



Acynitrilium ion-arene spiroannulations : studies toward the synthesis of the Lycopodium alkaloid serratine
by Gregory Randall Luedtke

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:

The use of C-acynitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic Lycopodium alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

ACYLNITRILIUM ION - ARENE SPIROANNULATIONS: STUDIES TOWARD
THE SYNTHESIS OF THE *LYCOPODIUM* ALKALOID
SERRATINE

by
Gregory Randall Luedtke

A thesis submitted in partial fulfillment
of the requirements for the degree

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APPROVAL

of a thesis submitted by

Gregory Randall Luedtke

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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Dedicated to the memory of my father, Randall Harvey Luedtke, and my grandfathers, Harvey August Luedtke and Marvin Draeger Hayes. They were all with me at the beginning of my college schooling, I only wish they could have been here with me at the end.

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I wish to thank my entire family for their unending support of me in all my endeavors in school and out. Without this foundation and all that springs from it, I could not have made this accomplishment. My mother and stepfather deserve special acknowledgments. Their loving care was the major reason that I have come this far in life. Words alone are not enough to say how much I appreciate all they have done for me.

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ABSTRACT

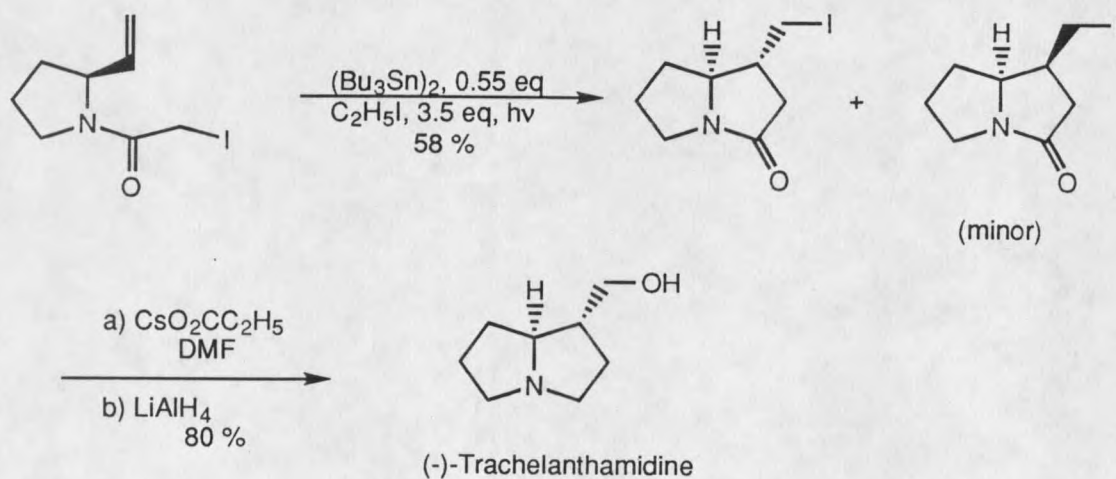
The use of *C*-acylnitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic *Lycopodium* alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

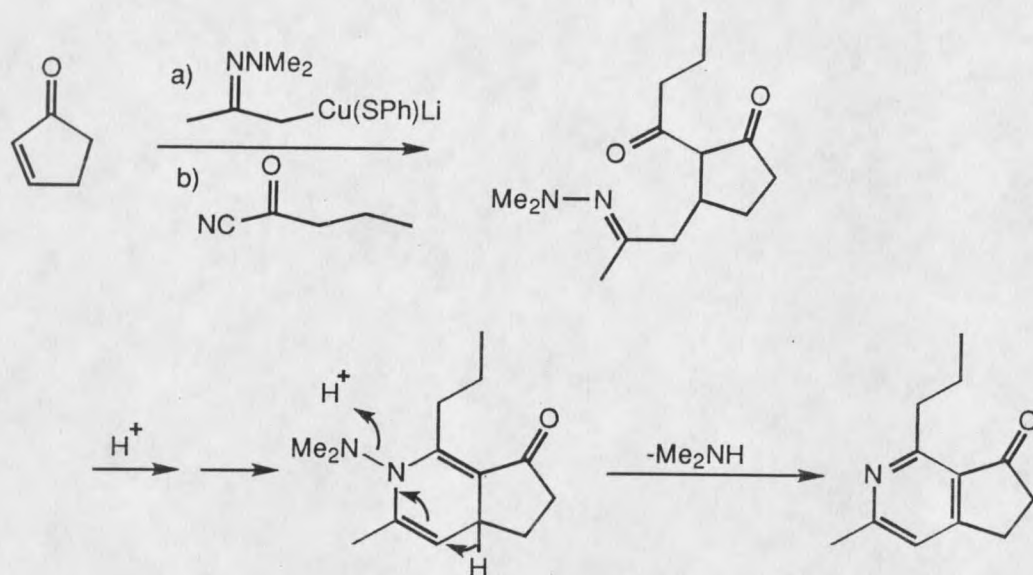
Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

INTRODUCTION

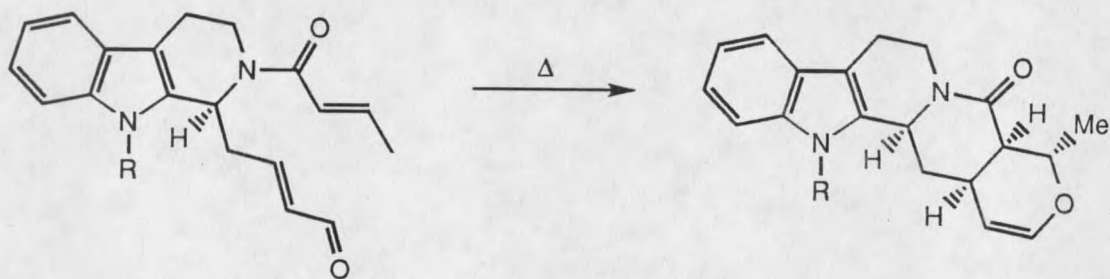
The interest in alkaloids as major synthetic targets has increased in recent years due to a heightened desire to study their biological properties. However, relatively few general methods have been developed for the assembly of nitrogen containing heterocycles. Representative methodologies include: free radical cyclizations, as illustrated by the key step leading to the synthesis of (-)-trachelanthamidine by Jolly and Livinghouse¹ (Eq. 1); anion initiated cyclizations, as utilized by Kelly and Liu² in their development of a new pyridine synthesis (Scheme 1); and cycloaddition reactions, as exemplified by Martin in the synthesis of 2-oxindole alkaloids (Eq. 2).³



Eq. 1



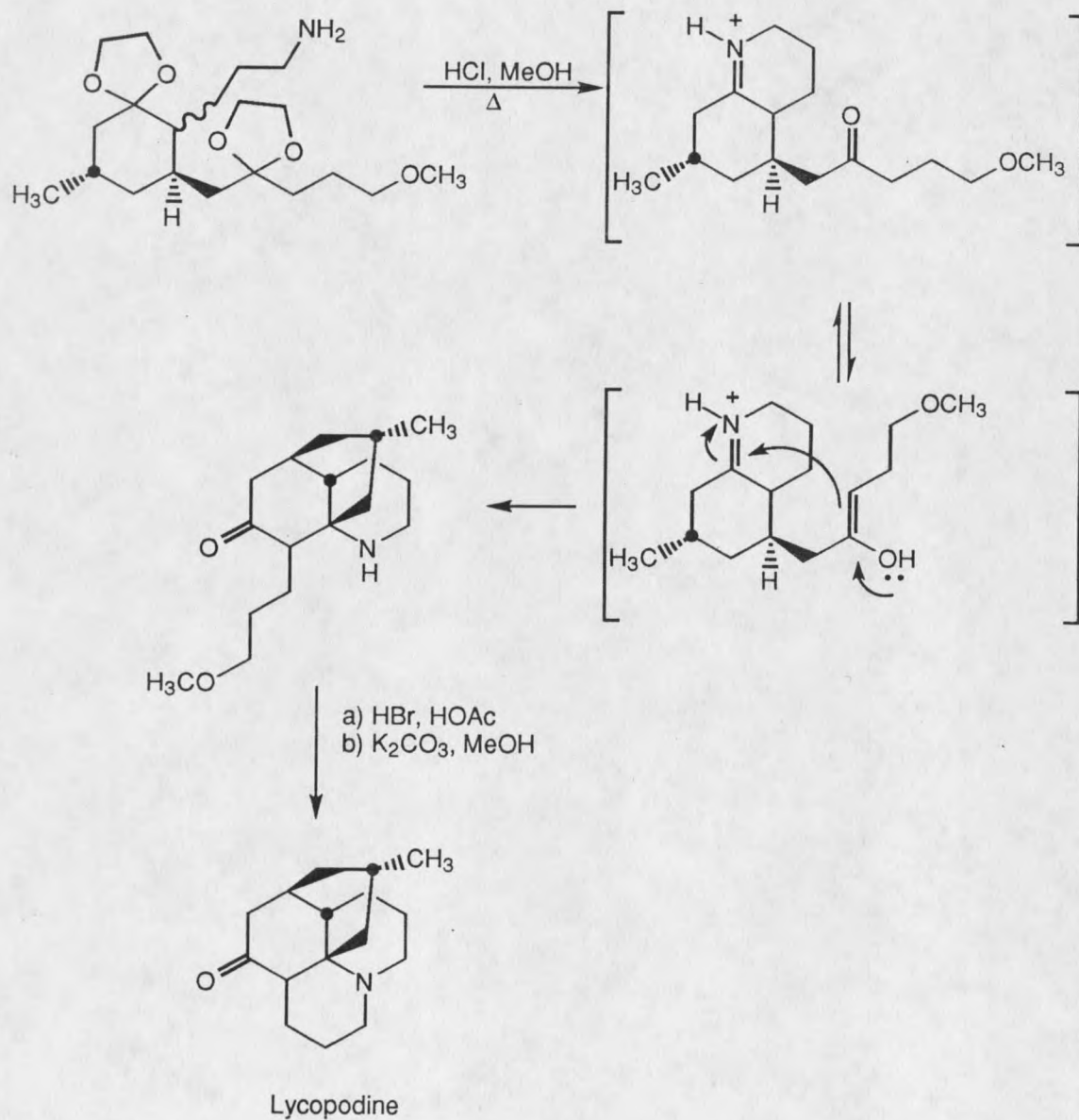
Scheme 1



Eq. 2

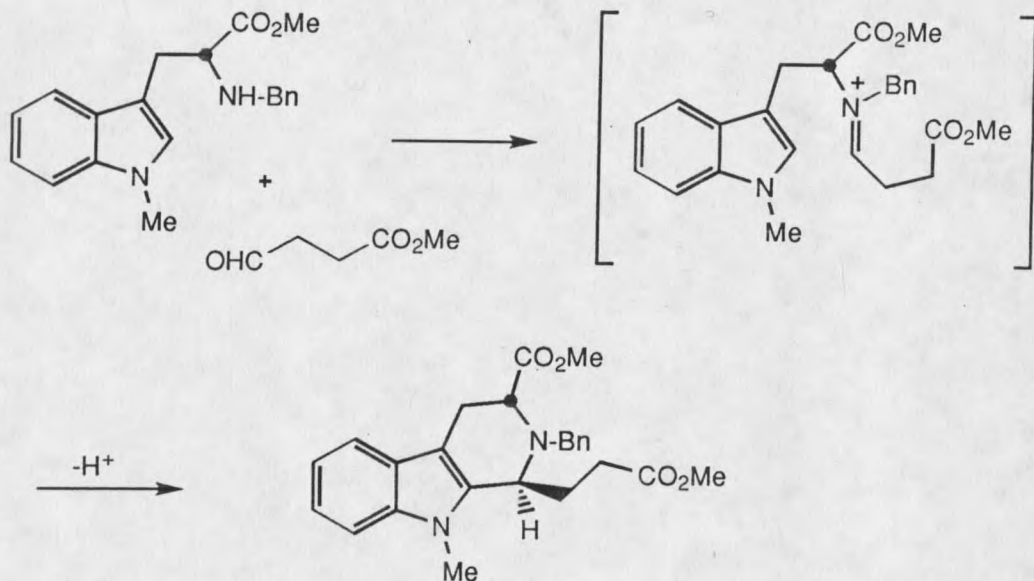
Perhaps the most widely used methods for the synthesis of alkaloids utilize nitrogen stabilized cations as reaction initiators. Some of the earliest methods in this class of reaction involved the use of iminium ions as reactive intermediates. These methods include the Mannich reaction, used by

Heathcock⁴ in the synthesis of Lycopodine (Scheme 2), and the Pictet-Spengler reaction, of which the stereochemical aspects were recently examined by Cook⁵ (Eq. 3).



Scheme 2

4

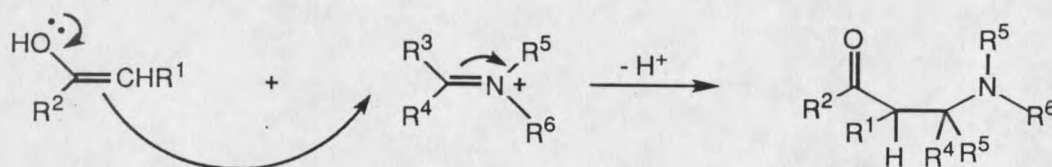


Eq. 3

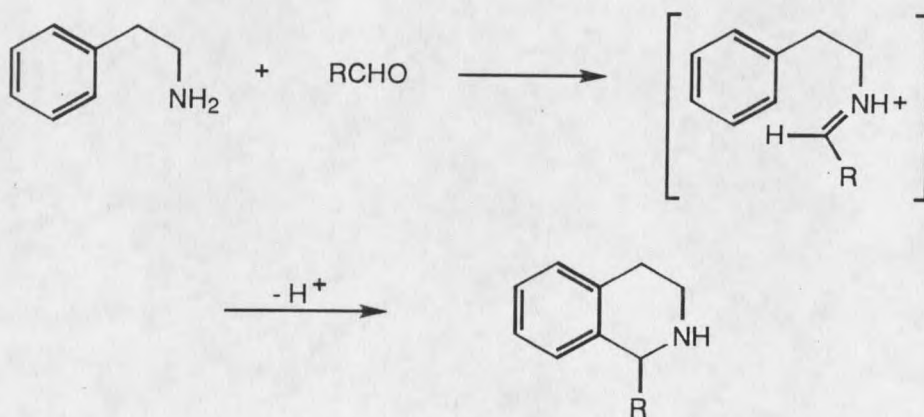
Many developments have occurred in recent years that have extended the use of nitrogen stabilized cations to the synthesis of natural products. However, even with the variety of procedures available, further methods which will facilitate the synthesis of complex heterocycles are needed. The work described herein is an effort toward that end.

