mL, 1.55 M in hexane, 0.878 mmol) dropwise. The solution was stirred for 1 h at 0 °C and left to stand for 2 h at 0 °C.

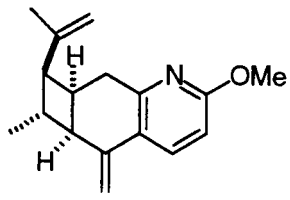
To a solution of the **196** (0.025 g, 0.095 mmol) in THF (7 mL) at –78 °C was added supernatant Wittig reagent prepared as described above (1.77 mL, 0.142 mmol) dropwise. After stirring 1 h at –78 °C, the reaction was quenched with water, and the mixture was allowed to warm to room temperature. The mixture was diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ (5 mL),

and brine (3 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 5% ethyl acetate in hexane and then 15% ethyl acetate in hexane as eluent, to give 0.001 g (4%, 8% based on recovered **196**) of **199**, 0.007 g (29%, 54% based on recovered **196**) of **197**, 0.003 g (13%, 24% based on recovered aa) of **198** and 0.012 g (48%) of **196**: IR (neat) 2948, 2869, 1669, 1591, 1570, 1481, 1410, 1321, 1261 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, d, *J* = 6 Hz), 1.71 (3H, s), 2.74 (3H, m), 2.88 (1H, dd, *J* = 8, 17 Hz), 3.02 (2H, m), 4.00 (3H, s), 4.70 (1H, s), 4.96 (1H, d, *J* = 1 Hz), 6.64 (1H, dd, *J* = 81, 9 Hz), 8.10 (1H, d, *J* = 9 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 20.1, 22.2, 29.3, 32.5, 37.7, 46.1, 50.6, 54.3, 110.2, 111.3, 123.0, 137.9, 143.2, 163.8, 166.6, 197.8; MS(CI) *m/z* 257 (M^+), 242, 228, 190, 175, 163, 149, 135, ; HRMS(CI) *m/z* 257.14197(calcd for $C_{16}H_{19}NO_2$: 257.14158).

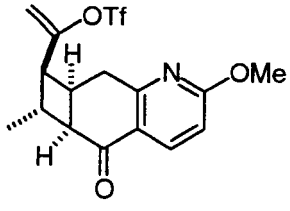


Ketone 198. IR (neat) 2957, 2919, 1704, 1594, 1474, 1304, 1262, 1029 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, d, *J* = 7 Hz), 2.10 (3H, s), 2.68 (2H, m), 2.80 (2H, m), 3.97 (1H, dd, *J* = 9, 9 Hz), 3.05 (1H, m), 3.91 (3H, s), 4.94 (1H, dd, *J* = 1, 2 Hz), 5.24 (1H, dd, *J* = 1, 2 Hz), 6.59 (1H, d, *J* = 8 Hz), 7.63 (1H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 20.8, 31.9, 34.0, 37.2, 42.1, 53.9, 55.1, 108.2,

109.2, 125.4, 136.0, 144.7, 154.1, 136.6, 208.3; MS(CI) *m/z* 258 (M^++H), 242, 200, 173, 158, ; HRMS(CI) *m/z* 258.14936(calcd for $C_{16}H_{20}NO2$: 258.14940).

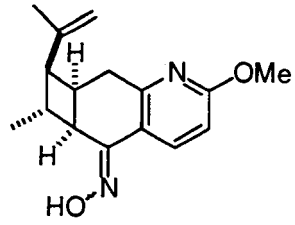


Olefin 199. IR (neat) 2949, 2919, 1591, 1475, 1404, 1316, 1259 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 7 Hz), 1.70 (3H, s), 2.39 (1H, m), 2.60 (1H, dd, *J* = 9, 9 Hz), 2.75 (4H, m), 3.90 (3H, s), 4.60 (1H, s), 4.87 (1H, s), 4.91 (1H, s), 5.24 (1H, s), 6.56 (1H, d, *J* = 8 Hz), 7.68 (1H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 20.1, 22.6, 30.8, 33.9, 39.6, 42.5, 50.3, 53.9, 107.2, 108.7, 110.4, 124.9, 135.8, 144.1, 145.0, 155.5, 163.5; MS(CI) *m/z* 255 (M^+), 240, 224, 173, 158, 144, 83, ; HRMS(CI) *m/z* 255.16184(calcd for $C_{17}H_{21}NO$: 255.16231).



Enol triflate 201. To a solution of the **196** (0.003 g, 0.012 mmol) in THF (4 mL) at –78 °C was added KHMDS (0.058 mL, 0.5M in toluene, 0.029 mmol) dropwise, and the mixture was stirred for 30 min at –78 °C. The mixture was warmed to 0

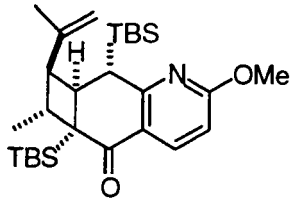
°C and a solution of N-(5-chloro-2-pyridyl)triflimide (0.006 g, 0.015 mmol) in THF (0.5 mL) was added. After stirring for 12 h at room temperature, the mixture was diluted with ether (20 mL), washed with water (5 mL). The phases were separated, and aqueous portion was extracted with ether (2 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, using 25% ethyl acetate in hexane as eluent, to give 0.0031 g (74%) of **201** as a colorless oil: IR (neat) 2962, 2924, 1669, 1592, 1556, 1418, 1266, 1212, 1142, 913 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, d, *J* = 6 Hz), 2.69 (1H, m), 2.78 (1H, dd, *J* = 8, 10 Hz), 3.10 (4H, m), 4.00 (3H, s), 4.99 (1H, dd, *J* = 1, 4 Hz), 5.35 (1H, d, *J* = 4 Hz), 6.68 (1H, d, *J* = 9 Hz), 8.10 (1H, d, *J* = 9 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 19.8, 29.6, 32.2, 38.6, 45.8, 46.8, 54.5, 106.0, 110.7, 123.0, 137.9, 155.2, 162.6, 166.9, 196.6; MS(CI) *m/z* 392 (M^++H), 258, 242, 214, 190, 175, 146, ; HRMS(CI) *m/z* 392.07753(calcd for $C_{16}H_{17}F_3NO_5S$: 392.07795).



Oxime 208. To a solution of the **197** (0.0033 g, 0.013 mmol) in MeOH (2 mL) was added NH_2OHHCl (0.0022 g, 0.032 mmol) and NaOAc3H_2O (0.0061 g, 0.045 mmol). The mixture was stirred at 85 °C for 48 h. After cooling down to

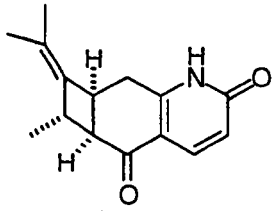
room temperature, the solvent was evaporated and the residue was diluted with $CHCl_3$ (20 mL), washed with brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, using 10% ethyl acetate in hexane as eluent, to give 1.8 mg (51%) of major isomer **208**,0.4 mg (12%) of minor **208**, and 0.6 mg (18%) of starting material: major isomer IR (neat) 3266 (br), 2928, 1596, 1482, 1324, 1256, 1070; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6 Hz, 3H), 1.74 (s, 3H), 2.63 (m, 2H), 2.70 (m, 1H), 2.81 (m, 2H), 3.25 (m, 1H), 3.94 (s, 3H), 4.69 (s, 1H), 4.90 (s, 1H), 6.57 (d, *J* = 9 Hz, 1H), 6.92, (br s, 1H), 7.95 (d, *J* = 9 Hz, 1H); MS(CI) *m/z* 272 (M^+), 255, 236, 190, 173, 83; HRMS (CI) *m/z* 272.1527 (calcd for $C_{16}H_{20}N_2O_2$: 272.1525).

minor 208 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6 Hz, 3H), 1.74 (s, 3H), 2.02, (br s, 1H), 2.53 (m, 1H), 2.66 (m, 1H), 2.76 (m, 2H), 2.89 (m, 2H), 3.96 (s, 3H), 4.60 (s, 1H), 4.89 (s, 1H), 6.63 (d, *J* = 10 Hz, 1H), 8.40 (d, *J* = 10 Hz, 1H).



