1996

Synthesis of diterpene alkaloids

Tiberiu Mircea Siclovan
Iowa State University

INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Synthesis of diterpene alkaloids

by

Tiberiu Mircea Siclovan

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry

Major: Organic Chemistry

Major Professor: Dr. George A. Kraus

Iowa State University

Ames, Iowa

1996

Graduate College
Iowa State University

This is to certify that the doctoral dissertation of

Tiberiu Mircea Siclovan

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Committee Member

Signature was redacted for privacy.

Committee Member

Signature was redacted for privacy.

Committee Member

Signature was redacted for privacy.

Committee Member

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Dedication

To all those who understood my desire to pursue a career in the demanding field of synthetic organic chemistry and, paying the price of personal sacrifices, supported me throughout this endeavor. To my parents, spouse and friends.

TABLE OF CONTENTS

GENERAL INTRODUCTION

There are little chances of being wrong when stating that organic synthesis is the heart of modern organic chemistry. Nowadays, it certainly is one of the most dynamic areas of interest in chemistry. Synthetic organic chemistry is a key instrument in answering questions such as the origins of life and those of the Universe known so far, the nature of the interactions within ourselves, as well as with our surroundings, and ultimately whether we may become a galactic civilization or succomb to our own mistakes. The impact that synthesis has on our everyday lives is unparalleled, leaving practically no aspect unmarked. Medicine, modern agriculture, computers, aircraft and space technology, to name just a few areas, benefit and require an increasingly important synthetic effort.

Natural product synthesis offers an excellent training, as well as rewarding results. Indeed, the synthesis of such complex targets requires that the scientist be familiar with a variety of functional transformation procedures and their mechanistic aspects, and be able to use them creatively and efficiently in a field which is still perceived as a complex hybrid between science and art, in spite of all the streamlining and computational involvement it benefited from in the past decade.

The interest that diterpene alkaloids received lately has prompted us to attempt an efficient entry into this class of natural products. Some of our most relevant results are described in this work.

The first part of this dissertation addresses some of the work done using adamantane as a model for developing new methods of generating bridgehead reactive species. The second part details relevant approaches towards the synthesis of complex natural products in connection with the methodology previously described. The numbering of the compounds, schemes and references used are independent in each section.

PART I. A STUDY ON THE GENERATION AND TRAPPING OF ADAMANTYL ANIONS

INTRODUCTION

As a result of our interest in diterpene alkaloids containing bicyclo[3.3.1]nonane structural subunits, we decided to investigate the possibility of using bridgehead anions as intermediates in our synthetic approach to this class of natural compounds. A secondary goal that we set for ourselves to achieve, was to investigate the relatively unknown chemistry of bridgehead anions and to apply it to the synthesis of simpler, but not less important compounds, which either are already known to possess remarkable biological activity, or are likely to act as analogs of the former.

BRIDGEHEAD INTERMEDIATES IN ORGANIC SYNTHESIS A REPRODUCIBLE SYNTHESIS OF ADAMANTANE-CONTAINING COMPOUNDS§

Compounds containing the adamantane subunit have long been of interest to chemists due to the rigid structure and well-defined substitution chemistry of adamantane.[1] The discovery of the potent antiviral activity of amantadine (1-aminoadamantane) and rimantadine (α-methyl-1-adamantylmethylamine) has stimulated interest in the synthesis of adamantane-containing compounds.[2] The significant neuroprotective properties of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine[3] (1-amino-3,5-dimethyladamantane) have also prompted interest in adamantane synthesis.

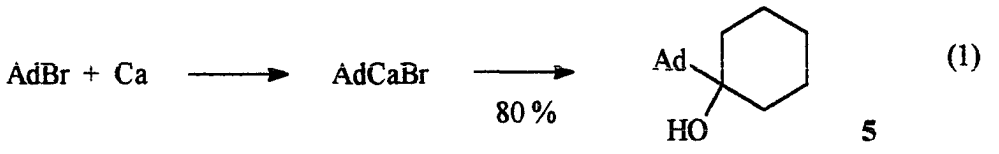
Although the carbocation chemistry of the adamantane system has been extensively studied, the chemistry of adamantyl bridgehead anions has been addressed in only a few isolated publications. No study of the scope and limitations of adamantyl bridgehead anions has been reported. Moreover, the literature of this bridgehead anion is complicated by problems related to reproducibility of experimental protocols.

Dubois and coworkers report that stirring a two-phase mixture of bromoadamantane (AdBr, **1**) and magnesium actually decreased the yield of Grignard reagent **2** compared with allowing the two-phase mixture to stand without stirring.[4] Dubois also reported that the use of the activated magnesium preparation developed by Rieke did not afford **2**. Yurchenko developed a quite different set of optimal conditions. He observed significant amounts (38-

AdBr	AdMgBr	AdCaBr	AdLi
1	**2**	**3**	**4**

§ Kraus, G.A.; Siclovan, T. M. *J. Org. Chem.* **1994**, *59*, 922.

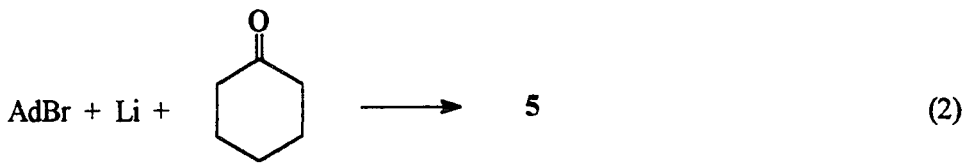
48%) of radical-derived products.[5] Organolithium **4** has been prepared and treated with nonenolizable ketones to provide hindered alcohols in modest yields.[6] Recently, Rieke and co-workers prepared an activated calcium reagent which reacted with adamantyl bromide to generate an organocalcium reagent **3** which, upon reaction with cyclohexanone, afforded an 80% yield of alcohol **5**.[7]



5 (1)

In the context of our continuing interest in bridgehead intermediates,[8] we tried the procedures of Dubois, Yurchenko and Rieke using adamantyl bromide. Attempts to make Grignard **2** and trap it with cyclohexanone gave low yields of alcohol **5** with much recovered starting material and some adamantane. Our experiments using the calcium reagent developed by Rieke afforded a 20% yield of **5** with much unreacted **1.** These experiments were not conducted using drybox techniques, and such techniques appear to be essential.[9] However, the most widely used synthetic organometallic reactions can be conducted without having to resort to drybox techniques, so we searched for reaction conditions that were more convenient.

Metal-halogen exchange, a useful method for the generation of organometallic compounds, was then tried.[10] Interestingly, Lansbury has reported that the exchange reaction between 1-iodoadamantane and *tert*-butyllithium does not proceed to completion.[11] However, the reaction of **1** with lithium wire containing 1-2 % sodium in tetrahydrofuran (THF) at 0° C in the presence of cyclohexanone produced alcohol **5** in 72% isolated yield, presumably via the intermediacy of **4**.



The reaction of 1 with Li and isobutyraldehyde furnished only a 32% yield of alcohol 6. Since alcohol 6 was an early intermediate in one of our synthetic routes, we studied the effects of varying reaction parameters. Table 1 depicts our results.

The optimal conditions involved the sonication of a mixture of 1, isobutyraldehyde and lithium at 0° C in ether. The reaction of representative carbonyl compounds using these conditions is collated in Table 2. The comparison of the results with isobutyraldehyde and pivaldehyde suggests that competitive deprotonation by the resulting alkoxide might be attenuating the yields. The failure of α-chloroisobutyraldehyde was unexpected and may be due to the facile reduction of the aldehyde carbonyl group. Although no chloro alcohol was isolated, the intermediate alkoxide would likely have generated a volatile epoxide by the displacement of chlorine.

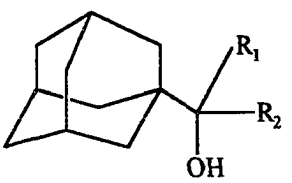
Table 1. Reactions of 1-Bromoadamantane, Lithium, and Isobutyraldehyde

i-PrCHO / 1	Li / 1	solvent	yield (%)
0.83	2.08	THF	32
1	1.5	THF	40
4	4.0	THF	7
1	1.5	Et_2O	46
1	1.5	Et_2O	56[a]

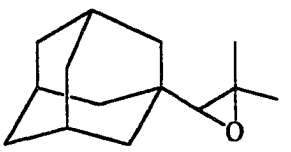
[a] Sonication

Table 2. Reactions of 1-Bromoadamantane, Lithium, and Carbonyl Compounds

carbonyl compound	RCOR' / **1**	Li / **1**	solvent	yield (%)	compd.
i-PrCHO	1	1.5	Et_2O	56	**6**
cyclohexanone	2	5	THF	72	**5**
cyclohexanone	2	5	Et_2O	74	**5**
2-cyclohexenone	0.83	2.08	THF	58	**7**
Me_3CCHO	2	5	THF	75	**8**
Me_3CCHO	2	5	Et_2O	80	**8**
PhCHO	0.83	2.08	THF	36	**9**
PhCHO	0.83	2.08	Et_2O	44	**9**
$Me_2C(Cl)CHO$	2	5	THF	0	**10**
$Me_2C(Cl)CHO$	2	5	Et_2O	10	**10**



5: R_1, R_2 = -$(CH_2)_5$-
6: R_1 = H, R_2 = i-Pr
7: R_1, R_2 = -$(CH_2)_3$-CH=CH-
8: R_1 = H, R_2 = Me_3C
9: R_1 = H, R_2 = Ph



10

Figure 1. Compounds prepared via in-situ generation and trapping of 1-adamantyllithium with carbonyl compounds

The reaction of the in-situ generated adamantyllithium reagent with other functional groups was also investigated. Although acetonitrile and propylene oxide did not react, adamantanecarboxaldehyde was isolated in 36% yield when dimethylformamide (DMF) was subjected to our standard conditions (eq. 3).

$$\text{AdBr} + \text{Li} + \text{DMF} \longrightarrow \text{AdCHO} \qquad (3)$$

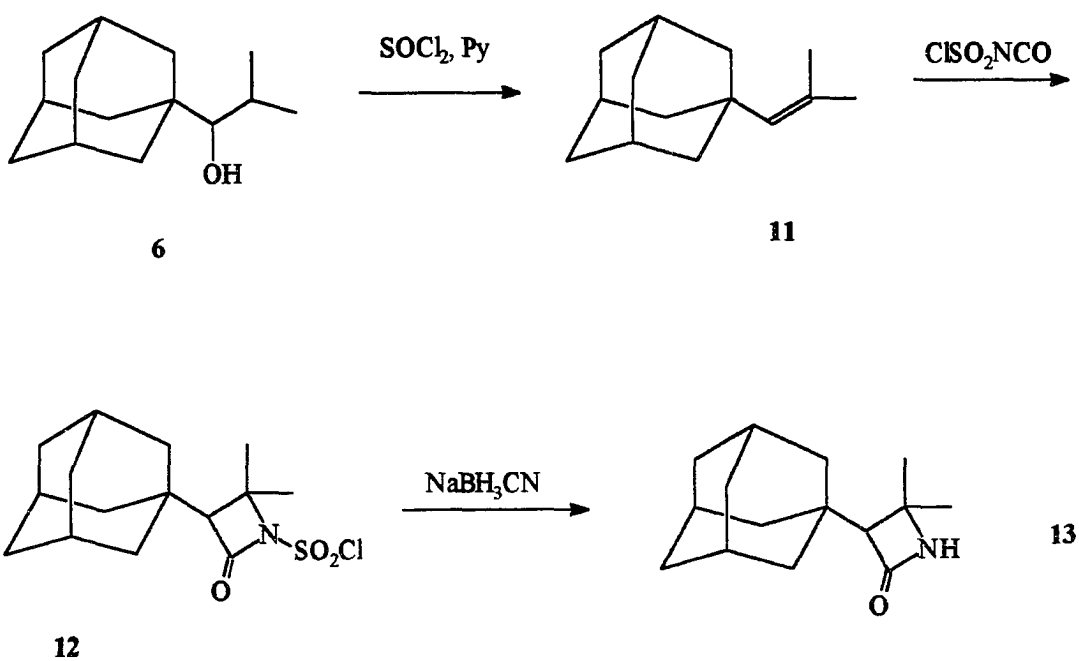
Our preparation of adamantyl carbinols via an in-situ generated organolithium reagent affords reproducible yields and is very convenient. It has been conducted on scales ranging from 1 mmol to 30 mmol. This work will facilitate the preparation of many compounds bearing the adamantane unit.

APPLICATIONS TOWARDS THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS CONTAINING THE ADAMANTANE UNIT

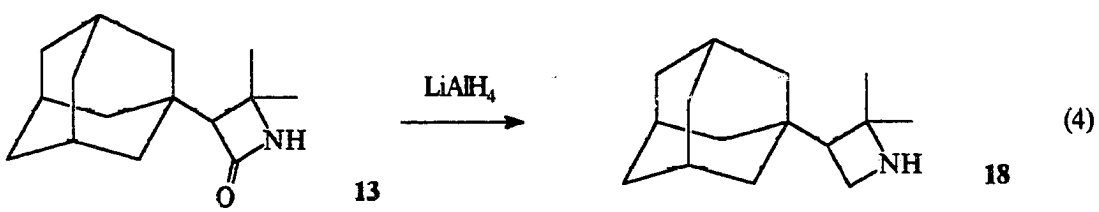
As briefly mentioned above, simple compounds containing the adamantane unit show remarkable biological activity. For instance, memantine prevents the acute toxic myopathy induced by organophosphate nerve agents *TABUN*, *SARIN*, *SOMAN* and *VX*,[3, 12] as well as the apoptosis induced in the rat cortical cell cultures by the HIV-1 protein gp120.[13]

Due to the interest expressed in the pharmacology of this interesting class of compounds,[14] we decided to apply our methodology towards the synthesis of adamantane derivatives. Thus, alcohol **6** was dehydrated to alkene **11**, which was then converted to the β-lactam **13** (Scheme 1) or the aziridine **14** (Scheme 2) following the methodology previously

Scheme 1.

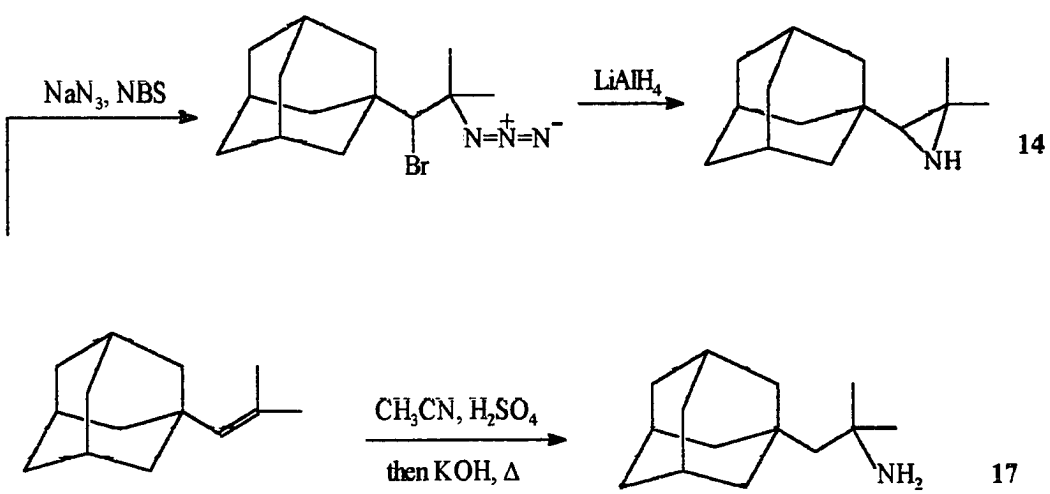


developed for the synthesis of derivatives of methyleneadamantane.[15] Lithium-aluminumhydride reduction of lactam **13** also provided the corresponding azetidine **18** (eq. 4). The β-adamantyl-α,α-dimethylethylamine **17** was prepared from alkene **11** using a Ritter reaction. It exhibited weak inhibition of several retro-virus strands. Amine **15** and the hydroxylamine **16** were prepared from alcohol **6** via reductive amination applied to the corresponding ketone and reduction of its oxime derivative, respectively (Figure 2).

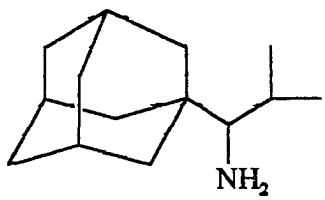


13 **18** (4)

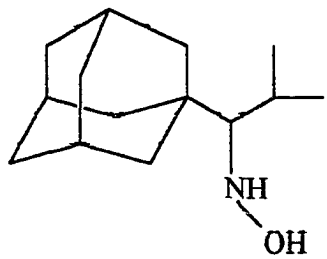
Scheme 2.



11 **14** **17**



15



16

Figure 2. Examples of compounds readily available from alcohol **6**

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes/ethyl acetate solvent mixtures for thin layer chromatography (TLC) and silica gel flash chromatography (SGC). The purity of all title compounds was determined to be > 95% by 300 MHZ proton NMR and/or elemental analysis.

General procedure. Li wire (6 mm in length, 3 mm diameter, 9.6 mmol) was cut into small pieces under N_2 and was added to a dry, N_2-flushed flask. Et_2O (8 mL) was then added, followed by a solution of anhydrous AdBr (410 mg, 1.9 mmol) in 2 mL of Et_2O. The flask was placed in an ultrasound bath containing water and crushed ice and sonication was started. The appropriate amount of aldehyde (3.8 mmol) was added dropwise via a syringe over 1 h. The mixture was further sonicated for 5 h. Depending on the aldehyde used, Li wire soon became clean and shiny as it reacted. The flask was then removed from the bath, 15 mL of H_2O was added, and the mixture was stirred for 5 min. The organic layer was separated, the aqueous was extracted with Et_2O (3x10 mL), and the combined organic layers were dried over Na_2SO_4. The product was separated by SGC with hexanes/ethyl acetate as eluent. Compounds **5**, **9**, and 1-adamantylcarboxaldehyde had been previously prepared.

1-Adamantyl-2-methylpropanol (6): ^{1}H-NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6 Hz, 1H), 1.5-2.1 (complex multiplet, 15H), 2.12-2.24 (broad singlet, 1H), 2.90 (br d, J = 3.9 Hz, 1H); IR (CCl_4) 3495 br, 2954, 2846, 1465, 1008, 786, 762 cm^{-1}; MS *m/e* 207, 165, 135, 107, 93, 70, 55; HRMS *m/e* for $C_{14}H_{24}O$ calcd 208.18272, found 208. 18246; mp 48-49°C; TLC (H:EA (10:1)) R_f = 0.47.

1-Adamantyl-2-cyclohexenol (7) ^{1}H-NMR ($CDCl_3$) δ1.4-2.2 (complex m, 21H), 4.15-4.3 (br s, 1H), 5.85 (complex m, 1H), 6.09 (d, J = 9.9 Hz, 1H); IR (CCl_4) 3630, 2910, 2853, 1454, 1289, 1027, 809, 761 cm^{-1}; MS *m/e* 135, 107, 79, 65; ^{13}C-NMR ($CDCl_3$) δ 18.90, 25.28, 28.51, 29.54, 35.72, 37.15, 38.45, 67.82, 72.58, 128.79, 131.31; mp 71-72°C; TLC (H:EA (10:1)) R_f = 0.44

1-Adamantyl-2,2-dimethylpropanol (8): ^{1}H-NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.45 (d, J = 6.3 Hz, 1H), 1.60-2.02 (complex m, 15H), 2.78 (d, J = 6.6 Hz, 1H); IR (CCl_4) 3648, 3530-3450 broad, 2906, 2849, 1481, 1363, 1005, 787, 763 cm^{-1}; MS *m/e* 222, 207, 165, 135, 107, 79, 67; HRMS *m/e* for $C_{15}H_{26}O$ calcd 222.19837, found 222. 19820; mp 113-114°C; TLC (H:EA (7;1)) R_f = 0.61.

PART II. SYNTHESIS OF DITERPENE ALKALOIDS

LITERATURE SURVEY

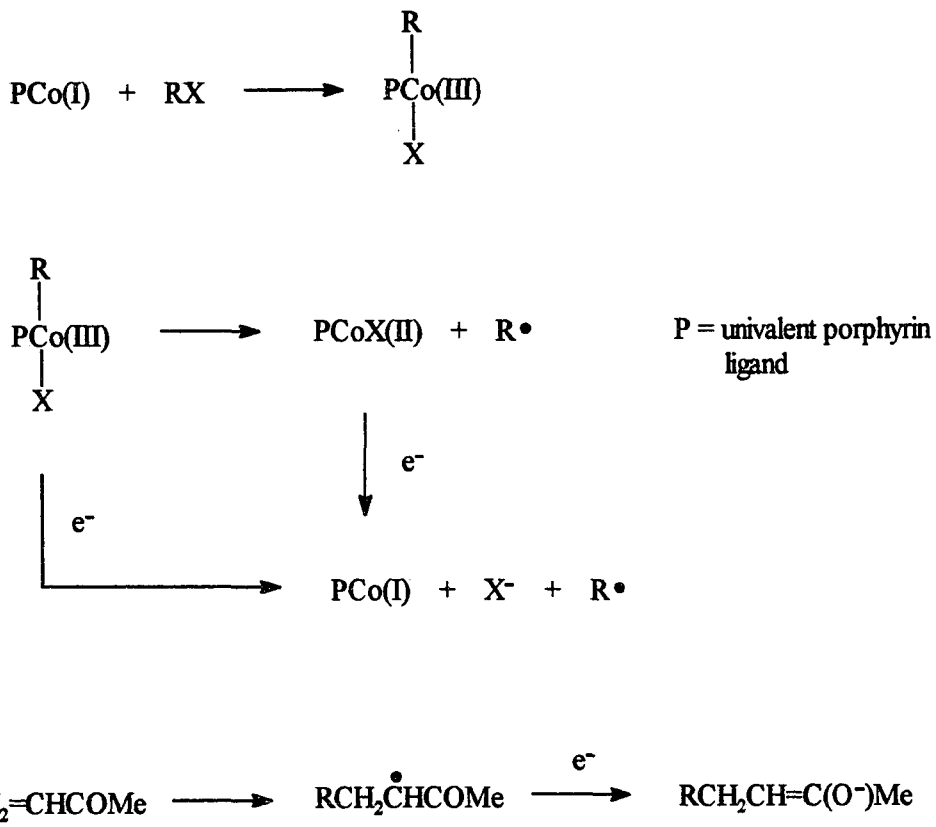
Conjugate addition of Co(III)-generated radicals to α,β-unsaturated ketones

Important progress has been made in radical chemistry during the past decade. As a result, synthetic organic chemists routinely consider radical-mediated carbon-carbon bond forming reactions in the strategy level planning of complex targets. An extensive review concerning applications of radical reactions in natural product synthesis has recently been published.[1] The most widely used methods include: the tin hydride method, the mercuric hydride method, the fragmentation method, the atom/group transfer method, the reductive method, and finally, the oxidative method of which electrochemical oxidation and the manganese(III) acetate oxidations are the most familiar. As is often the case, each of these methods have been developed to suit the needs of a particular application and to overcome the limitations of the other approaches currently in use at that time. Among the redox methods, the Cr(II) and Co(III) techniques proved to be superior in certain instances. Particularly in the due course of our research, an extension of the Co(III) method towards the generation of highly functionalized bridgehead radicals proved to be the only method that yielded the desired results.

A review detailing the acylation and alkylation of α,β-unsaturated ketones by Co(III)-generated radicals is also available.[2] In most cases, primary or secondary halides were used as precursors to radical species. In principle, both acylations and alkylations can be effected in either intermolecular or intramolecular fashion, although examples of intermolecular alkylations dominate. Radical generation may employ the photolysis of the isolated Co complexes, or may use an in-situ redox cycle and catalytic amounts of a Co(II) complex (Scheme 1).

With the exception of adamantyl bromide, our examples are the first to illustrate the applicability of this method in natural product synthesis via functionalized bridgehead radicals. A detailed account of our results, in the context of the latest achievements in this field, will be presented later in this work.

Scheme 1.



Particularities of nucleophilic additions to bicyclo[3.3.1]nonan-9-one and structurally related systems

The carbonyl functionality is of utmost importance to organic chemists who have long used the vast chemistry of the keto functionality as a pivotal point towards achieving today's impressive results in this field. Since nucleophiles may add to its π bond from two opposite faces, leading in most instances to different compounds, considerable attention has been devoted to defining the circumstances that govern facial selectivity in this type of reaction.[3, 4] Inclusion of the keto functionality in a bicyclic system further complicates its behavior through additional and more subtle through-bond interactions with neighboring or more remote functional groups. A brief critique involving some of the facts most relevant with respect to the research reported in this thesis will be given at this point.

Facial selectivity in bicyclo[3.3.1]nonanone-related systems

While easy to recognize, although not as easily quantified, the steric factor plays an important role in defining π facial stereoselection. Fortunately, its influence is always predictable in qualitative terms, addition proceeding from the less hindered face, all other factors being kept constant. Augmenting or balancing this factor are torsional and electronic effects: hyperconjugation, through-bond and spatial electrostatic effects.

A recent structure and charge density study[5] of variously 4-substituted cyclohexanones and heterocyclohexanones revealed that the electrostatic field difference between the two sides of the carbonyl plane affects the stereoselectivity. Transition state studies show that for 4-axially-substituted cyclohexanones the increased preference for axial attack results from the larger barrier for equatorial attack. For molecules in which the ring is flat, the observed

preference for axial attack results from increased torsional strain for equatorial attack, quantified in the electron density of the axial C-H bonds at C_2 and C_6. If coordination with a metal species is considered, the selective alkyl addition is likely to involve an electron-transfer mechanism. In the radical anion formed, which would have essentially the same geometry as that of the neutral complex, steric hindrance commands the addition to proceed from the less bulky face of the coordinated ketone.[6]

In a study of variously 4-substituted trans-decalones,[7] equatorial electron-withdrawing substituents have been shown to have very little effect on the stereoselectivity, while axial substituents had a large effect. Ab-initio calculations have indicated that the distortion about the C_{sp^2}-C_α bonds and the pyramidalization at the C_{sp^2} center are both enhanced by electron-withdrawing substituents, particularly fluoro substitution. The importance of long-range electrostatic effects results from examining the influence of hydroxy and amino substitution, which show strong dependence upon group orientation.

In the case of variously 2,3-endo,endo-disubstituted 7-norbornanones[8,9] (Figure 1), nucleophiles approached the carbonyl preferentially from the *syn* face in the case of electron-deficient substituents and from the *anti* face if electron-donating substituents were involved.

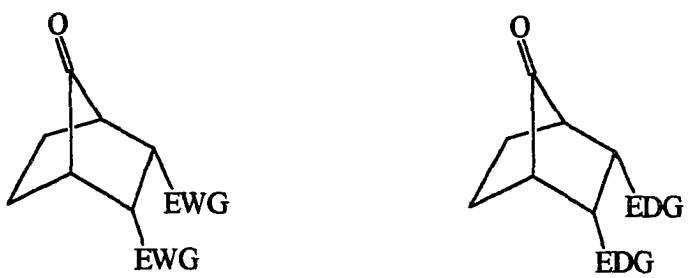


Figure 1. Substitution pattern of 7-norbornanones used in the study of hyperconjugation effects

If hyperconjugation is invoked, delocalization of σ electrons in the electron-rich antiperiplanar bond into the incipient σ* orbital lowers the transition state energy. Thus, electron-withdrawing substituents induce positive charges at C_2 and C_3 and *syn* addition becomes favorable. For electron-donating substituents, the opposite is true. Negative charges at C_2 and C_3 favor *anti* addition.

One of the problems of the hyperconjugation model, when quantitative results are sought, stems from the close connection between hyperconjugation and conformation. An attempt to dismiss the conformational factor by keeping it rigorously constant was made in the case of sterically unbiased 7-norbornanones.[10] Indeed, clean, quantitative results could be obtained this way. Unfortunately, the data thus obtained can hardly be applied to more complex systems, without risking contrasting results between prediction and experiment.

An extensive study on the behavior of various *cis*-[n.3.1] bicyclic ketones towards hydride and dissolving metal reductions, organometallic additions, condensation with dimethyloxosulfonium methylide, epoxidation, osmylation, oxymercuration, and cycloadditions involving chlorosulfonyl isocyanate and dichloroketene has recently been reported.[11] Generally, the results were similar to those reported for 4-*tert*-butylcyclohexanone. However, when an axially-oriented loop was present, a strong preference for the less hindered equatorial approach was noted. Highly biased results were obtained when bulky reagents were used. With increasing nucleophile size, a point was reached where steric approach became overriding. Since the effective size of any reagent is also dependent on a number of hardly predictable factors, such as solvation, self-association, coordination, and angle of attack, caution must be exerted when attempting to extrapolate these results to other systems.