BACKGROUND

Nitrogen stabilized cations are very frequently used in the synthesis of azacycles. One commonly used method involves the use of an iminium ion as a reactive intermediate. The most well known reactions of this type include the Mannich reaction, in which an enolizable carbonyl moiety serves as the reaction terminator, and the Pictet-Spengler reaction, in which an aromatic ring acts as the nucleophilic component (Scheme 3 and Eq. 4)

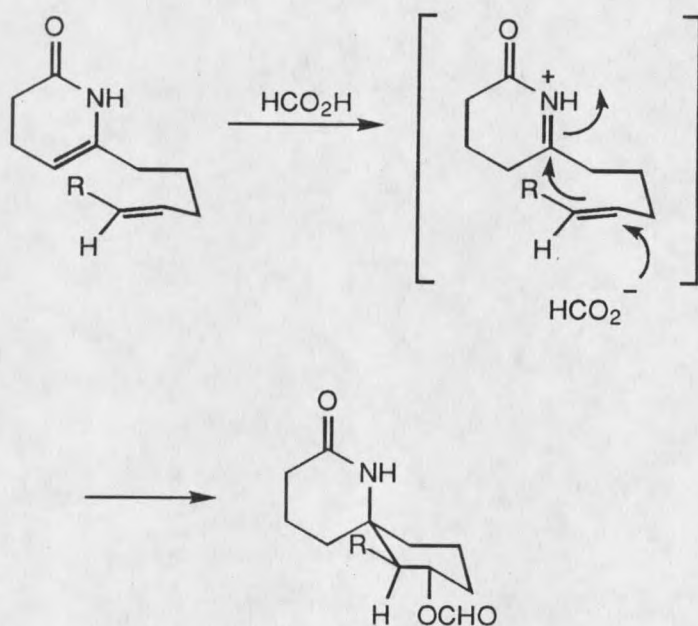


Scheme 3



Eq. 4

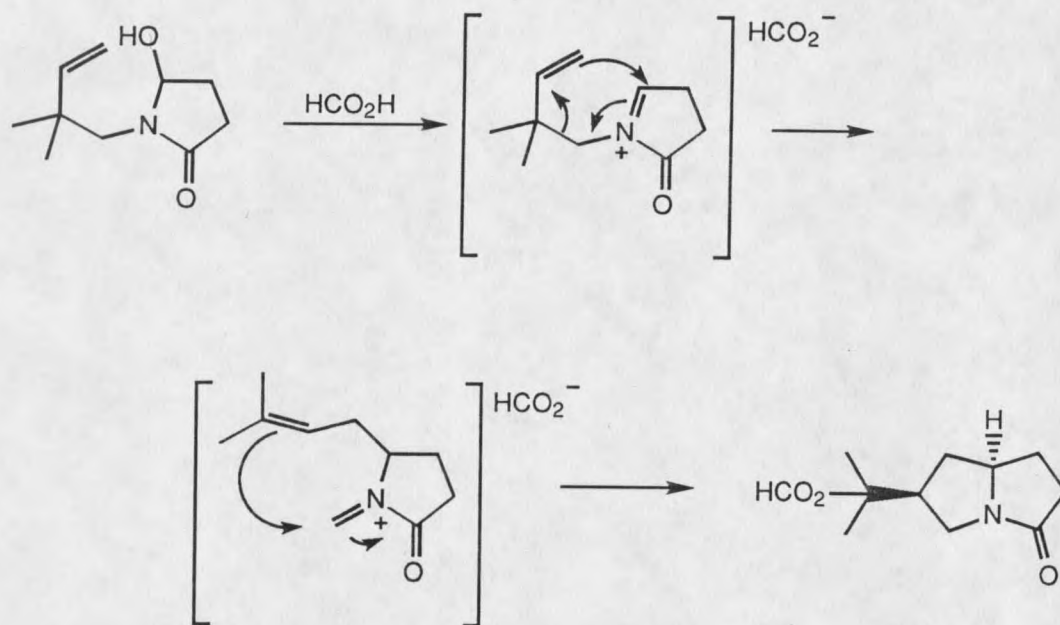
The more reactive *N*-acyliminium ion has been utilized in a manner similar to the iminium ion where aromatic ring system acts as a nucleophile.⁶ However, due to its increased reactivity, it was discovered that *N*-acyliminium ions react with a wider range of nucleophiles, including isolated olefins.⁷ In such reactions the olefin attacks the electron deficient carbon of the *N*-acyliminium ion while another nucleophile present during the reaction, typically the conjugate base of the acid used to form the active species adds to the olefin (Scheme 4).



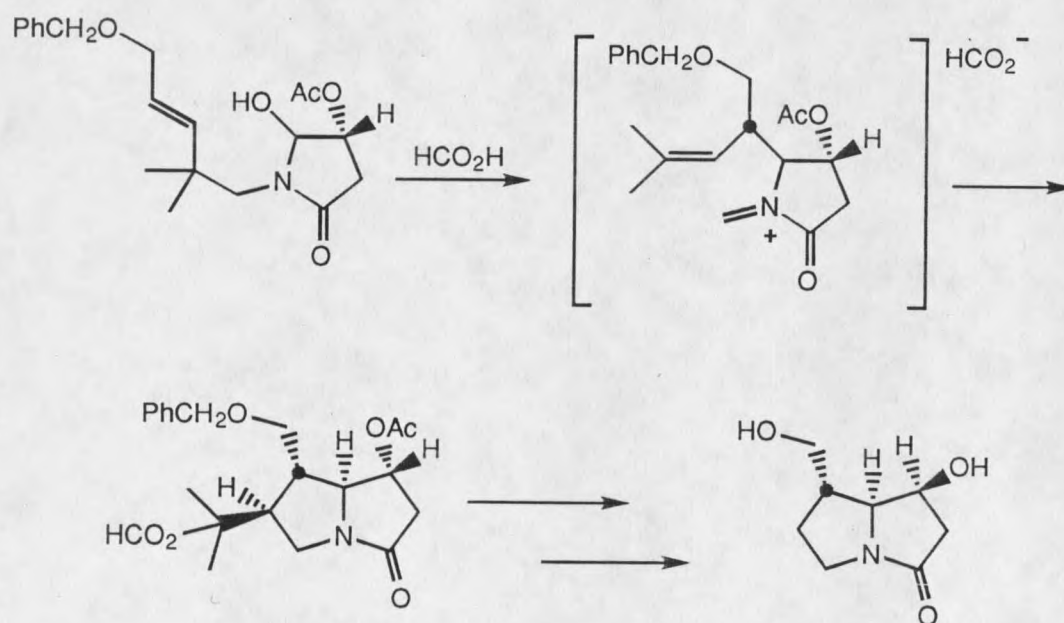
Scheme 4

An adaptation of the above work is the 2-aza-Cope *N*-acyliminium ion cyclization⁸ where the active ring forming intermediate is obtained after an initial aza-Cope rearrangement takes place (Scheme 5). This method of cyclization

has been used frequently in the synthesis of natural products, as exemplified by Hart's synthesis of (-)-hastanecine⁹ (Eq. 5).



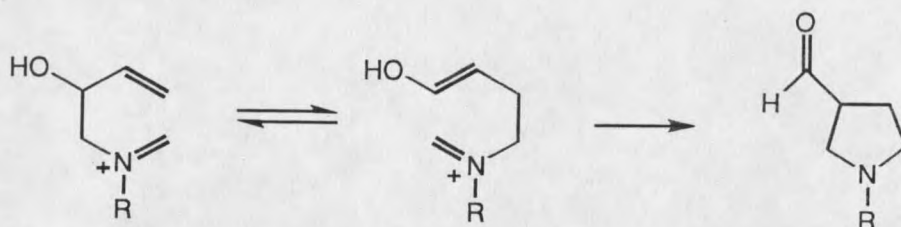
Scheme 5



Eq. 5

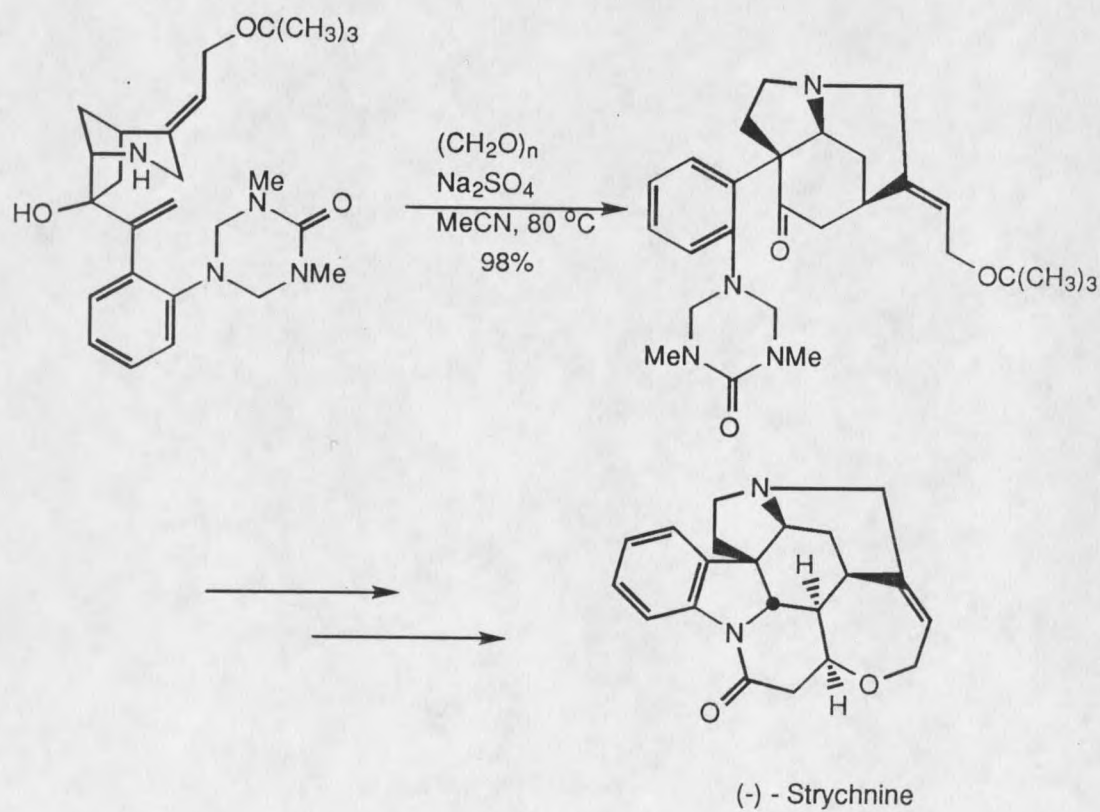
(+)-Hastanecine

Another example of the utility of iminium ions in azacycle synthesis is the tandem aza-Cope-Mannich reaction (Eq. 6), developed by Overman,¹⁰ which



Eq. 6

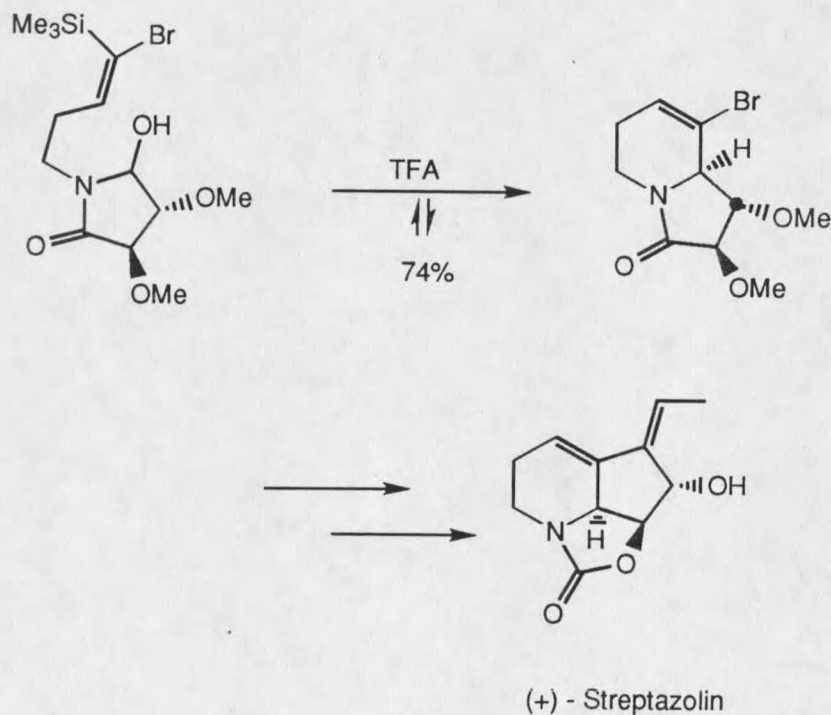
has also been of great utility in the synthesis of natural products. An example of this was demonstrated by the first enantioselective synthesis of (-)-strychnine¹¹ (Scheme 6). As with the related acyliminium ion reaction, the active cyclization



Scheme 6

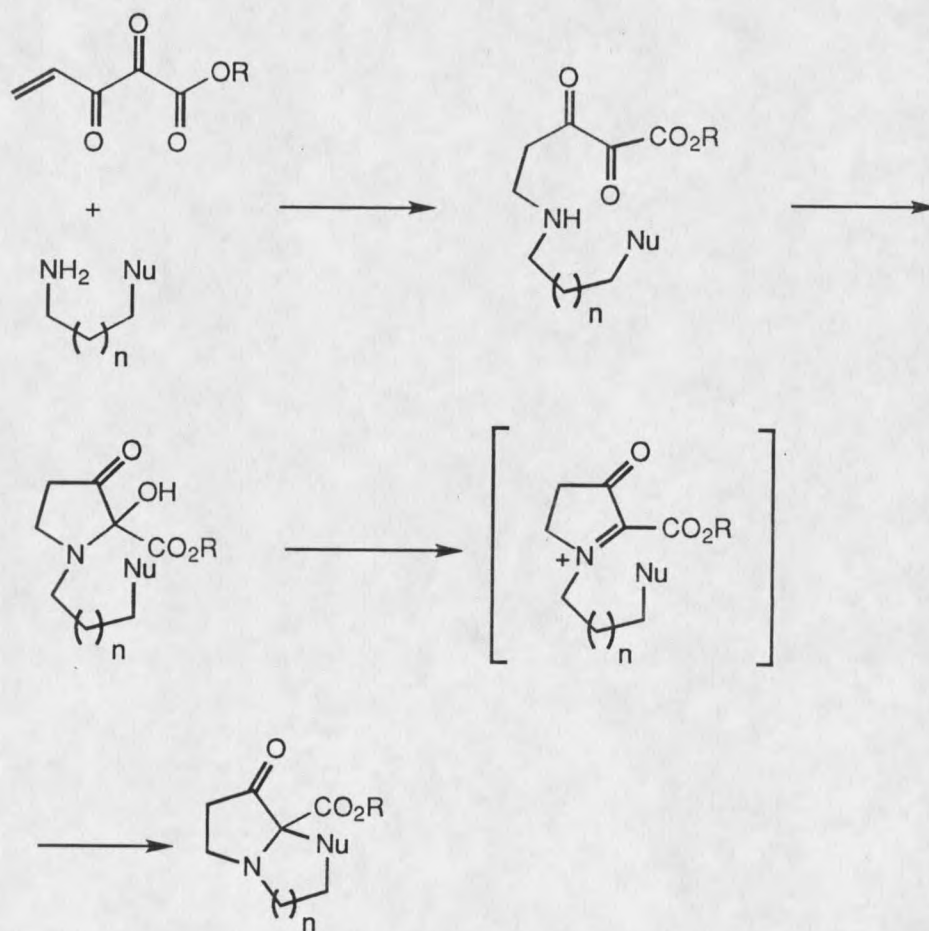
intermediate is formed following an initial rearrangement. In this case, however, the intramolecular nucleophilic component is generated after the aza-Cope rearrangement as an enol. The ensuing Mannich cyclization is sufficiently exothermic that the initial [3,3]-sigmatropic rearrangement is rendered virtually irreversible.¹²

Other studies by Overman have shown that vinylsilanes act as excellent terminators of iminium and acyl iminium ion cyclizations. Due to the relatively mild conditions required for the generation of the reactive intermediate as well as termination, this methodology has been used with great success when applied to highly complex natural product syntheses, as illustrated by Overman's synthesis of (+)-streptazolin¹³ (Scheme 7).