Ketone 209. To a solution of **197** (0.04 g, 0.016 mmol) in THF (1 mL) was added slowly KHMDS (0.06 mL, 0.5 mol solution in toluene, 0.03 mmol) at -78 °C. After stirring 2 h at -78 °C, a solution of TBSCl (0.007 g, 0.049 mmol) in THF (0.2 mL)

was added. After stirring for 1 h at -78 °C, the mixture was diluted with ether (20 mL), washed with water (5 mL). The phases were separated, and aqueous portion was extracted with ether (2 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, using 4% ethyl acetate in hexane as eluent, to give 0.7 mg (15%) of **209** as a colorless oil: IR (neat) 2963, 2932, 2862, 1700, 1600, 1484, 1328, 1273, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (d, J = 7 Hz, 6H), 0.25 (d, J = 7 Hz, 6H), 0.81 (s, 9H), 0.99, (s, 9H), 1.01 (d, J = 7 Hz, 3H), 1.80 (s, 3H), 2.50 (m, 1H), 3.12 (dd, J = 10, 10 Hz, 1H), 82 (dd, J = 1, 11 Hz, 1H), 4.00 (s, 3H), 4.35 (s, 1H), 4.84 (d, J = 1 Hz, 1H), 4.90 (d, J = 2 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 8.14 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.4, -5.3, -5.2, 12.9, 18.5, 18.8, 23.2, 26.5, 40.7, 42.0, 47.5, 54.5, 81.2, 84.0, 111.4, 112.7, 124.2, 138.1, 142.7, 157.3, 166.8, 192.8.



Ketone 210. To a solution of the **197** (0.005 g, 0.19 mmol) in $CHCl_3$ (3 mL) was added TMSI (0.027 mL, 0.19 mmol) at room temperature. The mixture was stirred at 80 °C for 3 h. After cooling down to room temperature, the solvent was evaporated and the residue was purified by chromatography on silica, using 5%

ethyl acetate in hexane as eluent, to give 0.5 mg (10%) of **210**: IR (neat) 2955, 2924, 2846, 1651, 1413, 1336cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 7 Hz, 3H), 1.51 (s, 3H), 1.70 (s, 3H), 2.75 (dd, J = 5, 10 Hz, 1H), 2.85-3.10 (m, 3H), 3.78 (m, 1H), 6.40 (d, J = 9 Hz, 1H), 8.10 (d, J = 9 Hz, 1H), 12.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 19.7, 20.6, 28.4, 33.1, 44.2, 45.9, 111.1, 112.1, 115.1, 127.5, 135.5, 140.8, 154.1, 195.5; MS(CI) *m/z* 243 (M^+), 228, 215, 200, 176, 162; HRMS (CI) *m/z* 243.1260 (calcd for $C_{15}H_{17}NO_2$: 243.1259).

References

1. Touchette, N. J. *NIH Res.* **1992,** *4*, 48.

2. Giacobini, E. *Progress in Brain Res.* **1990**, *84*, 321.

3. Davis, K. L.; Powchik, P. *Lancet* **1995**, *345*, 625.

4. Sugimoto, H.; Iimurs, Y.; Yamanish, Y.;Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821.

5. Prous, J.; Rabasseda, X.; Castaner, J.*Drugs Future* **1996**, *19*, 656.

6. Ahmad, S. R *Lancet* **1993**, *342*, 736.

7. Liu, J. -S.; Zhu, Y. -L.; Zhou, Y. -z.; Han, Y. -Y.; Wu, F. -W.; Qi, B. -F. *Can J. Chem.* **1986**, *64*, 837.

8. Kozikowski, A. P.; Thiels, E.; Tang, X. -C.; Hanin, I. In *Advances in Medicinal Chemistry*; Maryanoff, B. E.; Maryanoff, C. A., Eds.; JAI Press: Greenwich, CT, **1992**; Vol. *1*, 175-205.

9. Xu, S. -S.; Gao, Z. -X.; Du, Z. -M.; Xu, W. -A.; Yang, J. -S.;Zhang, M. -L.; Tong, Z. -H.; Fang, Y. -S.; Chia, Z. -S.; Li, S. -L. *Acta Pharmacol. Sin.* **1995**, *16*, 391.

10. Kozikowsk, A. P.; Xia, Y.; Reddy, E. R.; Hanin, I.; Tang, X. J. Org. Chem. **1991**, *56*, 4636.

11. Kozikowski, A. P.; Campiani, G.; Sun, L. Q.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357.

12. Wiesner, K.; Valenta, Z.; Yoshimurs, H. *Tetrahedron Lett*, **1960**, *12*, 14.

13. Liu, J. -S.; Ayer, W.; Browne, L. M.; Orszanska, H.; Valenta, Z. *Can. J. hem.* **1989**, *67*, 1538.

14. Kende, A. S.; Schneiderk, J. A. *Syn. Comm.* **1979**, *9*, 419.

15. Gravel, D.; Deziel, R.; Bordeleau, L. *Tetrahedron Lett.* **1983**, *24*, 699.

16. Gravel, D.; Bordeleau, L.; Ladouceur, G.; Randcourt, J.; Thoraval, D. *Can. J. Chem.* **1984**, *62*, 2945.

17. Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles.* **1984**, *21*, 91.

18. Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641.

19. Xia, Y.; Kozikowsk, A. P. *J. Am. Chem. Soc.* **1989**, *111*, 4116

20. Kozikowsk, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 195.

21. Raphael, R. A.; Colvin, E.; Martin, J.; Parker, W. J. *Chem. Soc., Chem. Commun.*, **1966**, 596.

22. Horii, Z. -I.; Imanishi, T.; Kim, S. -W.; Ninomiya, I. *Chem. Pharm. Bull.* **1968**, *16*, 1918.

23. Ji, R.; Qian, L. Tetrahedron Lett. **1989**, *30*, 2089.

24. Karus, G. A.; Hamsen, H.; Vines, D. *Synth. Commun.* **1992**, *22*, 2625.

25. Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663.

26. Campiani, G.; Sun, L. -Q.; Kozikowski, A. P.; Aaraard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660.

27. Yamada, F.; Kozikowski, A. P.; Reddy, E. R.; Pang, Y. -P.; Miller, J. P.; Mckinney, M. *J. Am. Chem. Soc.* **1991**, *113*, 4695.

28. Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron.* **1998**, *54*, 5471.

29. Corn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.

30. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113

31. He, X. -C.; Wang, B.; Bai, D. *Tetrahedron Lett.* **1998**, *39*, 411.

32. Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 8805.

33. Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**. *22*, 1

34. (a) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071. (b) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *J. Org. Chem.* **1999**, *63*, 6905. (c) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *63*, 657.

35. Berson, J. B.; Jones, M. *J. Am. Chem. Soc.* **1964**, *86*, 5019

36. Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865.

37. Brown, J. M.; Golding, B. T.; Stofko, J. J. *J. Chem. Soc., Chem. Commun.*, **1973**, 319

38. Vogel, E. *Justus Liebigs Ann. Chem.*, **1958**, *615*, 1.

39. Allin, S. M.; Button, M. A. C.; Shuttleworth, S. J. *Synlett.* **1997**, 725.

40. Serckx-Poncin, B.; Hesbain-Frisque, A. -M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261.

41. (a) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297. (b) Horspool, W. M. In *Photochemistry in Organic Synthesis*; Coyle, J. D., ED.; Royal Society of Chemistry: London, **1986**, 210.

42. Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

43. Marchand, A. P.; Xing, D.; Wang, Y.; Bott, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 2709.

44. (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332. (b) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.

45. (a) Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932. (b) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4930.

46. Gariboldi, P.; Jommi, G.; Sisti, M. *Gazz. Chim. Ital.* **1986**, *116*, 291.

47. Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.

48. Yadav, J. S.; Barma, D. K. *Tetrahedron* **1996**, *52*, 4457.

49. Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.

50. Kang, S. K.; Kim, S. G.; Park, D. C.; Lee, J. S. *J. Chem. Soc. Perkin Trans. 1* **1993**, 9. 49.

51. Anthonsen, T.; McCabe, P. H.; McCrindle, R.; Murray, R. D. H. *Tetrahedron.* **1969**, *25*, 2233.

52. Erdik, E *Tetrahedron*, **1987**, *43*, 2203.

53. (a) Hauser, C. R.; Breslow, O. S. *Org. Synth., Coll., Vol III*, **1955**, 408. (b) Bewman, M. S.; Arens, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946. (c) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikanthan, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992.

54. Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.

55. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*, **1977**, *18*, 4171.