In the case of 5-substituted adamantanones,[12] strongly enhanced selectivities were noted, particularly for 5-aza-adamantanone (Figure 2)[13, 14]. Addition of methyllithium to **1** proceeded as predicted, with a 55/45 Z/E selectivity. Borohydride reduction proceeded with

reversed selectivity, to give a 62/38 Z/E mixture. A hydrogen-bonded amine center was invoked in order to explain this unprecedented result. Following quaternization of the amine, borohydride reduction proceeded with a 4/96 Z/E selectivity. Unfortunately, no report has been made on the reaction of methyllithium with the same substrate. When considering the borohydride reduction, the effect is so much more visible than before because of the powerful deactivation of the bonds vicinal to the 5-substituent.

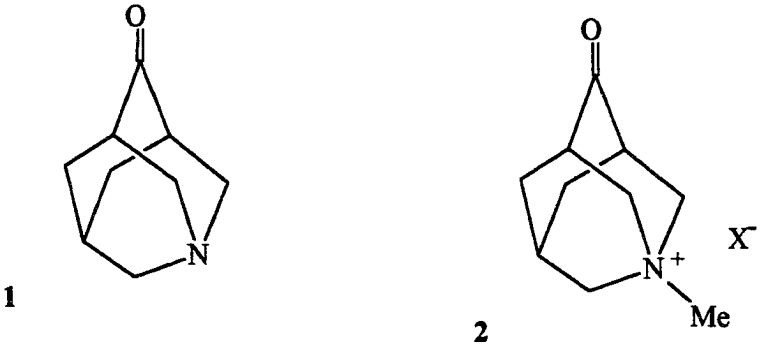


Figure 2. Aza-adamantanones employed in facial selectivity studies

Similar face selectivities have been reported when nucleophilic additions to the trigonal C_2 site in 5-azaadamantane derivatives and in the reduction of variously 5-substituted adamantanones were investigated.[15]

Electrostatic *vs* hyperconjugative effects as stereoinductive factors in the adamantane ring system have been thoroughly investigated with respect to both nucleophilic and electrophilic reactions.[16] The authors insist that electrostatic field interactions play a dominant role in governing nucleophilic additions to adamantanones and that it is unnecessary to invoke transition-state hyperconjugative models in these instances.

The complexity of the phenomena studied makes quantitative arguments difficult, if not hazardous, to defend in the case of more complex systems, obtained as a result of extensive synthetic work. Qualitatively, the wealth of knowledge presently available about these systems is reasonably helpful from a synthetic point of view.

Pharmacological properties of 3-aza-bicyclo[3.3.1]nonane derivatives

The 3-aza-bicyclo[3.3.1]nonane system is part of over one hundred known naturally-occurring compounds (*vide infra*), the majority of which exhibit potent biological activity. Interestingly, the 2,4-disubstituted 3-aza-bicyclo[3.3.1]nonanones alone are remarkably active. The stereochemical and conformational characteristics of these compounds are critical towards their activity.[18] Several of the structure-activity relationships developed for the γ-aminobutyric acid (GABA) receptor have been rationalized in terms of the ability of the low-energy conformations to dock optimally on the pharmacophore framework and may explain at least partially the observed activity associated with this class of compounds. The aryl substituents lock the molecular skeleton into a conformation which best mimics the GABA pharmacophore (Figure 3).

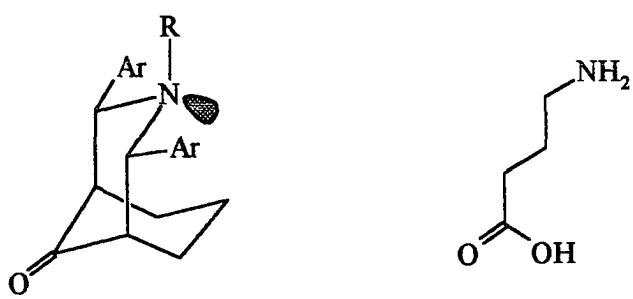


Figure 3. Structural similarities between 3-aza-bicyclo[3.3.1]nonane and GABA

Other derivatives, such as hydantoins, cyanohydrins and aminonitriles of 2,4-diaryl-3-aza-bicyclo[3.3.1]nonanone and 7,9-diphenyl-8-aza-bicyclo[4.3.1]decanone, have also been evaluated for their pharmacological properties.[19]

In addition to their activity upon the central nervous system, the compounds mentioned above, as well as the corresponding nonanes and 3,7-dihetera-bicyclo[3.3.1]nonanes[20] have been investigated with respect to their antiarrhythmic properties. When these compounds were administered to anesthetized dogs in which myocardial infarction was induced, the most common cause of death, ventricular tachycardia, was completely suppressed and could not be induced even artificially. The effective dosage ranged from 3 to 6 mg/kg, considerably lower than that of lidocaine, commonly used to alleviate, but not suppress, these side effects.

Several 2,3,7-trisubstituted 3,7-diaza-bicyclo[3.3.1]nonanes have also been investigated for their antiarrhythmic properties and compared with sparteine, diisopyramide and propranolol.[21] Although remarkably potent, these compounds exhibited a dangerously low therapeutic index, ranging from 0.89 to 1.24.

More complex molecules possessing the 3-aza-bicyclo[3.3.1]nonane motif, such as the alkaloids which are the objective of the synthetic effort reported herein, exhibit an even broader and more complex spectrum of biological activity, most of which can be utilized for medical purposes.

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF DITERPENOID ALKALOIDS

Introduction: Pharmacology

Diterpene alkaloids are of common occurrence in the plant world[22] and have long been of interest to chemists and pharmacists as well. Of these many natural compounds, about 70 alkaloids of diterpenoid structure have been identified in extracts from plants of genera *Aconitum*, *Delphinium* (family *Ranunculaceae*), *Spiraea* (family *Rosaceae*), *Garrya* (family *Garryaceae*) and *Consolida* (family *Consolidaceae*). The particular structure of these alkaloids makes the synthesis of these compounds both an attractive and a challenging endeavor. The pharmacological properties of some of these compounds have been exploited since ancient times in regions of the Far East.[23] Depending on the particular plant source and mode of preparation, the extracts used in traditional Chinese and Japanese medicine show analgesic, antiinflamatory, antiarrhythmic and sometimes antipyrhetic properties.[24] Besides atisine, the spiramines have recently been identified[25] in extracts from these sources and there seems to be an increasing interest among researchers in Southeast Asia in identifying, isolating and characterizing new active compounds belonging to this class.[26]

Methyllycaconitine (MLA), found in *Delphinium*, but not *Aconitum*, as its name would suggest, acts at the neuromuscular junction, inhibiting neurotransmission and inducing paralysis. It is stated to be the most potent non-protein antagonist of the neuronal nicotinic acetylcholine receptor yet found. According to some reports, its toxicity surpasses even that of the notorious snake venom α-bungarotoxin.[27]

Lycoctonine, the corresponding neopentyl alcohol derived from MLA, is equally toxic to cattle[28] and other mammals and insects,[29] although considerably less potent than MLA.

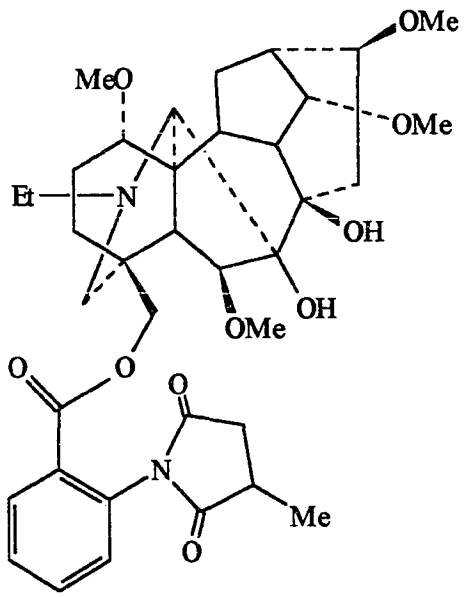
Several lycoctonine esters, as well as minute amounts of MLA, find use as muscle relaxants during surgery,[30] as they have curare-like activity. Their advantage over other similarly acting compounds stems from the fact that MLA is an extremely potent and selective ligand for neuronal over neuromuscular nicotinic acetylcholine receptors.

Recently, it has also been discovered that at least one of the alkaloids present in root extracts from plants belonging to the *Aconitum* genus is remarkably effective in restoring the protective activity against infections at dosages as low as 10 μg/kg/day.[31] Thus, "benzoylmesaconine administered orally to cytomegalovirus-infected mice effectively controlled viral, fungal and opportunistic infections". One of the main drawbacks of using natural extracts from these plants for medical purposes consists of the fact that the proportion of the active agents is highly dependent on the growing and processing conditions of the plants used. Unfortunately, some of the diterpenoid alkaloids present in these sources are also potent neurotoxic agents, hence the potential for poisoning while using extracts from these natural sources and the interest in making these compounds available in pure form through synthesis. This will allow for an accurate dosage and a fine tuning of the desired pharmacological effect by a more scientifically balanced drug composition.

Historical

Based on their chemical structure, the above mentioned diterpene alkaloids belong to three groups: aconitine type alkaloids, of which methyllycaconitine is one of the most complex representatives, atisine type alkaloids, shown here as the most complex, recently identified spiramine F representative[2] (Figure 4) and a minor series represented by garrya alkaloids. These formulas have been given here in order to provide a reference for the work which will

Methyllycaconitine:



Spiramine F:

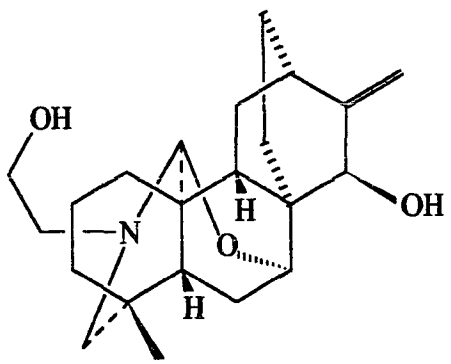
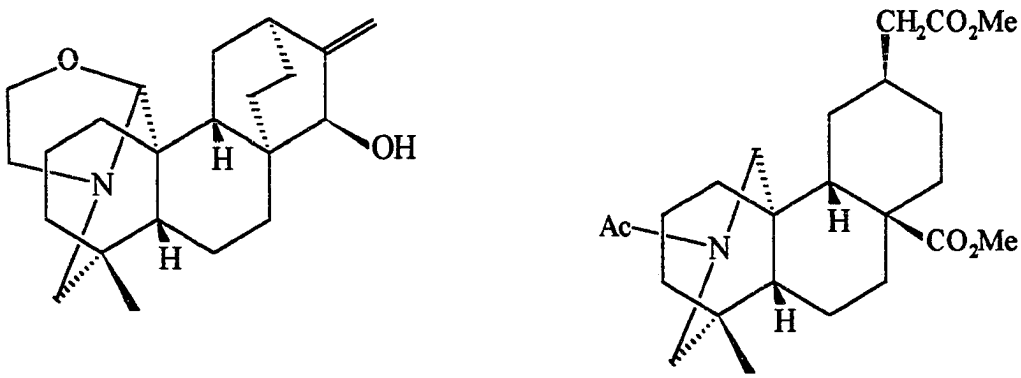


Figure 4. Structural and functional features of aconitine and atisine type alkaloids

be presented. The numbering system and the structures of some of the most representative alkaloids in each group are given in Appendix I.

The common feature of these compounds consists of the 3-azabicyclo[3.3.1]nonane system which also suggests a common intermediate for the synthesis of these alkaloids. Construction of the 5,6,7- fused tricyclic moiety present in the aconitine alkaloids represents a truly outstanding synthetic challenge. A serious obstacle is also represented by the construction of the bicyclo[2.2.2]octane ring system in the case of atisine alkaloids. This is probably the main reason why there are no reports regarding total syntheses of aconitine alkaloids and only two formal synthesis of atisine in spite of their practical interest. This is in strong contrast with the numerous reports on the isolation and characterization of diterpene alkaloids from natural sources.

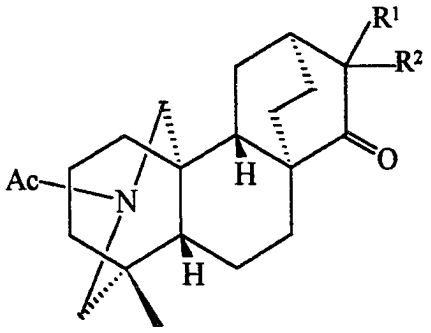
Natural product chemists have been among the first to investigate the chemistry of these highly functionalized compounds.[32] An early partial synthesis of atisine (**1**) belongs to Pelletier.[33] Thus, the diester **2**, obtained as a degradation product of the natural alkaloid, was reconverted to atisine (Figure 5).



1 **2**

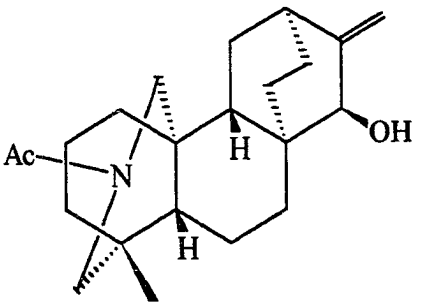
Figure 5. Atisine (**1**) and a degradation product (**2**) used in its synthesis

The desired transformation was achieved by first subjecting **2** to a Dieckmann cyclization with sodium in xylene, followed by hydrolysis and decarboxylation of the corresponding β-ketoacid to give ketone **3** (Figure 6). Methylation, followed by a bromination-dehydrobromination sequence, introduced the methylene group, resulting in the formation of compound **4**, which was reduced to the corresponding mixture of epimeric alcohols from which **5** was separated. Removal of the acetyl group and replacement with an ethyl group gave atisine **1**.



3: $R^1 = R^2 = H$

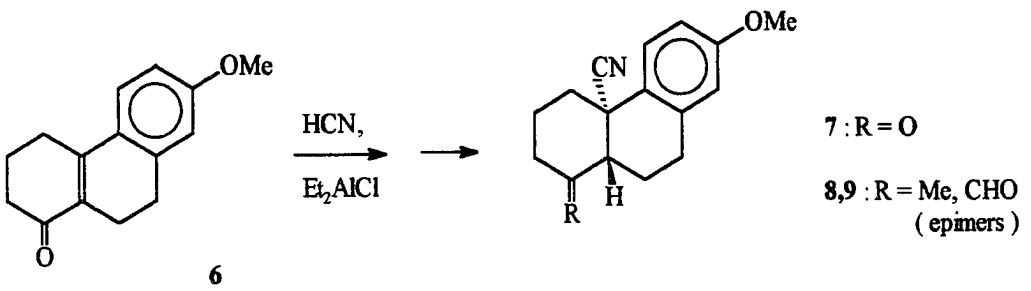
4: $R^1, R^2 = CH_2$

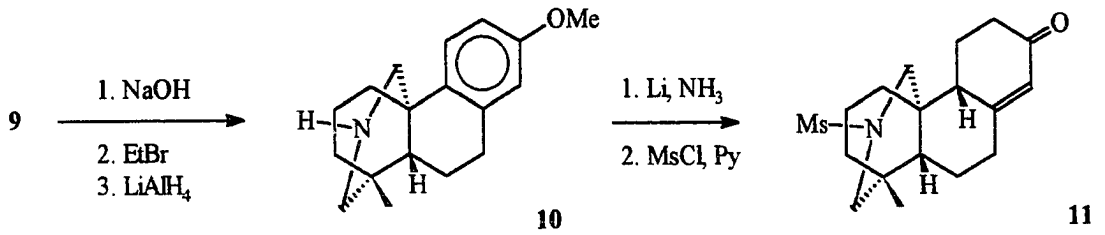


5

Figure 6. Products obtained via cyclization of compound **2**

Scheme 2.

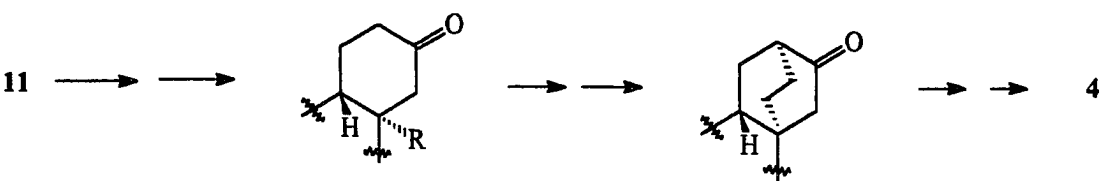




The first total synthesis of atisine, albeit formal, belongs to Nagata.[34] The synthetic work began with compound **6**, readily available in four steps from 6-methoxy-1-tetralone (Scheme 2). Hydrocyanation of **6** afforded a mixture of crude cyanoketones which epimerized to **7** upon recrystallization in the presence of hydrochloric acid. Wittig olefination with Ph_3P=CHOMe, acid hydrolysis and subsequent methylation gave, upon separation, compound **9**. A one step procedure in which alkaline hydrolysis to the amide, and condensation with the aldehyde moiety was followed by ethylation, resulted in the formation of an epimeric mixture of ethoxylactams which was reduced with lithium aluminumhydride to the corresponding cyclic secondary amine. The free base underwent Birch reduction which, upon acid treatment, followed by protection of the secondary amine with mesyl chloride, gave enone **11**. A rather lengthy and quite cumbersome sequence of reactions, of which a few key points are depicted in Scheme 3, was necessary to reach Pelletier's intermediate **4**.

In order to construct the bicyclo[2.2.2]octane ring system, compound **11** was again hydrocyanated; conversion of the highly hindered cyano group into the methyl ketone was achieved via the corresponding ketal, resulting in the formation of compound **13** (Scheme 3). Since cyclization of this intermediate resulted in the formation of a bicyclo[2.2.1]heptane system, a one carbon extension sequence was required, eventually leading to the formation of

Scheme 3.



12 : R = CN

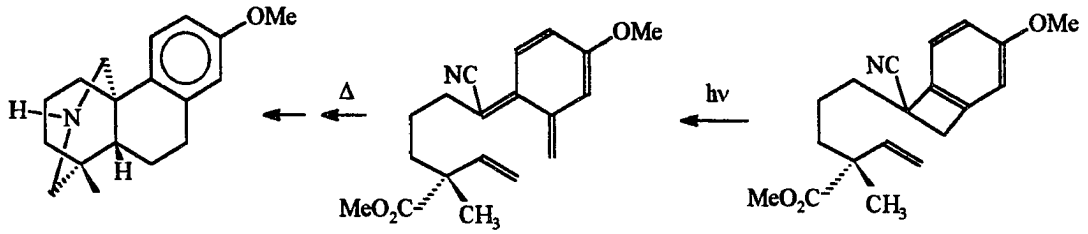
13 : R = $COCH_3$

14

compound **4**, which had already been taken to the natural compound atisine. In spite of the initially concise approach, this synthesis is shadowed by the long synthetic path required in the end. It has, nevertheless, the merit of being the first truly synthetic approach in its class.

According to Fukumoto, a Nagata-type intermediate of a structure similar to that of **7**, can be more readily attained using a regiospecific, stereocontrolled electrocyclic reaction applied to a functionalized benzocyclobutene derivative,[35] or to an appropriately functionalized *o*-quinodimethane, as illustrated in Scheme 4.

Scheme 4.



10 **15** **16**

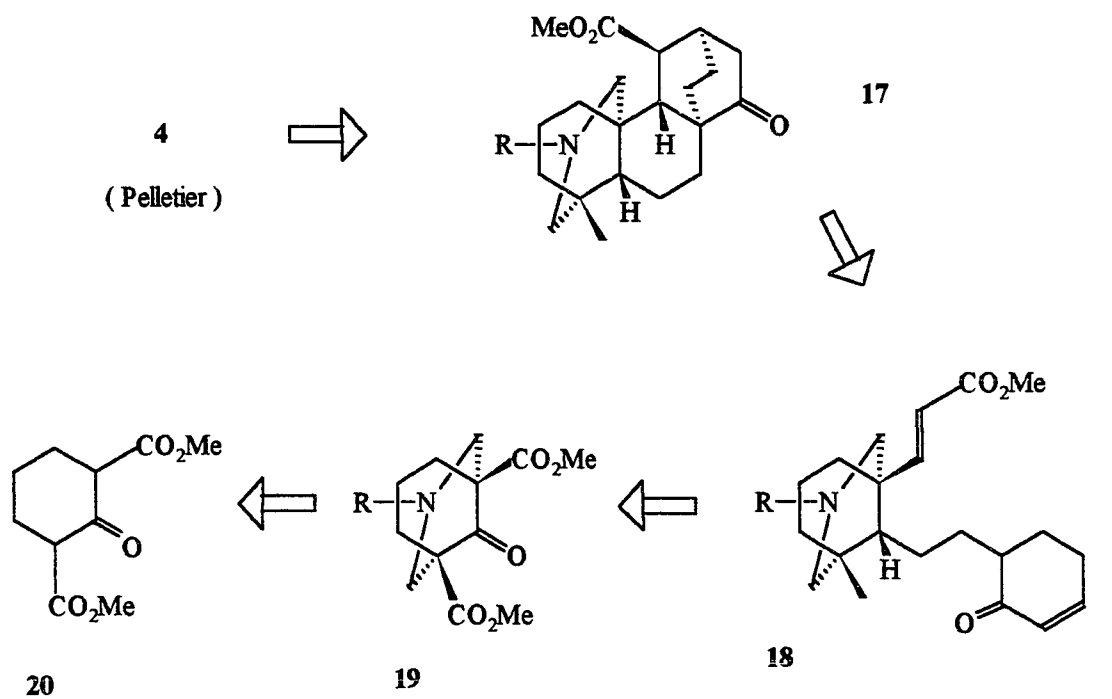
Although the strategy depicted in Scheme 4 proved to be successful, it did not address the real shortcomings of Nagata's synthesis, which only surface towards the end of that synthetic effort. A conceptually different approach was later undertaken by Fukumoto, in a beautiful asymmetric formal total synthesis of atisine via an intramolecular double Michael reaction used in the key step.[37] The synthetic strategy is shown in Scheme 5.

Pelletier's intermediate **4** is readily available from compound **17** via decarboalkoxylation, which, in turn, results from the double 1,4-addition of the anion of **18**, first to the unsaturated ester moiety in a six-exo-trig cyclization, immediately followed by a six-endo-trig cyclization of the resulting anion onto the enone moiety. Compound **18** is

available as a single enantiomer from the meso compound **19** by enzymatic desymmetrization. Construction of the 3-azabicyclo[3.3.1]nonane system is achieved again at an early stage, following a known procedure, consisting of a double Mannich reaction on the commercially available ketodiester **20**.

In spite of the beautiful science developed in the due course of this work, the synthesis of atisine by this route is well beyond practicality. Not only is the proposed route long by itself, which results in low overall yields, but the completion of the synthesis via Pelletier's route would add several steps which constantly proceed in discouragingly low yields.

Scheme 5.



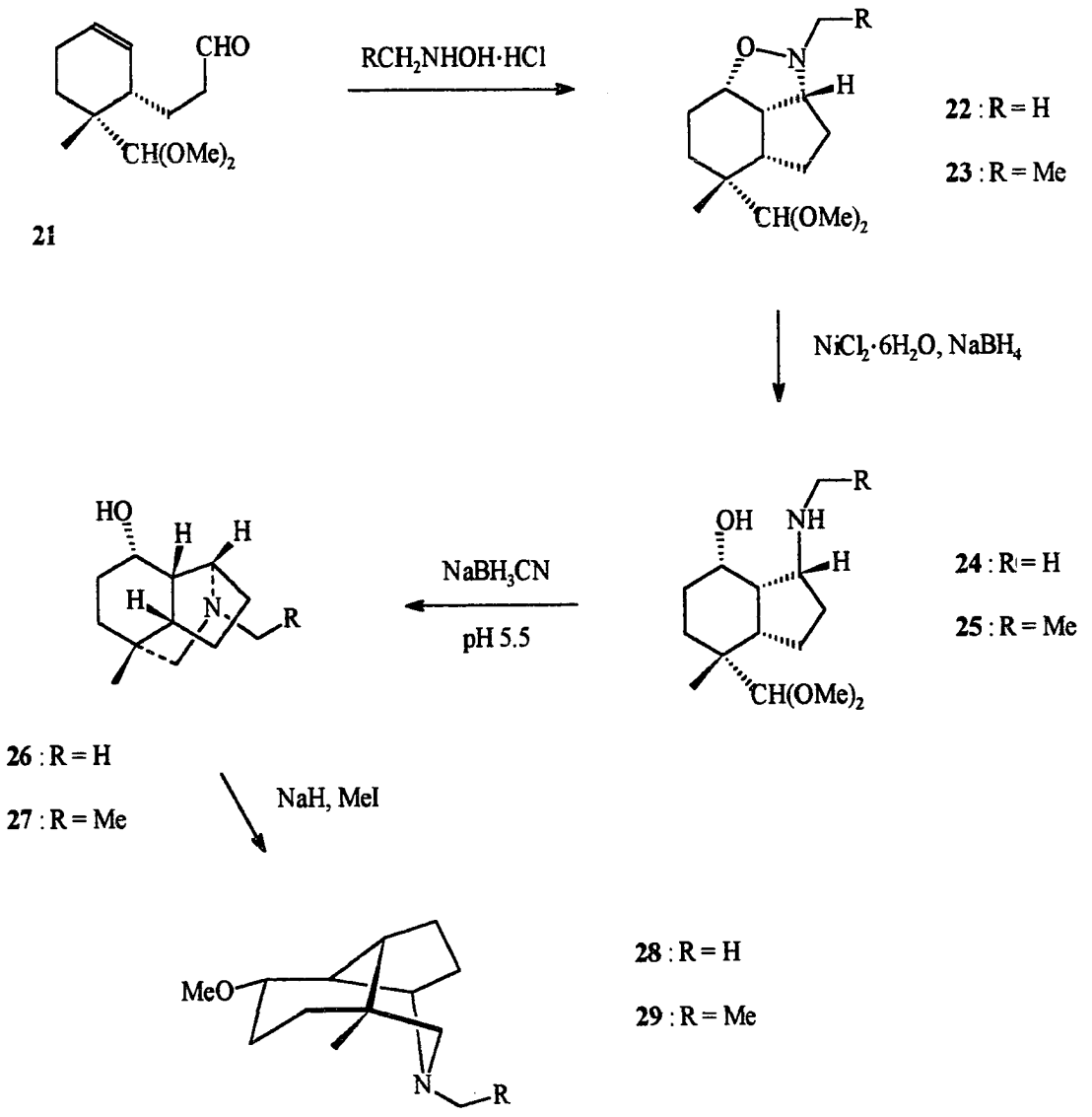
Wiesner and coworkers have successfully prepared a tetracyclic intermediate suitable for the synthesis of diterpene alkaloids.[38] However, an unexpected rearrangement noted by Birnbaum[39] precluded them from reaching any of the desired target compounds, in spite of some quite pertinent approaches. A different route was explored later.[40]

In the other series, a semi-synthesis of inuline, delsemine analogues and methyllycaconitine was recently reported by Blagbrough.[41] It actually consisted of acylation of the neopentyl alcohol functionality present in lycoctonine by a series of variously substituted acids. In a related work, the 3-aza-bicyclo[3.3.1]nonanone moiety and variously substituted anthranilate esters were connected via a 1-hydroxymethyl function on the bicyclic system[42]. The distance to any of the natural compounds is appreciable.

Presently, only the work of Whiting[43] really addresses this class of compounds from a synthetic point of view (Scheme 6). Thus, the mono-protected dialdehyde **21**, obtained from 1,4-pentadienol in four steps, was converted to the isoxazolidines **22** and **23** following direct treatment with methyl- or ethylhydroxylamine.

Efficient cleavage of the N-O bond was achieved using nickel chloride-sodium borohydride. A one-pot reductive amination carried out at pH 5.5 effected both the acetal hydrolysis and ring closure to give compounds **26** and **27**, which were then methylated with methyl iodide via the corresponding alkoxide. The competing N-alkylation step seems to be inhibited by steric compression of the resulting quaternary ammonium salts.

Scheme 6.