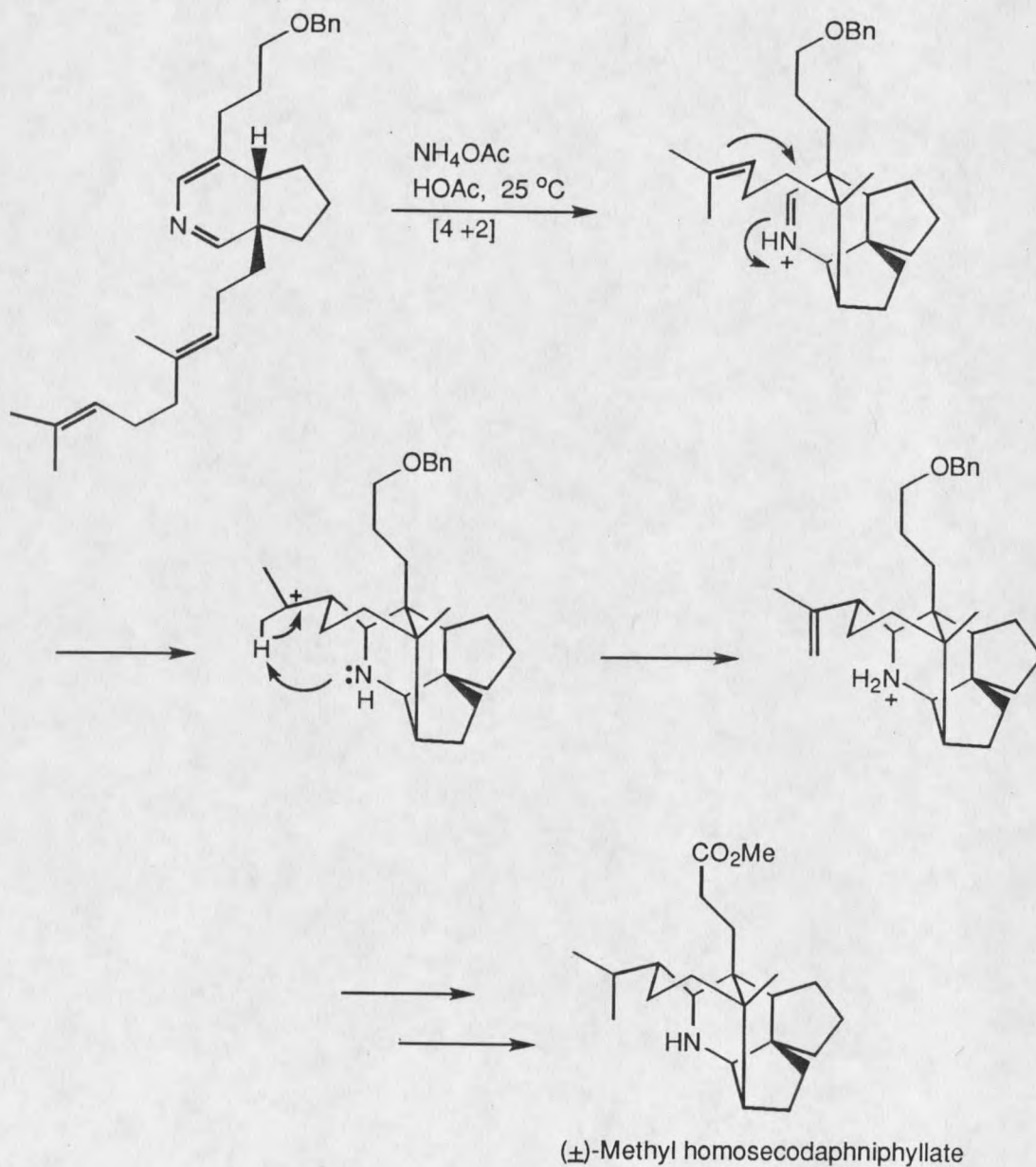
Scheme 7

A related intermediate that has recently been discovered is the C-acyliminium ion derived from vicinal tricarbonyls.¹⁴ The highly electrophilic central carbon atom allows for cyclizations to take place when vinyl, propargyl, and allyl silanes are used as terminators. It has also been shown that aromatic rings, enol ethers, amide NH groups, and lactam NH groups can serve as nucleophiles in these cyclizations^{15,16} (Eq. 7).



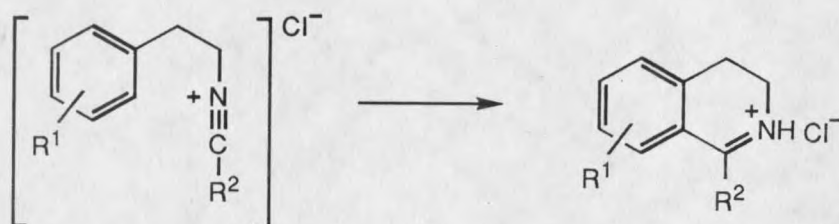
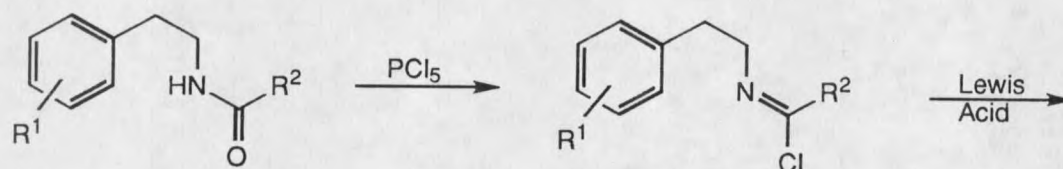
Eq. 7

Conjugated iminium ions have also been utilized as dienophiles in [4 + 2] cycloadditions. Heathcock¹⁷ has recently demonstrated the usefulness of this type of reactive species in the synthesis of several *Daphniphyllum* alkaloids, an example of which is shown in Scheme 8.

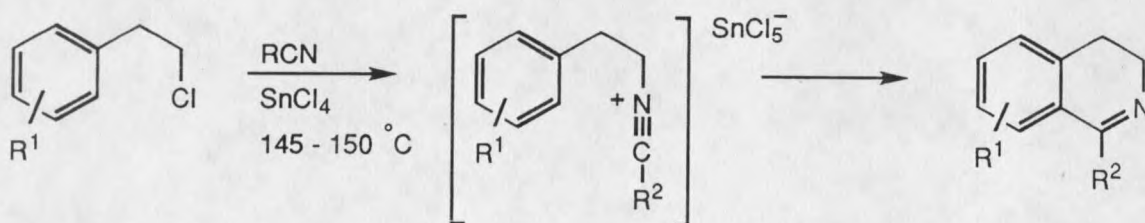


Scheme 8

Nitrilium ions are extremely reactive electrophilic intermediates that have been utilized for heteroannulations as well. Representative of these reactions are the Bischler-Napieralski reaction¹⁸ (Eq. 8) and a method developed by Lora-Tamayo¹⁹ (Eq. 9). However, both methods require strong Lewis Acids and high reaction temperatures which limit the usefulness of these reactions in the synthesis of molecules containing sensitive functional groups. To eliminate this problem in azacycle synthesis, a new method for nitrilium ion generation was sought by Livinghouse and coworkers.

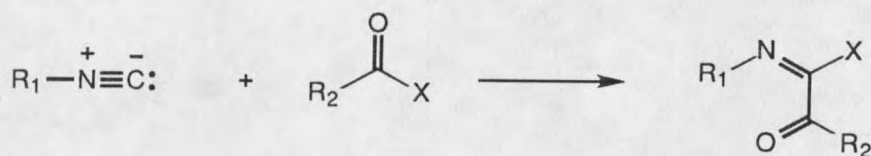


Eq. 8



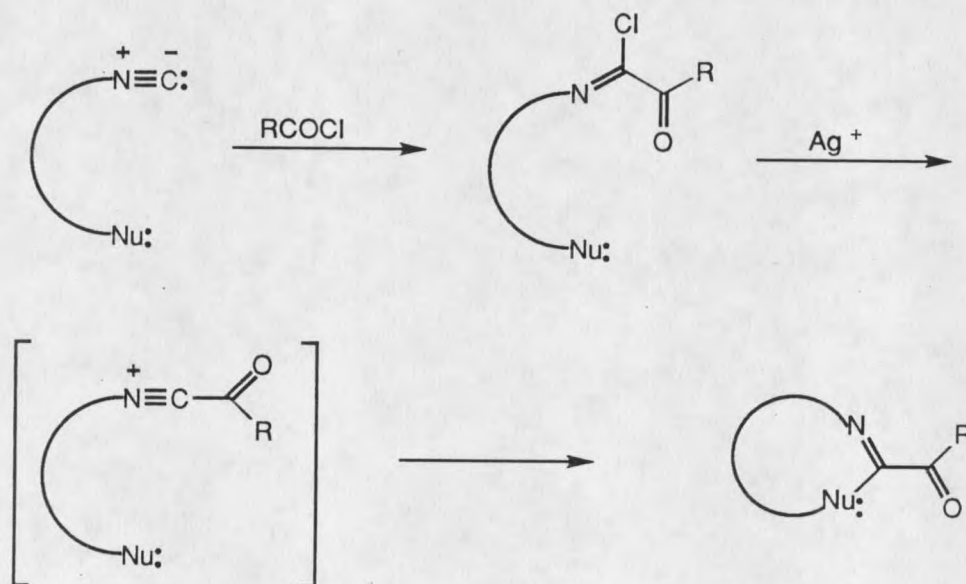
Eq. 9

The acylnitrilium ion intermediate had not previously been reported in the literature. However, in 1961 Ugi²⁰ reported the addition of acyl halides to isonitriles in good yields, resulting in stable α -ketoimidoyl halides (Eq. 10). It



Eq. 10

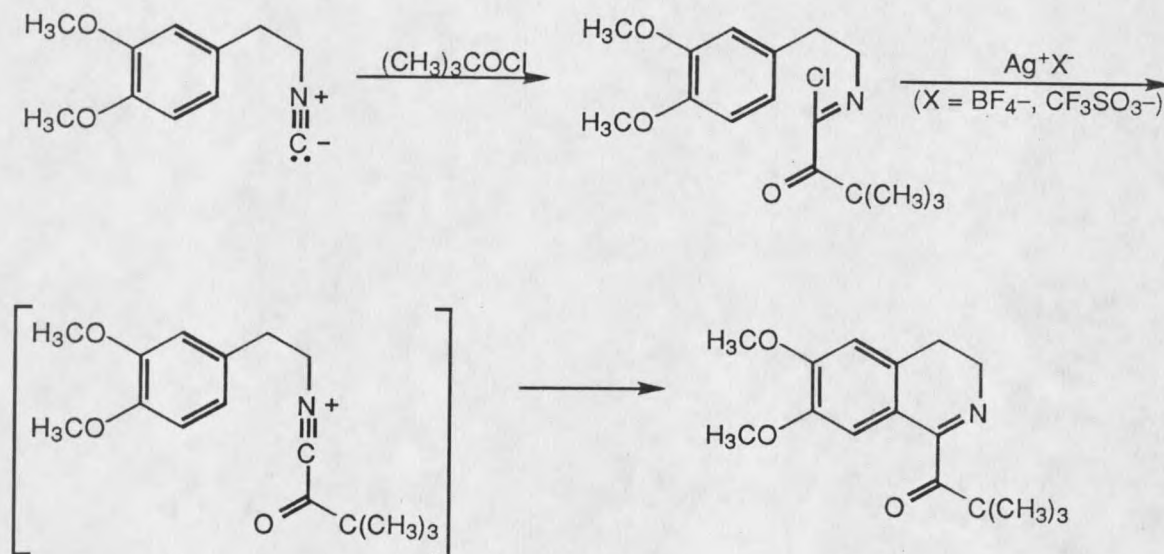
was believed by Livinghouse that upon treating this type of compound with a silver (I) salt, the halo-atom would be removed under mild conditions, resulting in the highly reactive *acylnitrilium* ion (Eq. 11). It was thought that the cation