56. McElvain, S. A.; Stevens, C. L. *J. Am. Chem. Soc.* **1946**, *68*, 1917.

57. (a) Cuerva, J. M.; Echavarren, A. M. *Synlett.* **1997**, 173. (b) Villacampa, M.; Perez, J. M.; Avendano, C.; Menendez, J. C. *Tetrahedron* **1994**, *50*, 10047.

58. Tamion, R.; Mineur, C.; Ghosez, L. *Tetrahedron Lett.* **1995**, *36*, 8977.

59. Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767.

60. Magnus, P.; Rigollier, P.; Lacour, J.; Tobler, H. *J. Am. Chem. Soc.* **1993**, *115*, 12629.

61. Trost, B. M.; Salzmann, T.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

62. Mikolajczyk, M.; Midura, W. H. *Synlett.* **1991**, 245.

63. Reich, H. J.; Willis, W. W.; Clark, P. D. *J. Org. Chem.* **1981**, *46*, 2775.

64. Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *22*, 1979.

65. Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

66. Petasis, N. A.; Lu, S. -P. *Tetrahedron Lett.* **1995**, *36*, 2393.

67. Scott, W. J.; Crips, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

68. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *32*, 6299.

Chapter IV. GENERAL CONCLUSION

The research described in this dissertation presents results on the synthesis of two natural products, (+)-byssochlamic acid and huperzine A.

Syntheses of both natural (+)- and nonnatural (-)-byssochlamic acid (**3**) were accomplished by a [2+2] photoaddition-cycloreversion strategy. An X-ray crystallographic analysis of the cyclohexylamine salt **99** unambiguously established the structure of **100** and **103** obtained from enzymatic hydrolysis of **44** and **82**, respectively. The preferred cis configuration of the ethyl and *n*-propyl side chains was demonstrated by using racemic (±)-**103** to access both enantiomers of byssochlamic acid (**3**)

In the approach to the synthesis of huperzine A, an intramolecular [2+2] photoaddition of the enantiopure enone **121** provided a direct route to the cyclobutane **122** with desired stereochemistry. The methoxypyridine moiety was synthesized by an intramolecular Michael addition followed by selenoxide elimination. The intended transformation of ketone **197** into a precursor of huperzine A by means of a [3.3] sigmatropic rearrangement of its enamine **202** was thwarted by difficulties which originate from poor overlap of the alkene termini.

Bibliography

Ahmad, S. R *Lancet* **1993**, *342*, 736.

Allin, S. M.; Button, M. A. C.; Shuttleworth, S. J. *Synlett.* **1997**, 725.

Anthonsen, T.; McCabe, P. H.; McCrindle, R.; Murray, R. D. H. *Tetrahedron.* **1969**, *25*, 2233.

Arai, K.; Shimizu, S.; Miyajima, H.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2870.

Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552.

Asano, M.; Kanematsu, T. *Chem. Ber.* **1932**, 65.

Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.

Baldwin, J. E.; Barton, D. H. R.; Bloomer, J. L.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *Experientia* **1962**, *18*, 345.

Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787.

Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*, **1977**, *18*, 4171.

Berson, J. B.; Jones, M. *J. Am. Chem. Soc.* **1964**, *86*, 5019

Bewman, M. S.; Arens, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946.

Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890.

Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, *28*, 828

Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

Brown, J. M.; Golding, B. T.; Stofko, J. J. *J. Chem. Soc., Chem. Commun.*, **1973**, 319.

Büchi, G.; Snader, K. M.; White, J. D.; Gougoutas, J. Z.; Singh, S. *J. Am. Chem..Soc.* **1970**, *92*, 6638.

Campiani, G.; Sun, L. -Q.; Kozikowski, A. P.; Aaraard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660.

Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 8805.

Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784.

Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *32*, 6299.

Corey, E. J.; Bock, M. *Tetrahedron Lett.* **1975**, 3269.

Corn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.

Crane, R. I.; Hedden, P.; MacMillan, J.; Turner, W. B. *J. Chem. Soc. Perkin Trans 1* **1973**, 194.

Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297.

Cuerva, J. M.; Echavarren, A. M. *Synlett.* **1997**, 173

Dabrah, T. T.; Kaneko, T.; Massefski, Jr., W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737.

Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, *63*, 657.

Davis, K. L.; Powchik, P. *Lancet* **1995**, *345*, 625.

Drapela, N. E. Synthetic Studies of nonadrides. **1998**, 139.

Erdik, E *Tetrahedron*, **1987**, *43*, 2203.

Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 12721.

Gariboldi, P.; Jommi, G.; Sisti, M. *Gazz. Chim. Ital.* **1986**, *116*, 291.

Gerdes, J. M.; Wade, L. G. *Tetrahedron Lett.* **1979**, 689.

Giacobini, E. *Progress in Brain Res.* **1990**, *84*, 321.

Gravel, D.; Deziel, R.; Bordeleau, L. *Tetrahedron Lett.* **1983**, *24*, 699.

Gravel, D.; Bordeleau, L.; Ladouceur, G.; Randcourt, J.; Thoraval, D. *Can. J. Chem.* **1984**, *62*, 2945.

Hamor, T. A.; Paul, I. C.; Monteath Robertson, J.; Sim. G. A. *Experientia* **1962**, *18*, 352.

Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.

Hauser, C. R.; Breslow, O. S. *Org. Synth., Coll., Vol III*, **1955**, 408.

Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113

He, X. -C.; Wang, B.; Bai, D. *Tetrahedron Lett.* **1998**, *39*, 411.

Horii, Z. -I.; Imanishi, T.; Kim, S. -W.; Ninomiya, I. *Chem. Pharm. Bull.* **1968**, *16*, 1918.

Horspool, W. M. In *Photochemistry in Organic Synthesis*; Coyle, J. D., ED.; Royal Society of Chemistry: London, **1986**, 210.

Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663.

Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Ji, R.; Qian, L. Tetrahedron Lett. **1989**, *30*, 2089.

Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron.* **1998**, *54*, 5471

Kang, S. K.; Kim, S. G.; Park, D. C.; Lee, J. S. *J. Chem. Soc. Perkin Trans. 1* **1993**, 9. 49.

Karus, G. A.; Hamsen, H.; Vines, D. *Synth. Commun.* **1992**, *22*, 2625.

Kende, A. S.; Schneiderk, J. A. *Syn. Comm.* **1979**, *9*, 419.

Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles.* **1984**, *21*, 91.

Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikanthan, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992.

Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439

Kozikowsk, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 195.

Kozikowsk, A. P.; Xia, Y.; Reddy, E. R.; Hanin, I.; Tang, X. J. Org. Chem. **1991**, *56*, 4636.

Kozikowski, A. P.; Thiels, E.; Tang, X. -C.; Hanin, I. In *Advances in Medicinal Chemistry*; Maryanoff, B. E.; Maryanoff, C. A., Eds.; JAI Press: Greenwich, CT, **1992**; Vol. *1*, 175-205.

Kozikowski, A. P.; Campiani, G.; Sun, L. Q.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357.

Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641.

Kraft, K.; Porsch, H. *Just. Lieb. Ann. Chim.* **1937**, *527*, 168.

Kraft, K. *Just. Lieb. Ann. Chim.* **1937**, *530*, 20.

Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1877, 1880.

Lange, G. L.; Huggins, M.-A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409.

Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749.

Laumen, K.; Schneider, M. P. *J. Chem. Soc. Chem. Commun.* **1986**, 1248.

Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.

Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071.

Liu, J. -S.; Zhu, Y. -L.; Zhou, Y. -z.; Han, Y. -Y.; Wu, F. -W.; Qi, B. -F. *Can J. Chem.* **1986**, *64*, 837.

Liu, J. -S.; Ayer, W.; Browne, L. M.; Orszanska, H.; Valenta, Z. *Can. J. Chem.* **1989**, *67*, 1538.

Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4930.

MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *J. Org. Chem.* **1999**, *63*, 6905.

Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767.

Magnus, P.; Rigollier, P.; Lacour, J.; Tobler, H. *J. Am. Chem. Soc.* **1993**, *115*, 12629.

Marchand, A. P.; Xing, D.; Wang, Y.; Bott, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 2709.

Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.

McElvain, S. A.; Stevens, C. L. *J. Am. Chem. Soc.* **1946**, *68*, 1917.

Mikolajczyk, M.; Midura, W. H. *Synlett.* **1991**, 245.

Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.

Moss, M. O. In *Microbial Toxins*; Ciegler, A., Ed.; Academic Press: New York & London, **1971**, *6*, 381.

Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1699.

Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H-S. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1676.

Olliver, Smith, J. Bot. 1933 71, 196.

Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865.

Overeem, J. C.; Mackor, A. *Recl. Trav. Chim. Pays-Bos* **1973**, *92*, 349.

Petasis, N. A.; Lu, S. -P. *Tetrahedron Lett.* **1995**, *36*, 2393.

Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

Prous, J.; Rabasseda, X.; Castaner, J.*Drugs Future* **1996**, *19*, 656.

Raistrick, H.; Smith, G. *Biochem. J.* **1933**, *27*, 1814.

Randall, M. L.; Lo, P. C-K.; Bonitatebus Jr., P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534.

Raphael, R. A.; Colvin, E.; Martin, J.; Parker, W. J. *Chem. Soc., Chem. Commun.*, **1966**, 596.

Reich, H. J.; Willis, W. W.; Clark, P. D. *J. Org. Chem.* **1981**, *46*, 2775.

Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**. *22*, 1.

Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc. Chem. Commun.* **1984**, 236.

Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 225.

Schorno, K. S.; Adolphen, G. H.; Eisenbraun, E. J. *J. Org. Chem.* **1969**, *34*, 2801.

Scott, W. J.; Crips, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

Serckx-Poncin, B.; Hesbain-Frisque, A. -M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261.

Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157.

Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *22*, 1979.

Soai, K.; Yokoyama, S.; Mochida, Y. *Synthesis* **1987**, 647.

Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932.

Stein, K. A.; Toogood, P. L. *J. Org. Chem.* **1995**, *60*, 8110.

Stork, G.; Tabak, J. M.; Blount, J. F. *J. Am. Chem. Soc.* **1972**, *94*, 4735.

Sugimoto, H.; Iimurs, Y.; Yamanish, Y.;Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821.

Sutherland, J. K. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 131.

Sutter, H.; Wijkman, N. *Just. Lieb. Ann. Chim.* **1933**, *505*, 248.

Sutter, H.; Wijkman, N. *Just. Lieb. Ann. Chim.* **1935**, *519*, 97.

Sutter, H.; Rottmayr, F.; Porsch H. *Just. Lieb. Ann. Chim.* **1936**, *521*, 189.

Tamion, R.; Mineur, C.; Ghosez, L. *Tetrahedron Lett.* **1995**, *36*, 8977.

Touchette, N. J. *NIH Res.* **1992,** *4*, 48.

Trost, B. M.; Salzmann, T.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332.

Villacampa, M.; Perez, J. M.; Avendano, C.; Menendez, J. C. *Tetrahedron* **1994**, *50*, 10047.

Vogel, E. *Justus Liebigs Ann. Chem.*, **1958**, *615*, 1.

Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015.

Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. Am. Chem. Soc. 1984, 106, 3695.

Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267.

Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365.

Wender, P. A.; Letendre, L. J. *J. Org. Chem.* **1980**, *45*, 367.

White, J. D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673.

Wiesner, K.; Valenta, Z.; Yoshimurs, H. *Tetrahedron Lett*, **1960**, *12*, 14.

Wijkman, N. *Just. Lieb. Ann. Chim.* **1931**, *485*, 61.

Williams, J. R.; Callahan, J. F. *J. Chem. Soc. Chem. Commun.* **1979**, 405.

Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4475, 4479.

Wilson, B. J.; Wilson, C.H. *J. Bacteriol.* **1962**, *83*, 693.

Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373.

Xia, Y.; Kozikowsk, A. P. *J. Am. Chem. Soc.* **1989**, *111*, 4116

Xu, S. -S.; Gao, Z. -X.; Du, Z. -M.; Xu, W. -A.; Yang, J. -S.;Zhang, M. -L.; Tong, Z. -H.; Fang, Y. -S.; Chia, Z. -S.; Li, S. -L. *Acta Pharmacol. Sin.* **1995**, *16*, 391

Yadav, J. S.; Barma, D. K. *Tetrahedron* **1996**, *52*, 4457.

Yamada, F.; Kozikowski, A. P.; Reddy, E. R.; Pang, Y. -P.; Miller, J. P.; Mckinney, M. *J. Am. Chem. Soc.* **1991**, *113*, 4695.

Appendices

APPENDIX A

SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON CYCLOHEXYLAMINE SALT 99

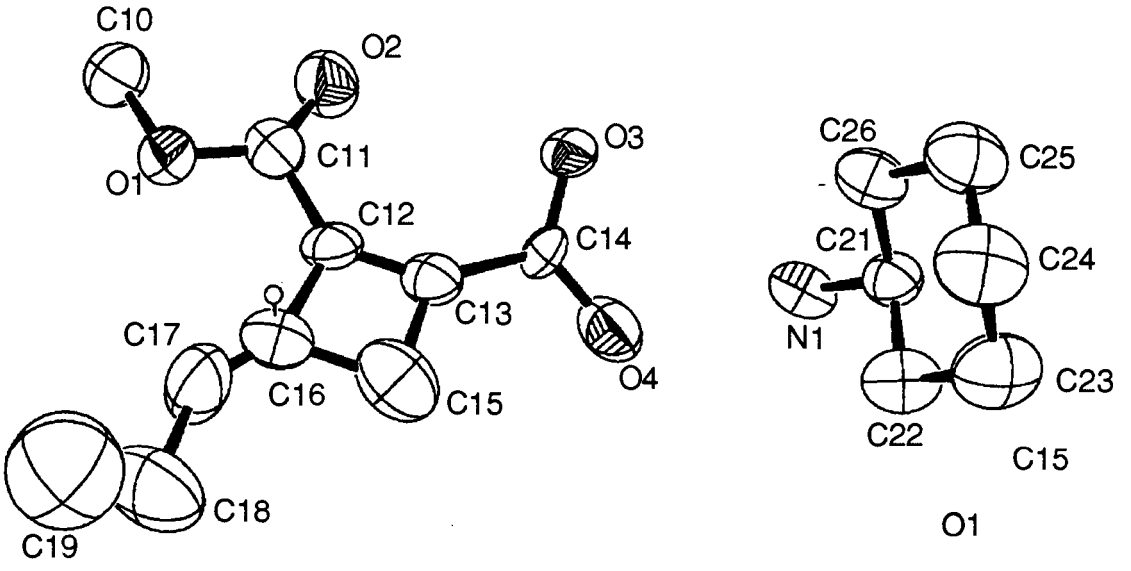


Table A.1 Crystal data and structure refinement for 99

Empirical formula	$C_{16}H_{27}NO_4$	
Formula weight	297.39	
Temperature	566(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1 (#2)	
Unit cell dimensions	a = 5.999(2) Å	α= 98.530(10)°.
	b = 11.212(2) Å	β= 91.64(2)°.
	c = 13.274(3) Å	γ = 96.50(2)°.
Volume	876.3(4) $Å^3$	
Z	2	
Density (calculated)	1.127 Mg/m^3	
Absorption coefficient	0.649 mm^{-1}	
F(000)	324	
Crystal size	0.50 x 0.10 x 0.10 mm^3	
Theta range for data collection	3.37 to 67.48°.	
Index ranges	0<=h<=1, -13<=k<=13, -15<=l<=15	
Reflections collected	1302	
Independent reflections	973 [R(int) = 0.0583]	
Completeness to theta = 67.48°	30.8 %	
Absorption correction	Empirical (Psi-scans)	
Max. and min. transmission	0.9379 and 0.7372	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	973 / 139 / 191	
Goodness-of-fit on F^2	1.780	
Final R indices [I>2sigma(I)]	R1 = 0.0803, wR2 = 0.2339	
R indices (all data)	R1 = 0.0948, wR2 = 0.2555	
Extinction coefficient	0.004(3)	
Largest diff. peak and hole	0.181 and -0.129 $e.Å^{-3}$	

Table A.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 99.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	18080(20)	5029(6)	1332(4)	134(8)
O(2)	16350(20)	4397(4)	2654(4)	164(8)
O(3)	13036(18)	5822(4)	4089(3)	109(8)
O(4)	10460(20)	6696(9)	3390(8)	166(10)
C(11)	16750(30)	5131(6)	2072(5)	119(10)
C(12)	15400(30)	6191(7)	2064(6)	112(10)
C(13)	13890(30)	6658(8)	2589(5)	119(10)
C(14)	12330(30)	6322(11)	3391(11)	105(12)
C(15)	13870(50)	7689(13)	1991(11)	242(13)
C(16)	15660(50)	7159(14)	1395(10)	214(13)
C(17)	16270(50)	7368(12)	701(12)	262(13)
C(10)	19270(40)	4067(11)	1295(6)	178(11)
C(18)	16400(50)	8473(15)	132(12)	276(13)
C(19)	18400(70)	9020(40)	-30(40)	410(30)
C(192)	16180(120)	8390(30)	-850(20)	230(20)
N(1)	7450(20)	6111(4)	4789(3)	133(9)
C(21)	7580(30)	7147(7)	5625(6)	119(11)
C(22)	7110(30)	8238(6)	5228(6)	158(10)
C(23)	7420(40)	9368(9)	6070(9)	207(12)
C(24)	9600(40)	9511(12)	6618(10)	200(13)
C(25)	10160(40)	8442(9)	6995(6)	181(11)
C(26)	9850(30)	7340(8)	6138(6)	145(11)

Table A.3 Bond lengths [Å] and angles [°] for 99.