CHO
CH(OMe)2
RCH2NHOH·HCl
R
O
N
H
CH(OMe)2
22 : R = H
23 : R = Me
NiCl2·6H2O, NaBH4
OH
NH
R
H
CH(OMe)2
24 : R = H
25 : R = Me
NaBH3CN
pH 5.5
HO
H
H
H
N
R
26 : R = H
27 : R = Me
NaH, MeI
MeO
N
R
28 : R = H
29 : R = Me

21

RESULTS AND DISCUSSION

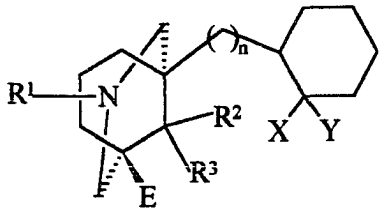
Retrosynthetic analysis

Stimulated by the recent discovery of novel pharmacologically active compounds belonging to the spiramine group, which are closely related to the natural compound atisine as shown before, we decided to engage ourselves in a search for a synthetic route which would have sufficient generality to allow not only for the synthesis of the parent compounds, but also for a number of analogs. This would be of significant importance for structure-activity correlations. We also imposed on ourselves an additional constraint, by attempting as short a synthetic sequence as possible, with the express goal of increasing the availability of these compounds, to the extent that might make them marketable.

A study directed towards the total synthesis of aconitine alkaloids would be an impressive task by itself, especially since there are no such previous attempts. Due to the similar structural features of these two classes of natural compounds, we dared envision a possible common pathway which would give us access to both series of alkaloids. In the approach shown in Scheme 7, an intermediate such as **I** would satisfy this condition. Furthermore, this could in turn be prepared from a single compound, such as the functionalized bridgehead bromide **II**, conceivably via anion or radical chemistry.

The approach illustrated in Scheme 8 would allow for the formation of a tetracyclic intermediate via compound **III**, which in turn could again be prepared via the same bridgehead bromide **II** employed in Scheme 7. Although the use of anion chemistry for the ring closure step would be purely speculative in this instance, the use of radical chemistry to effect the same transformation would have all the prospects to be successful.

Scheme 7.

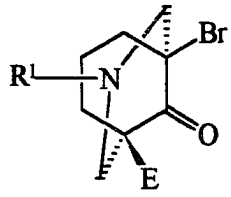


I

n = 1;
R^2 = H, R^3 = Ac;
X, Y = O
aconitine type alkaloids

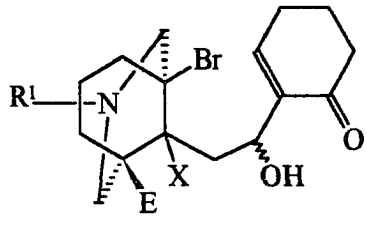
n = 0;
R^2, R^3 = O;
X = H, Y = Ac
atisine type alkaloids

R^1 = Et, β-hydroxyethyl

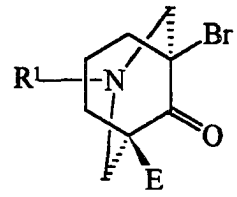


II

Scheme 8.



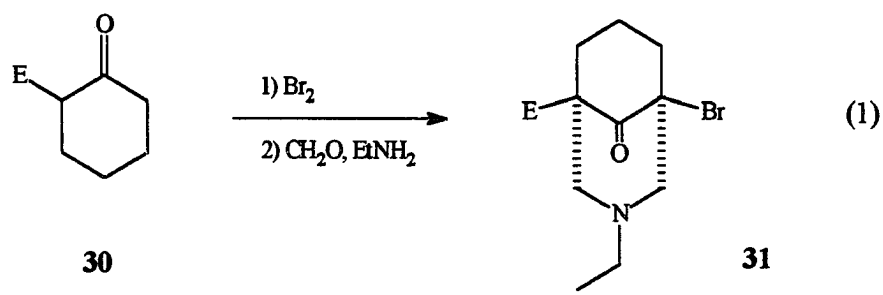
III



II

Synthetic studies based on nucleophilic additions as key steps

Although the strategy outlined in Scheme 7 seemed more challenging since it involved more unknowns than that of Scheme 8, we decided to investigate first the somewhat safer approach of the latter. Thus, bridgehead bromide **31**[44] was prepared from commercially available ketoester **30** in 55 to 65% yield over two steps, on scales up to 0.25 moles (eq. 1).

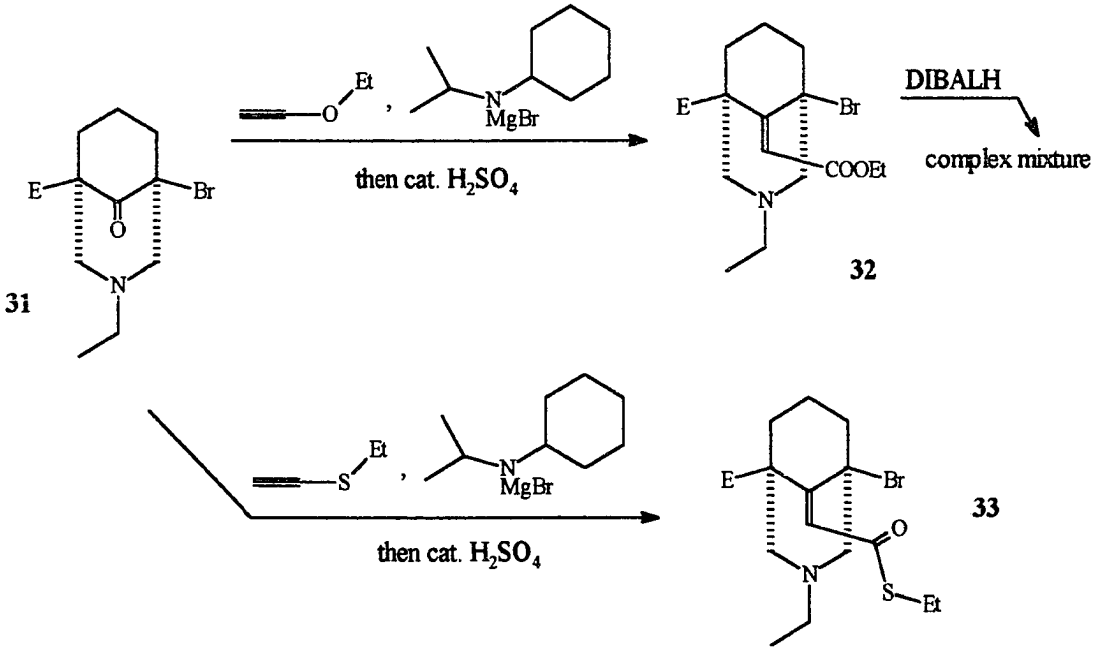


30 **31** (1)

Preliminary research in our group[45] has determined that both organolithium and organomagnesium compounds add well to the ketone **31**, but the reaction products are quite different. While the Grignard reagents yield the expected tertiary alcohols, the intermediary lithium alkoxides undergo a rapid rearrangement even at -78° C, which results in the expulsion of the bromide anion and the formation of a ring-contracted product bearing a bicyclo[3.3.0]octane ring system. It is for this reason that the sequence of transformations outlined in Scheme 9 was addressed, as a means of obtaining the important intermediate **34** (Scheme 10).

Although both the addition of ethoxyacetylene[46] bromomagnesium salt and the acid-catalyzed rearrangement of the corresponding carbinol[47a] proceeded smoothly and in high

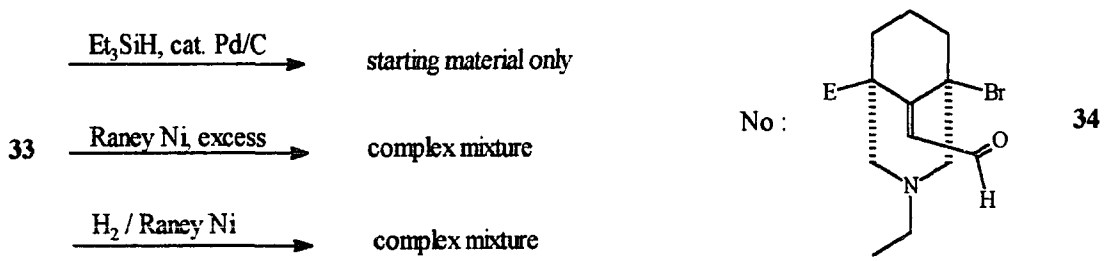
Scheme 9.



yields, the unsaturated diester **32** could not be converted to the desired aldehyde **34** upon reduction with diisobutylaluminum hydride. Stronger reducing agents also afforded a complex mixture of products from which the corresponding diol could not be isolated. Since selectivity between the two ester groups was also a concern, we decided to repeat the same sequence of reactions using ethylthioacetylene[47b] which would give an ethylthio ester, considerably more reactive than the other ester group present in the molecule. Indeed, compound **33** was obtained in excellent yield. Several functional transformations resulting in the formation of aldehyde **34** have been investigated[48] (Scheme 10).

Much to our surprise, the desired unsaturated aldehyde was not formed. Although both **32** and **33** were cleanly obtained as a single diastereomer as evidenced by their ^{1}H-NMR spectrum, no attempt at assigning the configuration of the double bond was made at this step. The configuration of the double bond is not important, since it must be saturated eventually in

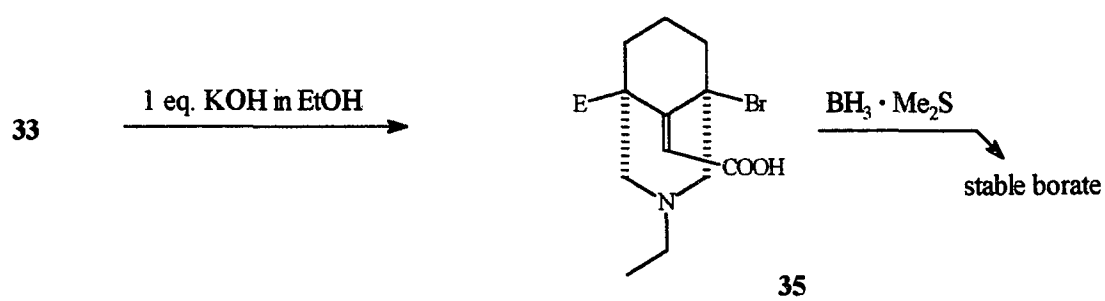
Scheme 10.



order to form an atisine-like structure. It is, however, possible that the actual configuration be E- rather than Z- (shown), for which steric congestion of the thioester moiety would be considerably enhanced.

Differentiation between the two sites could be achieved following alkaline hydrolysis (Scheme 11), but reduction of the corresponding amino-acid **35** gave a stable borate.

Scheme 11.

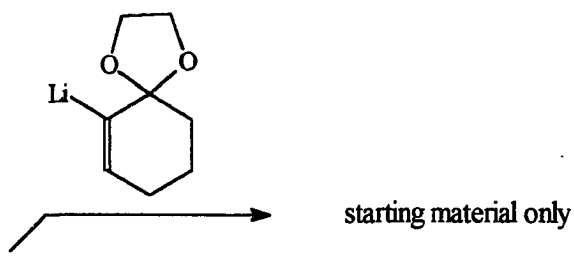


Unfortunately, bulkier anions did not add to the thioester moiety. Attempts to trap an acyl cation formed as a result of treating **33** with a suitable Lewis acid were unsuccessful as well (Scheme 12). At this point we decided to concentrate our efforts in a parallel direction that we were pursuing simultaneously (Scheme 13). Treatment of the ketone **31** with

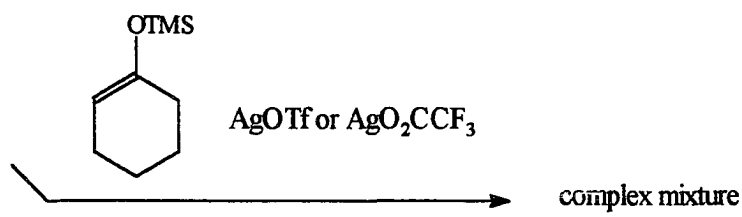
ethynylmagnesium bromide gave carbinol **36** as a mixture of isomers. As we have noticed in the case of other Grignard compounds, addition proceeded preferentially from the face away from the nitrogen with approximately 2 to 1 selectivity. Separation of these compounds appeared impossible by flash column chromatography (FCC).

In the case of **36**, however, treatment with a catalytic amount of mercury(II) sulfate under acidic conditions[49] resulted in complete epimerization to **37**, instead of the expected hydration product. While unusual, although predictable by molecular modeling calculations at the MM2 level,[50] this result was encouraging, since the one-carbon bridge had the configuration required by the natural product.

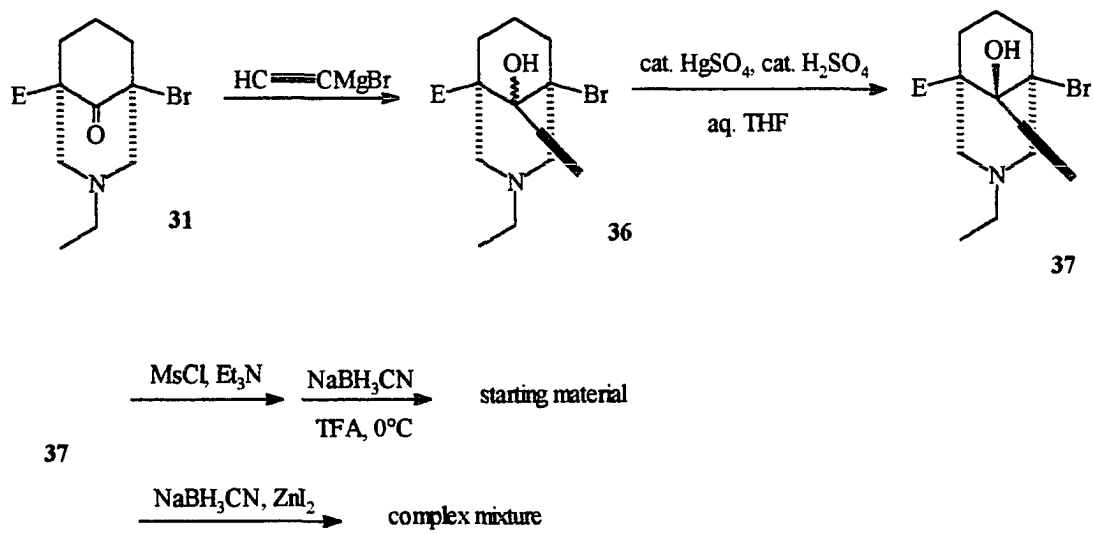
Scheme 12.



33



Scheme 13.

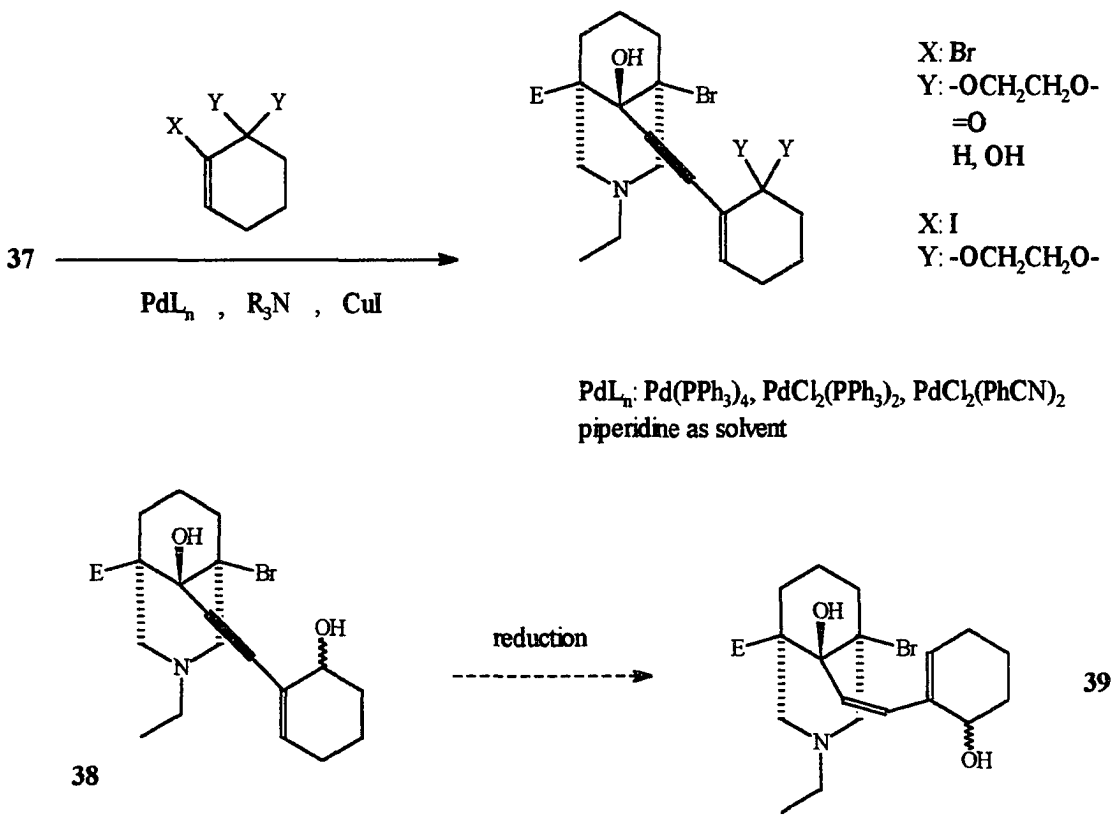


Reductive elimination of the hydroxy group[51] in compound **37** was unsuccessful. In the due course of this work we gathered additional evidence that the hydroxy group in compounds such as **37** is extremely hindered. Reactions involving this position often resulted either in the recovery of the starting material or in the formation of complex mixtures of products. Even though the hydroxy function could not be removed at this stage, we decided not to abandon this route yet. The sequence of reactions shown in Scheme 14 was designed to provide a significant advance on the pathway towards atisine type alkaloids.

Although we obtained compounds such as **38** via the addition of the corresponding alkyne anion to **31**, the palladium catalyzed coupling[52] was preferred since it formed one diastereomer only. Initial results in the coupling reactions were disappointing with respect to both the yield and rate of the reaction. We found that the use of bis(benzonitrile)palladium[53] dichloride, copper (I) iodide and piperidine as a solvent[54] resulted in the formation of the corresponding adduct in less than two hours at room temperature and in yields in excess of

80%. Reduction of the triple bond set the stage for a six-endo-trig cyclization. Molecular models showed that the configuration at the one carbon atom bridge effectively controls the stereochemistry of the tetracyclic compound thus formed if the reaction proceeds through the lower energy chair-like transition state. Thus, the cyclohexenol hydrogen and the hydroxy group tend to be *syn* to each other following cyclization. The same relationship exists in the natural compounds of this class.

Scheme 14.

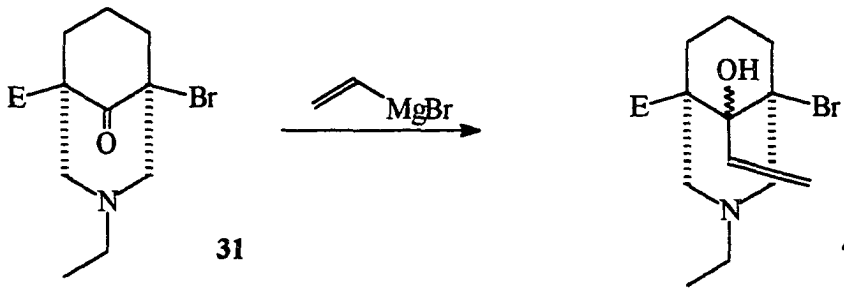


Considerable effort was invested in finding the proper conditions which would effect the transformation leading to **39** (Table 1). Unfortunately, the desired transformation could not be achieved. Based on our previous experience with similar systems, an alternative route was envisioned as shown in Scheme 14. Although the rearrangement following oxidation[57] of **38** proceeded smoothly giving **40** as a single diastereomer, based on the unsuccessful cyclization attempt, it is very likely that the product contains an (E)- double bond.

Since reduction of the very hindered triple bond in **38** was one of the problems that could not be overcome, we sought to introduce a double bond at an early stage instead. Compound **41** was easily prepared according to equation 2, again as a mixture of isomers.

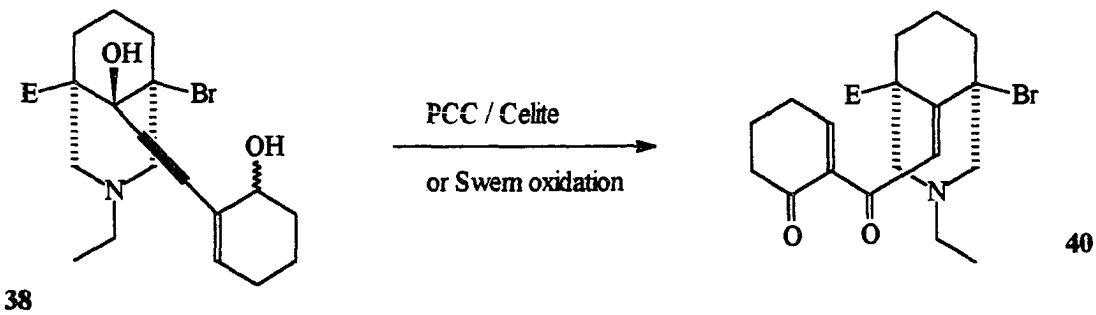
Table 1. Attempted reduction of alkyne **38**

Reagent / conditions	product / comments
H_2 / Lindlar cat., quinoline	starting material
Rieke Zn[55]	starting material
Rieke Zn / THF-aq. MeOH, reflux	starting material
$LiAlH_4$	triol, alkyne
H_2 / Pd-C, normal pressure	starting material
H_2 / Raney Ni	reduced double bond triple bond unaffected
i-BuMgCl / cat. Cp_2TiCl_2[56]	starting material
substrate: **38**, 2° alcohol protected as MOM ether	
i-BuMgCl / cat. Cp_2TiCl_2	starting material
3 equiv. i-BuMgCl / 1.1 equiv. Cp_2TiCl_2	unidentified product



31 41 (2)

Scheme 15.

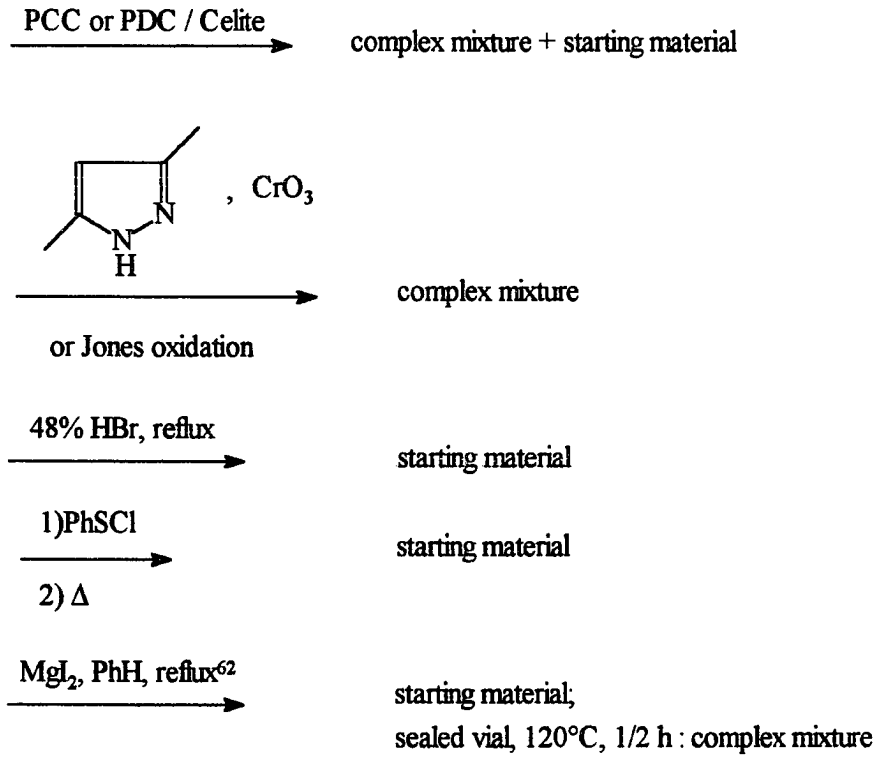


38 40

40 Bu_3SnH, AIBN or vitamin B_{12} / Zn → reduced **40**, no cyclization

Many tertiary allylic alcohols rearrange under oxidative conditions[58] to give the corresponding unsaturated aldehydes. Similarly, treatment with concentrated HBr or HCl yields the primary rearranged halides.[59] The rearranged primary allylic chloride can also be obtained via the [2,3] sigmatropic rearrangement of the corresponding sulfinyl ester.[60] All these procedures failed to give any of the desired products (Scheme 16). Milder oxidants,

Scheme 16.

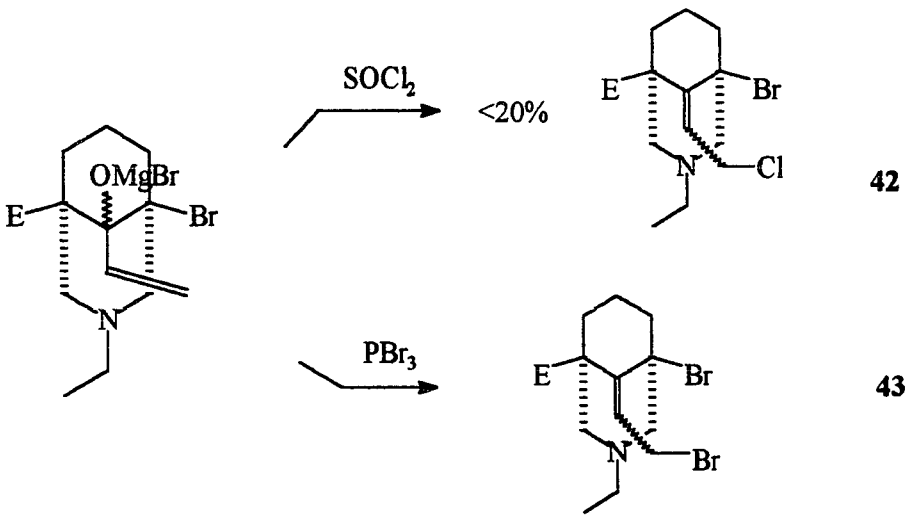


such as PCC, PDC or other chromium(VI) complexes,[61] as well as the more vigorous Jones reagent were equally ineffective.

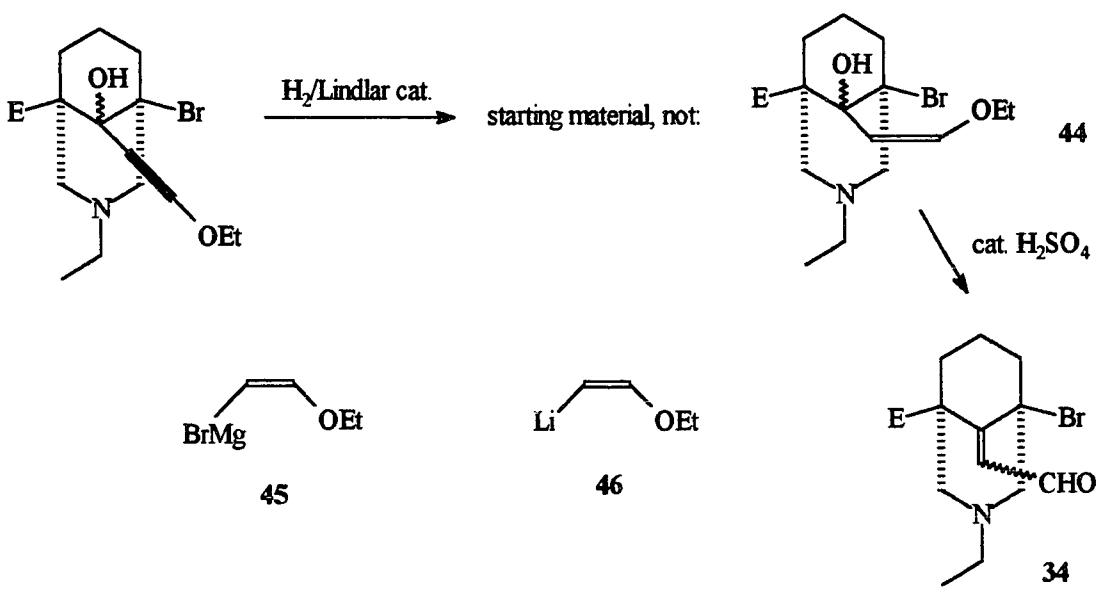
Compounds **42** and **43** were obtained in less than 20% yield following direct treatment of the magnesium alkoxide with thionyl chloride or phosphorous tribromide respectively (Scheme 17). Both of the products proved to be very reactive, intermolecular alkylation of the amine moiety being the most probable cause for their lack of stability.