Eq. 11

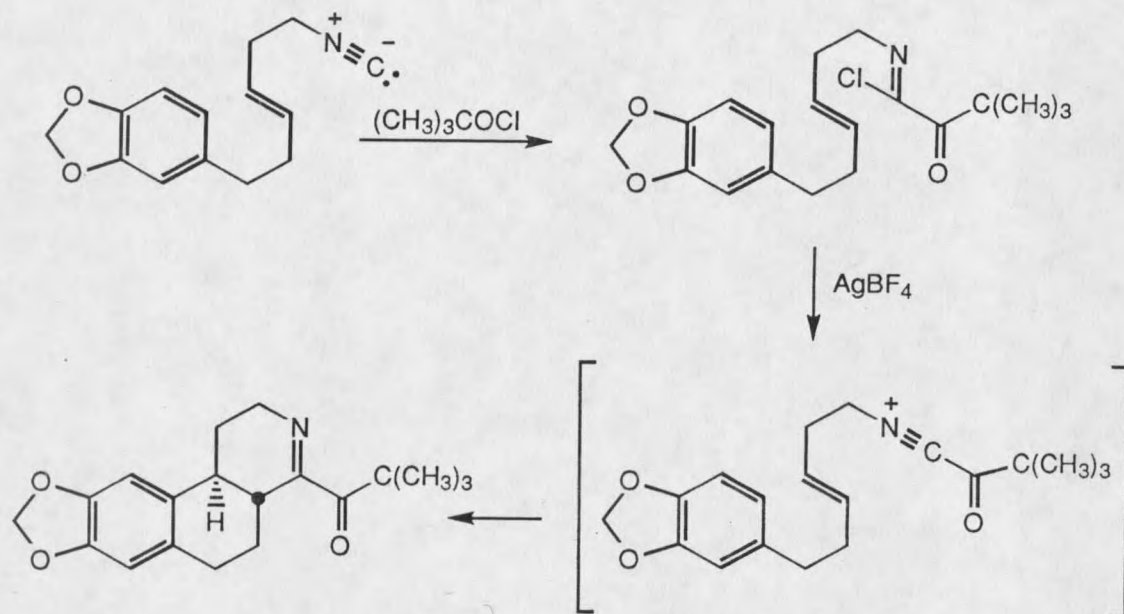
could then be intercepted by simple nucleophiles such as arenes, similar to the Pictet-Spengler and Bischler-Napieralski reactions. Initial studies²¹ to test this

hypothesis found that the silver halide salt did indeed form, and the π -bond from an aromatic ring was sufficiently nucleophilic to add to the reactive component that was created (Eq. 12). Internal nucleophiles were then used to further

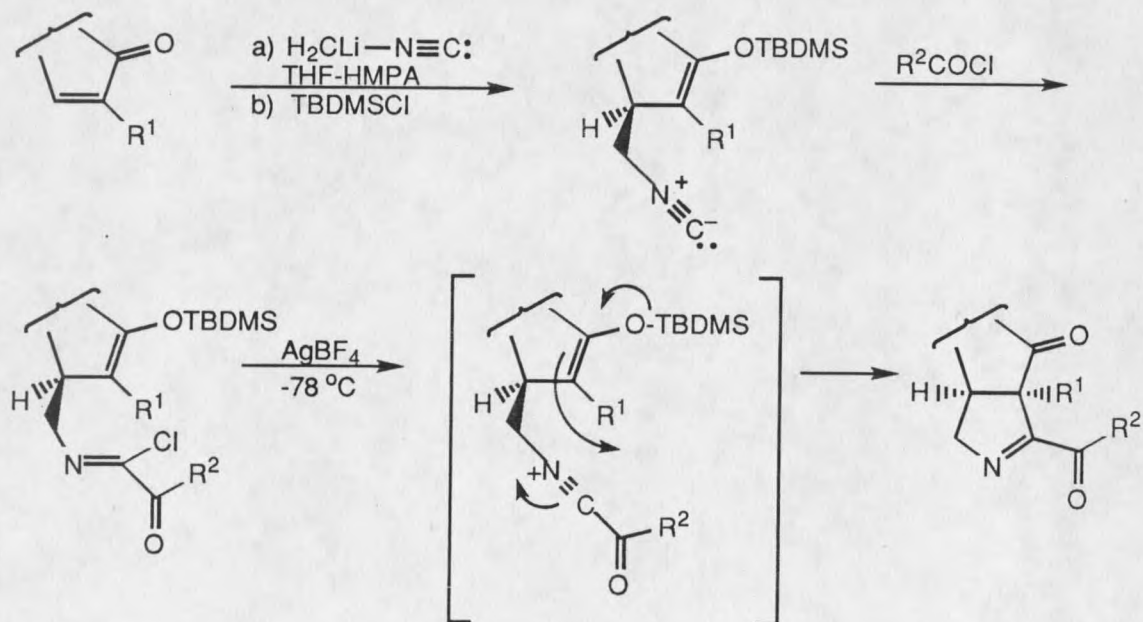


study the generality of these acylnitrilium ion initiated annulations. As shown in Eq. 13, simple alkenes²² can also be used for this purpose in a relay synthesis resulting in an extended ring system.

It was also predicted that silyl enol ethers²³ would act as excellent acylnitrilium ion-arene terminators. The 1,4-addition of $\text{LiCH}_2\text{NC}:$ to α,β -unsaturated ketones, and trapping with *t*-butyldimethylchlorosilane gave 3-(isocyanomethyl)silyl enol ethers in high yields. Reaction of the isonitriles with the desired acyl chloride, followed by treatment with silver tetrafluoroborate, gave the expected Δ^1 -pyrrolines in excellent yield (Scheme 9).

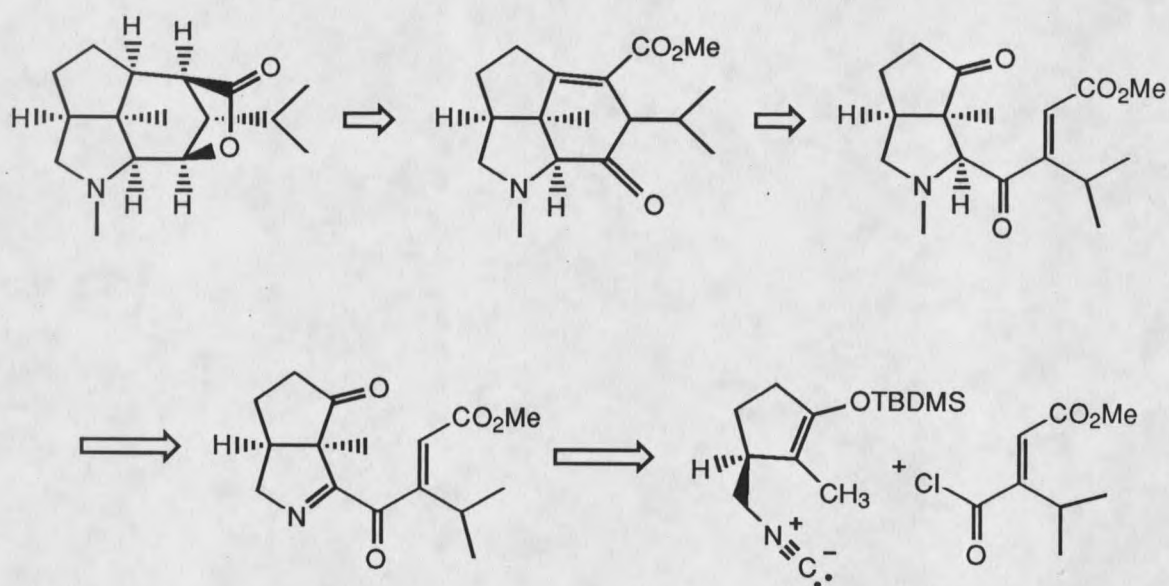


Eq. 13



Scheme 9

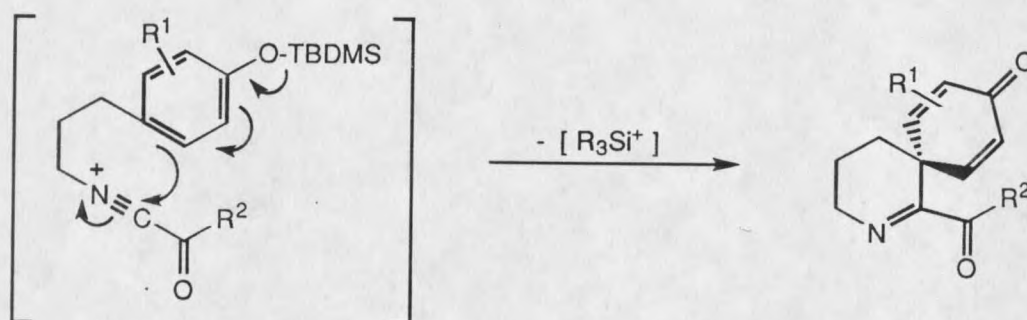
The utility of this methodology has been further demonstrated in these laboratories by its use in the total synthesis of the tetracyclic *Orchidaceae* alkaloid, dendrobine.²⁴ This efficient synthesis, consisting of eight linear steps, was carried out in 6.2 % overall yield with the key cyclization step as the highest yielding reaction (Scheme 10).



Scheme 10

These examples demonstrate that this method offers the advantage of a convergent assembly of azacycles of various ring sizes containing 2-acyl and endocyclic imine moieties, which can be utilized as sites for further functionalization. Most importantly, these cyclizations can be carried out under *extremely* mild conditions (-78 °C to -20 °C) and are therefore compatible with molecules containing other highly sensitive functionalities.

The focus of the research described herein was to expand upon the use of acyltrilium ion initiated cyclizations and ascertain whether spirocyclizations could be accomplished utilizing phenolic silyl ethers as terminators (Scheme 11). Once this could be shown, the possibility existed of using this methodology in the total synthesis of the *Lycopodium* alkaloid serratine (1) (Figure 1).



Scheme 11

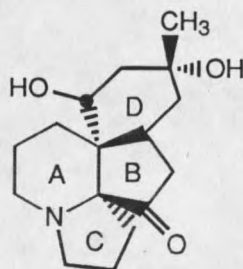


Figure 1. Serratine (1)

Nature of *Lycopodium* alkaloids

The *Lycopodium* alkaloids are unique in nature in that they are the only alkaloids found in club mosses. Of the 400 or so known varieties of club moss (genus *lycopodium*) only 10 % have been analyzed for alkaloid content.²⁵ From

these, over 100 different alkaloids have been isolated and are classified in 12 major skeletal systems shown in Figure 2.²⁶ One of the more recently discovered alkaloids, serratine (1), is found in *Lycopodium serratum* Thumb. and belongs to the minor serratinane skeletal group. This species has been

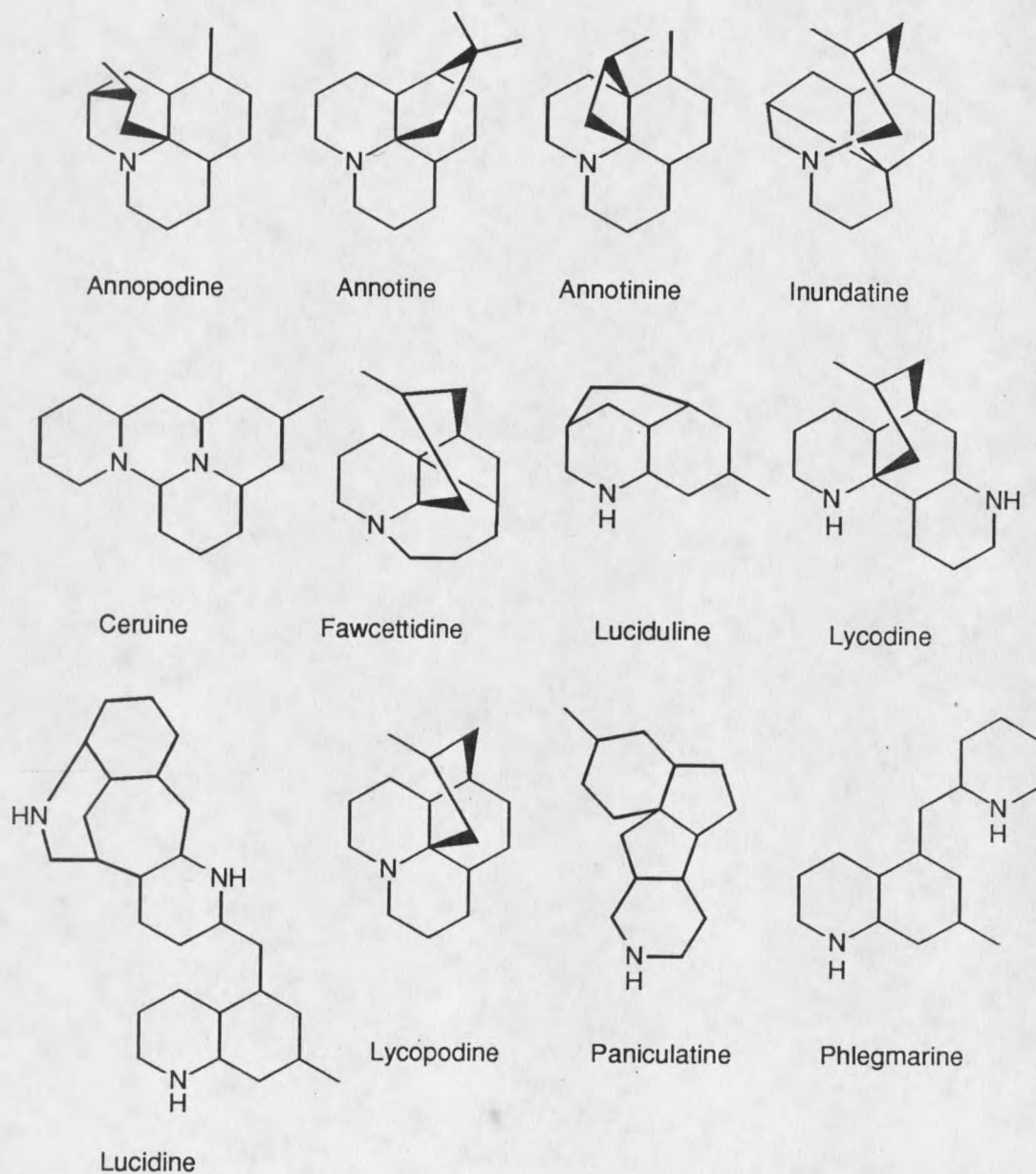


Figure 2. Major Skeletal Classes of *Lycopodium* Alkaloids

used in traditional Chinese herbal medicine due to its hemostatic and antipyretic activities.²⁷ Many other alkaloids are found in this species including lycololine, lycoclavine, serratinine, huperzine A, and huperzine B. The latter two compounds are currently being examined in China for the treatment of myasthenia gravis and Alzheimer's dementia²⁸ (Figure 3).