O(1)-C(11)	1.285(12)
O(1)-C(10)	1.353(15)
O(2)-C(11)	1.219(7)
O(3)-C(14)	1.240(12)
O(4)-C(14)	1.243(17)
C(11)-C(12)	1.514(16)
C(12)-C(13)	1.27(2)
C(12)-C(16)	1.500(13)
C(12)-C(15)	2.02(2)
C(13)-C(15)	1.497(12)
C(13)-C(14)	1.50(2)
C(15)-C(16)	1.48(3)
C(16)-C(17)	1.049(17)
C(17)-C(18)	1.540(16)
C(18)-C(192)	1.30(3)
C(18)-C(19)	1.32(3)
N(1)-C(21)	1.477(9)
C(21)-C(22)	1.454(10)
C(21)-C(26)	1.482(18)
C(22)-C(23)	1.550(12)
C(23)-C(24)	1.46(2)
C(24)-C(25)	1.435(13)
C(25)-C(26)	1.541(11)

C(11)-O(1)-C(10)	114.1(9)
O(2)-C(11)-O(1)	125.8(10)
O(2)-C(11)-C(12)	121.2(11)
O(1)-C(11)-C(12)	112.4(7)
C(13)-C(12)-C(16)	94.9(12)
C(13)-C(12)-C(11)	137.3(8)
C(16)-C(12)-C(11)	127.6(14)
C(13)-C(12)-C(15)	47.9(7)
C(16)-C(12)-C(15)	47.1(10)
C(11)-C(12)-C(15)	174.1(12)

C(12)-C(13)-C(15)	93.1(12)
C(12)-C(13)-C(14)	137.7(9)
C(15)-C(13)-C(14)	128.6(15)
O(3)-C(14)-O(4)	122.7(19)
O(3)-C(14)-C(13)	119.4(14)
O(4)-C(14)-C(13)	117.3(12)
C(16)-C(15)-C(13)	86.9(14)
C(16)-C(15)-C(12)	47.8(9)
C(13)-C(15)-C(12)	39.0(8)
C(17)-C(16)-C(15)	128(2)
C(17)-C(16)-C(12)	144(2)
C(15)-C(16)-C(12)	85.1(13)
C(16)-C(17)-C(18)	136.1(19)
C(192)-C(18)-C(19)	82(4)
C(192)-C(18)-C(17)	124(2)
C(19)-C(18)-C(17)	118(2)
C(22)-C(21)-N(1)	110.2(6)
C(22)-C(21)-C(26)	110.1(11)
N(1)-C(21)-C(26)	109.6(11)
C(21)-C(22)-C(23)	111.7(8)
C(24)-C(23)-C(22)	112.3(13)
C(25)-C(24)-C(23)	114.7(15)
C(24)-C(25)-C(26)	110.5(8)
C(21)-C(26)-C(25)	112.9(12)

Symmetry transformations used to generate equivalent atoms:

Table A.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 99.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	110(30)	170(4)	120(3)	20(3)	5(6)	27(7)
O(2)	200(30)	146(3)	162(3)	50(3)	39(7)	40(6)
O(3)	60(20)	151(3)	121(2)	49(2)	-8(6)	-6(5)
O(4)	150(30)	223(9)	127(4)	58(5)	7(10)	-4(11)
C(11)	100(30)	134(5)	113(4)	21(3)	-7(8)	-22(8)
C(12)	80(30)	137(5)	120(4)	35(4)	-23(9)	9(9)
C(13)	90(30)	146(5)	127(5)	49(4)	-13(10)	-6(10)
C(14)	50(40)	147(6)	120(5)	21(4)	17(13)	28(13)
C(15)	280(40)	239(11)	239(10)	144(9)	63(17)	18(16)
C(16)	230(40)	269(12)	190(8)	134(8)	48(14)	117(17)
C(17)	260(40)	284(13)	320(14)	183(12)	161(19)	162(17)
C(10)	200(30)	189(7)	158(6)	18(5)	25(11)	102(14)
C(18)	320(40)	266(12)	262(12)	137(10)	8(17)	-11(17)
N(1)	160(30)	124(3)	115(3)	31(2)	-20(7)	-9(6)
C(21)	90(30)	139(5)	124(4)	32(4)	-2(9)	8(10)
C(22)	150(30)	126(4)	189(6)	32(4)	-32(11)	-9(8)
C(23)	240(40)	138(7)	235(10)	16(7)	-35(17)	28(13)
C(24)	190(40)	168(8)	212(9)	-1(8)	-51(16)	-40(15)
C(25)	200(30)	175(7)	161(6)	11(5)	-38(11)	2(11)
C(26)	150(30)	151(5)	125(4)	22(4)	-30(10)	-4(10)

Table A.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 99.

	x	y	z	U(eq)
H(15A)	12478	7684	1599	290
H(15B)	14338	8482	2385	290
H(16)	16899	7655	1816	256
H(17A)	15516	6716	203	314
H(17B)	17823	7201	737	314
H(10A)	20210	4043	722	267
H(10B)	18248	3331	1224	267
H(10C)	20179	4142	1912	267
H(18A)	15599	8217	-524	331
H(18B)	15580	9077	514	331
H(19A)	18232	9705	-365	608
H(19B)	19202	8455	-457	608
H(19C)	19229	9279	607	608
H(19D)	16176	9187	-1036	351
H(19E)	14791	7904	-1093	351
H(19F)	17409	8017	-1160	351
H(1A)	7763	5451	5038	199
H(1B)	8435	6278	4326	199
H(1C)	6070	5978	4499	199
H(21)	6465	6964	6122	142
H(22A)	5580	8123	4944	190
H(22B)	8109	8374	4684	190
H(23A)	7267	10088	5761	248
H(23B)	6239	9294	6550	248
H(24A)	10748	9755	6166	240
H(24B)	9618	10162	7189	240
H(25A)	9204	8281	7548	217
H(25B)	11706	8574	7259	217
H(26A)	10964	7456	5636	174
H(26B)	10109	6617	6424	174