The desired aldehyde **34** could have conceivably been obtained following rearrangement of compound **44** (Scheme 18). However, reduction[63] of the previously prepared tertiary carbinol did not afford **44**.

Scheme 17.



Scheme 18.

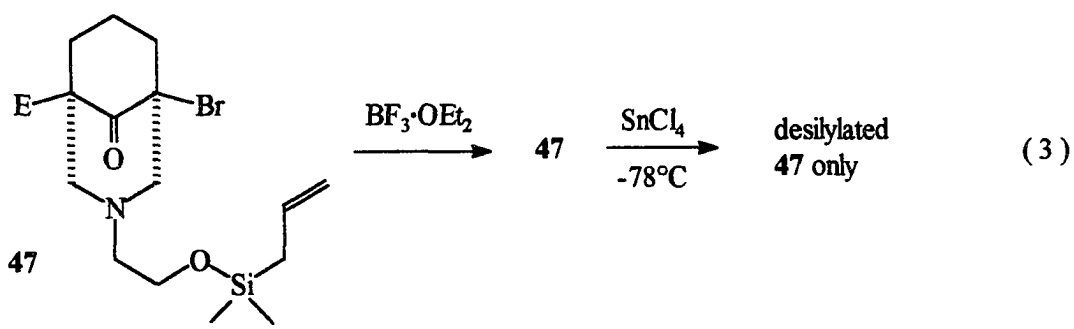


Unfortunately, this compound could not be prepared directly, due to unsuccessful attempts to prepare **45**. The organolithium **46** cleanly added to various carbonyl compounds, including **31**, yielding the expected products. As previously described, the ring-contracted product was formed in the latter case. Furthermore, all products rearranged to the corresponding unsaturated aldehydes upon treatment with a catalytic amount of sulfuric acid.

Ozonolysis of **41** gave a complex mixture of products instead of the expected α-hydroxyaldehyde. However, a carbonyl homologation sequence[64] would have added an extra step to the synthesis.

An intramolecular version of the Lewis acid catalyzed alkylation[65] using the allyl silane **47**, prepared in conjunction with our synthetic studies on the spiramine alkaloids, fell prey to the same steric and electronic factors which prevented us from obtaining **34** (equation 3).

In spite of its initial promise, this route became too unproductive to be able to maintain our interest in it. It was replaced by a set of less conventional, but more intriguing ideas.

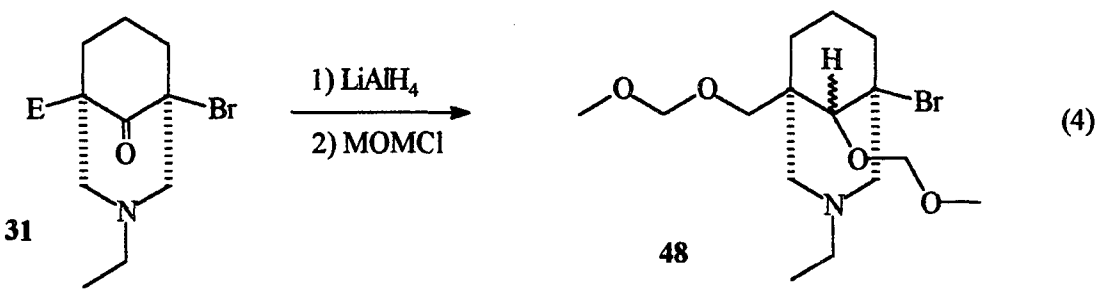


(3)

Synthetic studies based on bridgehead intermediates

Studies on the generation and trapping of highly functionalized bridgehead anions

Encouraged by the consistent results obtained while studying bridgehead adamantyl anions, we decided to expand the methodology we developed such as to comprise more complex systems. For this purpose, compound **48** was prepared as a mixture of isomers, in excess of 80% yield over two steps (equation 4).

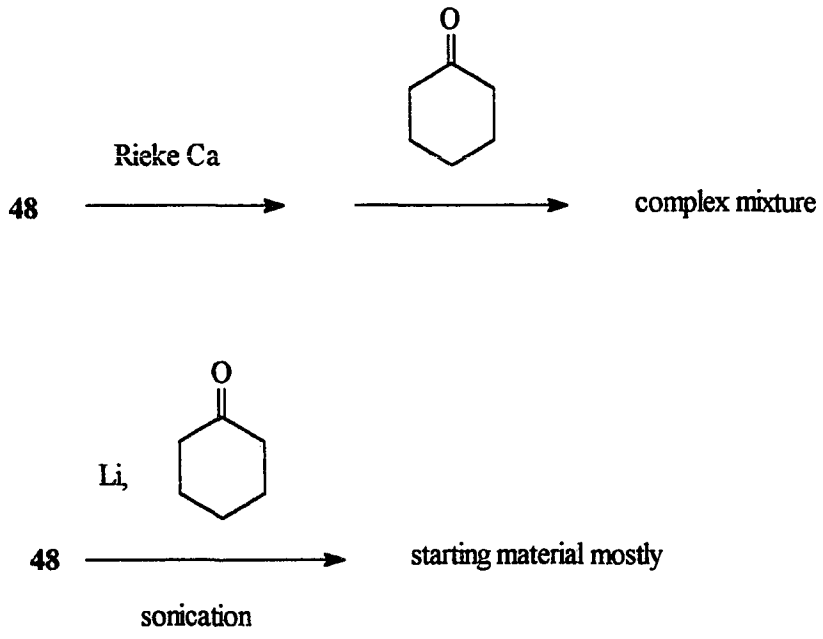


31 **48** (4)

The methodology that was so successful in the case of adamantyl systems failed to give any of the desired compounds in the case of **48**. The use of Rieke calcium[66] afforded a complex reaction mixture, which was also obtained while attempting to prepare the corresponding Grignard reagents (Scheme 19).

It is well known that many organometallic compounds, those deriving from the main two groups of the periodic table notably, associate to a degree varying from dimers to hexamers,[67] depending on the actual cationic and anionic species involved and on the

Scheme 19.



particular conditions employed in their preparation, of which the donor ability of the solvent plays a key role. Such aggregates decrease the overall energy of the system through the formation of multicentered bonds at the expense of the lower entropic factor. Since in our case the anionic species generated would be considerably bulky, it is possible that steric factors overcome electronic ones to such an extent that the reaction becomes impossible.

While considering our options in this direction, we were simultaneously pursuing an alternative route in which bridgehead radicals played a crucial role.

Methods for bridgehead radical formation.

Preparation of an intermediate for the synthesis of gibberellins§.

Radicals are now well recognized as versatile intermediates for the construction of highly functionalized molecules.[1, 68] Research in radical chemistry has resulted in many useful methods by which radicals can be generated. Although tin hydride chemistry remains the dominant means of radical generation,[69] both photochemical procedures[70] and metal-mediated procedures[71] are becoming increasingly important. Of the latter group, the manganic acetate chemistry of Corey[72] and Snider[73] and the persulfate chemistry of Torsell[74] and Minisci[75] are the most extensively studied. The use of these reagents has been suggested by the structure of manganese(III) acetate in which the three Mn ions, positioned at the vertices of a triangle, share an O^{2-} ligand at its center, facilitating a one-electron transfer involving substrates that can be readily deprotonated, and are thus fairly acidic, such as β-diketones or β-ketoesters. Indeed these species, as well as equivalent acidic compounds, have been successfully employed in the construction of polycyclic γ-lactones[72] and related interesting annulations[73] based on oxidative free-radical type cyclizations. Although cobalt complexes have been used by Baldwin,[76] by Pattenden[77] and by Braunchard[78] to effect intramolecular cyclizations, intermolecular bond formation using catalytic cobalt species has been little studied.[79] In most cases, the complexes obtained from relatively simple primary or secondary halides had to be isolated and subsequently photolized. Recently, Giese and coworkers have shown that adamantyl bromide reacts with substituted fumarates in the presence of zinc, triethylamine and a catalytic amount of vitamin B_{12}.[80] In the context of our studies of bridgehead radicals,[81] we evaluated cobalt chemistry and compared methods for radical generation.

---

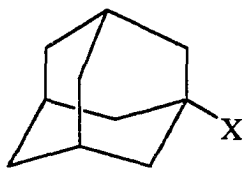
§Kraus, G. A.; Siclovan, T. M.; Watson, B. W. Synlett **1995**, 201.

Our initial studies focussed on bond formation using one equivalent of the bridgehead bromide and 1-2 equivalents of the radical acceptor. These studies are summarized in Table 2 and Figure 7. Bridgehead substrates employed included adamantyl bromide **49**, bromo keto ester **31**[44] and bromoketone **56**.[82] As evidenced from Table 2, bridgehead radicals generated by organocobalt intermediates react with a variety of radical acceptors. In general, steric hindrance at the β-position of the radical acceptors attenuated the yields of adducts. In these cases, the major product was the reduction product **51**. The radical addition reaction could be conducted at subambient temperatures, as shown by the reaction of bromide **31** with

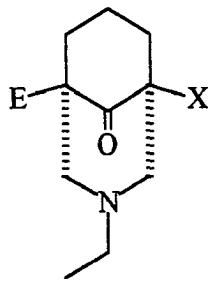
Table 2. Bridgehead radical generation and trapping

Halide	Radical Acceptor	Conditions	Yield, %	Product
49	dimethyl fumarate	A	56	50
31	Bu_3SnH	B	88	51
31	methyl-vinyl-ketone	B	87	52
31	tributyl-2,4-pentadienyltin	B	61	53
31	cyclopentadiene	B (0° C)	47	54
31	3-acetylcyclohexenone	C	21	55
56	diethyl fumarate	B	80	57

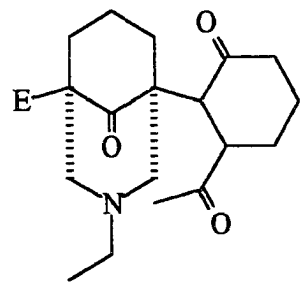
Conditions	Halide to Radical Acceptor		to B_{12}	to Zn	to Et_3N	ratios	Solvent
A	1.2	1	0.05	11	1.5		DMF
B	1	1.2	0.05	10	5		DMF
C	1	1.2	0.05	4	5		DMF



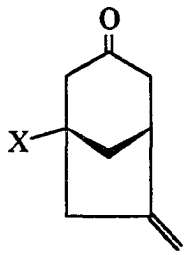
49: X=Br
50: X=CH(CO_2Me)CH_2CO_2Me



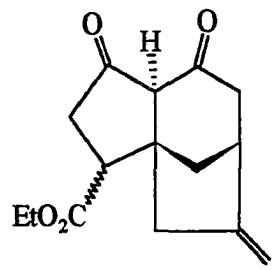
31: X=Br
51: X=H
52: X=CH_2CH_2COMe
53: X=CH_2CH=CHCH=CH_2
54: X= 3-cyclopentenyl



55



56: X= Br
57: X=CH(CO_2Et)CH_2CO_2Et



58

Figure 7. Bridgehead intermediates.

cyclopentadiene which afforded a better yield at 0 °C. We also examined radical acceptors where the resulting radical would be stabilized by a captodative effect. Surprisingly, neither 2-acetoxyacrylonitrile nor 2-chloroacrylonitrile were effective acceptors. Interestingly, α-methyl styrene also failed as a radical acceptor.

We next compared different methods of radical generation. The reaction of bromide **31** with methyl vinyl ketone using several stannane reagents (Bu_3SnH, AIBN; Ph_3SnH, AIBN) failed to provide diketone **52**. The reaction conditions using catalytic vitamin B_{12} generated

52 in 87% yield. Similarly, stannane reagents could not be used to generate adduct **55** in Table 2. The only observable product was the reduction product.

Adduct **57** was treated with potassium *tert*-butoxide and magnesium ethoxide to produce tricyclic diketone **58** as a 1:1 mixture of diastereomers, in 65% isolated yield. Diketone **58** possesses functionality suitable for the synthesis of gibberellins which lack the C-13 hydroxyl group.[83]

The success of this methodology encouraged us to direct almost all of our research effort in this direction. Indeed, suitable reaction partners as well as a common bridgehead bromide opened both synthetic pathways leading to either atisine or aconitine type alkaloids, while suggesting a very concise synthesis in each direction. Our goal of achieving a very effective synthesis seemed also within our reach, warranted by the high yields of these coupling reactions.

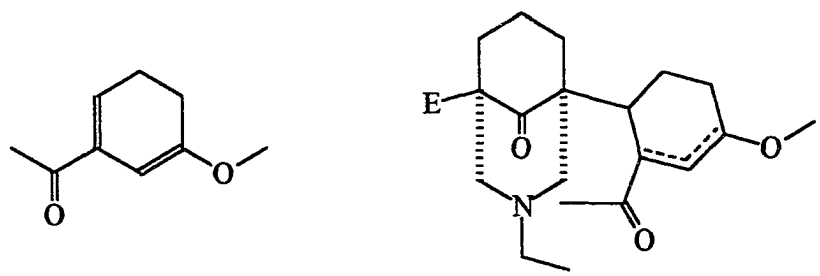
Studies directed towards the synthesis of atisine and spiramine alkaloids

Since atisine and the spiramines alkaloids are closely related to each other, studies towards the synthesis of atisine can also be considered as model studies towards the synthesis of spiramine alkaloids.

The low yield of compound **55** and the inefficient trapping of the nucleophilic, sterically hindered bridgehead radicals by the only moderately electron-deficient enones such as **59** (Figure 8), prevented us from obtaining compound **60**. This would have been one of the most direct routes conceivable towards constructing the atisine and spiramine skeleton.

With compound **52** in hand, the tricyclic core of these alkaloids was constructed as indicated in Scheme 20. Compound **61** was thus obtained in 95% yield.

One of the issues that became imperative at this point was the selective 1,4-reduction of enone **61** with high diastereoselectivity from the face away from the nitrogen atom. In addition to this, a way of continuing our chemistry on the cyclohexanone side opposite to the bicyclononane system ought to be considered. These restrictions are summarized in Scheme 21.



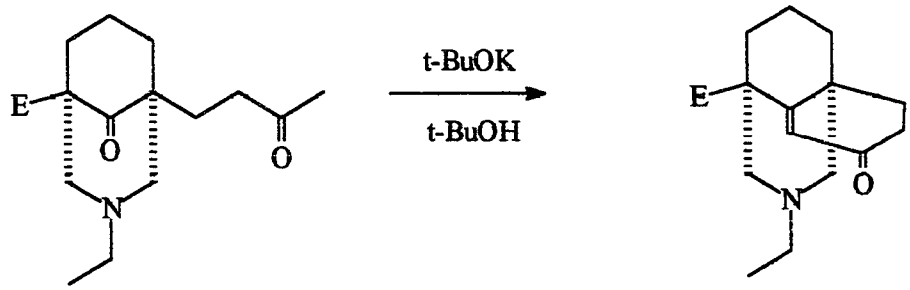
59 **60**

Figure 8. A direct approach towards a tetracyclic intermediate.

Introduction of an electron-withdrawing group in compound **62** allows for an easy differentiation of the two reactive sites α to the carbonyl group due to the marked difference in the acidity of the corresponding protons. Unfortunately, if compound **62** is considered, introduction of a carboalkoxy group is the only regioselective reaction known.[84] In the case of compound **61** a variety of options becomes available via the corresponding enolate. The question of maintaining the same facial selectivity during enone reduction as in **61** remained open at that time.

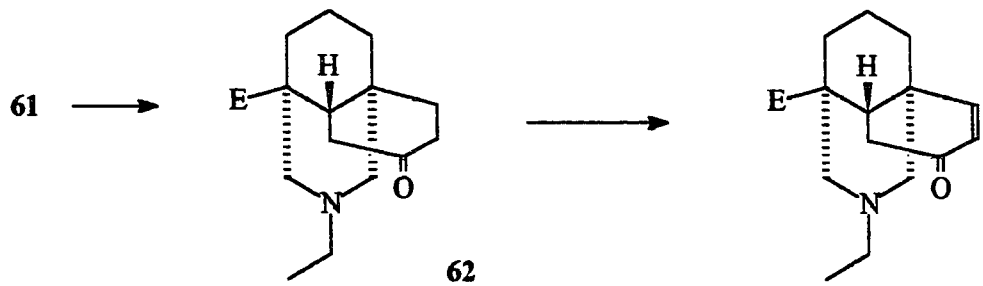
Previous investigations involving nucleophilic additions to the bicyclic ketone **31** provided solid evidence of the steric congestion at the one-carbon bridge in the bicyclononane

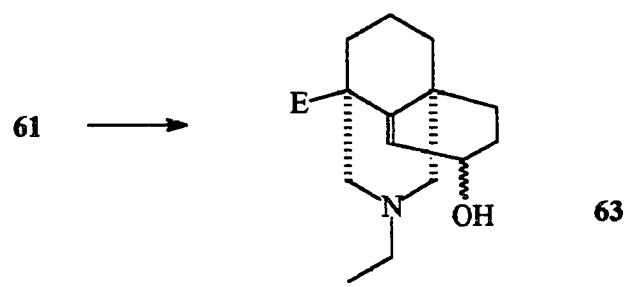
Scheme 20.



52 **61**

Scheme 21.





Reductions:

62 = Ketone
63 = Allylic alcohol

ring system. This was a cause of concern, since many hydride donors which are likely to effect conjugate reduction of enones are relatively bulky species. Given the importance of this reaction, though, we decided to investigate various conditions which would lead to the desired transformation. Some of the most notable, with respect to the results obtained, are given in Table 3.

Table 3. Reductions of compound **61**

Entry	Reagent / Conditions	Product / Diastereomer ratio	Reference
1	LAH + CuI	A ~ 2/1	85
2	$LiAlH(OMe)_3$ + CuI	A ~ 2/1	86
3	$LiAlH(OMe)_3$	A ~ 5/1	87
4	DIBALH	A ~ 3/1	88
5	LAH then BH_3 then EtCOOH	?	89
6	$BF_3 \cdot OEt_2$, $NaBH_4$	A ~ 1/2	37
7	$BF_3 \cdot OEt_2$, L-Selectride	A ~ 1/1	37
8	Zn / Vitamin B_{12} / AcOH	A	90
9	Bu_3SnH, $ZnCl_2$, cat. $Pd(PPh_3)_4$	starting material	91
10	$TiCl_4$, Mg / t-BuOH	?	92
11	$Na_2S_2O_4$ / PTC	K ~ 2/1	93
12	Et_3SiH / Wilkinson cat.	starting material	94
13	H_2 / Wilkinson cat.	starting material	95
14	H_2 / Crabtree cat.	starting material	96
15	H_2 / Crabtree cat., 100 psi	starting material	96
16	H_2 / $RhCl_3$, PTC	K ~ 4/1	97
17	H_2 / Pd-C	K ~ 1/1	98
18	H_2 / Pd-C / 2N HCl	starting material	98
19	H_2 / Pd-C / triethylamine, i-PrOH	K ~ 4/1	98
20	H_2 / Pd-C / AcOH, i-PrOH	starting material	98
21	H_2 / Co(dmg)PyCl	starting material	99

Unexpectedly, the equivalent of copper hydride (entries 1 through 3) did not afford the conjugate reduced product, in spite of its efficiency in the case of other systems. The facial selectivity in the case of in-situ generated borane reduction was opposite to that observed in the copper hydride equivalent reductions (entry 6). A tin hydride, paladium-mediated conjugate reduction proved unsuccessful too (entry 9).

Ruthenium trichloride[100]- or diiron nonacarbonyl[101]-promoted isomerizations of allylic alcohols, which proceed with retention of stereochemistry, were not attractive due to the difficult separation of the allylic alcohol (A) diastereomers.

Homogeneous hydrogenations (entries 13 through 15) were probably adversely affected by the steric factors mentioned above, resulting in complete recovery of the starting material. Eventually, heterogeneous hydrogenation proved to be the method of choice. The desired ketone was obtained in quantitative yield, with a satisfactory diastereoselectivity. At this point, no attempt has been made to assign the stereochemistry of the major isomer, mainly due to the fact that the product mixture proved to be inseparable by FCC. Our previous observations on the bicyclic ketone **31**, however, strongly supported the hypothesis that reduction also occurred preferentially from the less hindered face, namely away from the nitrogen atom. It was also noted that the solvent composition influenced the diastereomer ratio of the reduction product.

Our interest in confirming our synthetic route ranked higher in priority over fine tuning of the reduction conditions. One of the most direct routes which led to an advanced tetracyclic intermediate is depicted in Scheme 22.

The carbomethoxylation of **64** proceeded in 55% yield with 20% ester exchange. Introduction of the double bond via selenium[102] chemistry afforded the α-unsaturated-β-ketoester **66**, which was subjected to a series of Diels-Alder reactions (Table 4).

The yields of the desired adducts were much lower than expected. This may be due to underestimation of the steric factors when planning the experiments.

Scheme 22.

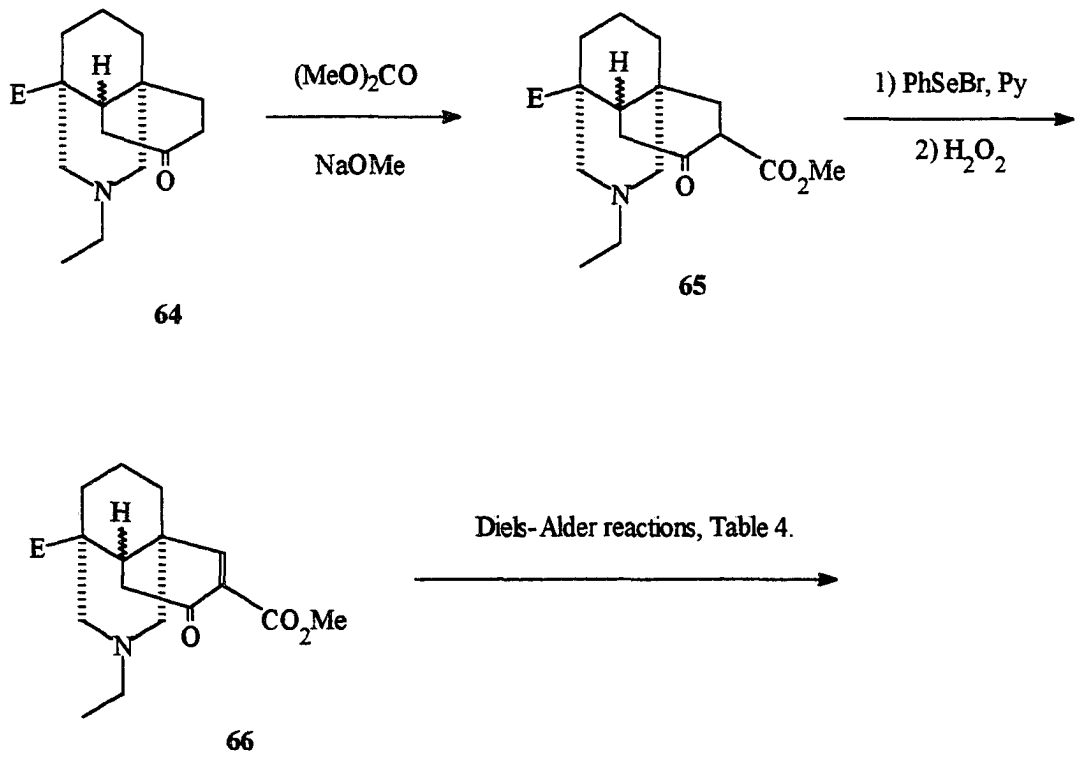
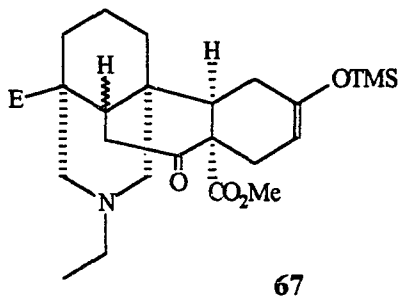


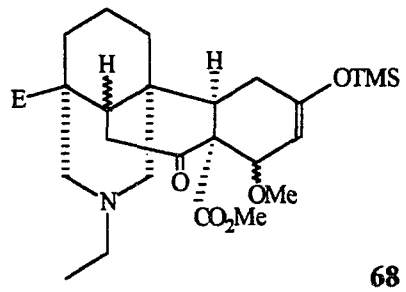
Table 4. Diels-Alder reactions of the enone 66

Diene / conditions	Product / yield
Butadiene / 2M in toluene, 200°C / 24h	starting material
Butadiene, neat, 100°C / 24h	starting material
2-TMSO-butadiene[103] / 2M in toluene, 220°C/ 24 h	**67**[a] < 5 %
Danishefsky's diene[104] / 3M in toluene, 200°C / 24 h	**68**[a], traces

[a]for structures, refer to Figure 9.



67



68

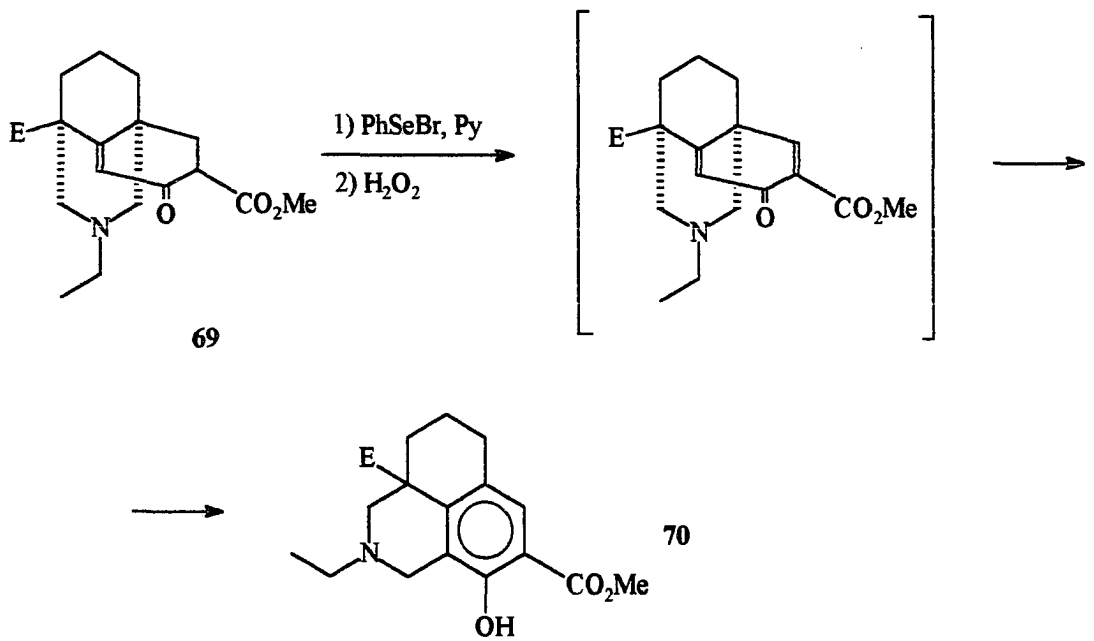
Figure 9. Structures of compounds **67** and **68**.

An interesting rearrangement was noticed while attempting to prepare a more reactive dienophile (Scheme 23). The strong electron withdrawing property of the α-unsaturated-β-ketoester moiety and the tendency towards aromatization, combined with the electron-donor ability of the nitrogen atom favors a bond cleavage yielding an iminium cation and the tautomer form of the corresponding phenolate. Ortho attack then generates the rearranged compound **70**. This constitutes a very direct entry into the isoquinoline class of alkaloids, but is of little importance to this project. Previous work on the synthesis of these systems also led to the discovery of some notable, although less dramatic rearrangements.[39, 105]

Since our cycloaddition approach was not successful, we decided to construct the fourth ring of the target molecules via a 1,4-addition to **66** (Scheme 24). Although the base-catalyzed addition[106] of 5-nitro-methylvalerate proceeded in quantitative yield, subsequent Dieckmann cyclization attempts resulted only in the recovery of **66** via a retro 1,4-addition of the corresponding β-ketoester anion. Attempts to remove the nitro group[107] prior to the cyclization reaction also resulted only in the recovery of **66**. These results are very unusual.

The α-acetoxy organozinc reagent[108] failed to add to **66**, regardless of whether a higher order cuprate was employed or not. The fact that the crotonaldehyde enolate did not add was not only unexpected but also in contradiction with previous results reported in our group.[109]

Scheme 23.