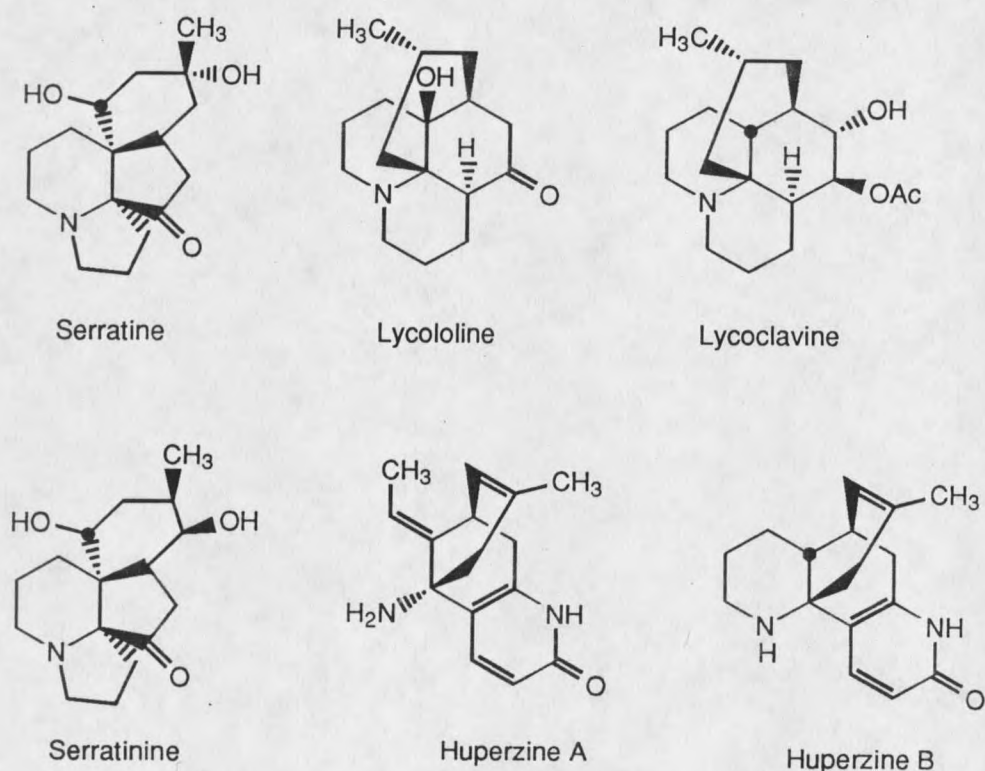
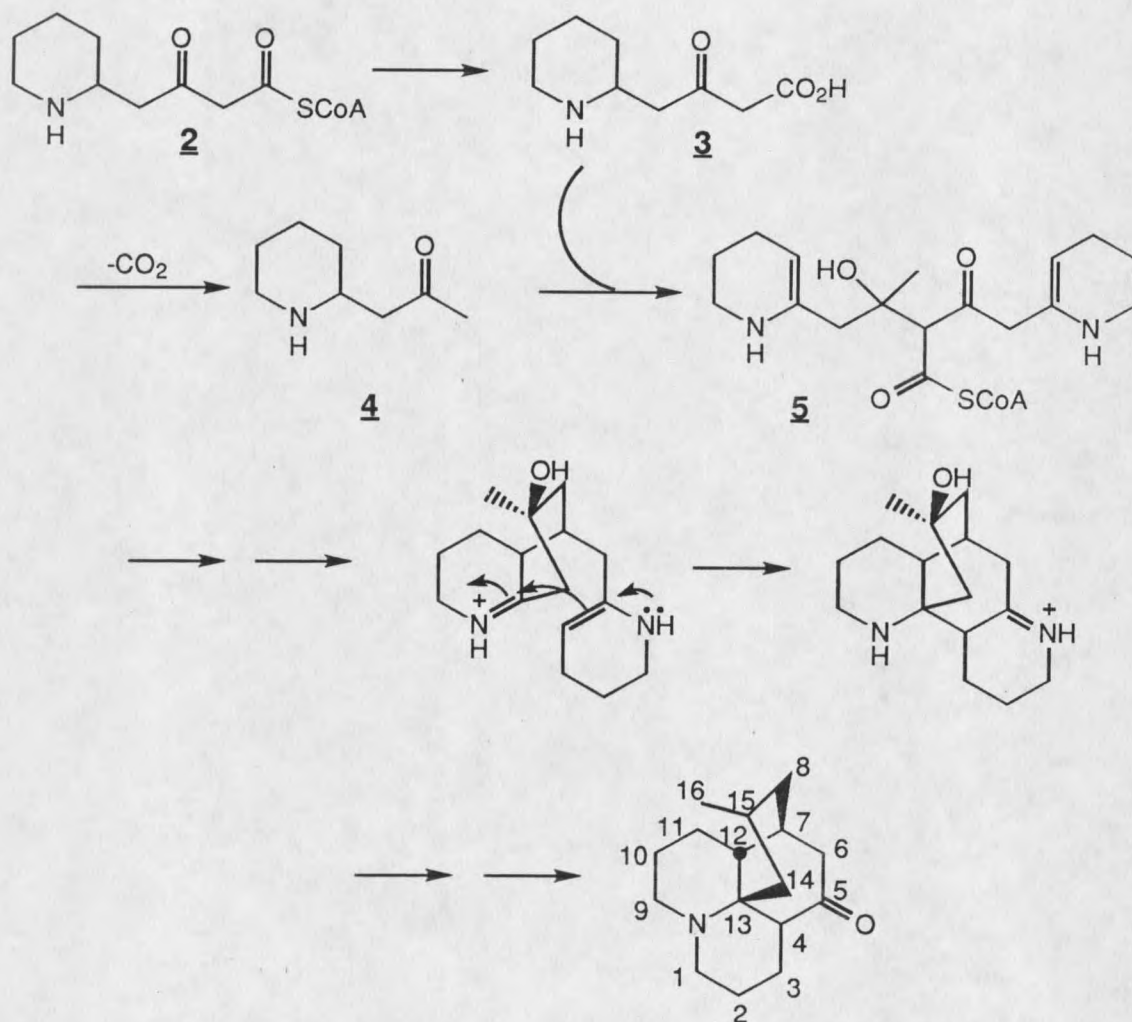


Figure 3. Representative Alkaloids within the Species *Lycopodium serratum* Thumb.

The biosynthesis of serratine most likely proceeds via a pathway common to the majority of the lycopodium alkaloids. A proposal for the biosynthesis of lycopodine has been put forth by Spencer and MacLean²⁹

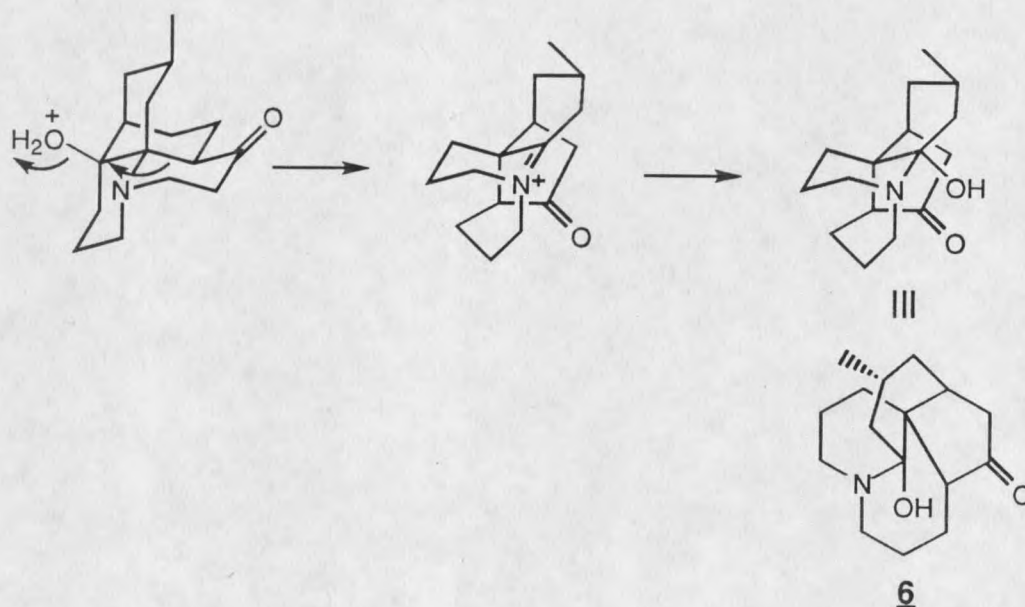
(Scheme 11). It suggests that lycopodine stems from the piperidine-2-acetoacetate derivative **2**, which in turn is derived from lysine. Decarboxylation



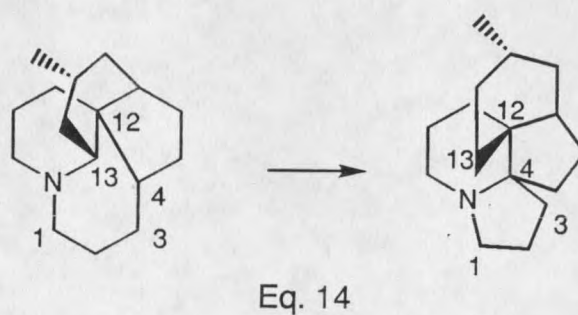
Scheme 11

of **3** would yield pelletierine **4**. Condensation of **4** with another molecule of **2** would produce **5**, the immediate precursor of the lycopodine alkaloids. Subsequent hydrolysis of the immonium salt and cyclization with the nitrogen contained in the A ring produces the lycopodine alkaloids.

A biosynthetic conversion between lycodoline (12-hydroxylycopodine) and fawcettimine (**6**) has been proposed by Inubushi³⁰ (Scheme 13). This is believed to be accomplished via protonation of the hydroxyl group, followed by loss of water, and then a migration of the C (4)-C (13) bond to yield the immonium salt, which upon hydration provides fawcettimine (**6**). The serratinane skeletal system is arrived at through one more bond migration, a Wagner-Meerwein shift of the C (13) - N bond to the C (4) position³¹ (Eq. 14).



Scheme 13



Eq. 14

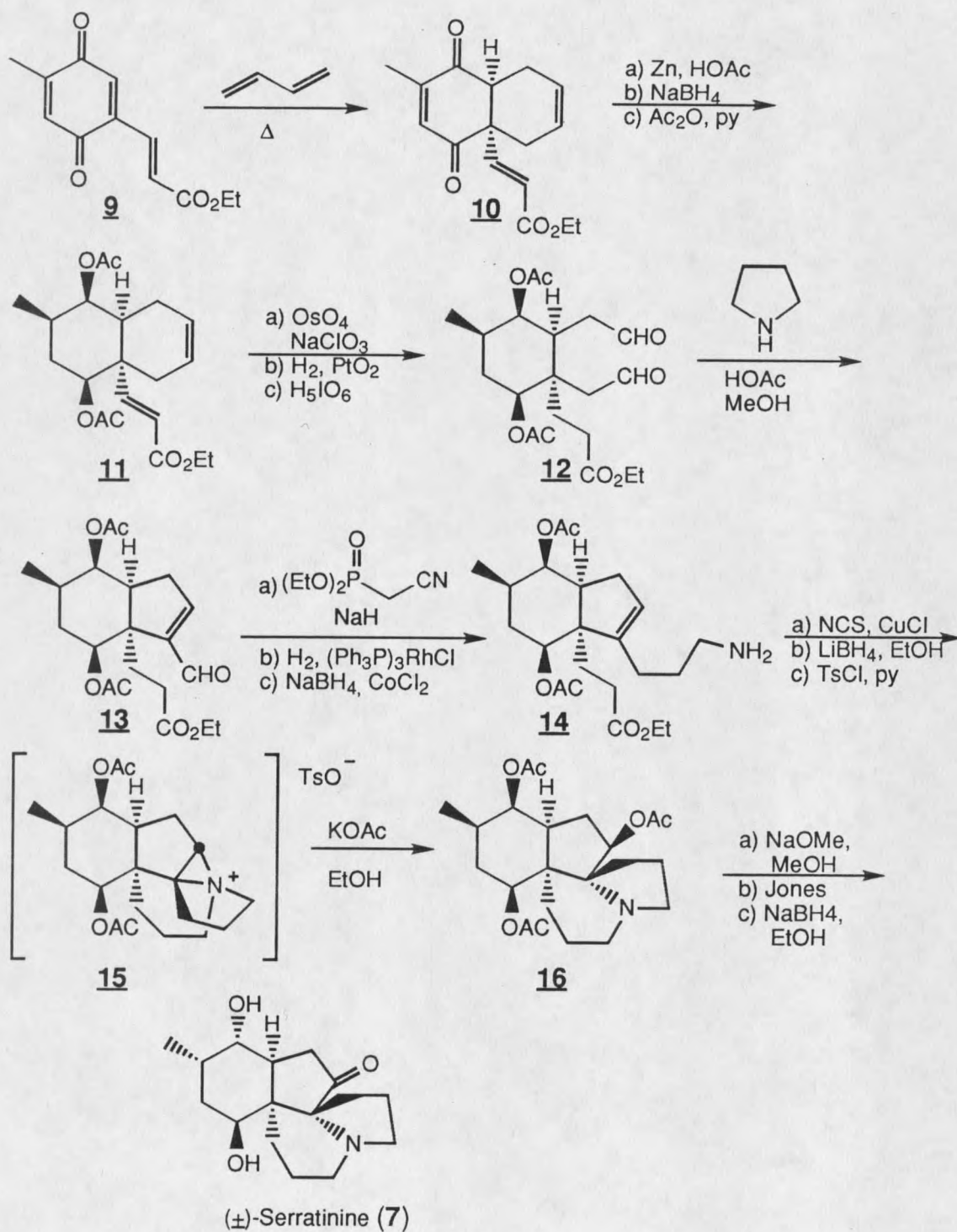
Previous Syntheses of *Lycopodium* Alkaloids with the Serratinane Skeleton

Many of the *Lycopodium* alkaloids have been synthesized. The most extensive synthetic studies have been performed on the most abundant alkaloid of the class, lycopodine. The initial routes to its skeleton were devised independently by Stork³² and Ayer³³ in 1968. However, only two alkaloids of the serratinane group have been synthesized, (\pm)-serratinine (**7**)³⁴ and (\pm)-8-deoxyserratinine (**8**).³⁵ Both of these syntheses were carried out by Inubushi (Scheme 14 and Scheme 15).