APPENDIX B

SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON CYCLOBUTANE 157

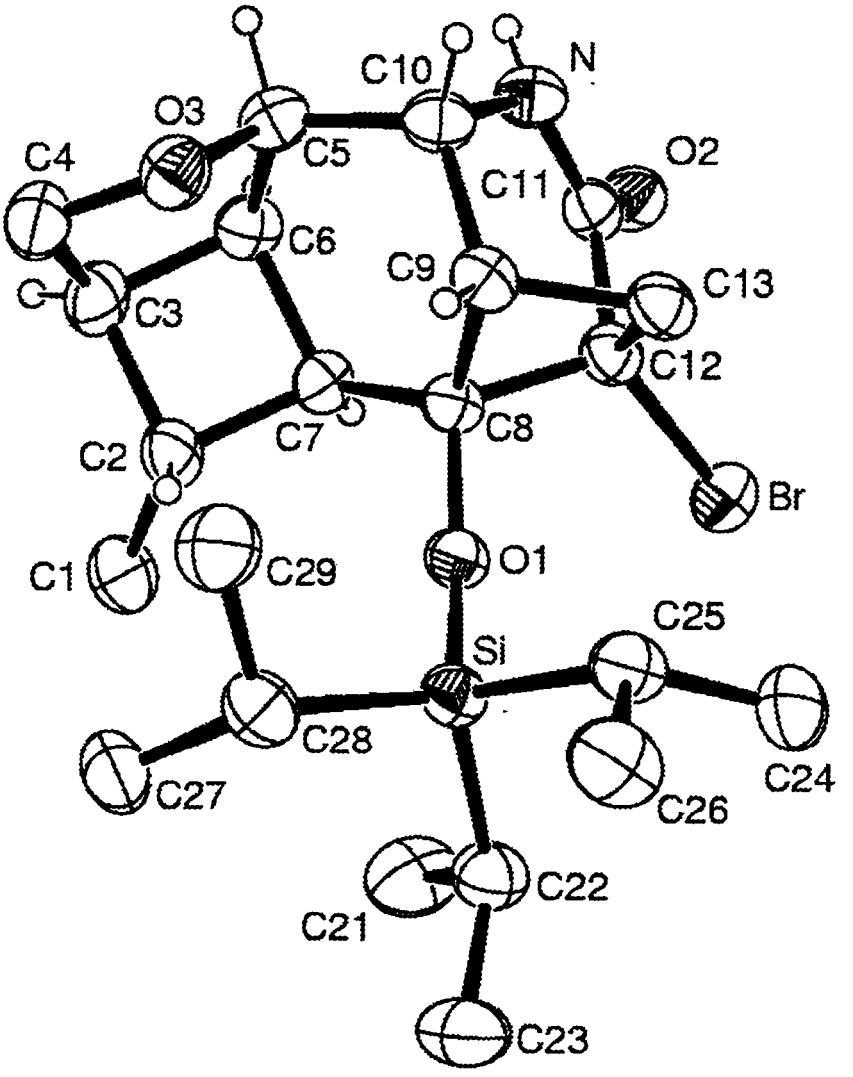


Table B.1 Crystal data and structure refinement for Cyclobutane 157

Empirical formula	C22 H36 Br N O3 Si	
Formula weight	470.52	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (#14)	
Unit cell dimensions	a = 11.266(1) Å	α= 90°.
	b = 10.731(1) Å	β= 106.13°.
	c = 19.674(1) Å	γ = 90°.
Volume	2284.9(3) $Å^3$	
Z	4	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	3.126 mm^{-1}	
F(000)	992	
Crystal size	0.30 x 0.17 x 0.10 mm^3	
Theta range for data collection	4.10 to 57.34°.	
Index ranges	-9<=h<=9, -11<=k<=11, -21<=l<=21	
Reflections collected	6087	
Independent reflections	2885 [R(int) = 0.0558]	
Completeness to theta = 57.34°	92.4 %	
Max. and min. transmission	0.7451 and 0.4540	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2885 / 0 / 276	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.1078	
R indices (all data)	R1 = 0.0507, wR2 = 0.1160	
Extinction coefficient	0.00088(14)	
Largest diff. peak and hole	0.356 and -0.564 e.$Å^{-3}$	

Table B.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Cyclobutane 157.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	9261(1)	4541(1)	6142(1)	66(1)
Si	10639(1)	8247(1)	6621(1)	51(1)
N	6143(4)	6226(3)	4936(2)	60(1)
O(1)	9381(2)	7393(2)	6472(1)	52(1)
O(2)	6498(3)	4356(3)	5476(2)	65(1)
O(3)	6219(3)	9457(2)	5550(2)	65(1)
C(1)	7749(5)	8113(5)	7773(2)	86(2)
C(2)	7402(4)	8371(4)	6985(2)	60(1)
C(3)	6042(4)	8721(4)	6630(2)	66(1)
C(4)	5844(5)	9846(4)	6156(2)	74(1)
C(5)	5758(4)	8217(4)	5404(2)	59(1)
C(6)	5934(4)	7609(4)	6120(2)	59(1)
C(7)	7279(4)	7222(4)	6496(2)	51(1)
C(8)	8188(4)	7104(3)	6053(2)	48(1)
C(9)	7860(4)	7666(4)	5295(2)	53(1)
C(10)	6466(4)	7554(4)	4966(2)	56(1)
C(11)	6857(4)	5385(4)	5361(2)	54(1)
C(12)	8191(4)	5836(4)	5658(2)	52(1)
C(13)	8527(4)	6568(4)	5060(2)	57(1)
C(21)	11121(4)	7027(4)	7962(2)	97(2)
C(22)	11709(4)	7472(4)	7411(2)	70(1)
C(23)	12873(5)	8226(5)	7744(3)	90(2)
C(24)	11937(5)	6874(5)	5807(3)	83(2)
C(25)	11343(4)	8148(4)	5857(2)	63(1)
C(26)	12268(5)	9184(5)	5824(3)	85(2)
C(27)	10175(5)	10325(5)	7487(3)	84(2)
C(28)	10420(5)	9950(4)	6784(2)	65(1)
C(29)	9520(5)	10601(4)	6159(3)	83(2)

Table B.3 Bond lengths [Å] and angles [°] for Cyclobutane 157.

Br-C(12)	1.910(4)
Si-O(1)	1.644(3)
Si-C(22)	1.875(4)
Si-C(28)	1.883(4)
Si-C(25)	1.889(4)
N-C(11)	1.337(5)
N-C(10)	1.467(5)
O(1)-C(8)	1.403(4)
O(2)-C(11)	1.220(5)
O(3)-C(5)	1.428(5)
O(3)-C(4)	1.432(5)
C(1)-C(2)	1.515(6)
C(2)-C(3)	1.543(6)
C(2)-C(7)	1.547(5)
C(3)-C(4)	1.505(6)
C(3)-C(6)	1.542(6)
C(5)-C(10)	1.505(6)
C(5)-C(6)	1.514(5)
C(6)-C(7)	1.547(6)
C(7)-C(8)	1.522(5)
C(8)-C(9)	1.556(5)
C(8)-C(12)	1.568(5)
C(9)-C(10)	1.528(5)
C(9)-C(13)	1.536(5)
C(11)-C(12)	1.532(6)
C(12)-C(13)	1.547(5)
C(21)-C(22)	1.497(6)
C(22)-C(23)	1.526(6)
C(24)-C(25)	1.537(6)
C(25)-C(26)	1.538(6)
C(27)-C(28)	1.538(6)
C(28)-C(29)	1.527(6)
O(1)-Si-C(22)	102.96(16)

O(1)-Si-C(28)	115.12(19)
C(22)-Si-C(28)	111.97(19)
O(1)-Si-C(25)	110.99(16)
C(22)-Si-C(25)	108.6(2)
C(28)-Si-C(25)	107.1(2)
C(11)-N-C(10)	122.0(4)
C(8)-O(1)-Si	150.0(2)
C(5)-O(3)-C(4)	105.3(3)
C(1)-C(2)-C(3)	116.7(4)
C(1)-C(2)-C(7)	116.3(4)
C(3)-C(2)-C(7)	90.4(3)
C(4)-C(3)-C(6)	104.2(3)
C(4)-C(3)-C(2)	115.7(4)
C(6)-C(3)-C(2)	89.7(3)
O(3)-C(4)-C(3)	104.8(4)
O(3)-C(5)-C(10)	109.6(3)
O(3)-C(5)-C(6)	105.5(3)
C(10)-C(5)-C(6)	112.1(3)
C(5)-C(6)-C(3)	103.8(3)
C(5)-C(6)-C(7)	114.7(4)
C(3)-C(6)-C(7)	90.5(3)
C(8)-C(7)-C(6)	118.3(3)
C(8)-C(7)-C(2)	117.6(3)
C(6)-C(7)-C(2)	89.4(3)
O(1)-C(8)-C(7)	109.5(3)
O(1)-C(8)-C(9)	114.3(3)
C(7)-C(8)-C(9)	119.9(3)
O(1)-C(8)-C(12)	110.4(3)
C(7)-C(8)-C(12)	116.8(3)
C(9)-C(8)-C(12)	83.9(3)
C(10)-C(9)-C(13)	110.1(3)
C(10)-C(9)-C(8)	108.5(3)
C(13)-C(9)-C(8)	89.2(3)
N-C(10)-C(5)	108.5(3)
N-C(10)-C(9)	108.0(4)
C(5)-C(10)-C(9)	111.5(3)