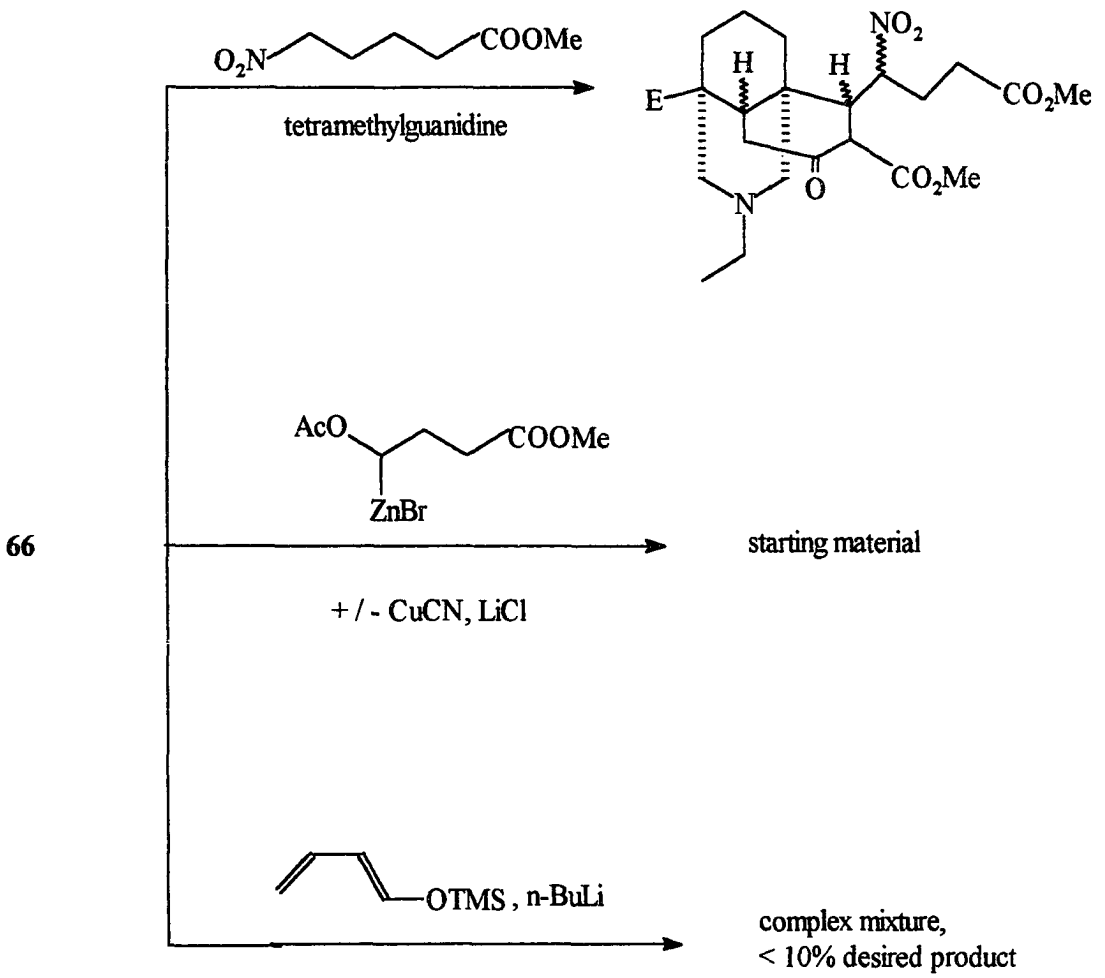


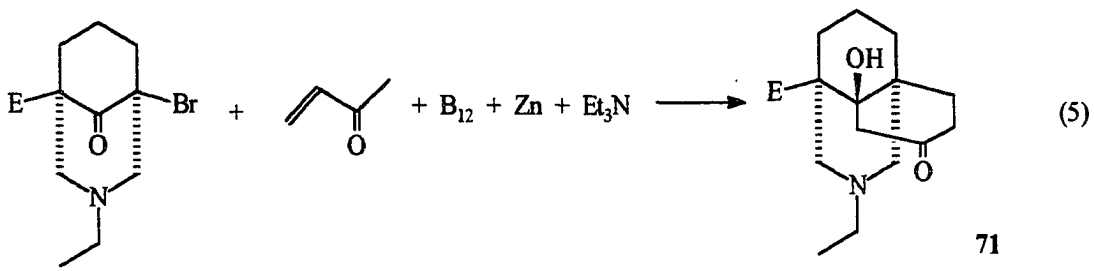
Although conjugate addition of lithium diallylcuprate and lithium di-(2-ethoxyvinyl)-cuprate was essentially quantitative, the directing effect of the amine[110] produced the undesired diastereomer with a 4:1 diastereoselectivity as evidenced by ^{1}H-NMR studies.

At this point our attention was attracted by the product obtained as a result of modifying the reaction conditions for the vitamin B_{12}-catalyzed addition of the bridgehead bromide **31** to methyl-vinyl-ketone (MVK). Thus, if the reaction was conducted in the presence of a larger excess of triethylamine and a certain amount of water, controlled aldol cyclization of the initially obtained diketone became possible (equation 5).

The structure of compound **71** was determined by single crystal X-ray diffraction (Appendix 2). Compound **71** was the only diastereomer formed, probably as a result of the attack of the zinc enolate only from the bottom face of the carbonyl due to coordination with the amine group. Although serendipitous, this result was initially very encouraging.

Scheme 24.

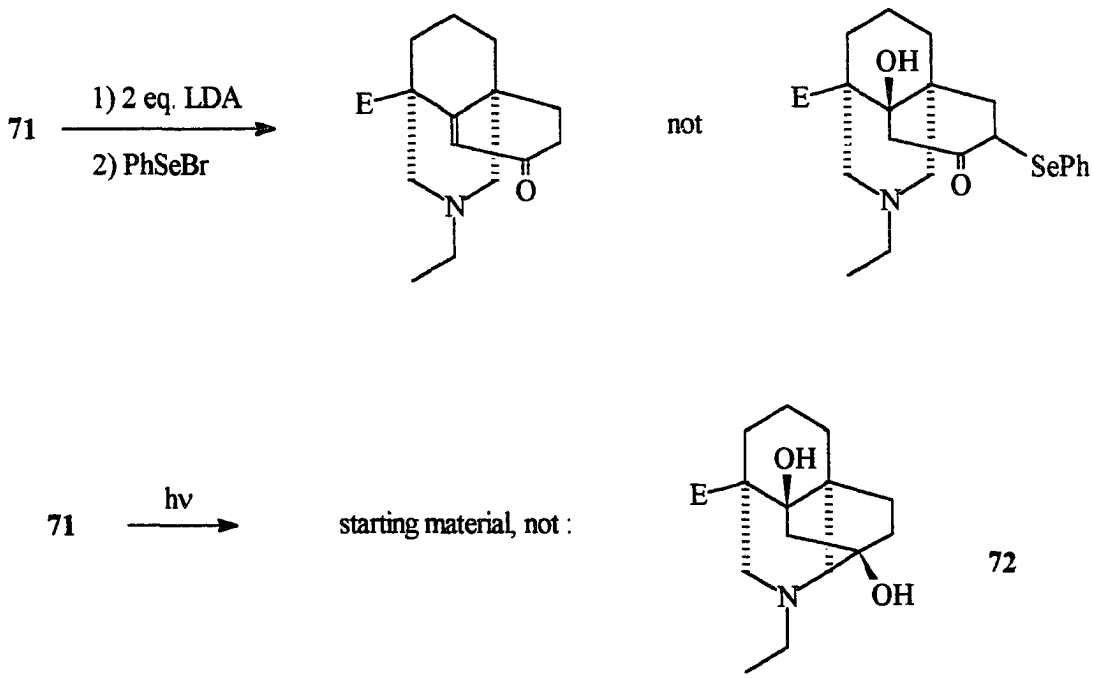




(5)

71

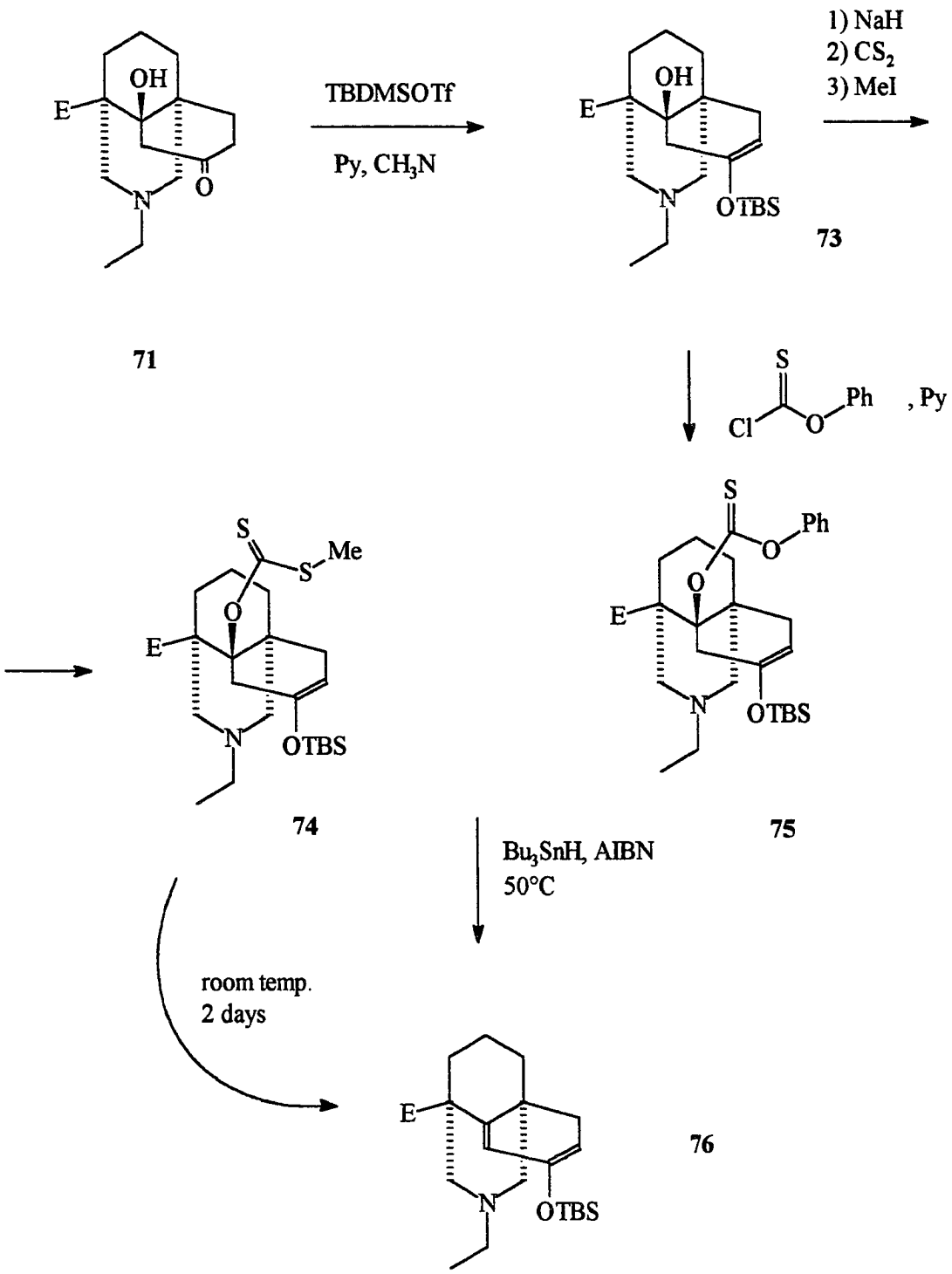
Scheme 25.



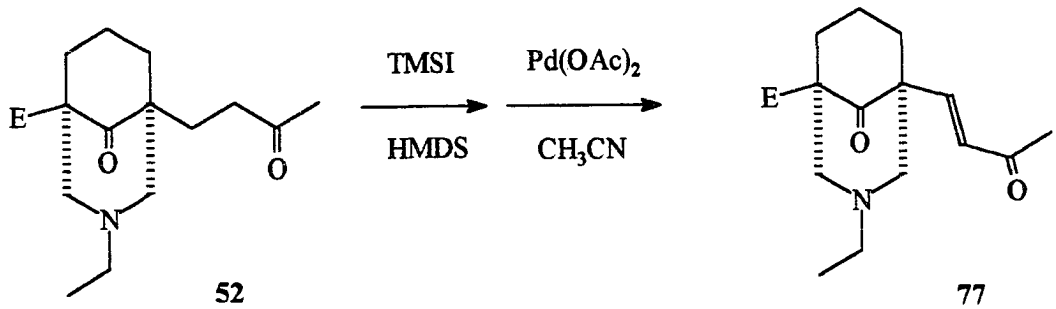
Unfortunately, the hydroxy group proved to be very labile (Scheme 25). Irradiation only returned starting material although **72** could have been formed as a result of the intramolecular quenching of the corresponding iminium ion[111] generated by photooxidation. Similar experiments performed with compound **83** (page 65), under slightly different conditions[112] returned the starting material exclusively. This carbon connectivity was met in some of the atisine and aconitine alkaloids and apparently cannot be introduced via **71**. The most probable cause for the observed lability of the hydroxy group in **71** is the β-carbonyl functionality; for more than a century it has been known that dehydration of this class of compounds to the corresponding α,β-unsaturated carbonyl compound proceeds easily.

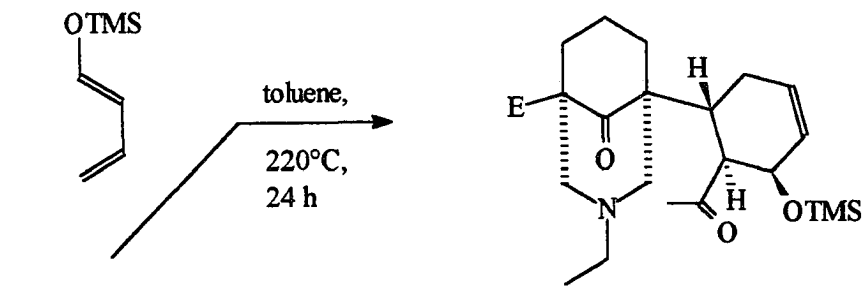
By taking advantage of the steric congestion at the bridge position, compound **73** was prepared in 95% yield (Scheme 26). The question that we were seeking an answer for was whether radical deoxygenation of **71** would proceed with high diastereofacial selectivity.

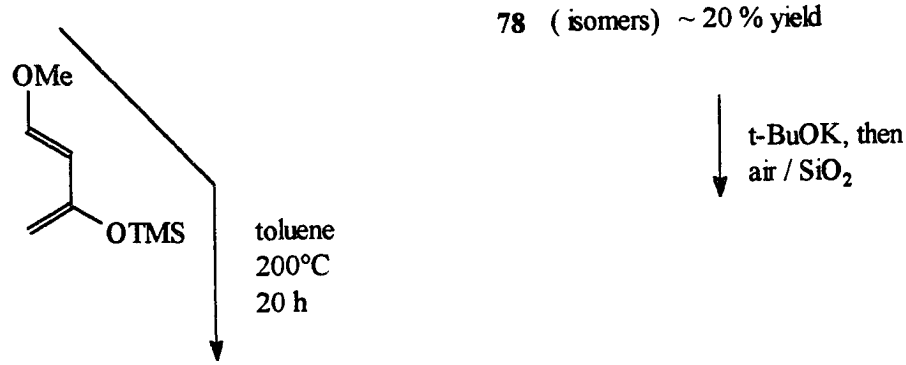
Scheme 26.


OH
E
N
O
TBDMSOTf
Py, CH_3N
OTBS
1) NaH
2) CS_2
3) MeI
73
71
S
Cl
O
Ph
, Py
S
Me
S
O
E
N
OTBS
74
S
Ph
O
O
E
N
OTBS
75
Bu_3SnH, AIBN
50°C
room temp.
2 days
E
N
OTBS
76

Scheme 27.


TMSI
HMDS
Pd(OAc)2
CH3CN
E
O
N
O
52
77


OTMS
toluene,
220°C,
24 h
77
H
E
O
N
H
O
OTMS
78 (isomers) ~ 20 % yield


t-BuOK, then
air / SiO2
OMe
OTMS
toluene
200°C
20 h
H
OTMS
E
O
N
H
O
OMe
80
(isomers)
~ 18%
H
E
N
O
79

Unfortunately, the concerted Chugaev elimination proved to be much faster than the tributyltin radical attack on either the xanthate or the thionocarbonate species, yielding compound **76** exclusively.

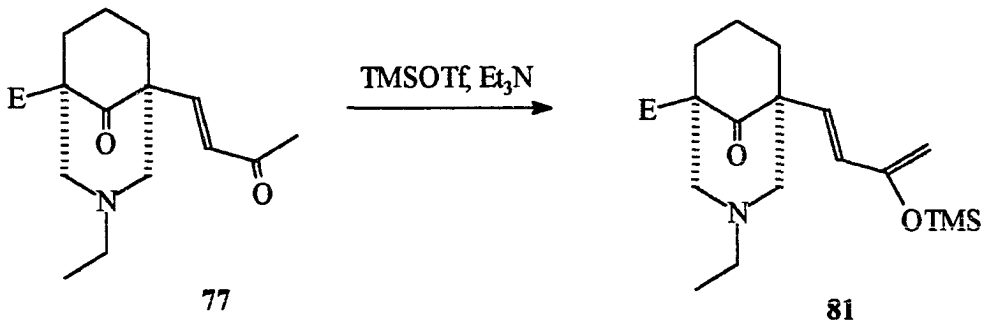
In spite of the apparent lack of productivity of the reactions discussed previously, the wealth of knowledge about the systems we were trying to synthesize was augmented considerably. It is not uncommon in the field of synthetic organic chemistry that the lack of reactivity at a particular position in the molecule, although unexpected, was later turned to an advantage. Before making any further attempts to construct the fourth ring of our systems using either tricyclic intermediate obtained so far, we wanted to investigate two synthetic approaches that were suggested by the structure of **52**.

The first one turns the acyclic enone **77**, obtained from **52** in 75% yield over two steps,[113] into an acyclic Diels-Alder reaction partner having more degrees of freedom over its cyclic counterpart (Scheme 27).

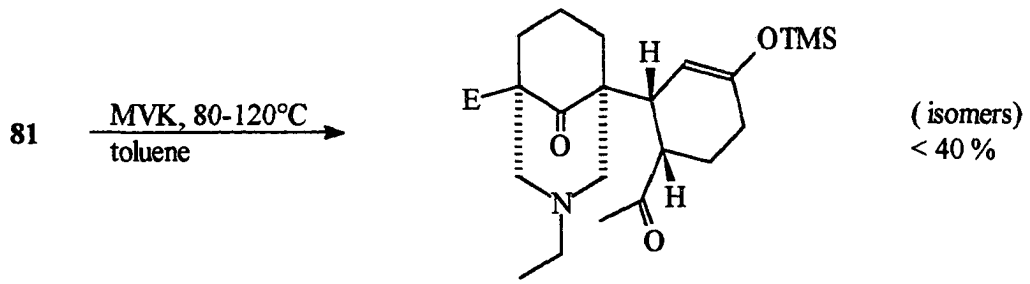
Although the cycloaddition reactions proceeded in better yields this time, the low conversion obtained was unsatisfactory. However, the tetracyclic intermediate **79** was obtained for the first time. A possible continuation of the synthetic work would have used the dienone **80** as an inverse electron demand Diels-Alder reaction partner, leaving sensible questions about facial selectivity to be addressed further. The low yield of **80** made any such considerations practically unattractive.

The second opportunity for constructing four of the five rings present in our target molecules is illustrated in Scheme 28. Enone **77** was transformed into diene **81**, which reacted with methyl-vinyl ketone under moderate conditions to give the corresponding adduct **82** as a mixture of isomers. Although the yields improved constantly along this sequence of attempts, one of the main drawbacks of this approach consisted in the unsuccessful control of the polymerization reaction of MVK. The large amounts of polymer that accompanied **82** made work-up difficult.

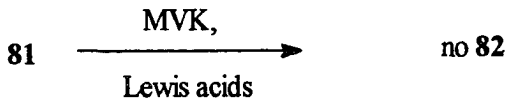
Scheme 28.



77 81



82

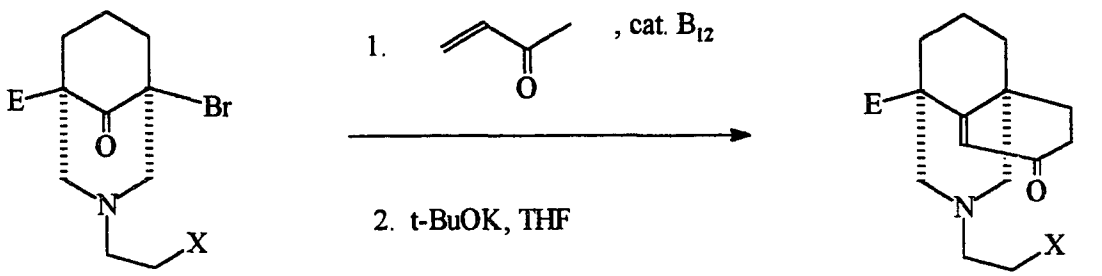


Attempts to effect the reaction at lower temperatures by using various Lewis acid catalysts[114] turned out to be even more problematic: coordination with the tertiary amine moiety was exceptionally strong in all but boron trifluoride cases. However, for the latter compound practically no catalytic effect was noted.

Micellar catalysis,[115] in which **77** and 3,5-hexadienoic acid or its sodium salt were used, gave us but traces of the desired adduct. The use of a C_7 or C_8 acid would have been impractical in our situation.

Since the acyclic intermediates proved to be of little advantage over the cyclic enone species, we decided to return to our previous strategy and to look for a successful way of balancing the steric factors by using more reactive intermediates. The steric interactions in the cycloaddition step could also be reduced by using a less sterically-demanding diene. We decided to run both a model and an appropriately functionalized system simultaneously. Our sequence of reactions required that compounds **84** and **86** be made (Scheme 29).

Scheme 29.



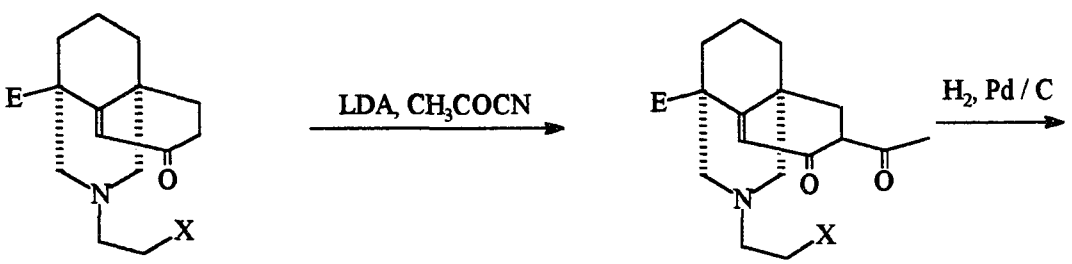
31: X = H
83: X = OH

61: X = H
84: X = OH
85; X = OMOM

Compound **31** was obtained previously and was taken to **61** without any incident. Similarly, by using ethanolamine in the double Mannich reaction,[116] compound **83** was obtained in 80% yield. When our bridgehead radical formation methodology was used in order to effect the coupling with MVK, no product was formed. Apparently, the catalytic

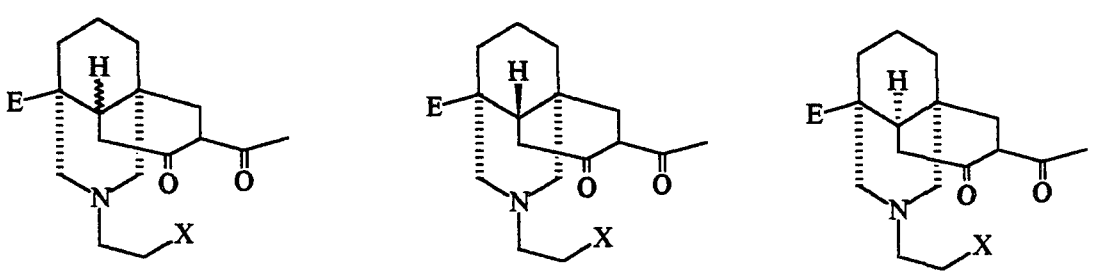
system was poisoned by the bicyclic alkanolamine used. This result was at least curious. Even more interesting was the fact that protecting the hydroxy group in **83** as a methoxymethyl (MOM) ether[117] allowed the desired reaction to proceed in better than 90% yield. Cyclization to **85** was uneventful, resulting in a 66% overall yield of **85** starting from **83**. Although compound **84** could not be obtained directly, **85** turned out to be a better alternative in the long run. An acetyl group was then introduced as a handle to be used in the construction of the carbocyclic skeleton of atisine and spiramine alkaloids (Scheme 30).

Scheme 30.



61: X = H
85; X = OMOM

86: X = H
87: X = OMOM



X = H, OMOM

88: X = OMOM

89: X = OMOM

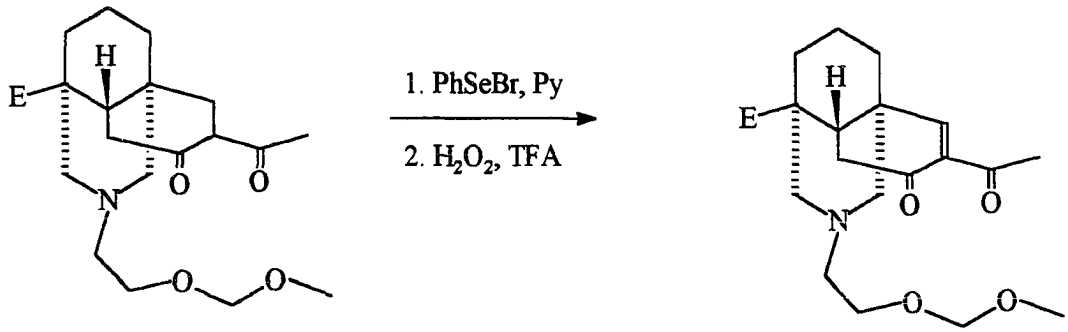
Acylation of the corresponding enone enolate[118] with pyruvonitrile at low temperature provided **86** and **87** in about 85% yield and 60% conversion. Reduction of the double bond under the same conditions used in the case of **61** proceeded with a 2.5 to 1 diastereoselectivity in the case when X = H and 2 to 1 in the case of X = OMOM, to give the corresponding mixture of isomers in quantitative yield. Initially, the mixture proved to be inseparable by FCC. After carefully screening various solvent compositions for their separating ability under conditions which would greatly shift the enolization equilibrium in the favor of the enol form, separation of **88** and **89** became possible by the technique mentioned above. This way, the major isomer **88** became available in pure form in multigram quantities. The relative configuration of **88** and **89** was inferred from two-dimensional NMR experiments (COSY, NOESY) as well as APT, HETCOR and NOE data.

Initial experiments designed to test our synthetic route were performed using **86** as a model system and then repeated with the isomer mixture of **88** and **89**. Satisfied with the results, we then subjected the pure isomer **88** to the same sequence of reactions (Scheme 31).

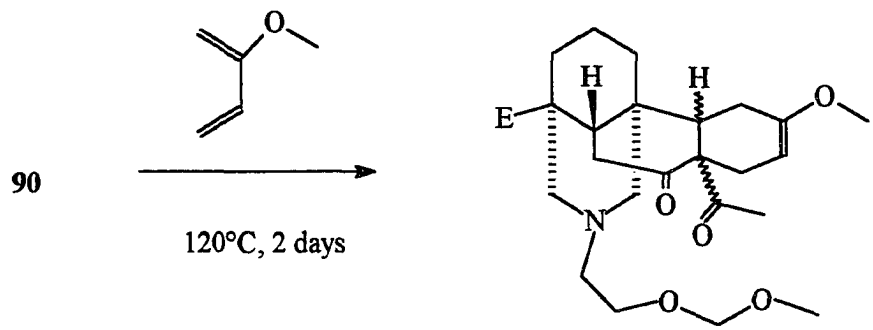
Introduction of the double bond was effected using the same procedure as for **65**. Compound **90** was thus obtained in 70% yield. The double bond in **90** proved to be very electron-deficient, as evidenced by the singlet at 7.26 ppm present in its ^{1}H-NMR spectrum. When 2-methoxy-butadiene[119] was used as a Diels-Alder reaction partner, the desired adduct **91** was obtained. After keeping the reaction mixture for two days at 120°C, the isolated yield of **91** was always better than 70%, although conversions ranged only in the 51 to 55%. The mixture of isomers, obtained in a 1.2 to 1 ratio could not be separated at this stage by FCC.