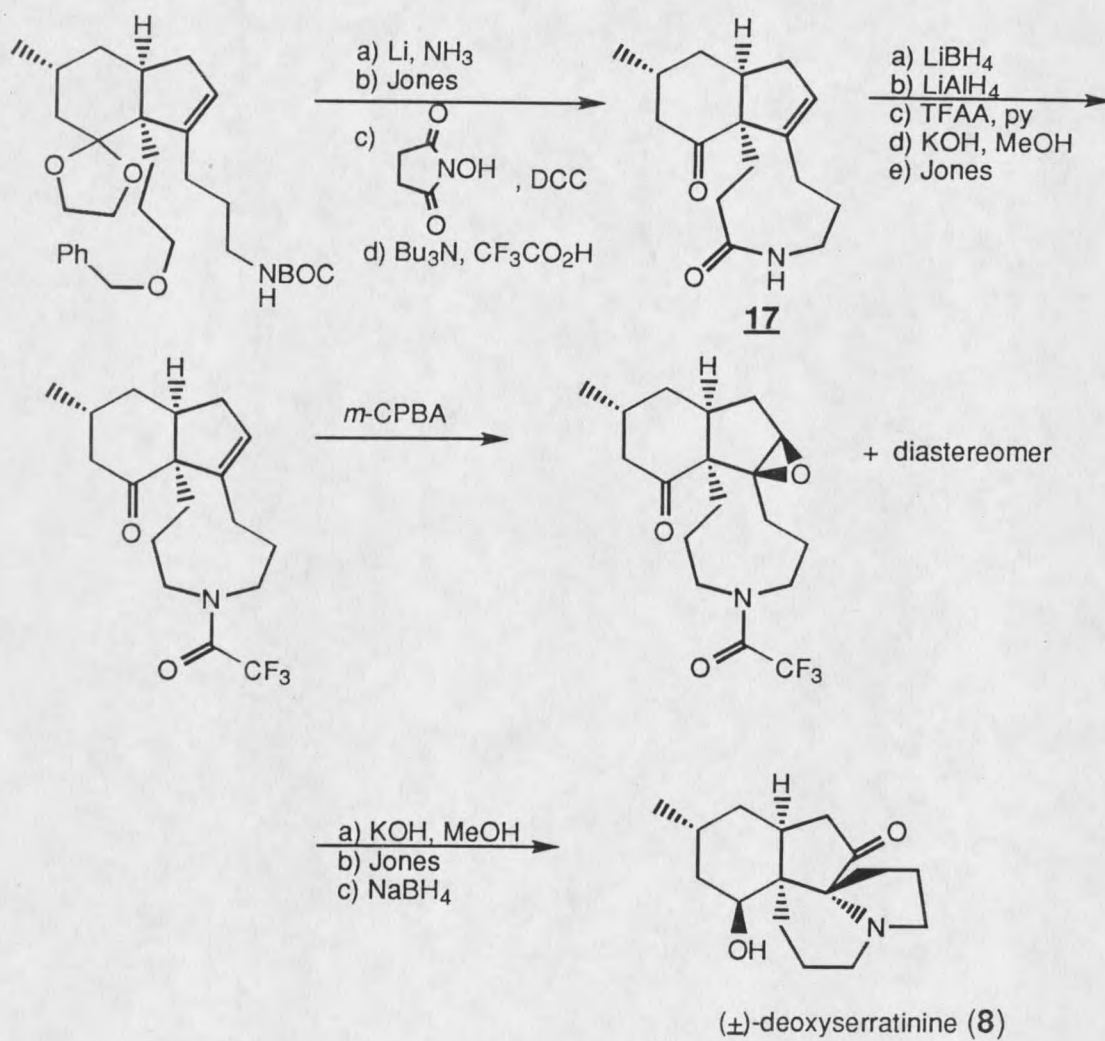
The synthesis of (\pm)-serratinine (**7**) started with the benzoquinone **9**, which was heated with butadiene to yield the Diels-Alder product **10** in 39 % yield. The enedione system was reduced and then acylated to produce **11**. The isolated olefin was dihydroxylated upon treatment with osmium tetroxide, followed by hydrogenation of the remaining double bond. The resulting diol was cleaved with periodic acid to give the dialdehyde **12**. The use of Mannich conditions utilizing pyrrolidine and excess acetic acid in methanol resulted in a mixture of products, with the desired regioisomer **13** being favored in an 8 to 1 ratio. The aldehyde was then treated with diethyl cyanomethylphosphonate to yield the cinnamitrile. The least substituted olefin and the cyano function were then reduced sequentially to furnish the amine **14**. In the following step, a nitrene was produced which adds to the double bond to yield the aziridine. The ester moiety was then reduced to yield the corresponding alcohol which was in turn tosylated, then displaced by nitrogen to produce the aziridinium salt **15**. Treatment of this salt with potassium acetate yielded triacetate **16**, containing

the serratinane ring skeleton. The synthesis was completed, following modifications of functional groups contained in this ring system, in an overall yield of less than 0.1 %.

The synthesis of (\pm)-8-deoxyderratinine (**8**) is similar to that of (\pm)-seratinine (**7**) except for the closure of the final two rings of the skeleton. This was accomplished by the formation of a nine-membered ring in **17**, which was followed by reduction of the amide and ketone. The resulting alcohol was then reoxidized and the amine protected with a trifluoroacetyl moiety. *m*-CPBA was then employed to epoxidize the olefin. Upon generation of the amine, the tetracyclic alcohol was produced in quantitative yield. Following oxidation of the alcohol and selective reduction of the less hindered ketone, the target molecule **8** was obtained. This synthesis was also accomplished in less than 0.1 % overall yield.



Scheme 14

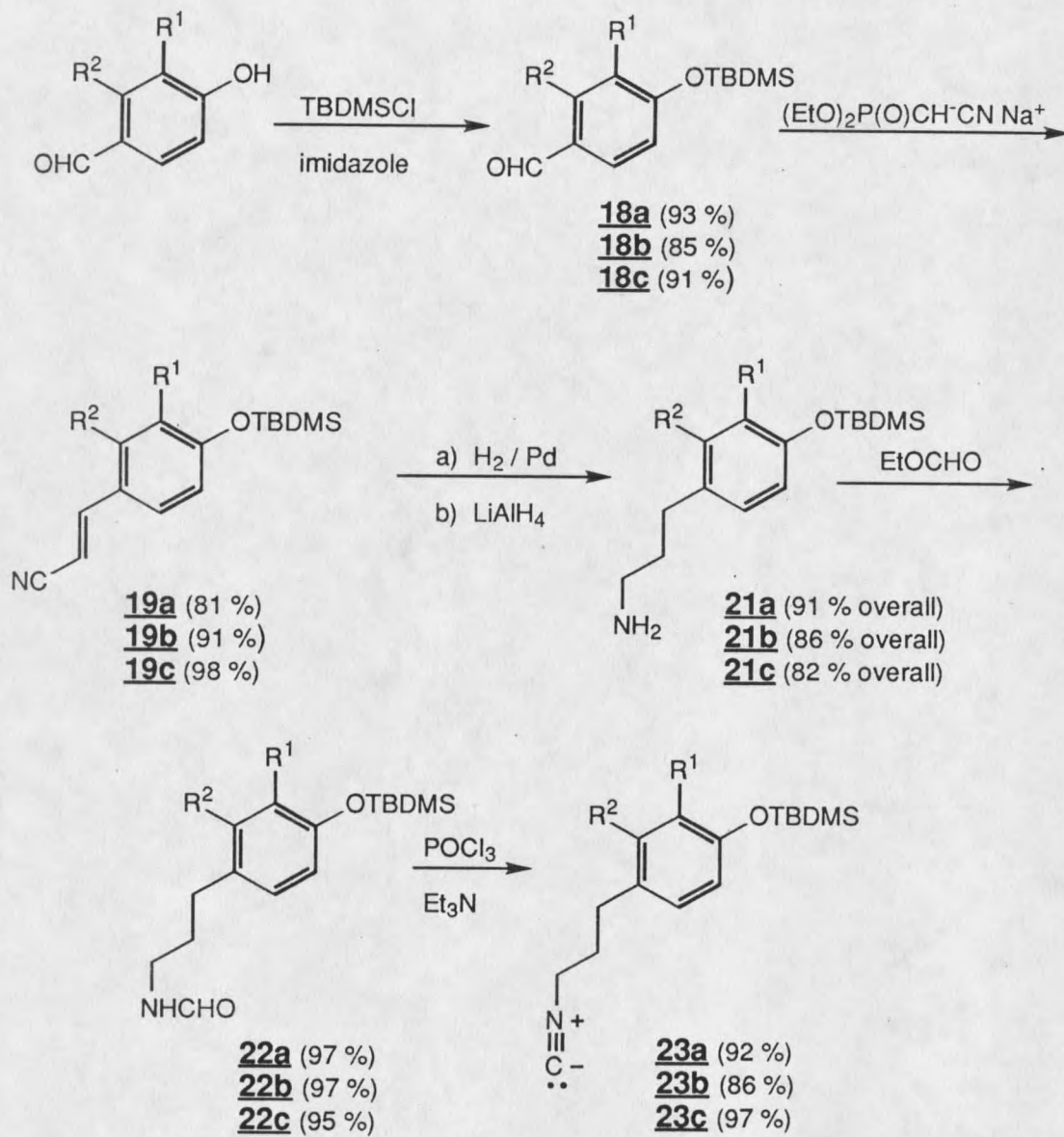


Scheme 15

RESULTS AND DISCUSSION

Methods Development

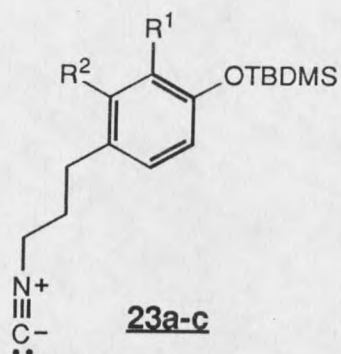
The aim of this research was to determine the feasibility of using phenolic silyl ethers as terminators in acylnitrilium ion-arene spiroannulation reactions (Scheme 11). As seen in Scheme 16, the requisite isonitriles were synthesized by first silylating the phenols,³⁶ whereupon the Horner-Wadsworth-Emmons reagent³⁷ was employed to produce the cinnamonnitriles **19a-c**. This was followed by hydrogenation of the olefins, reduction of the nitriles, and formylation of the resulting amines **21a-c**. The formamides **22a-c** were then dehydrated, giving rise to the respective isonitriles **23a-c**. Each isonitrile was subsequently treated with trimethylacetylchloride (25 °C) in CDCl₃ and the reaction monitored to completion by NMR. This was followed by addition to AgBF₄ in a solution of dichloromethane and 1,2-dichloroethane (-78 °C to -20 °C), which resulted in the spirocyclic products in the case of **23a** and **23b** (Scheme 17). However, in the case of **23c**, the 7-membered ring adduct was formed. This result was in congruence with what was found using the piperonal derived isonitrile **23d** (Eq. 15), formed by treating piperinal **26** with KOH in acetonitrile³⁸ to give the corresponding cinnamonnitrile **19d** (Eq. 16), and then following the same series of steps taken for **19a-c**.



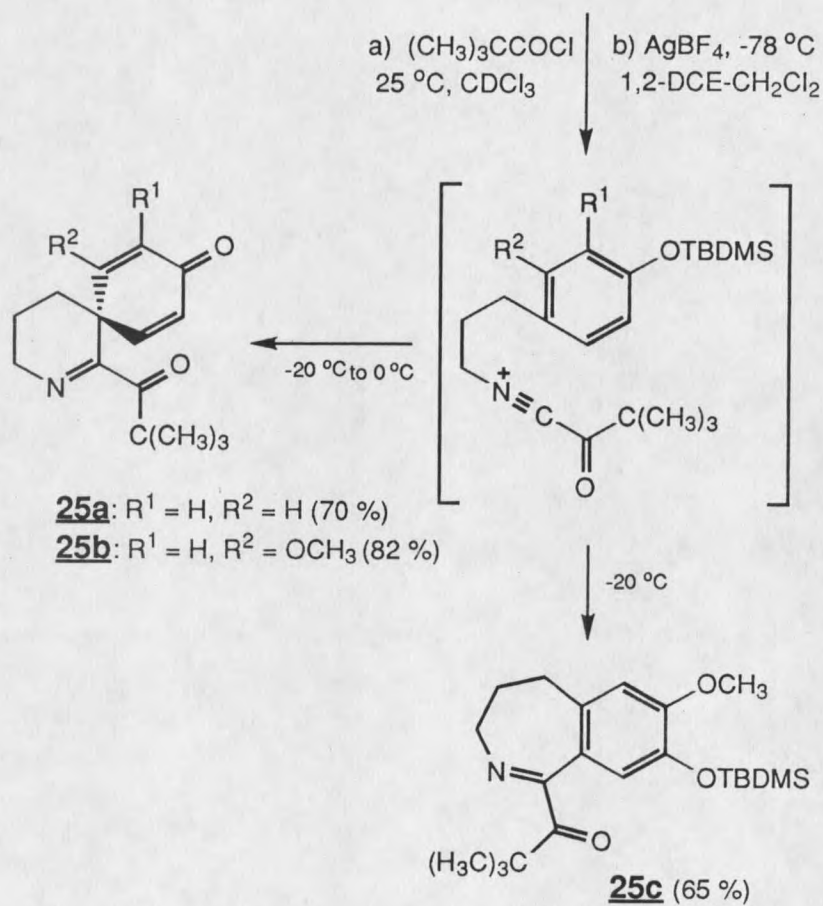
(a: $\text{R}^1 = \text{R}^2 = \text{H}$; b: $\text{R}^1 = \text{H}, \text{R}^2 = \text{OCH}_3$; c: $\text{R}^1 = \text{OCH}_3, \text{R}^2 = \text{H}$)

Scheme 16

28

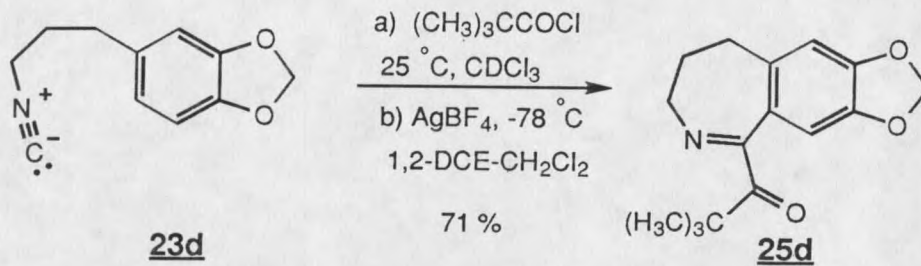


(**a**: $R^1 = R^2 = H$; **b**: $R^1 = H, R^2 = OCH_3$; **c**: $R^1 = OCH_3, R^2 = H$)