O(2)-C(11)-N	123.7(4)
O(2)-C(11)-C(12)	123.8(4)
N-C(11)-C(12)	112.5(4)
C(11)-C(12)-C(13)	106.9(3)
C(11)-C(12)-C(8)	109.0(3)
C(13)-C(12)-C(8)	88.3(3)
C(11)-C(12)-Br	112.2(3)
C(13)-C(12)-Br	119.6(3)
C(8)-C(12)-Br	118.2(2)
C(9)-C(13)-C(12)	85.3(3)
C(21)-C(22)-C(23)	111.0(3)
C(21)-C(22)-Si	115.43(14)
C(23)-C(22)-Si	113.5(3)
C(24)-C(25)-C(26)	109.1(4)
C(24)-C(25)-Si	112.9(3)
C(26)-C(25)-Si	115.6(3)
C(29)-C(28)-C(27)	111.0(4)
C(29)-C(28)-Si	113.3(3)
C(27)-C(28)-Si	118.1(3)

Symmetry transformations used to generate equivalent atoms:

Table B.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Cyclobutane 157.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	63(1)	63(1)	71(1)	4(1)	19(1)	7(1)
Si	52(1)	56(1)	45(1)	-1(1)	13(1)	-4(1)
N	52(3)	65(2)	59(2)	0(2)	8(2)	-8(2)
O(1)	47(2)	64(2)	46(1)	-4(1)	14(1)	-5(1)
O(2)	57(2)	61(2)	75(2)	-1(1)	16(2)	-7(1)
O(3)	65(2)	58(2)	72(2)	4(1)	20(2)	1(1)
C(1)	93(4)	113(4)	57(3)	-11(3)	31(3)	10(3)
C(2)	61(3)	69(2)	56(2)	-7(2)	26(2)	-2(2)
C(3)	61(3)	76(3)	70(3)	-2(2)	32(2)	5(2)
C(4)	71(4)	69(3)	84(3)	-8(2)	25(3)	10(2)
C(5)	48(3)	63(2)	65(2)	4(2)	13(2)	0(2)
C(6)	50(3)	69(3)	61(2)	2(2)	21(2)	-6(2)
C(7)	51(3)	58(2)	49(2)	7(2)	21(2)	1(2)
C(8)	47(3)	55(2)	44(2)	0(2)	14(2)	-5(2)
C(9)	60(3)	55(2)	46(2)	5(2)	18(2)	-4(2)
C(10)	56(3)	61(2)	49(2)	8(2)	10(2)	-3(2)
C(11)	58(3)	57(2)	49(2)	-6(2)	18(2)	-2(2)
C(12)	53(3)	58(2)	47(2)	-1(2)	16(2)	-3(2)
C(13)	57(3)	68(3)	46(2)	-4(2)	18(2)	-6(2)
C(21)	97(4)	125(4)	68(3)	33(3)	19(3)	9(3)
C(22)	68(3)	80(3)	58(2)	2(2)	9(2)	0(2)
C(23)	73(4)	101(4)	78(3)	-1(3)	-8(3)	-5(3)
C(24)	78(4)	102(4)	75(3)	-18(3)	32(3)	1(3)
C(25)	58(3)	75(3)	55(2)	-1(2)	15(2)	-7(2)
C(26)	81(4)	107(4)	75(3)	-8(3)	35(3)	-26(3)
C(27)	88(4)	80(3)	85(3)	-29(3)	28(3)	-4(3)
C(28)	69(3)	58(2)	68(3)	-4(2)	19(2)	-12(2)

C(29)	89(4)	62(3)	93(4)	6(2)	15(3)	4(2)

Table B.5 Hydrogen coordinates (x 10 ^{4}) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for Cyclobutane 157.

	x	y	z	U(eq)
H	5460(40)	6120(40)	4820(20)	41(13)
H(1A)	8613	7914	7937	129(12)
H(1B)	7272	7423	7864	129(12)
H(1C)	7582	8837	8017	129(12)
H(2A)	7960(20)	8990(20)	6875(5)	52(3)
H(3A)	5520(20)	8677(4)	6931(13)	52(3)
H(4A)	4950(20)	10103(9)	6015(4)	52(3)
H(4B)	6360(13)	10567(19)	6399(7)	52(3)
H(5A)	4930(40)	8237(4)	5164(10)	52(3)
H(6A)	5370(30)	7060(30)	6140(2)	52(3)
H(7A)	7283(4)	6520(30)	6746(11)	52(3)
H(9A)	8193(14)	8450(30)	5259(2)	52(3)
H(10A)	6251(10)	7888(14)	4505(19)	52(3)
H(13A)	9360(20)	6688(5)	5129(2)	52(3)
H(13B)	8151(10)	6279(9)	4611(12)	52(3)
H(21A)	11735(4)	6635(4)	8341(3)	113(5)
H(21B)	10481(5)	6435(5)	7754(2)	113(5)
H(21C)	10768(4)	7724(4)	8144(3)	113(5)
H(22A)	11992(4)	6731(4)	7230(2)	63(7)
H(23A)	13395(15)	7767(13)	8140(11)	113(5)
H(23B)	12646(7)	9020(20)	7909(5)	113(5)
H(23C)	13319(13)	8371(7)	7395(10)	113(5)
H(24A)	12268(10)	6870(5)	5411(11)	113(5)
H(24B)	11330(17)	6238(18)	5750(3)	113(5)
H(24C)	12582(18)	6727(7)	6228(12)	113(5)
H(25A)	10740(30)	8221(5)	5477(19)	63(7)
H(26A)	12568(10)	9060(6)	5411(12)	113(5)
H(26B)	12960(20)	9157(5)	6249(12)	113(5)
H(26C)	11862(12)	9990(20)	5791(3)	113(5)

H(27A)	10094(6)	11220(30)	7504(3)	113(5)
H(27B)	10850(20)	10055(9)	7875(12)	113(5)
H(27C)	9420(20)	9938(12)	7522(3)	113(5)
H(28A)	11160(40)	10295(18)	6804(2)	63(7)
H(29A)	9456(5)	11460(30)	6269(4)	113(5)
H(29B)	8730(20)	10219(12)	6068(4)	113(5)
H(29C)	9813(10)	10531(5)	5752(13)	113(5)

APPENDIX C

SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON PYRIDONE 197

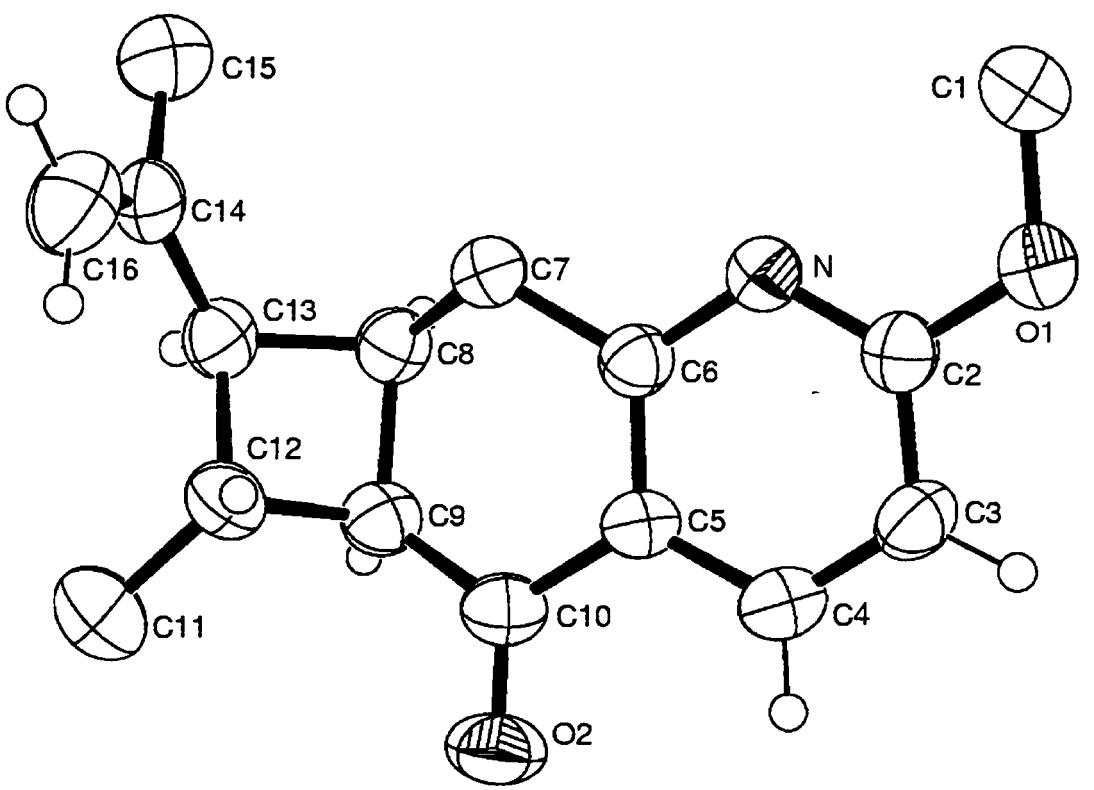


Table C.1 Crystal data and structure refinement for Pyridone 197.