Several conditions under which selective hydrolysis of the enol ether could be achieved without removal of the protective acetal group have been investigated. Finally, it was found that a catalytic amount of pyridine p-toluenesulfonate in refluxing tetrahydrofurane effected the desired transformation with better than 95% selectivity. Base-catalyzed cyclization effected the ring closure giving **93** as a mixture of isomers from which **94** could not be

Scheme 31.



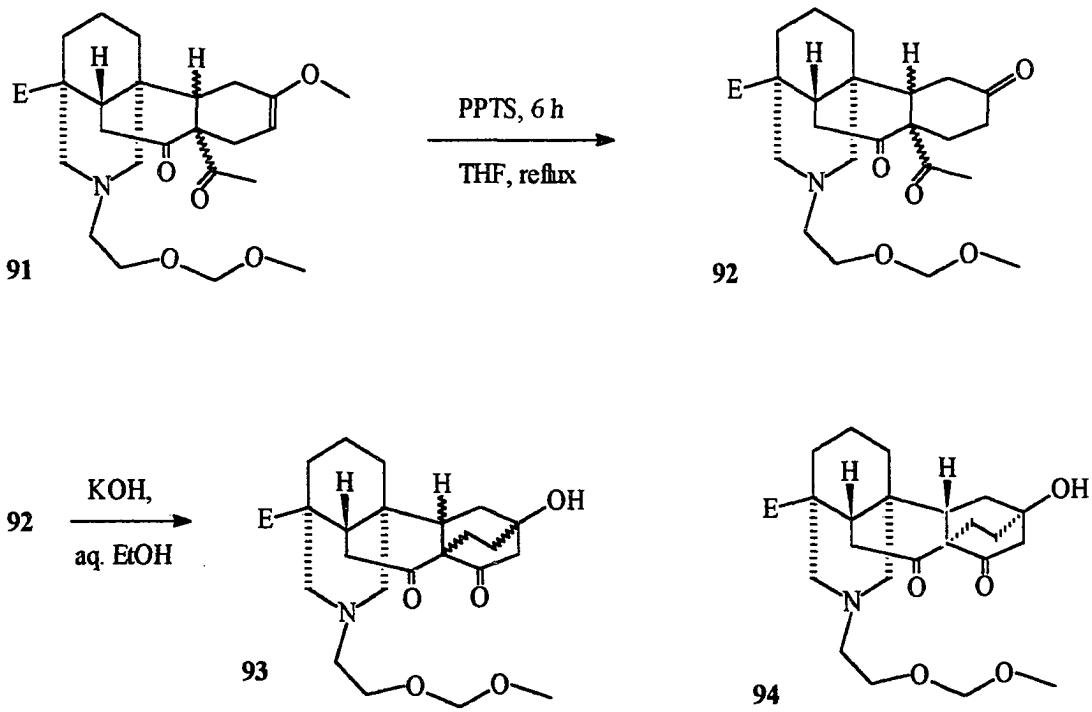
88 **90**



90 **91**

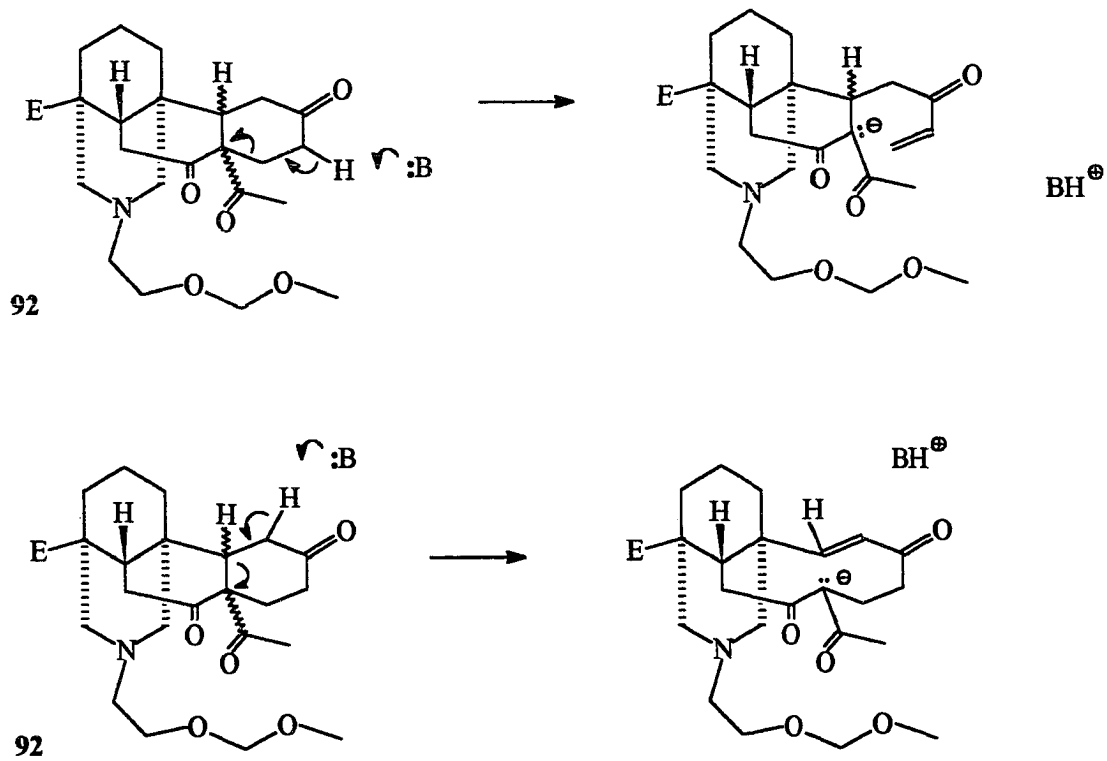
isolated by flash column chromatography (Scheme 32). The separation of **94** and its C6a-*epi*, C10a-*epi* isomer proved to be troublesome even by preparative HPLC. Studies towards a better selectivity in the cycloaddition step as well as towards achieving reasonable isomer purity for **94** are under way. An interesting epimerization of **92** was noticed under equilibration conditions (Scheme 33). At this moment it is not clear yet whether only one of the centers shown, or both of them are involved.

Scheme 32.



For stereoelectronic reasons, epimerization at the 10a position, implying ring closure of a decentrione, is less likely. The evidence that we have so far, however, is only circumstantial. Due to the complexity of the NMR data, we attempted an X-ray structure elucidation. In the case of these more complex substrates, obtaining the proper crystalline materials proved to be tedious. When the sequence of reactions shown in Schemes 30 through 32 was applied to compound **86**, a crystalline material was obtained following purification by FCC. Unfortunately, it could not be obtained in a form suitable for X-ray structure determination. Removal of the MOM protective group in compound **92**, as well as in **93**, resulted in the formation of the corresponding primary alcohols which were then esterified with *p*-bromobenzoyl chloride.

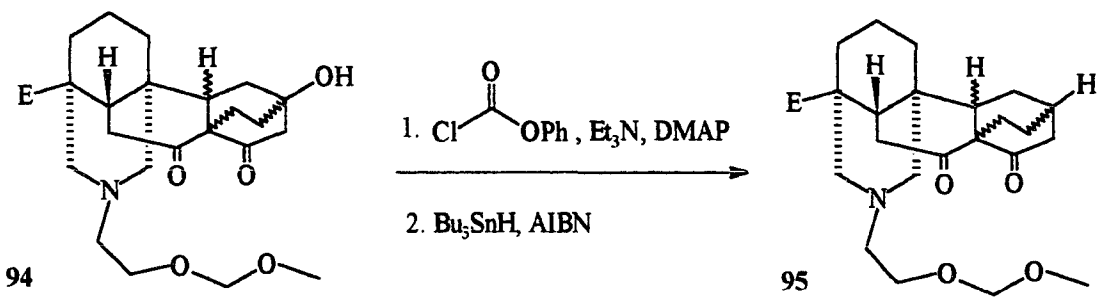
Scheme 33.



No crystals suitable for X-ray structure determination could be obtained, in spite of employing a variety of conditions under which selective crystallization was likely to occur. Surprisingly, attempts at separation by preparative HPLC were again futile.

Compound **94** contains the skeleton of the the atisine and spiramines alkaloids together with appropriate functional groups to allow for a convenient generation of several members of these genera. Barton deoxygenation[120] of **93** gave compound **95** for which the introduction of the double bond present in the natural compounds should be facilitated by the fact that one of the positions α to the carbonyl is less hindered than the other one (Scheme 34).

Scheme 34.

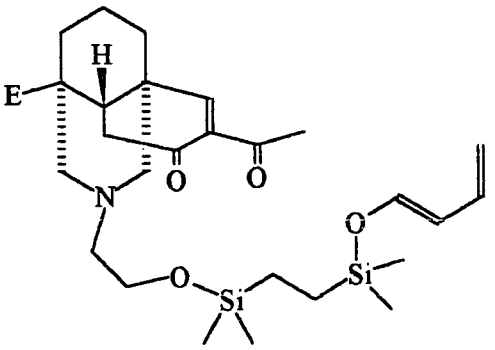


94 95

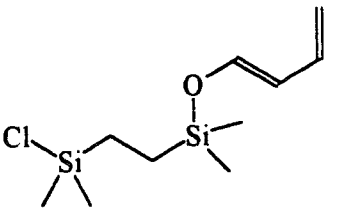
Attempts to control the facial selectivity of the cycloaddition reaction were not successful yet. An elegant approach would have used the hydroxyl functionality masked in the endione **90** in order to tether the diene moiety and thus force it to reach the reactive site from one face only. The desired configuration at the new carbon centers formed would have been identical to that present in the natural compounds regardless of whether the cycloaddition reaction proceeded via an exo or an endo transition state (Scheme 35). Molecular modelling calculations indicated that for the tether shown there would not be insurmountable steric barriers and that the presence of the silicon atoms influenced the flexibility of the tether chain quite favorably. Unfortunately, several attempts to prepare compound **97** failed to yield a clean product. Other tethers considered initially were later dismissed for reasons of thermal and hydrolytic stability. The use of the equivalent of a 1-siloxy-butadiene would not have precluded us from completing the synthesis of these classes of compounds since ring closure could have been effected, for instance, via an SN_2' process on the corresponding mesylate.

Given the fact that the corresponding 2-siloxy-butadiene tether would have been considerably more difficult to prepare than its 1-siloxy counterpart, any attempts to make use of this strategy were halted at that time.

Scheme 35.

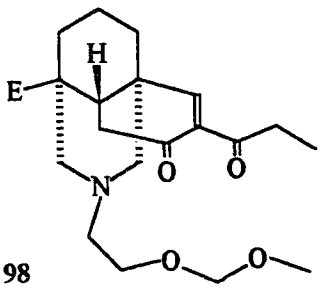


96

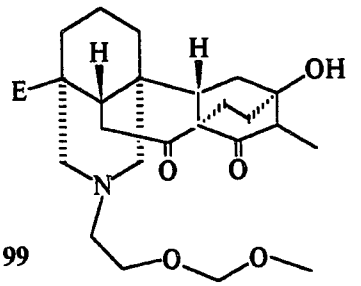


97

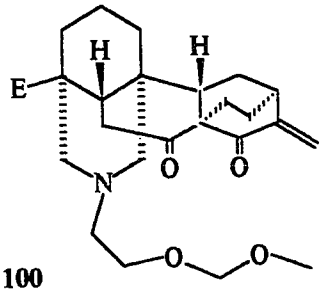
Scheme 36.



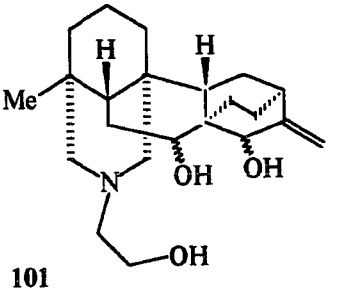
98



99



100



101

A possible strategy which would have allowed for the introduction of a methyl group which in turn could have been transformed into the corresponding methylene functionality has been briefly examined (Scheme 36).

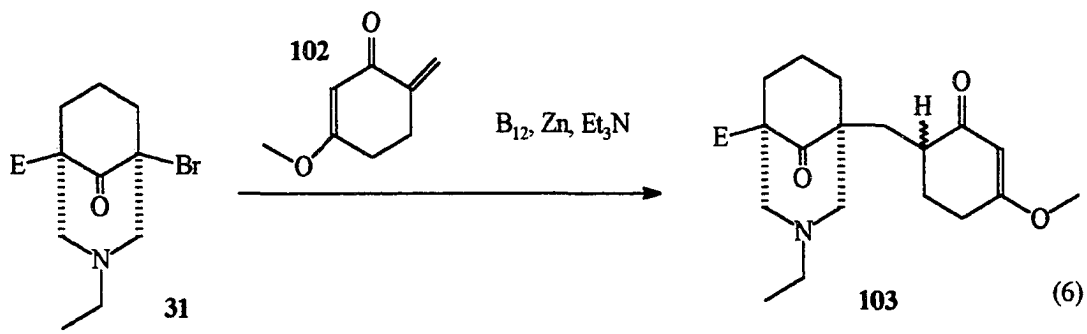
Thus, the same sequence of reactions that led us to the successful construction of **95**, this time substituting 2-oxo-butyronitrile for pyruvonitrile in the acylation step would give **98** as an intermediate, and **99** as a preliminary target compound. Although deoxygenation should proceed in good yield, the previous base-catalyzed cyclization would have had to overcome a sensibly more sterically hindered transition state. With this concern in mind and a number of issues yet to be addressed in the previous route, we postponed further investigations in this direction. At this point it is only worth mentioning that the compounds **101** which could be obtained by the reduction of **100** are naturally occurring compounds by themselves (see also Appendix 1).

In conclusion, the carbocyclic skeleton bearing the appropriate functionality and configuration of the stereogenic centers of the atisine and spiramines alkaloids has been synthesized following a 13 step sequence starting with the commercially available ethyl-2-oxo-cyclohexanecarboxylate. Further manipulation of the present functional groups allows for a convenient and very direct access to many of the compounds comprising these classes of diterpene alkaloids. Although the most direct route known so far, better stereo control in some of the key steps is needed for an improved overall yield.

Studies directed towards the synthesis of aconitine type alkaloids

Based on our considerable experience acquired while studying the synthesis of atisine type alkaloids, we decided to pursue a similarly direct route which would also contribute more examples to our successful bridgehead radical chemistry. We began by preparing compound **103** (equation 6) and then subjecting it to various organometallic reagents under conditions

that would allow for as good a regioselective addition as possible (Table 5). Enone **102** was obtained in excellent yield following a very mild exo-methylenation[121] of 3-methoxy-2-cyclohexen-1-one. Our efforts were initially focused on devising a method of effecting a ring closure in **103**, by using both its carbonyl functions in order to obtain a tetracyclic intermediate, leaving stereochemical issues, such as epimerization of the center α to the carbonyl, to be addressed at a later stage.

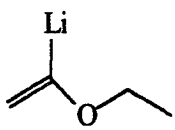
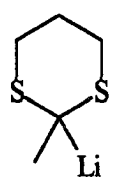


(6)

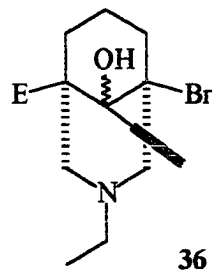
Compound **103** was indeed obtained in excellent yield (92%) by using our standard procedure. Although we expected the ketone functionality present in **103** to be considerably more reactive than the vinylogous ester, in practice the steric factors at the carbonyl position decreased its reactivity so as to almost match that of the less hindered and more electron-rich vinylogous ester (Table 5).

Introduction of an acetyl group equivalent on **31** by using 2-propenyl-magnesium bromide was unsuccessful, probably due to excessive steric hindrance. Interestingly, **36** did not hydrate to **104** even when a variety of reagents and conditions was employed,[122] nor did it undergo a Rupe rearrangement (Scheme 37).[123]

Table 5. Organometallic additions / reductions of **103**.

Reagent	Product / Comments
TMS—≡—Li	~ 1 / 1 mixture of the two mono-adducts
TMS—≡—MgBr	~ 1 / 1 mixture of the two mono-adducts
TMS—≡—$CeCl_2$	~ 1.5 / 1 mixture of regioisomers
	~ 1.2 / 1 mixture of regioisomers
	~ 1.4 / 1 mixture of regioisomers
$NaBH_4$	no selectivity, complete reduction
$LiAlH(OtBu)_3$	low selectivity, complete reduction
	~ 20% mixture of alcohols + starting mat.

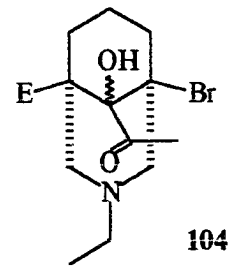
Scheme 37.



36

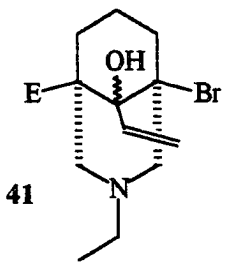
no hydration with:

HgO / H_2SO_4
$HgSO_4$
Hg^{2+} / Dowex
conc. HCl
$Co_2(CO)_8 / NaBH_4 / Fe(NO_3)_3$



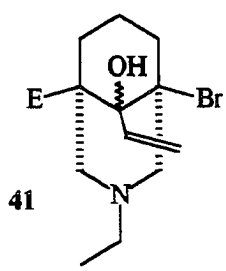
104

Scheme 38.

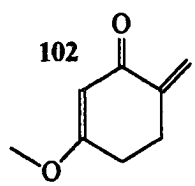


41

$PdCl_2 / CuCl / O_2$ → complex mixture

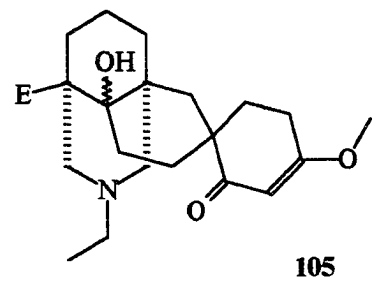


41



102

B_{12}, Zn, Et_3N

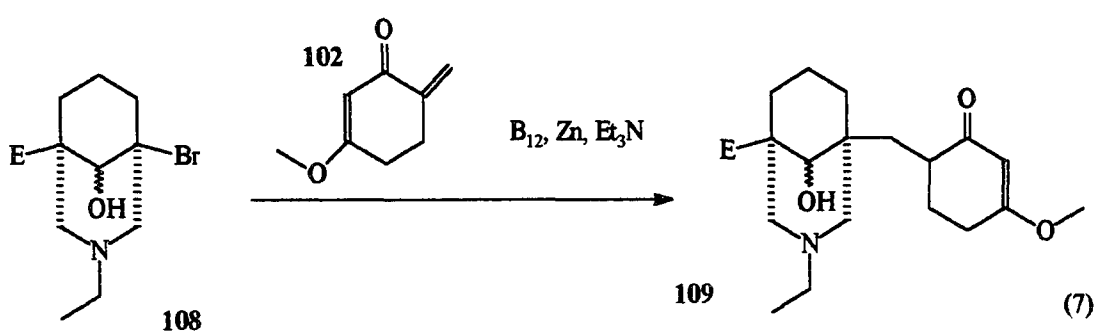


105

Compound **104** was however separated in low yield from the complex mixture obtained while treating **36** with phenylmercuric hydroxyde.[124] A Wacker oxidation[125] of **41** also resulted in the formation of a complex mixture (Scheme 38). Although it has been reported that some allylic alcohols do not respond well when subjected to this procedure we reasoned that the bridgehead bromide may be a source of additional interference. Interestingly, when compound **41** was subjected to our bridgehead radical-forming conditions in the presence of enone **102**, the spiro compound **105** was obtained in high yield, conceivably as a result of the addition of the expected intermediate radical species to the allylic double bond in a 1,6-endo-trig cyclization. Apparently both isomers bearing opposite configurations at the spiro carbon center were formed with no significant selectivity.

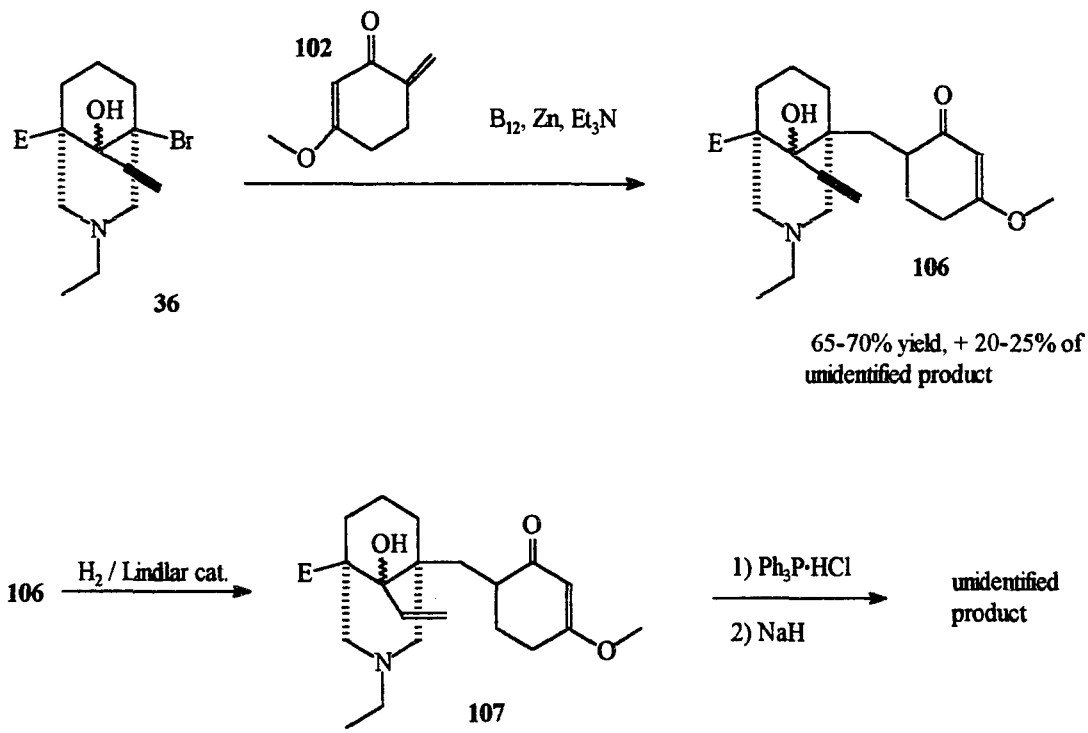
Due to our interest in effecting the seven-membered ring closure leading to an advanced aconitine type intermediate, an indirect route to compound **107** was sought (Scheme 39). Unfortunately, the conceptually elegant intramolecular Wittig reaction resulted in the formation of an unidentified product instead of our desired tetracyclic intermediate.

An alternative route was then envisaged, in which one would not rely on differentiation between the two carbonyl groups of **103** anymore. For this purpose, compound **109** had to be prepared (equation 7).



108 **109** (7)

Scheme 39.

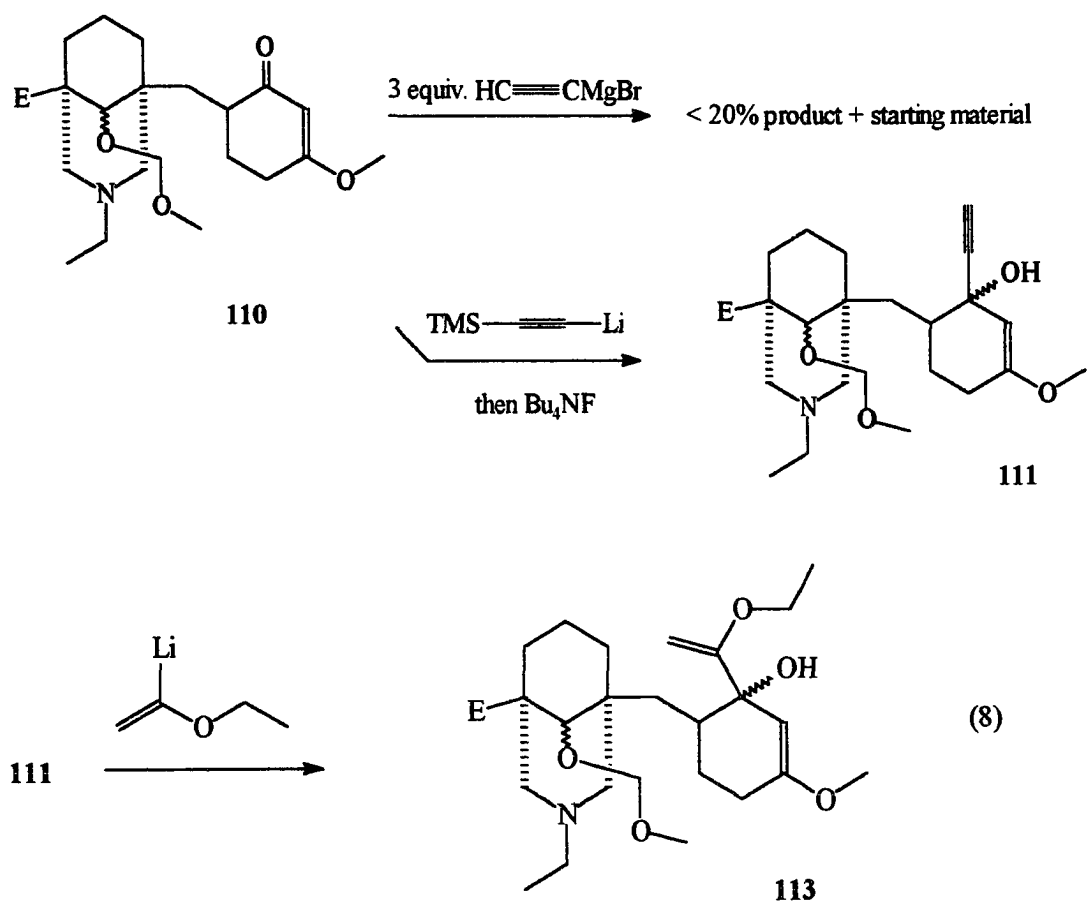


Although we were initially concerned about the poisoning effect on the catalyst encountered with the free alkanolamine used in the spiramine series, compound **109** was obtained in excellent yield as a mixture of separable diastereomers. Organometallic additions to **109** failed completely regardless of the nature of the reagent used. We assumed that deprotonation of the enone moiety by the alkoxide formed as the first equivalent of reagent was added, was so effective that no electrophillic substrate was left to react with the second equivalent of the organometallic reagent used. For this reason, protection of the secondary alcohol was necessary. We chose a methoxymethyl (MOM) group again, due to the fact that its removal could be effected under the same acidic conditions employed in the rearrangement of the 3-methoxy tertiary allylic alcohol resulted from nucleophillic additions to the enone moiety of **110** (Scheme 40).

Addition of ethynyl magnesium bromide to **110** failed again, but when trimethylsilyl-ethynyllithium was used instead the desired adduct was formed in quantitative yield. Although both deprotection and rearrangement of **111** proceeded smoothly, hydration of the triple bond to the corresponding acetyl group could not be achieved; only **112** was obtained instead (Scheme 41).

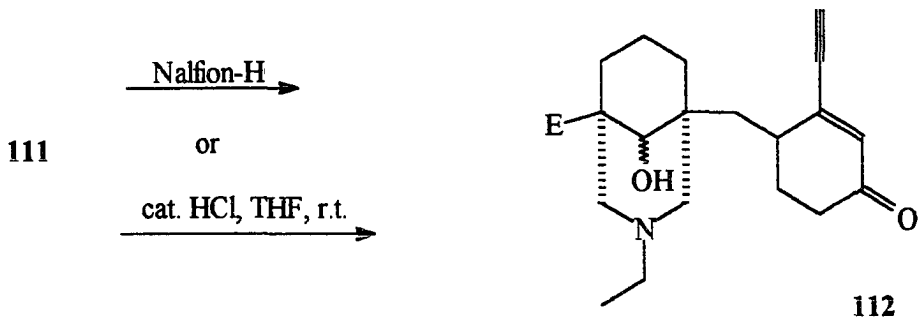
In order to overcome these difficulties, 1-ethoxyvinyllithium[126] had to be used as an acetyl anion equivalent (equation 8).[127] The desired compound **113** was obtained in 90% yield.

Scheme 40.