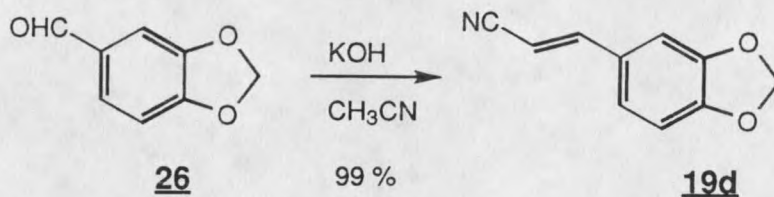


Scheme 17

29



Eq. 15

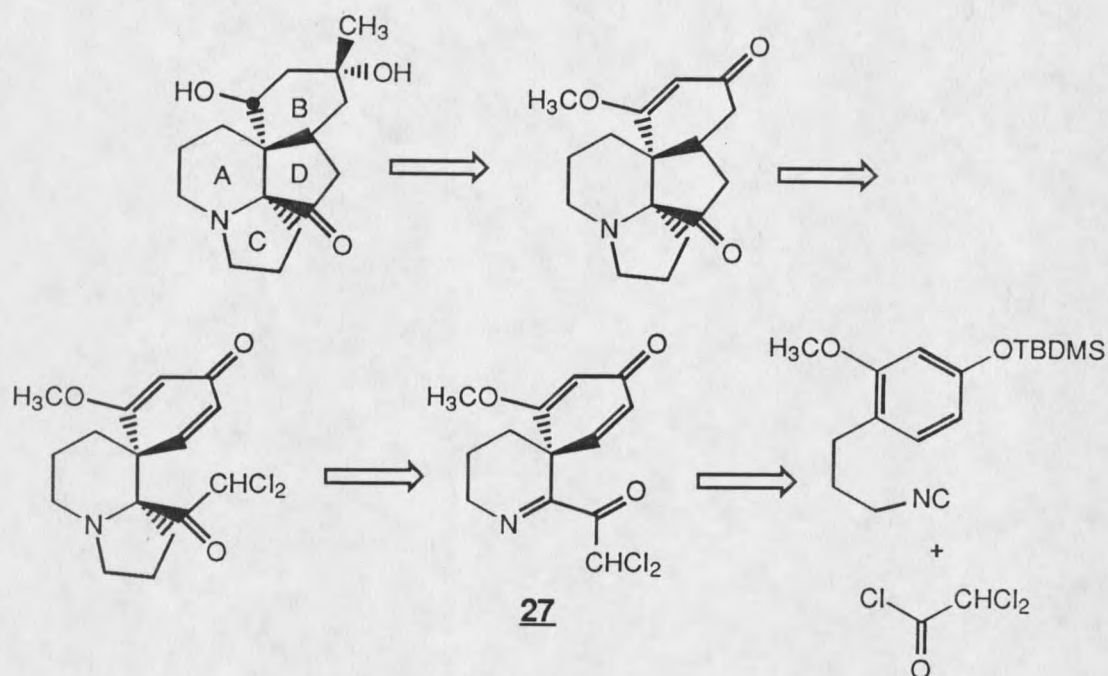


Eq. 16

Studies Toward the Synthesis of Serratine

Fortunately, it was determined that the desired spirocyclic precursor required for the synthesis of serratine (**1**) could be formed utilizing our acylnitrilium ion methodology. It was hoped that from spirocycle **27**, the tetracyclic core structure of serratine could be formed in the manner shown in Scheme 18.

30

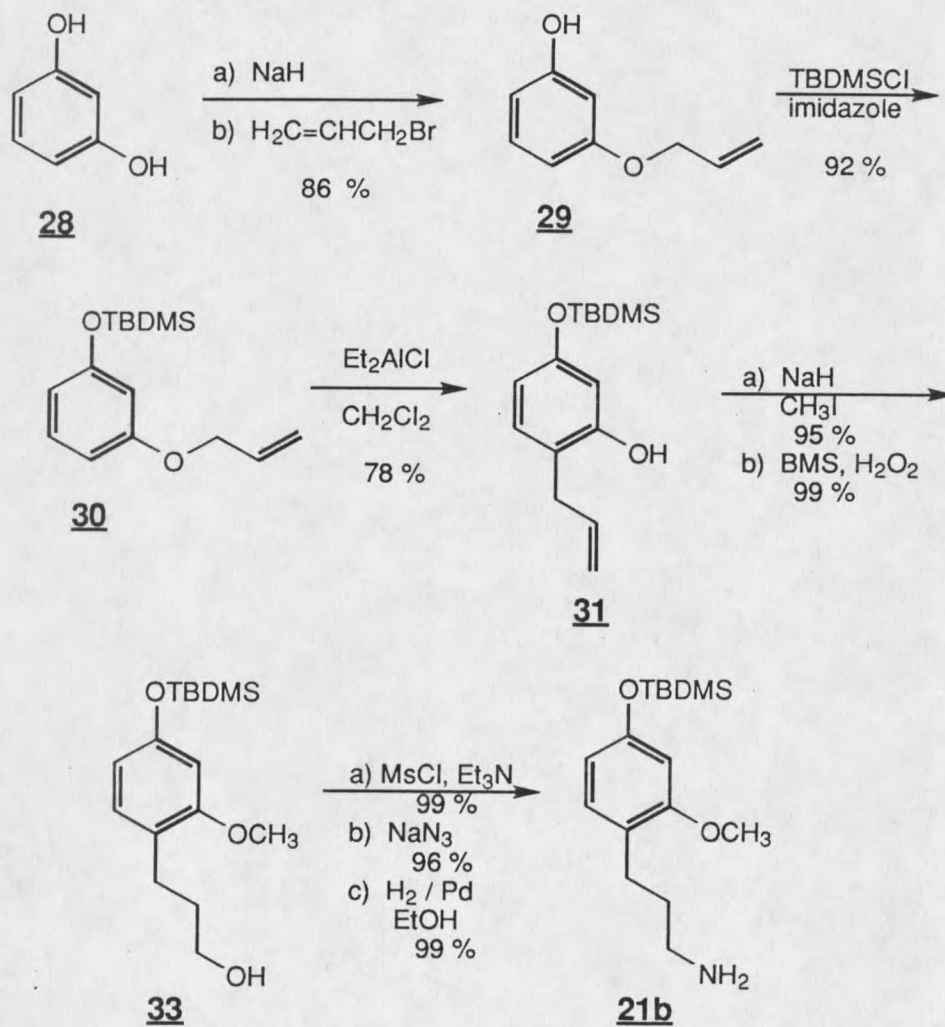


Scheme 18

Upon formation of the spirocycle, it was hoped that the imine contained within the molecule could be functionalized in a manner that would yield closure of the C ring. We then believed that it would be possible to form the D ring utilizing the dichloroacetyl moiety in a radical ring closure following known procedures.³⁹ All that would remain to complete the total synthesis would be modification of the functionality embedded within this tetracyclic core.

Before proceeding with the synthesis toward the natural product, a new pathway to the required isonitrile needed to be developed. The reasons for this were two-fold, first the cost of commercial 4-hydroxy-2-methoxybenzaldehyde used in the initial studies was exceedingly high, and second, if it was found necessary to place a different substituent on the 3-position of the aromatic ring later in the synthesis, it seemed prudent that it should be done at an early stage

of the synthesis. This was accomplished as shown in Scheme 19. Resorcinol **28** was monofunctionalized through treatment with one equivalent of NaH followed by alkylation with allyl bromide (0.75 equiv.). The resulting phenol was

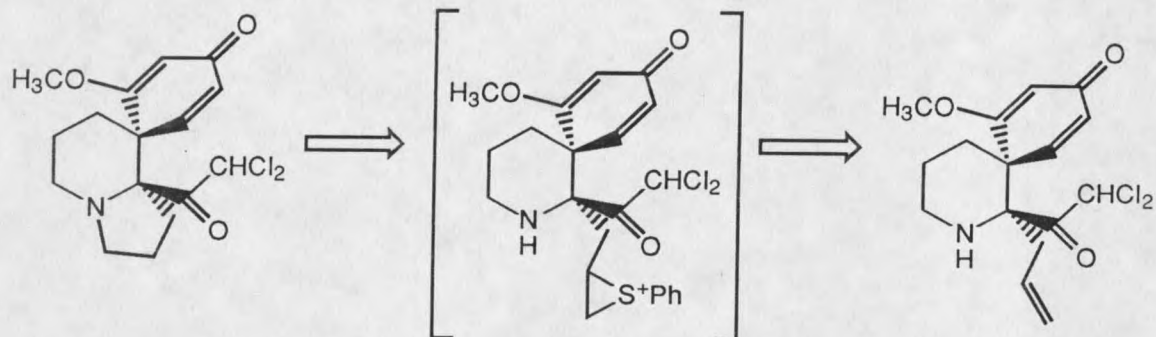


Scheme 19

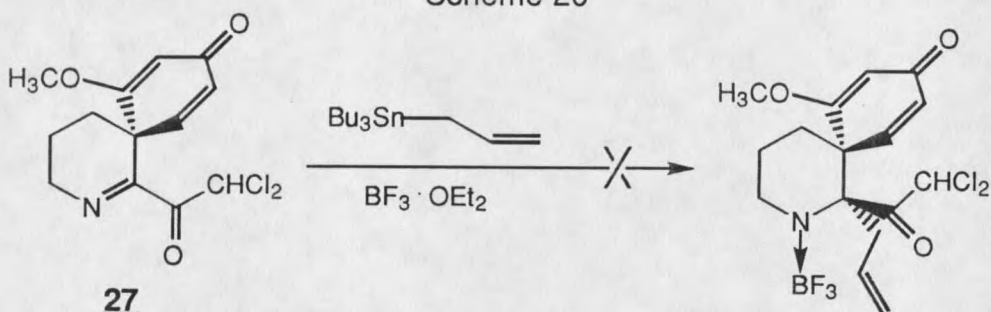
protected with *t*-butyldimethylsilylchloride.³⁶ *Para* functionalization of this protected phenol was realized through a diethylaluminum chloride catalyzed Claisen rearrangement.⁴⁰ It should be noted that if the reaction temperature exceeded -30 °C, considerable amounts of product with undesired *ortho* substitution were obtained. The methoxy derivative was prepared by treatment with NaH and iodomethane in THF. Hydroboration of the olefin, with borane-methyl sulfide complex, followed by oxidative workup afforded the alcohol in excellent yield. Preparation of the mesylate was accomplished by treating the alcohol with MsCl and Et₃N in CH₂Cl₂. Displacement of the mesylate with sodium azide in DMF yielded the corresponding azide. Subsequently, the amine was obtained via hydrogenation of the azide in nearly quantitative yield. The remaining two steps to the isonitrile were performed as previously described.

As mentioned, the spirocycle **27** was to be the initial substrate utilized, as it was believed that the dichloroacyl group could ultimately be used to form the B ring of the system. With this in mind, attempts were made to functionalize the imine contained within the A ring. The first method employed was to treat the spirocycle with boron trifluoride diethyl etherate and allyltributyltin, which was hoped to yield the secondary amine. Following the precedent by Ishibashi, utilizing known episulfonium ion methodology,⁴¹ it was believed that the C ring could be secured (Scheme 20). However, much to our concern, no reaction was observed (Eq. 17).

33



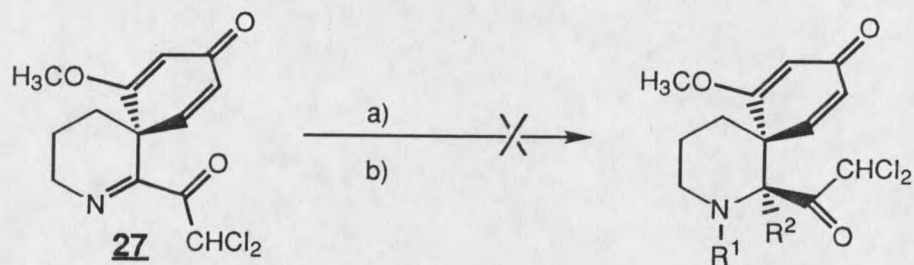
Scheme 20



Eq. 17

We then sought to increase the electrophilicity of the imine carbon by creating the corresponding iminium ion, formed for the initial investigation by treating **28** with methyl triflate in CH_2Cl_2 or CDCl_3 . As shown in Table 1 many different nucleophiles were utilized but none were successful.

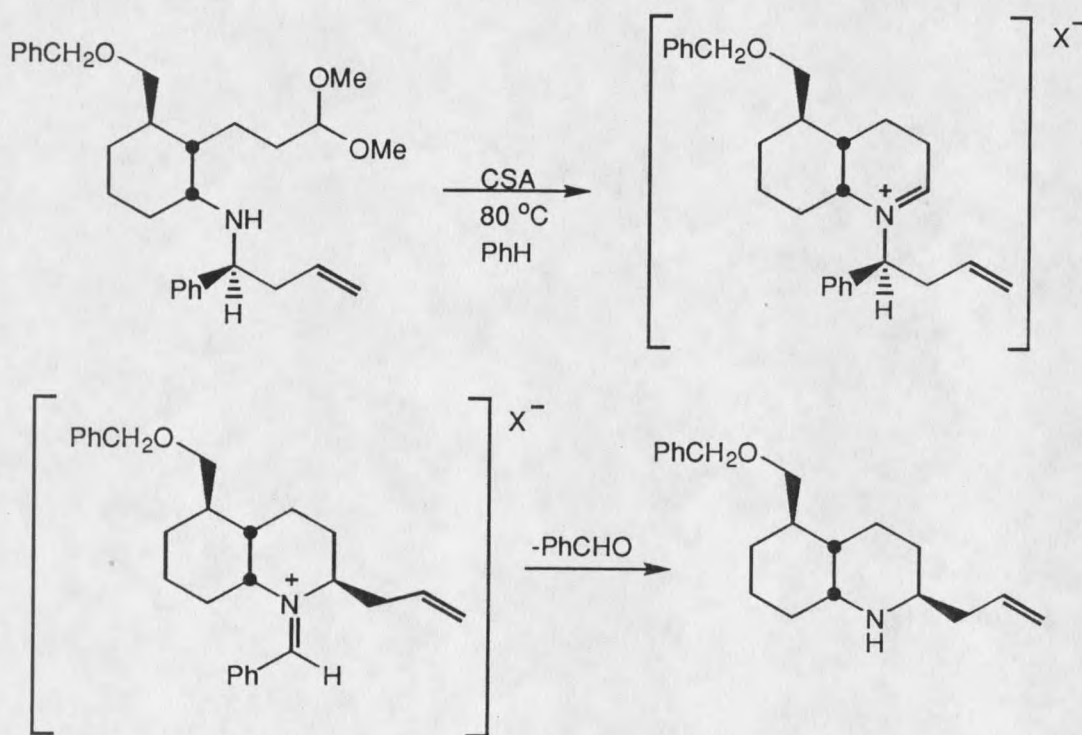
Allyl tributyltin was also used on the iminium ion derived from MEM-Cl, MOM-Br, and also on the *N*-acyliminium ion derived from treatment of the spirocycle with trifluoromethylacetyltriflate (TFAT). None of these attempts were successful either. It was then realized that perhaps intramolecular functionalization methods, stemming from the initial alkylation of the imine, would be required due to steric constraints.