Empirical formula	$C_{16}H_{19}NO_2$	
Formula weight	257.33	
Temperature	288(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (#14)	
Unit cell dimensions	a = 10.618(4) Å	α= 90°.
	b = 8.024(3) Å	β= 107.44(2)°.
	c = 17.216(7) Å	γ = 90°.
Volume	1399.4(9) $Å^3$	
Z	4	
Density (calculated)	1.221 Mg/m^3	
Absorption coefficient	0.638 mm^{-1}	
F(000)	552	
Crystal size	0.30 x 0.30 x 0.05 mm^3	
Theta range for data collection	4.39 to 69.33°.	
Index ranges	-12<=h<=12, -8<=k<=9, -20<=l<=20	
Reflections collected	4696	
Independent reflections	2437 [R(int) = 0.0347]	
Completeness to theta = 69.33°	93.3 %	
Max. and min. transmission	0.9688 and 0.8317	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2437 / 0 / 174	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0427, wR2 = 0.1097	
R indices (all data)	R1 = 0.0527, wR2 = 0.1188	
Largest diff. peak and hole	0.150 and -0.158 $e.Å^{-3}$	

Table C.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Pyridone 197.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3557(1)	3415(2)	9718(1)	58(1)
N	3448(1)	925(2)	10321(1)	43(1)
O(2)	6806(1)	-853(2)	12617(1)	67(1)
C(4)	5899(2)	1533(2)	11382(1)	47(1)
C(5)	5255(1)	62(2)	11432(1)	41(1)
C(2)	4100(2)	2287(2)	10287(1)	45(1)
C(6)	4019(1)	-187(2)	10888(1)	41(1)
C(9)	5249(2)	-2846(2)	11958(1)	48(1)
C(3)	5335(2)	2662(2)	10808(1)	50(1)
C(7)	3221(2)	-1659(2)	10951(1)	49(1)
C(8)	4024(2)	-3200(2)	11245(1)	46(1)
C(10)	5850(2)	-1177(2)	12050(1)	47(1)
C(12)	4467(2)	-3356(2)	12539(1)	52(1)
C(14)	2090(2)	-4370(2)	11724(1)	52(1)
C(1)	2307(2)	3031(3)	9162(1)	64(1)
C(13)	3524(2)	-4279(2)	11834(1)	48(1)
C(16)	1541(2)	-3730(3)	12233(1)	69(1)
C(15)	1319(2)	-5232(3)	10977(1)	80(1)
C(11)	5165(2)	-4289(4)	13296(1)	89(1)

Table C.3 Bond lengths [Å] and angles [°] for Pyridone 197.

O(1)-C(2)	1.3317(19)
O(1)-C(1)	1.418(2)
N-C(2)	1.304(2)
N-C(6)	1.328(2)
O(2)-C(10)	1.2074(19)
C(4)-C(3)	1.342(2)
C(4)-C(5)	1.379(2)
C(5)-C(6)	1.379(2)
C(5)-C(10)	1.455(2)
C(2)-C(3)	1.381(2)
C(6)-C(7)	1.477(2)
C(9)-C(10)	1.472(2)
C(9)-C(8)	1.523(2)
C(9)-C(12)	1.536(2)
C(7)-C(8)	1.501(2)
C(8)-C(13)	1.543(2)
C(12)-C(11)	1.493(3)
C(12)-C(13)	1.516(2)
C(14)-C(16)	1.296(3)
C(14)-C(15)	1.472(3)
C(14)-C(13)	1.479(2)
C(2)-O(1)-C(1)	117.44(14)
C(2)-N-C(6)	117.64(13)
C(3)-C(4)-C(5)	120.19(15)
C(6)-C(5)-C(4)	118.08(15)
C(6)-C(5)-C(10)	120.88(15)
C(4)-C(5)-C(10)	121.04(14)
N-C(2)-O(1)	118.90(14)
N-C(2)-C(3)	124.56(15)
O(1)-C(2)-C(3)	116.54(15)
N-C(6)-C(5)	122.26(15)
N-C(6)-C(7)	116.44(13)
C(5)-C(6)-C(7)	121.15(14)

C(10)-C(9)-C(8) 119.63(14)
C(10)-C(9)-C(12) 118.28(15)
C(8)-C(9)-C(12) 88.71(12)
C(4)-C(3)-C(2) 117.26(16)
C(6)-C(7)-C(8) 113.74(13)
C(7)-C(8)-C(9) 112.32(14)
C(7)-C(8)-C(13) 114.26(14)
C(9)-C(8)-C(13) 87.40(12)
O(2)-C(10)-C(5) 121.31(16)
O(2)-C(10)-C(9) 121.04(16)
C(5)-C(10)-C(9) 117.65(14)
C(11)-C(12)-C(13)119.37(18)
C(11)-C(12)-C(9)118.59(16)
C(13)-C(12)-C(9) 87.92(12)
C(16)-C(14)-C(15)122.14(19)
C(16)-C(14)-C(13)123.24(18)
C(15)-C(14)-C(13)114.61(17)
C(14)-C(13)-C(12)122.28(15)
C(14)-C(13)-C(8)119.19(14)
C(12)-C(13)-C(8) 88.72(13)

Symmetry transformations used to generate equivalent atoms:

Table C.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Pyridone 197.

The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	55(1)	50(1)	61(1)	14(1)	6(1)	-5(1)
N	41(1)	41(1)	46(1)	3(1)	9(1)	-3(1)
O(2)	54(1)	63(1)	64(1)	2(1)	-13(1)	-1(1)
C(4)	38(1)	48(1)	52(1)	-8(1)	8(1)	-4(1)
C(5)	37(1)	41(1)	43(1)	-5(1)	8(1)	-1(1)
C(2)	47(1)	40(1)	47(1)	1(1)	13(1)	-1(1)
C(6)	39(1)	39(1)	43(1)	-1(1)	10(1)	0(1)
C(9)	42(1)	45(1)	54(1)	1(1)	11(1)	6(1)
C(3)	47(1)	41(1)	59(1)	-4(1)	13(1)	-9(1)
C(7)	43(1)	48(1)	51(1)	7(1)	4(1)	-8(1)
C(8)	49(1)	42(1)	47(1)	-3(1)	15(1)	-2(1)
C(10)	38(1)	51(1)	49(1)	-4(1)	7(1)	3(1)
C(12)	50(1)	55(1)	48(1)	8(1)	9(1)	5(1)
C(14)	53(1)	46(1)	56(1)	12(1)	16(1)	-2(1)
C(1)	55(1)	69(1)	60(1)	15(1)	4(1)	-2(1)
C(13)	50(1)	38(1)	54(1)	4(1)	15(1)	4(1)
C(16)	61(1)	68(1)	84(1)	4(1)	32(1)	-3(1)
C(15)	67(1)	99(2)	67(1)	3(1)	9(1)	-21(1)
C(11)	78(1)	105(2)	69(1)	36(1)	-1(1)	-5(1)

Table C.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Pyridone 197.

	x	y	z	U(eq)
H(4)	6727	1742	11747	62(2)
H(9)	5924	-3688	11973	62(2)
H(3)	5757	3656	10762	62(2)
H(7A)	2600	-1883	10420	62(2)
H(7B)	2715	-1405	11321	62(2)
H(8)	4209	-3842	10807	62(2)
H(12)	4025	-2377	12678	62(2)
H(1A)	2041	3912	8769	101(3)
H(1B)	1668	2917	9452	101(3)
H(1C)	2364	2005	8888	101(3)
H(13)	3856	-5416	11824	62(2)
H(16A)	633	-3807	12133	62(2)
H(16B)	2057	-3194	12699	62(2)
H(15A)	1388	-4630	10510	101(3)
H(15B)	410	-5287	10965	101(3)
H(15C)	1657	-6340	10971	101(3)
H(11A)	5816	-3580	13651	101(3)
H(11B)	5588	-5252	13157	101(3)
H(11C)	4539	-4633	13567	101(3)