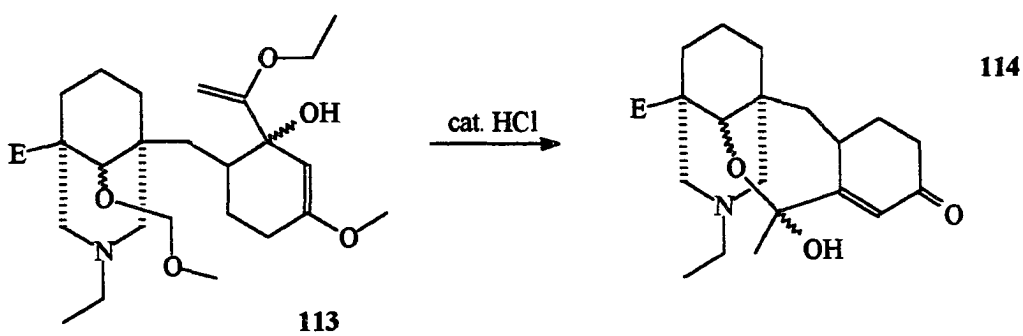


(8)

Scheme 41.



Interestingly, compound **113** proved to be stable to neutral silica. Rearrangement and simultaneous deprotection of **113** occurred rapidly following treatment with a catalytic amount of hydrochloric acid in tetrahydrofurane at room temperature (eq. 9), however, oxidation of the hemiketal **114** thus formed proved to be extremely difficult (Table 6).

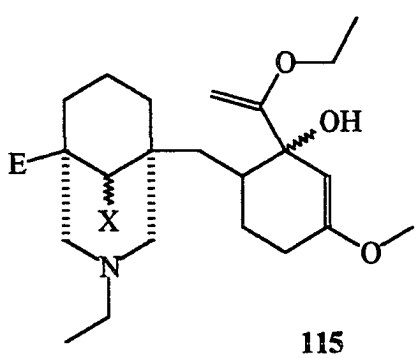


(9)

Table 6. Oxidation of compound **114**

Reagent / conditions	product / comments	reference
PCC / Celite	starting material	128
PCC / Celite, AcONa	~ 30% s.m. + tarr	129
PhCOPh, tBuOK / PhH, reflux	starting material	130
$Al(OiPr)_3$, acetone, reflux[128]	starting material	131
DMSO, TFAA, Et_3N	starting material	57
Jones reagent	starting material + tarr	132

The stability of the hemiketal **114** is indeed remarkable. While preventing us from reaching an all-carbon frame tetracyclic intermediate suitable for the synthesis of aconitine type alkaloids, it also suggests that such a structure can be made following a less favorable cyclization in which a seven-membered ring is formed in the key step. The difficulties encountered so far could be overcome if oxidation of the secondary alcohol precedes the enone-forming rearrangement. A suitable alternative would employ a protective group that can be removed under basic or neutral conditions, as indicated for compound **115** (Figure 10).



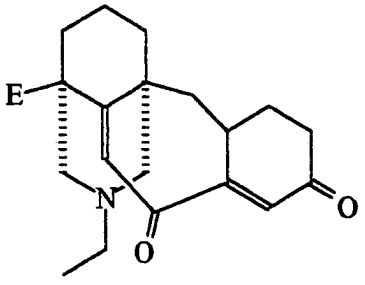
115

X : OTMS
OTBS

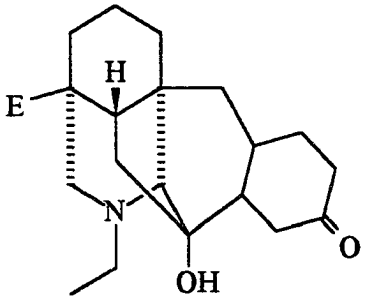
OCOCOPh

Figure 10. With appropriate "X" unmasking the keto group can precede rearrangement

Upon effecting the ring closure, intermediate **116** would be obtained with promise for an even more advanced pentacyclic intermediate such as **117** in sight (Figure 11). Even at the present stage, considerable progress has been made in this direction. For a quick reference, the structure of one of the target compounds has been given, enclosed in a rectangle. Given the fact that no work has been reported towards the total synthesis of aconitine alkaloids, further research in this area is justified and promises to return interesting results.



116



117

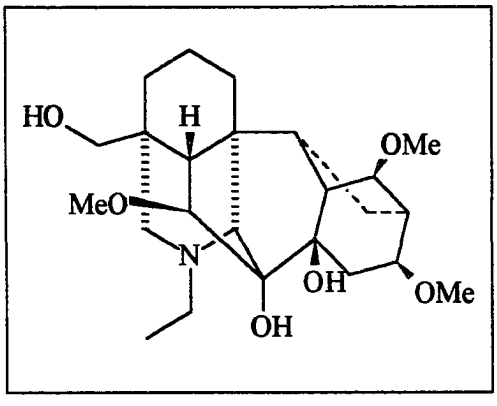


Figure 11. Intermediates accessible via the proposed route, together with one of the target compounds.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for thin layer chromatography (TLC) and silicagel flash chromatography (SGC). Commercially available silicagel (40μm) was used as stationary phase. The NMR spectra were recorded at 300 MHz and the purity of all title compounds was determined to be > 95% by this method. The following symbols were used to designate peak multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), qv (quintet), ABq (AB quartet), m (multiplet). Combinations, such as dt should read "doublet of triplets".

General procedure for the bridgehead generation/trapping sequence: A 10 mL flask was charged with vitamin B_{12} (23 mg, 16.4 μmoles), activated zinc (220 mg, 3.38 mmol), 1.4 mL of dimethylformamide (DMF), 30 μL of water and a stirring bar. The mixture was degassed and stirred vigorously under argon at room temperature until the color turned emerald green. A degassed solution of the bridgehead bromide (0.34 mmol), radical acceptor (0.67 mmol) and triethylamine (0.24 mL, 1.7 mmol) in 0.9 mL of DMF was added dropwise and the mixture was stirred at room temperature for 12-24h. The excess zinc was removed by filtration. To the solution were added 2.5 mL of water and 0.5 mL of ammonium hydroxide 6M solution. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography, using H:EA as eluent.

Ethyl 5-bromo-3-(2-hydroxyethyl)-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (83): To a mixture of freshly distilled 6-bromo-2-carboethoxy-cyclohexanone (2.49 g, 10 mmol) and formaldehyde (1.67 g of 37% wt. solution, 20.2 mmol) in 50 mL absolute methanol was added ethanolamine (0.61 g, 10 mmol) and the mixture was kept at room

temperature for two days. A cleaner reaction mixture was obtained in the presence rather than the absence of air. The mixture was concentrated, and the brown oil was taken in 20 mL 1N HCl and extracted with ethyl ether. About 0.4 g of the starting bromo derivative could be recovered. The aqueous layer was neutralized with solid sodium carbonate, saturated with brine, and extracted with ether. The dried extract was concentrated and purified by SGC with H:EA 2.5:1 to 1.5:1 to give 2.1 g of **83** (64%) as a colorless oil. MS. *m/e* calcd. for $C_{13}H_{20}NO_4{}^{79}Br$: 333.05757, measured: 333.05800. MS *m/e* calcd. for $C_{13}H_{20}NO_4{}^{81}Br$: 335.05565, measured: 335.05491. MS *m/e*: 335.1, 333.1, 304.0, 302.0, 276.0, 254.1, 222.1, 208.1, 180.1, 152.1, 122.1, 93.1, 79.1, 56.1, 42.0. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.8 Hz, 3H), 1.69 (qvt, *J* = 6.4, 2.0 Hz, 1H), 1.75-1.95 (m, 1H), 2.28 (ddt, *J* = 14.4, 6.0, 2.0 Hz, 1H), 2.5-2.7 (m, 3H), 2.8 (ddt, *J* = 14.3, 6.0, 2.0 Hz), 2.82-3.05 (m, 1H), 3.08 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.17 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.29 (dd, *J* = 11.8, 2.4 Hz, 1H), 3.64 (dd, *J* = 11.2, 2.4 Hz, 1H), 3.73 (t, *J* = 2.4 Hz, 2H), 4.23 (q, *J* = 7.8 Hz, 2H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 13.74, 22.57, 35.80, 45.80, 57.85, 58.94, 59.53, 61.16, 61.28, 68.68, 68.76, 169.32, 201.67. IR (neat): cm^{-1} 715, 859, 1013, 1262, 1440, 1712, 2818, 2935, 3200-3600 broad. R_f (H:EA 2/1) 0.36.

Ethyl 5-bromo-3-(2-(methoxymethyloxy)-ethyl)-9-oxo-3-azabicyclo-[3.3.1]-nonane carboxylate (83a): To the aminoalcohol **83** (1.5352 g, 4.6 mmol) in 15 mL dry (CaH_2) methylene chloride were added diisopropylethylamine (2.56 mL, 13.8 mmol) and the mixture was cooled at 0°C in an ice bath. Freshly distilled methyl-chloromethyl ether (0.95 mL, 12.5 mmol) were added dropwise, under vigorous stirring. The mixture was warmed to room temperature, stirred overnight, and partitioned between methylene chloride and a saturated solution of $NaHCO_3$. The aqueous layer was further extracted with methylene chloride, the combined organic layers were dried over Na_2SO_4 and concentrated. The crude reaction mixture was flushed through a 1.5 in. pad of silicagel, using H:EA (3:1) to give 1.65 g (95%) of **83a**, as a colorless oil. MS *m/e* calcd. for $C_{15}H_{24}NO_5{}^{79}Br$: 377.08378, measured:

377.08378. MS *m/e* calcd. for $C_{15}H_{24}NO_5{}^{81}Br$: 379.08187, measured: 379.08214. MS *m/e*: 379.1, 377.1, 304.0, 302.0, 252.1, 222.1, 150.1, 122.1, 86.1, 56.1. ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.61 (qvt, *J* = 6.6, 1.8 Hz, 1H), 2.25 (ddt, *J* = 15.0, 5.8, 2.0 Hz, 1H), 2.5-2.62 (m, 4H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.78 (ddt, *J* = 14.8, 5.9, 2.0 Hz, 1H), 3.21 (d, *J* = 2.8 Hz), 3.27 (d, *J* = 3.0 Hz), 3.31 (d, *J* = 3.0 Hz), 3.06-3.35 (m, 3H), 3.38 (s, 3H), 3.67 (t, *J* = 5.7 Hz, 2H), 4.23 (q, *J* = 7.5 Hz, 2H), 4.64 (s, 2H). ^{13}C-NMR ($CDCl_3$): δ 13.97, 22.66, 36.22, 46.20, 55.24, 55.56, 59.90, 61.45, 61.61, 65.26, 69.00, 69.17, 96.44, 169.59, 201.78. IR (neat) cm^{-1}: 702, 917, 1041, 1112, 1260, 1456, 1728, 1738, 2822, 2934, 2983. R_f (H:EA 4:1) 0.5.

Ethyl 3-(2-(methoxymethyloxy)-ethyl)-5-(3-oxobutyl)-9-oxo-3-azabicyclo-[3.3.1]-nonane carboxylate (52a). The general procedure outlined above was employed. Thus, the crude reaction mixture obtained from 12.129 g bromide **83** (32.25 mmol) gave upon SGC (H:EA 2:1), 9.6 g (82%) of **52a** as a light yellow oil. MS *m/e* calcd. for $C_{19}H_{31}NO_6$: 369.21514, measured: 369.21447. MS *m/e*: 369.2, 312.2, 294.2, 248.1, 179.1, 121.1, 86.1, 45.0. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.48-1.72 (m, 4H), 1.82 (m, 1H), 2.04 (dqv, *J* = 16.0, 2.0 Hz, 1H), 2.14 (s, 3H), 2.21 (dqv, *J* = 15.8, 2.0 Hz, 1H), 2.4-2.56 (m, 3H), 2.6 (td, *J* = 8.0, 0.8 Hz, 2H), 2.86-3.0 (m, 1H), 3.03 (dd, *J* = 14.8, 2.0 Hz, 1H), 3.07 (dd, *J* = 11.8, 1.8 Hz, 1H), 3.22 (dd, *J* = 11.8, 1.8 Hz, 1H), 3.37 (s, 3H), 3.67 (t, *J* = 8.0 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.64 (s, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 14.00, 20.21, 28.29, 29.72, 36.66, 38.22, 39.32, 48.79, 55.14, 56.29, 58.94, 61.02, 62.23, 65.36, 65.41, 96.39, 170.88, 208.30, 212.54. IR (neat), cm^{-1}: 918, 1040, 1112, 1258, 1441, 1469, 1715, 1732, 2821, 2933, 2982. R_f (H:EA 2:1) 0.38.

Ethyl 2*H*, 3*H*, 4*H*, 6*H*, 7*H*, 8*H*-2-(2-(methoxymethyloxy)-ethyl)-6-oxo-4,8a-1*H*-propanoiso-quinoline 4-carboxylate (85): In a flame-dried flask were placed **52a** (9.406 g, 25.5 mmol) and 250 ml dry (benzophenone ketyl) THF. Potassium *tert*-butoxide (2.28 g, 20.3 mmol) was added at 0°C under dry argon, and the dark yellow solution was kept in the

refrigerator overnight. The mixture was neutralized with aqueous saturated ammonium chloride solution at 0°C, separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried, concentrated and the crude product was flushed through a 2 in. pad of silicagel using H:EA 2:1 as eluent. Compound **85** (8.06 g, 91 %) was obtained as a light yellow oil. MS *m/e* calcd. for $C_{19}H_{29}NO_5$: 351.20457, measured: MS *m/e*: ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.5 Hz, 3H), 1.56 (qvt, *J* = 6.6, 2.0 Hz, 1H), 1.65-1.84 (m, 3H), 1.92-2.15 (m, 2H), 2.17-2.5 (m, 4H), 2.54 (td, *J* = 6.0, 1.5 Hz, 2H), 2.80 (dd, *J* = 4.8, 1.5 Hz, 1H), 2.95 (dd, *J* = 11.0, 0.8 Hz), 2.89-3.08 (m, 2H), 3.14 (dd, *J* = 11.5, 1.2 Hz, 1H), 3.38 (s, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 4.20 (qd, *J* = 7.2, 1.5 Hz, 2H), 4.64 (s, 2H), 5.66 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.12, 20.56, 32.97, 33.38, 36.76, 37.67, 38.34, 52.05, 55.25, 56.94, 61.20, 61.92, 65.36, 66.86, 96.52, 120.75, 167.35, 172.58, 198.96. IR (neat), cm^{-1}: 748, 915, 1041, 1248, 1614, 1672, 1728, 2821, 2930, 2983.
R_f (H:EA 2:1), 0.38.

Ethyl 2*H*, 3*H*, 4*H*, 6*H*, 7*H*, 8*H*-7-acetyl-2-(2-(methoxymethyloxy)-ethyl)-6-oxo-1*H*-4,8a-propanoisoquinoline-4-carboxylate (87): To a flame-dried, argon-flushed flask were added dry (benzophenone ketyl) THF (17 mL) and dry (CaH_2) diisopropylamine (0.7 mL, 4.7 mmol). The mixture was cooled at -10°C, and 2.0 mL of butyllithium (2.38M solution in hexanes) were added via syringe. After stirring for 1/2 h at -10°C, the mixture was cooled at -78°C and a solution of the enone **85** (1.3751 g, 3.91 mmol) in THF (6 mL) was added dropwise. The flask containing compound **85** was rinsed with 7 mL THF and this solution was transferred to the reaction flask via canula. The reaction mixture was stirred for 1/2 h at -78°C, warmed to 0°C for 5 min then quickly cooled to -78°C. Freshly distilled, dry pyruvonitrile (0.32 mL, 4.3 mmol) was added over 5 min, immediately followed by dry hexamethylphosphoramide (HMPA, 0.76 mL). The mixture was stirred at -78°C for 1 h, warmed to -10°C and stirred at this temperature overnight. To the cold mixture was added a saturated solution of ammonium chloride and the pH was adjusted to 7-7.5 with NH_4OH.

The mixture was extracted with ethyl acetate, the extract was dried, concentrated and purified by SGC (H:EA 6:1 to 2:1). Compound **87** (light yellow oil, 981 mg, 64%) eluted first, followed by **85** (432 mg, 31%). Compound **87** is in equilibrium with its tautomer. MS *m/e* calcd. for $C_{21}H_{31}NO_6$: 393.21514, measured: 393.21416. MS *m/e*: 362.2, 318.2, 272.1, 244.1, 187.1, 132.1, 86.1, 43.0. ^{1}H-NMR ($CDCl_3$): δ 1.29, 1.30 (t, *J* = 7.2 Hz, 3H), 1.52 (qvt, *J* = 6.5, 2.0 Hz, 1H), 1.65-1.75 (m, 1H), 1.86-2.09 (m, 1H), 2.04 (s, 3H), 2.08-2.40 (m, 6H), 2.54 (td, *J* = 5.9, 1.2 Hz, 2H), 2.80 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.82-3.05 (m, 3H), 3.14 (dd, *J* = 11.1, 0.9 Hz, 1H), 3.38 (s, 3H), 3.663, 3.658 (t, *J* = 6 Hz, 2H), 4.21, 4.20 (q, *J* = 7.2 Hz, 2H), 4.64 (s, 2H), 5.67, 5.68 (s, 1H), 15.80 (s, corresponding to 0.72 H). ^{13}C-NMR ($CDCl_3$): δ 13.95, 13.97, 20.51, 20.81, 34.47, 37.87, 38.98, 40.05, 51.95, 55.04, 56.79, 60.97, 61.61, 65.17, 66.57, 96.32, 100.74, 118.44, 164.40, 172.39, 183.14, 183.64. IR (neat), cm^{-1}: 733, 917, 1040, 1108, 1253, 1464, 1623, 1669, 1727, 2821, 2929, 2980. R_f (H:EA 2:1) 0.35.

Ethyl 4a-(α) 2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 7*H*, 8*H*-7-acetyl-2-(2-methoxymethyl-oxy)-ethyl)-6-oxo-1H-4,8a-propanoisoquinoline-4-carboxylate (88) and **4a-(β) Ethyl 2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 7*H*, 8*H*-7-acetyl-2-(2-methoxymethyloxy)-ethyl)-6-oxo-1*H*-4,8a-propanoisoquinoline-4-carboxylate (89)**: To a flask containing the endione **87** (1.193 g, 3.036 mmol) were added 30 mL isopropanol, 10 μL acetic acid and the flask was flushed with argon. Palladium on carbon (120 mg, 10% Pd) was then added, and a hydrogen atmosphere (normal pressure) was maintained for 24 h. The reaction mixture was filtered under argon, the precipitate was washed with isopropanol and the crude reaction mixture was concentrated to give a mixture of **88** and **89** in a 2.6 to 1 ratio, as a colorless oil. MS *m/e* calcd. for $C_{21}H_{33}NO_6$: 395.23079, measured: 395.23041. MS *m/e*: 395.2, 352.2, 320.2, 246.1, 203.1, 132.1, 86.1, 58.1, 42.9. ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.42-1.72 (m, 2H), 2.11 (s), 1.80-2.14 (m, 7H), 2.49 (t, *J* = 6.0 Hz, 2H), 2.20-2.60 (m, 6H), 2.65-2.80 (m, 1H), 3.15 (d, *J* = 9 Hz, 1H), 3.28 (d, *J* = 8.0 Hz, 1H), 3.38 (s, 3H), 3.64 (t, *J* = 6 Hz, 2H), 4.10

(q, J = 7.5 Hz, 2H), 4.64 (s, 2H), 15.72, 15.83 (s, total 0.8H). ^{13}C-NMR ($CDCl_3$): δ 12.45, 14.14, 19.94, 25.12, 25.38, 28.44, 28.84, 32.50, 36.41, 39.72, 45.72, 55.14, 55.19, 57.60, 60.59, 63.33, 65.30, 67.61, 96.44, 104.52, 174.85, 179.79, 199.14. IR (neat), cm^{-1}: 741, 920, 1042, 1110, 1258, 1472, 1725, 2820, 2930, 2980.

Compounds **88** and **89** were separated by SGC on a 8 in. column, using benzene: isopropanol:ethyl acetate:acetic acid 60:3:2:0.54.

General procedure for the introduction of the double bond in **88** and **89**: To a cold (0°C) solution of diphenyl diselenide (148 mg, 0.47 mmol) in 11.3 mL methylene chloride was added a freshly prepared solution of bromine in methylene chloride (0.46 mL 1.0 M). After stirring for 10 min., pyridine (80 μL, 0.99 mmol) was added and the mixture was stirred at 0°C for 20 min. The diketone (312 mg, 0.79 mmol) was slowly added as a solution in methylene chloride. The mixture was stirred at 0°C for 6 h, concentrated, and the excess pyridine was removed under reduced pressure (10-20 mtorr). The residue was partitioned between water and methylene chloride and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried, concentrated, and any trace of pyridine was removed under vacuum. The residue was taken in methylene chloride (12 mL), and trifluoroacetic acid (75 μL) was added at 0°C, followed by hydrogen peroxide (0.35 mL 30%, in three portions at 10 min. interval) under vigorous stirring. Sodium sulfite (0.5 mL saturated solution) was added and the mixture was stirred for 20 min. Upon neutralization (ammonium hydroxide 6M), partitioning between water and methylene chloride and extraction of the aqueous layer with methylene chloride, the crude product was purified by SGC using H:EA 5:1 as eluent to give the corresponding endione (245 mg, 79%) as a colorless oil which rapidly turns orange upon exposure to air.

Ethyl 4a-(α)-2*H*, 3*H*, 4*H*, 6*H*, 7*H*, 8*H*, 7-acetyl-2-(2-(methoxymethyloxy)-ethyl)-6-oxo-1*H*-4,8a-propanoisoquinoline-4-carboxylate (90): MS *m/e* calcd. for $C_{21}H_{31}NO_6$: 393.21514, measured: 393.21508. MS *m/e*: 393.2, 333.2, 290.2, 260.2, 170.1, 149.1, 91.1,

72.1, 42.6. ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, *J* = 7.5 Hz, 3H), 1.42-1.68 (m, 3H), 1.70-2.03 (m, 3H), 2.21-2.31 (m, 1H), 2.36 (ABq, *J* = 18.6, 4.2 Hz, 1H), 2.46 (s), 2.41-2.67 (m, 8H), 2.80 (nonet, *J* = 6.6 Hz, 1H), 3.08 (ABq, *J* = 12.0, 11.4 Hz, 1H), 3.37 (s, 3H), 3.64 (t, *J* = 5.7 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.63 (s, 2H); 1H is at δ 7.26 ppm. ^{1}H-NMR (CD_3COCD_3): δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.58-1.75 (m, 3H), 1.92-2.02 (m, 2H), 2.33 (s), 2.12-2.32 (m, 6H), 2.53 (t, *J* = 6.0 Hz), 2.42-2.52 (m, 3H), 2.70 (dd, *J* = 17.4, 15.0 Hz, 1H), 2.80 (s), 2.73-2.93 (m, 1H), 3.10 (d, *J* = 10.8 Hz, 1H), 3.23 (d, *J* = 10.5 Hz, 1H), 3.30 (s, 3H), 3.63 (t, *J* = 6.0 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.58 (s, 2H), 7.19 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.02, 20.82, 25.41, 29.58, 30.52, 36.32, 36.60, 42.17, 45.20, 55.04, 57.18, 60.73, 62.15, 63.08, 65.03, 96.29, 137.62, 161.25, 173.86, 196.12, 198.20. IR (neat), cm^{-1}: 728, 923, 1035, 1110, 1258, 1635, 1672, 1728, 2820, 2930, 2980. R_f (H:EA 2:1) 0.42.

Ethyl 4a-(α), 6a-(α), 10a-(α)-2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 6a*H*, 7*H*, 10*H*, 10a*H*-6a-acetyl-2-(2-(methoxymethyloxy)-ethyl)-9-methoxy-6-oxo-1*H*-4,10b-propano-benz[h]isoquinoline-4-carboxylate and **Ethyl 4a-(α), 6a-(β), 10a-(β)-2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 6a*H*, 7*H*, 10*H*, 10a*H*-6a-acetyl-2-(2-(methoxymethyloxy)-ethyl)-9-methoxy-6-oxo-1*H*-4,10b-propanobenz[h]iso-quinoline-4-carboxylate (91)**: To a dry pressure reactor were added endione **90** (419 mg, 1.066 mmol), 2-methoxybutadiene (1.1 mL), and hydroquinone (2 mg). The reactor was flushed with dry argon, sealed and kept at 120°C for 40h. The solvent was distilled under reduced pressure and the residue was purified by SGC (column neutralized with 1% triethylamine in hexanes, H:EA 2.5:1 as eluent) to give the corresponding adduct, as a 1.2 to 1 mixture of isomers (346 mg, 68%), colorless oil. MS *m/e* calcd. for $C_{26}H_{39}NO_7$: 477.25265, measured: 477.27289. MS *m/e*: 462.2, 434.3, 402.2, 345.2, 294.2, 243.2, 179.6, 97.1, 58.1. ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.28-1.63 (m, 4H), 2.17 (s), 2.18 (s), 1.75-2.31 (m, 12H), 2.50 (t, *J* = 6.0 Hz), 2.33-2.65 (m, 4H), 2.75-2.95 (m, 2H), 3.15 (broad s, 1H), 3.36 (s, 3H), 3.54 (s, 3H), 3.65 (t, *J* = 6.0 Hz, 2H), 4.10 (qd, *J* = 7.2, 3.0 Hz, 2H), 4.62 (s, 2H), 4.74 (broad s, 1H). ^{13}C-NMR ($CDCl_3$): 12.46,

14.15, 20.56, 24.12, 25.65, 25.92, 29.89, 31.93, 37.16, 38.83, 39.22, 45.85, 45.89, 54.02, 55.19, 55.20, 57.77, 60.33, 60.70, 62.86, 63.43, 64.89, 65.43, 91.87, 96.45, 96.51, 156.71, 174.70, 207.14, 209.56. IR (neat), cm^{-1}: 733, 916, 1041, 1256, 1362, 1445, 1464, 1667, 1690, 1717, 2824, 2935, 2983.

Ethyl 4a-(α), 6a-(α), 10a-(α)-2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 6a*H*, 7*H*, 8*H*, 10*H*, 10a*H*-6a-acetyl-6,9-dioxo-2-(2-(methoxymethyloxy)-ethyl)-4,10b-propano-benz[h]isoquinoline-4-carboxylate and **Ethyl 4a-(α), 6a-(β), 10a-(β)-2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 6a*H*, 7*H*, 8*H*, 10*H*, 10a*H*-6a-acetyl-6,9-dioxo-2-(2-(methoxymethyloxy)-ethyl)-4,10b-propano-benz[h]isoquinoline-4-carboxylate(92)**: To compound **91** (43.7 mg, 91.6 μmol) dissolved in 1 mL THF, was added pyridine para-toluenesulfonate (PPTS, 22 mg, 87.6 μmol) and water(18 μL, 1 mmol). The mixture was refluxed for 6 h. Saturated $NaHCO_3$ solution (0.25 mL) was added, and the mixture was extracted with ethyl acetate. The dried organic layer was concentrated under reduced pressure and the residue was purified by SGC (H:EA 1.5:1) to give **92** and **92a** (39 mg, 92%) as a colorless oil. MS *m/e* calcd. for $C_{25}H_{37}NO_7$: 463.25700, measured: 463.25576. MS *m/e*: 432.2, 388.2, 346.2, 229.1, 132.1, 58.1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.33-1.39 (m, 1H), 1.51-1.74 (m, 4H), 1.74-1.92 (m, 2H), 2.24 (s), 2.10-2.57 (m, 14H), 2.62-2.78 (m, 2H), 2.83-3.04 (m, 2H), 3.36 (s, 3H), 3.60 (t, *J* = 6.0 Hz, 2H), 4.3 (two overlapped qd, *J* = 7.2, 4.0 Hz, 2H), 4.61(s, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 14.12, 20.68, 25.49, 25.61, 29.59, 31.69, 36.06, 37.04, 38.80, 39.09, 40.34, 46.11, 47.85, 55.15, 57.66, 60.87, 62.93, 63.64, 65.19, 65.43, 96.40, 174.08, 206.04, 208.84, 210.09.

Ethyl 4a-(α)-2*H*, 3*H*, 4*H*, 4a*H*, 5*H*, 6*H*, 6a*H*, 8*H*, 9*H*, 10*H*, 10a*H*-6,7-dioxo-9-hydroxy-2-(2-(methoxymethyloxy)-ethyl)-1*H*, 7*H*-6a,9-Ethano-4,10b-propano-benz[h]isoquinoline-4-carboxylate (93); configuration at the centers 6a, 10a yet to be determined. To compound **92** (24.5 mg, 52.9 μmol) was added 0.53 mL of an 8% solution of KOH in distilled water. The mixture was refluxed for 3h, then 0.5 mL EtOH 95% were added

and the mixture was refluxed for 3h. To the cooled orange solution was added benzene and the organic phase was stripped off and replaced with EtOAc. Concentrated ammonium chloride solution (0.5 mL) was added and Ar was bubbled through the mixture in order to remove the ammonia. The pH gradually changed from 9 to 6. During this time, the organic phase was removed (four times) and replaced with fresh EtOAc. The combined organic phases were dried, the solvent was removed under reduced pressure and the residue was purified by SGC (H:EA 2:1) to give **93** as a colorless oil (9.2 mg, 37.6%). MS *m/e*: 432.2, 388.2, 346.2, 229.1, 132.1, 58.1. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3H), 1.35-1.62(m, 4H), 1.70-1.90(m, 2H), 1.95-2.05(m, 2H), 2.10-2.80(m, 14H), 2.90-3.20(m, 4H), 3.41(s, 3H), 3.62(t, J = 6.0 Hz, 2H), 4.30(qd, J = 7.2, 4.0 Hz, 2H), 4.65(s, 2H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 13.80, 20.50, 25.40, 25.65, 29.60, 31.70, 36.50, 37.20, 38.80, 39.20, 40.30, 42.20, 46.10, 47.80, 55.90, 58.25, 61.20, 62.70, 63.80, 66.20, 66.40, 96.40, 174.20, 207.20.

GENERAL SUMMARY

An advanced pentacyclic intermediate bearing the entire carbocyclic skeleton of the atisine and spiramine alkaloids, together with appropriate functional groups has been obtained as a result of the research described in this dissertation. A direct route to this class of natural compounds, potentially useful from an industrial point of view, has been developed.

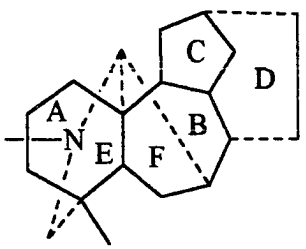
A tetracyclic intermediate bearing the *AEBD* ring system of aconitine alkaloids has been synthesized.

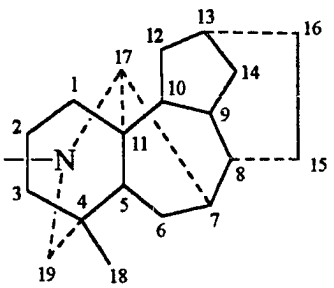
A highly reproducible synthesis of adamantane-containing compounds of potential biological interest and a highly versatile method for the generation and trapping of functionalized bridgehead radicals was developed and successfully applied to the synthesis of complex natural targets.

APPENDIX I. NUMBERING SYSTEM AND STRUCTURES OF SOME DITERPENE ALKALOIDS

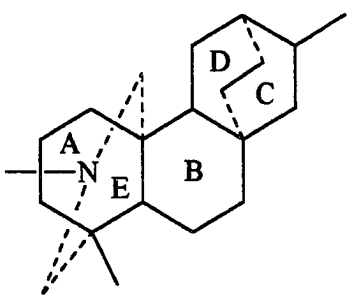
1. Ring and numbering system:

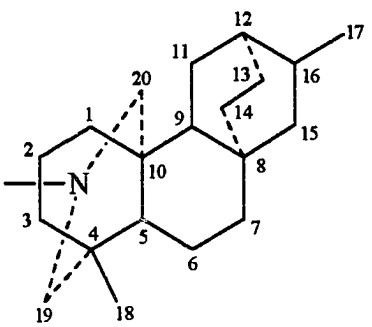
C_{19} diterpene alkaloids, aconitine group:



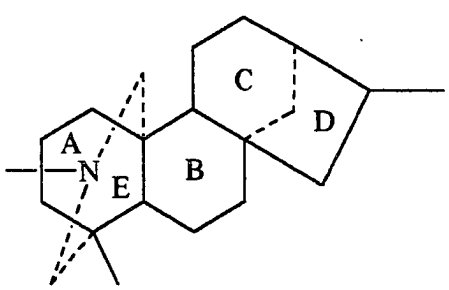


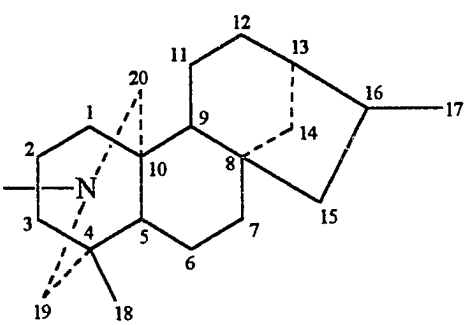
C_{20} alkaloids, atisine group:



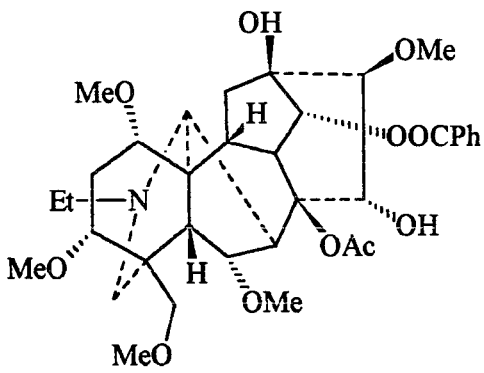


C_{20} alkaloids, garrya group:

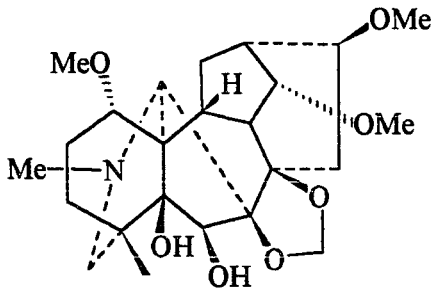




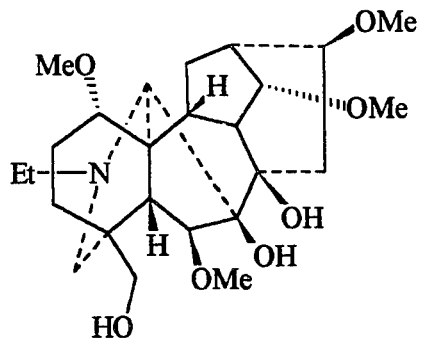
2. Structures of representative C_{19} and C_{20} alkaloids.



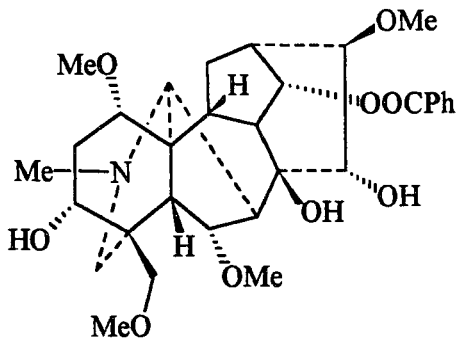
Aconitine



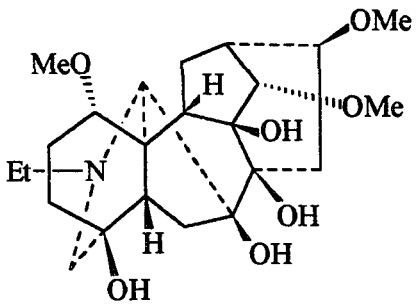
Bonvalol



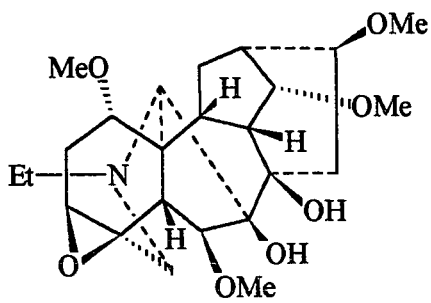
Lycoctonine



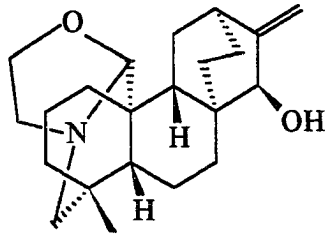
O^{14}-Benzoylmesaconine



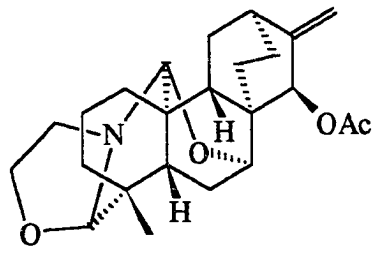
Ranaconine



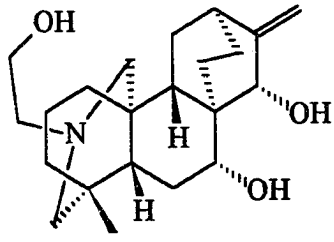
Tuguaconitine



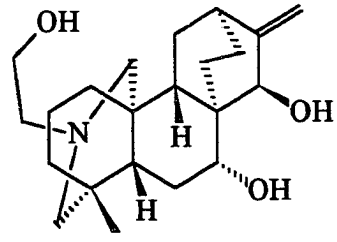
Atisine



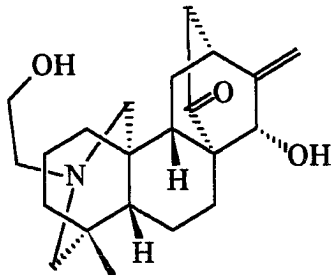
Spiramine A



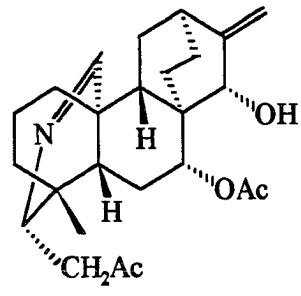
A naturally occuring intermediate in the biosynthesis of spiramine. Chemical conversion to spiramines is known



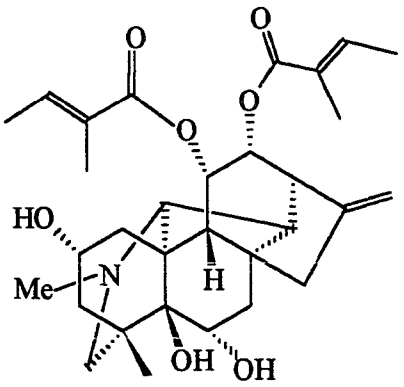
Ajaconine



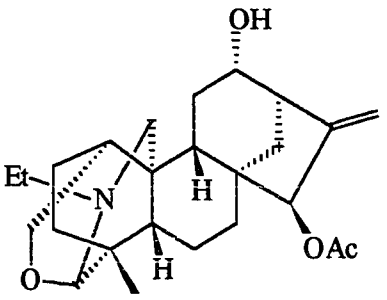
Spiramine H



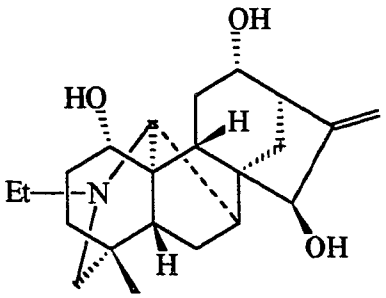
Spiramine M



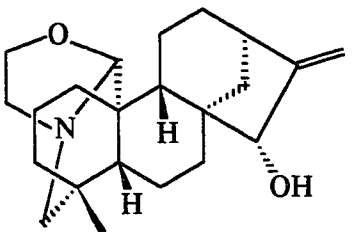
Anopterine



Dehydrolucidusculine

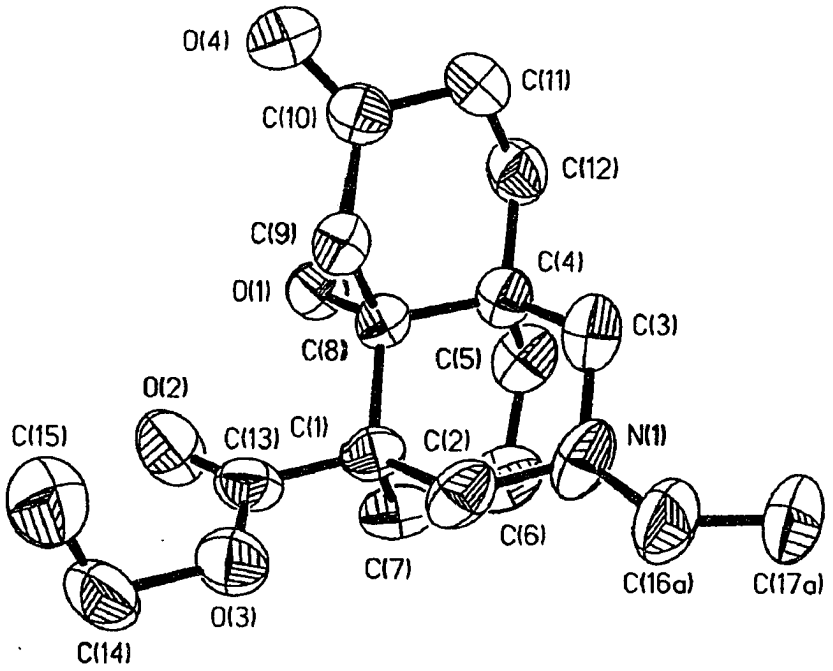


Napelline



Veatchine

APPENDIX II. X-RAY STRUCTURE OF COMPOUND 71



REFERENCES

PART I

1. Bingham, R. C.; Von R. Schleyer, P. *Fortschr. Chem. Forsch.* **1971**, *18*, 1-102.
2. Kirschbaum, J. *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1983; Vol. 12, pp 1-36.
3. Gupta, R. C.; Dettbarn, W. D. *Neurotoxicology* **1992**, *13*, 649.
4. Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4120.
5. Yurchenko, A. G.; Fedorenko, T. V.; Rodionov, V.N. *J.Org. Chem. USSR* **1985**, *21*, 1529.
6. Molle, G.; Briand, S.; Bauer, P.; Dubois, J. E. *Tetrahedron* **1984**, *40*, 5113.
7. Wu, T.-C.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045.
8. Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hansen, J. *Chem. Rev.* **1989**, *89*, 1591.
9. Dr. Rieke informed us that the preparation and reactions of his reactive Ca reagent have been done using a drybox.
10. Wakefield, B. J. *Chemistry of Organolithium Compounds*; Wiley: New York, 1972; pp 51-62.
11. Lansbury, P. T.; Sidler, J. D. *Tetrahedron Lett.* **1965**, 691.
12. Chen, H. S.; Pellegrini, J. W.; Aggarval, S. K.; Lei, S. Z.; Warach, S.; Jensen, F. E.; Lipton, S. A. *J. Neurosci.* **1992**, *12*, 4427.
13. Müller, W. E.; Schröder, H. C.; Ushijima, H.; Dapper, J.; Bormann, J. *Eur. J. Pharmacol.* **1992**, *226*, 209.
14. Bubser, M.; Kesenberg, U.; Notz, P. K.; Schmidt, W. J. *Eur. J. Pharmacol.* **1992**, *229*, 75
15. Sasaki, T.; Eguchi, S.; Hirako, Y. *Tetrahedron*, **1976**, *32*, 437.

PART II

1. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
2. Russell, G. A. *The Chemistry of Enones*; Patai, S.; Rappoport, Z., Ed.; Wiley: New York, 1989, pp 471-512.
3. Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, Germany, 1987, pp. 138-143.
4. Nasipuri, D. *Stereochemistry of Organic Compounds: Principles and Applications*; Wiley: New Delhi, 1991; pp. 391-410.
5. Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614.
6. Power, M. B.; Bott, S. G.; Atwood, J. L.; Barron, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 3446.
7. Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.
8. Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140.
9. Paddon-Row, M. N.; Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638.
10. Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006.
11. Paquette, L. A.; Underiner, T. L.; Gallucci, J C. *J. Org. Chem.* **1992**, *57*, 86.
12. Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.
13. Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.
14. Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 232.
15. Lau, J.; Gonikberg, E. M.; Hung, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421.
16. Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867.
17. Southon, I. W.; Buckingham, J., Ed. *Dictionary of Alkaloids*; Chapman and Hall: London, 1989, vol I.
18. Arias, M. S.; Smeyers, Y. G.; Fernández, M. J.; Smeyers, N. J.; Gálvez, E.; Fonseca, I.; Sanz-Aparicio, J. *J. Org. Chem.* **1994**, *59*, 2565.

19. del Campo, C.; Martínez, E.; Trigo. G. G. *Helv. Chim. Acta* **1984**, *67*, 1291.

20. Thompson, M. D.; Smith, G. S.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; van der Helm, D; Muchmore, S. W.; Fidelis, K. A. *J. Med. Chem.* **1987**, *30*, 780.

21. Ruenitz, P. C.; Mokler, C. M. *J. Med. Chem.* **1977**, *20*, 1668.

22. Manske, R. H. F., Ed. *The Alkaloids*; Academic Press: New York, 1970, vol 12, pp. 2-202; 1979, vol. 18, pp. 2-98; 1981, vol 18, pp. 100-211.

23. "Zhong Yao Da Ci Dian", ed. by Jiangshu New Medical College, Shanghai People's Publishing House, **1971**, pp. 117 (Chinese).

24. Yunusov, M. S. *Natural Product Reports* **1993**, *10*, 471.

25. Hao, X.-J.; Node, M.; Zhou, J.; Chen, S.-Y.; Taga, T.; Miwa, Y.; Fuji, K. *Heterocycles* **1993**, *36*, 825.

26. a) Hao, X.; Node, M.; Zhou, J.; Chen, S.; Fuji, K. *Yunnan Zhiwu Yanjiu* **1994**, *16*, 301. In *CA* **1995**, *122*, 605. b) Hao, X.; Zhou, J.; Fuji, K.; Node, M. *Yunnan Zhiwu Yanjiu* **1992**, *14*, 314. In *CA* **1993**, *118*, 537.

27. Wonnacott, S.; Albuquerque, E. X.; Bertrand, D. *Methods in Neurosciences* **1993**, *12*, 263.

28. Keeler, R. F. *Lloydia* **1975**, *38*, 56.

29. Jennings, K. R.; Brown, D. G.; Wright, D. P. *Experientia* **1986**, *42*, 611.

30. Mashkovsky, M. D.; Churyukanov, V. V. In *Handbook of Experimental Pharmacy*; Kharkevich, D. A. Ed.; Springer-Verlag: Heidelberg, **1986**, *79*, pp. 391-397.

31. Fujio, S. *PCT Int. Appl. WO 95 25517*. In *CA* **1996**, *124*, 452.

32. Pelletier, S. W. *J. Am. Chem. Soc.* **1960**, *82*, 2398.

33. Pelletier, s. W.; Parthasaranthy, P. C. *Tetrahedron Lett.* **1963**, *4*, 205.

34. Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1962**, *85*, 2342.

35. Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 8185.

36. Shishido, K.; Hiroya, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1443.

37. Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164.

38. Wiesner, K.; Phillipp, A.; Ho, P.-T. *Tetrahedron Lett.* **1968**, 1209.

39. Birnbaum, K. B.; Wiesner, K.; Ho, P.-T. *Tetrahedron Lett.* **1969**, 1071.

40. Wiesner, K. *Tetrahedron* **1985**, *41*, 485.

41. Blagbrough, I. S.; Coates, P. A.; Hardick, D. J.; Lewis, T.; Rowan, M. G.; Wonnacott, S.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, 8705.

42. Coates, P. A.; Blagbrough, I. S.; Rowan, M. G.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, 8709.

43. Baillie, L. C.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2487.

44. Kraus, G. A.; Shi, J. *J. Org. Chem.* **1991**, *56*, 4147.

45. Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 5423.

46. Jacobs, T. L.; Cramer, R.; Hanson, J. E. *J. Am. Chem. Soc.* **1942**, *64*, 223.

47. Viehe, H. G., Ed. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969, pp. 365-417, 751-848.

48. Fukuyama, T.; Liu, S. C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

49. Thomas, R. J. *J. Am. Chem. Soc.* **1938**, *60*, 718.

50. DeTar, D. F. *J. Org. Chem.* **1992**, *57*, 902. Tai, J. C.; Yang, L.; Allinger, N. L. *J. Am. Chem. Soc.* **1993**, *115*, 11906 and references therein.

51. Lau, C. K.; Dufresne, C.; Bélanger, P.C.; Piétré, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038.

52. a) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900. b) Nwokogu, G. C. *Tetrahedron Lett.* **1984**, *25*, 3263.

53. Anderson, G. K.; Lin, M. *Inorg. Synth.* **1990**, *28*, 60.

54. Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109.

55. Chou, W. -N.; Clark, D. L.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 299.

56. Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. *J. Chem. Soc., Chem. Comm.*

1981, 718.

57. Ireland, R. E.; Norbeck, D. H. *J. Org. Chem.* **1985**, *50*, 2198.
58. Lee, J. G.; Kang, K. K. *J. Org. Chem.* **1988**, *53*, 3634.
59. Dakka, G.; Sason, Y. *Tetrahedron Lett.* **1987**, *28*, 1223. Dennis, J. N.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1983**, 229.
60. Brown, W. L.; Fallis, A. G. *Tetrahedron Lett.* **1985**, *26*, 607.
61. Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499.
62. Martinez, A. G.; Villalobos, A. C.; Ruiz, M. O. *Synthesis* **1988**, 58.
63. Chauhau et al *J. Am. Chem. Soc.* **1985**, *107* (4),
64. Kluge, A. F. *Tetrahedron Lett.* **1978**, 3629.
65. Majetich, G.; Song, J. -S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030.
66. Wu, T.-C.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045.
67. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 3rd Ed.*; Plenum Press: New York, 1993, part A, pp. 404-407 and references therein.
68. Walton, J. C. *Chem. Soc. Rev.* **1992**, *21*, 105.
69. Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493.
70. Kraus, G. A.; Wu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8705. Wagner, P. J.; Park, B. S. *Organic Photochemistry* **1991**, *11*, 227.
71. Giese, B.; Thoma, G. *Helv. Chim. Acta* **1991**, *74*, 1143. Inokuchi, T.; Kawafuchi, H.; Torii, S. *J. Org. Chem.* **1991**, *56*, 4983.
72. Corey, E. J.; Kang, M. *J. Am. Chem. Soc.* **1984**, *106*, 5384.
73. Snider, B. ; Buckman, B. *J. Org. Chem.* **1992**, *57*, 322.
74. Torsell, K. *Acta Chem. Scand.* **1983**, *32*, 237.
75. Minisci, F.; Citterio, A.; Giordano, C. *Accts. of Chem. Res.* **1983**, *16*, 27.
76. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.
77. Bhandal, H.; Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1986**, *27*, 2299. Patel, V. F.;

Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1986**, *27*, 2303.

78. Braunchard, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273 and references therein.
79. Patel, V. F.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1987**, 871. Coveney, D. J.; Patel, V. F.; Pattenden, G.; Thompson, D. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2721. Bhandal, H.; Howell, A. R.; Patel, V. F.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2709.
80. Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H.-G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638.
81. Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741.
82. Kraus, G. A.; Su, Q. *Synlett* **1994**, 234.
83. Mander, L. *Chem. Rev.* **1992**, *92*, 573.
84. VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841.
85. Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1975**, 4453.
86. Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619.
87. Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.
88. Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537.
89. Brown, H. C.; Murray, K. *J. Am. Chem. Soc.* **1959**, *81*, 4108.
90. Fischli, A.; Süss, D. *Helv. Chim. Acta* **1979**, *62*, 2361.
91. Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825.
92. Pons, J. -M.; Santelli, M. *Tetrahedron Lett.* **1986**, *27*, 4153.
93. Lois-Andre, O.; Gelbard, G. *Tetrahedron Lett.* **1985**, *26*, 831. Camps, F.; Coll, J.; Guitart, J. *Tetrahedron* **1986**, *42*, 4603.
94. Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5085.
95. Voelter, W.; Djerassi, C. *Chem. Ber.* **1968**, *101*, 58.

96. Suggs, J. W.; Cox, S. D.; Crabtree, R. H.; Quirk, J. M. *Tetrahedron Lett.* **1981**, *22*, 303.

97. Amer, I.; Bravdo, T.; Blum, J.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1987**, *28*, 1321.

98. Augustine, R. L. *J. Am. Chem. Soc.* **1958**, *23*, 1853.

99. Ricroch, M, N,; Gaudemer, A. *J. Organomet. Chem.* **1974**, *67*, 119.

100. Smadja, W.; Ville, G.; Georgoulis, C. *J. Chem. Soc., Chem. Commun.* **1980**, 594.

101. Barborak, J. C.; Herndon, J. W.; Wong, J.-W. *J. Am. Chem. Soc.* **1979**, *101*,7430.

102. Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S. *J. Org. Chem.* **1981**, *46*, 2920. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. Plieninger, H.; Gramlich, W. *Chem. Ber.* **1978**, *111*, 1944.

103. Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2692. Hansson, C.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 188.

104. Danishefsky, S. J.; Bednarsky, M.; Izawa, T. *J. Org. Chem.* **1984**, *49*, 2290.

105. Risch, N.; Langhals, M.; Mikosch, W.; Bögge, H.; Müller, A. *J. Am. Chem. Soc.* **1991**, *113*, 9411.

106. Pollini, G. P.; Barco, A. J.; DeGiuli, G. *Synthesis* **1972**, 44.

107. Ono, N.; Miyake, H.; Kaji, A. *J. Org. Chem.* **1984**, *49*, 4997.

108. Knochel, P.; Chou, T. S.; Jubert, C.; Rajagopal, D. *J. Org. Chem.* **1993**, *58*, 588.

109. Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1977**, *45*, 3929.

110. Cossy, J.; Guha, M. *Tetrahedron Lett.* **1994**, *35*, 1715.

111. Hutchinson, D. K.; Fuchs, P.L. *Tetrahedron Lett.* **1986**, *27*, 1425. Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1429.

112. Santamaria, J.; Kaddachi, M. T.; Ferroud, C. *Tetrahedron Lett.* **1992**, *33*, 781.

113. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

114. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

115. Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. Grieco, P. A.; Yoshida, K.; He, Z. *Tetrahedron Lett.* **1984**, *25*, 5715.

116. Tramontini, T.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

117. Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981, pp.16-17.

118. Mander, L. N.; Sethi, P. S. *Tetrahedron Lett.* **1983**, *24*, 5425.

119. Dolby, L. J.; Marshall, K. S. *Organic Preparations and Procedures* **1969**, *1*, 229.

120. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 1574. Barton, D. H. R.; Motherwell, W. B. *Pure & Appl. Chem.* **1981**, *53*, 15. Forrest, D.; Ingold, K. U.; Barton, D. H. R. *J. Phys. Chem.* **1977**, *80*, 915.

121. Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180.

122. Newman, M. *J. Am. Chem. Soc.* **1953**, *75*, 4740. Larock, R. C. *Solvomercuration / Demercuration Reactions in Organic Synthesis*; Springer-Verlag: New York, 1986, pp. 123-161.

123. Olah, G. A.; Fung, A. P. *Synthesis* **1981**, 473.

124. Janout, V.; Regen, S. L. *J. Org. Chem.* **1982**, *47*, 3331.

125. Tsuji, J. *Synthesis* **1984**, 369.

126. Shimano, M.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 7727. Kraus, G. A.; Krolski, M. E. *Synthetic Commun.* **1982**, *12*, 521.

127. Baldwin, J. E.; Höffe, G. A.; Lever, W. A., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

128. Bartlett, P.D.; Giddings, W.P. *J. Am. Chem. Soc.* **1960**, *82*, 1240 and references therein.

ACKNOWLEDGEMENTS

Working on this project was definitely a rewarding experience. It could hardly be remembered as a facile task though, and it is the time to admit that these achievements were also made possible by the helpful comments and suggestions I received throughout my tenure at Iowa State University. It is virtually impossible to mention the names of all of the persons I am indebted to.

With these regrets in my heart, I would like to take advantage of this opportunity to express my deepest gratitude to professor George A. Kraus, with whom I shared the enthusiastic moments our results brought, as well as considerable concern and frustration, too little of which may have become apparent to the reader of this work.

Professors Richard C. Larock, Glenn A. Russell and Alan W. Schwabacher deserve special mentioning for their uncommon willingness to provide pertinent advice whenever I needed it.

I would also like to extend my appreciation to Dr. Victor Young, for his help in X-ray structure determination, Dr. Dave Scott, who skillfully adapted some of the NMR software to the particular requirements of this project, Dr. Hiroshi Maeda and Ms. Rurng-jen Chang for their help in interpreting original Japanese and Chinese literature.

My special thanks are addressed to professor Lyle C. Hall, from the University of Wisconsin at River Falls, whom I owe my presence in the United States.