Table 1. Unsuccessful Attempts to Functionalize Spirocycle **27**

| Trial | Reagents |
|-------|---|
| 1 | a) CH ₃ OTf b) Bu ₃ Sn-CH ₂ -CH=CH ₂ |
| 2 | a) CH ₃ OTf b) Bu ₃ Sn-CH ₂ -CH=CH ₂ , BF ₃ · Et ₂ O |
| 3 | a) CH ₃ OTf b) Bu ₃ Sn-CH ₂ -CH=CH ₂ , SnCl ₄ |
| 4 | a) CH ₃ OTf b) Me ₃ Si-CH ₂ -CH=CH ₂ |
| 5 | a) CH ₃ OTf b) BuCu(CN)Li |
| 6 | a) CH ₃ OTf b) BrZn-CH ₂ -CH=CH ₂ CuCN / 2 LiCl |
| 7 | a) CH ₃ OTf b) TMSCN |
| 8 | a) CH ₃ OTf b) <i>n</i> -BuCuCN(Mg)Br |
| 9 | a) MEM-Cl b) Bu ₃ Sn-CH ₂ -CH=CH ₂ |
| 10 | a) MOM-Br b) Bu ₃ Sn-CH ₂ -CH=CH ₂ |
| 11 | a) TFAT b) Bu ₃ Sn-CH ₂ -CH=CH ₂ |

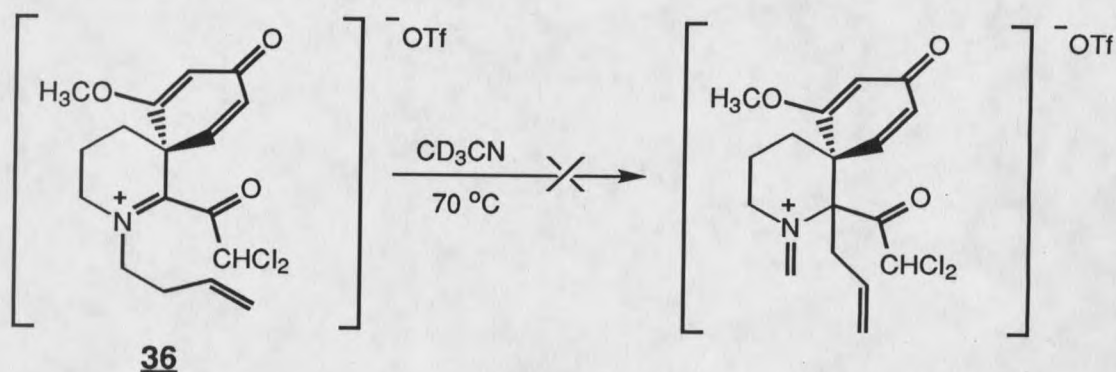
Our initial strategy for intramolecular functionalization of the imine was to use an aza-Cope rearrangement, previously demonstrated to be effective by Overman⁴² (Eq. 18). The triflate salt **36** was prepared cleanly upon treatment of the spirocycle with the corresponding alkyl triflate. The subsequent reaction was monitored by NMR in CD₃CN but again no addition to the iminium ion was seen even after extended periods at 75 °C (Eq. 19).

The second strategy was based on similar work by Macdonald⁴³ in which an *N*-acyliminium ion was formed in situ upon treatment of a hydroxylactam with TiCl₄. This reactive species was attacked by the nucleophilic carbon adjacent to a trimethyltin moiety (Eq. 20).

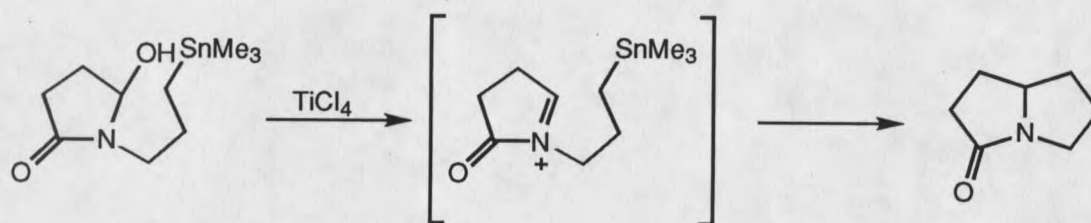


Eq. 18

36

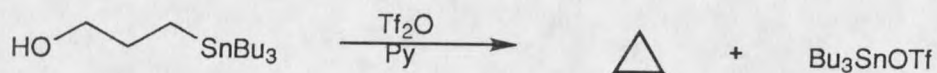


Eq. 19

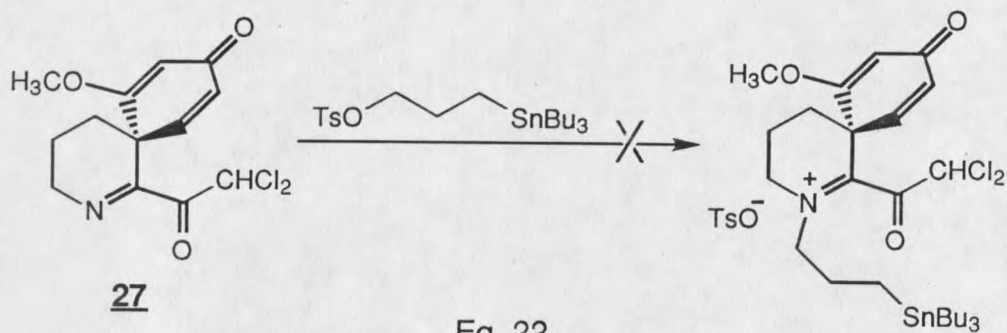


Eq. 20

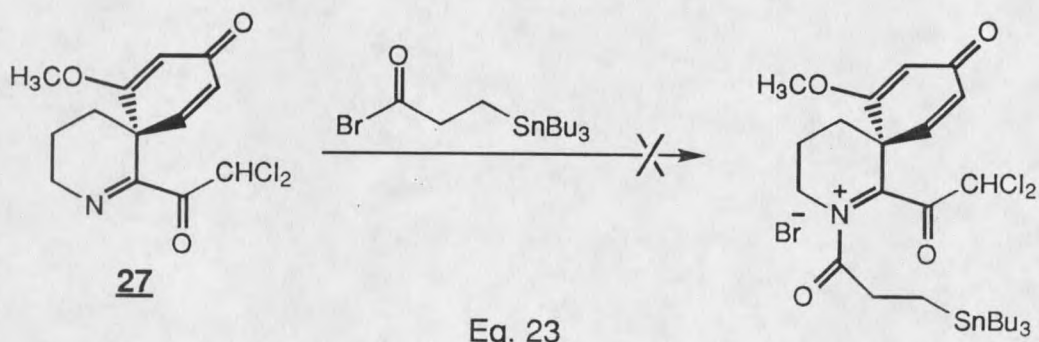
Knowing that it was possible to cleanly alkylate the spirocycle with triflates, an endeavor was made to form a reagent containing both the required triflate and tributyltin moiety from the corresponding alcohol.⁴⁴ However, upon its generation, the nucleophilicity of the tributylorganostannane was clearly demonstrated as cyclopropane was believed to be immediately generated, as evidenced by escaping gas and the recovery of tributyltin triflate (Eq. 21). The tosylate derivative was formed in expectation that it would serve as an adequate leaving group in the alkylation of the imine, but it was found to be ineffective (Eq. 22) The same result was observed with the acid bromide derivative⁴⁵ (Eq. 23).



Eq. 21



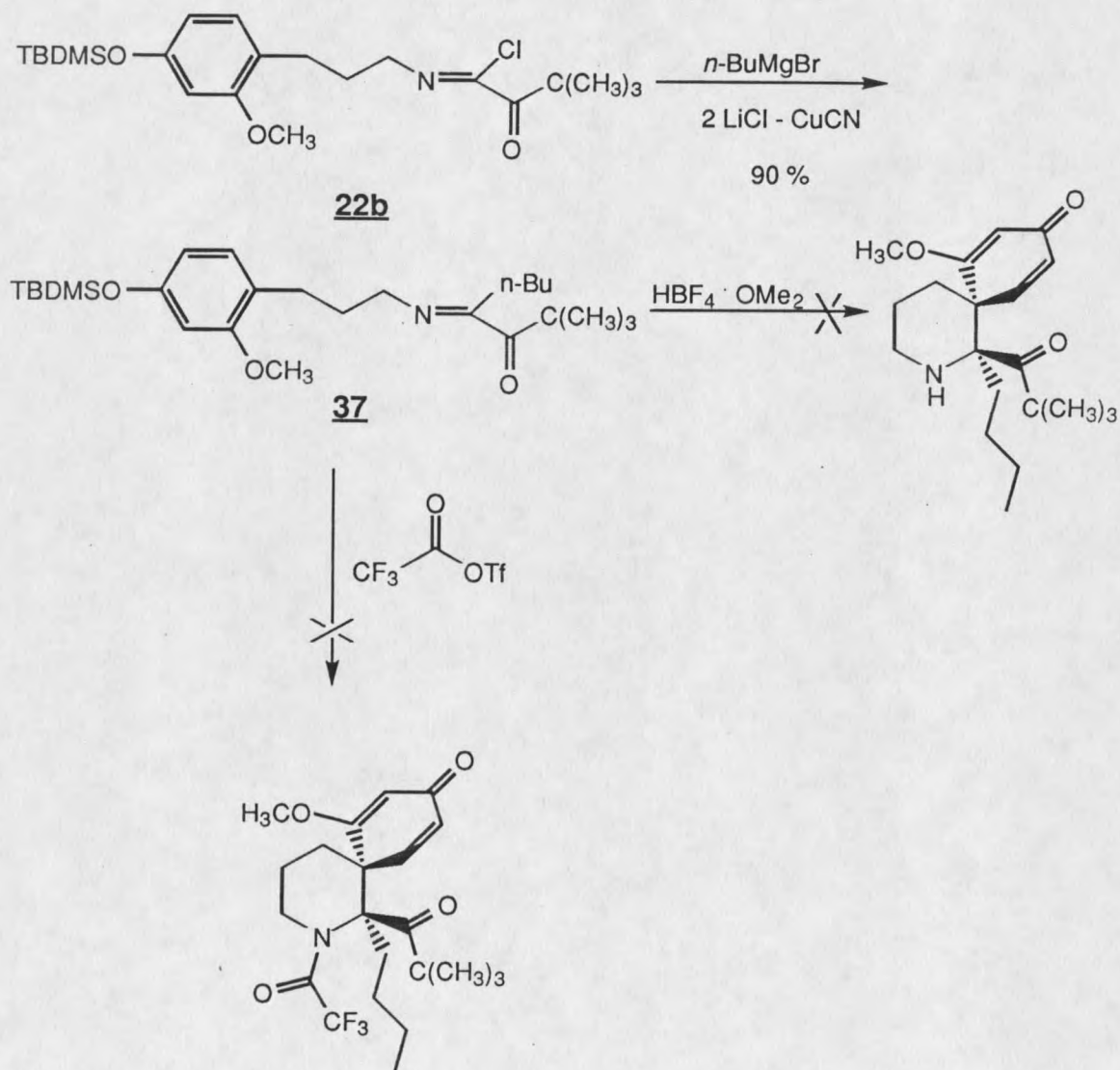
Eq. 22



Eq. 23

At this point, the difficulty in forming a quaternary center adjacent to a preexisting quaternary center was becoming quite apparent due to the severe steric congestion at that site. The use of the extremely electrophilic C-acylnitrilium ion as the cyclization initiator was abandoned briefly in hopes that

a C-acyliminium ion could be substituted and thereby form the two adjacent quaternary centers in the initial ring forming step (Scheme 21). The required

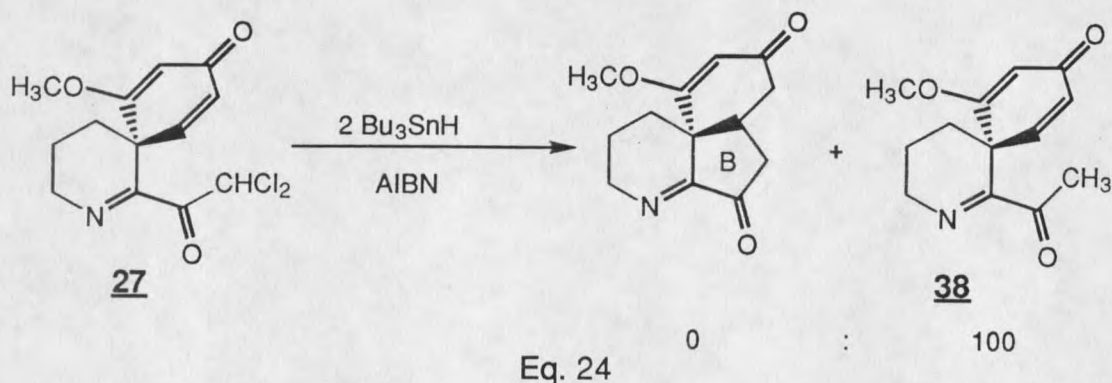


Scheme 21

imine **37** was formed by treating the α -ketoimidoyl chloride **22b** with a lower order cyanocuprate. This compound was then treated with $\text{HBF}_4 \cdot \text{OMe}_2$ with the

hope that this reagent could form the iminium ion and serve as a deprotection agent, thus driving the cyclization to the desired product. However this idea did not come to fruition. The imine was also treated with trifluoroacetyltriflate in the same vein but once again no reaction was observed.

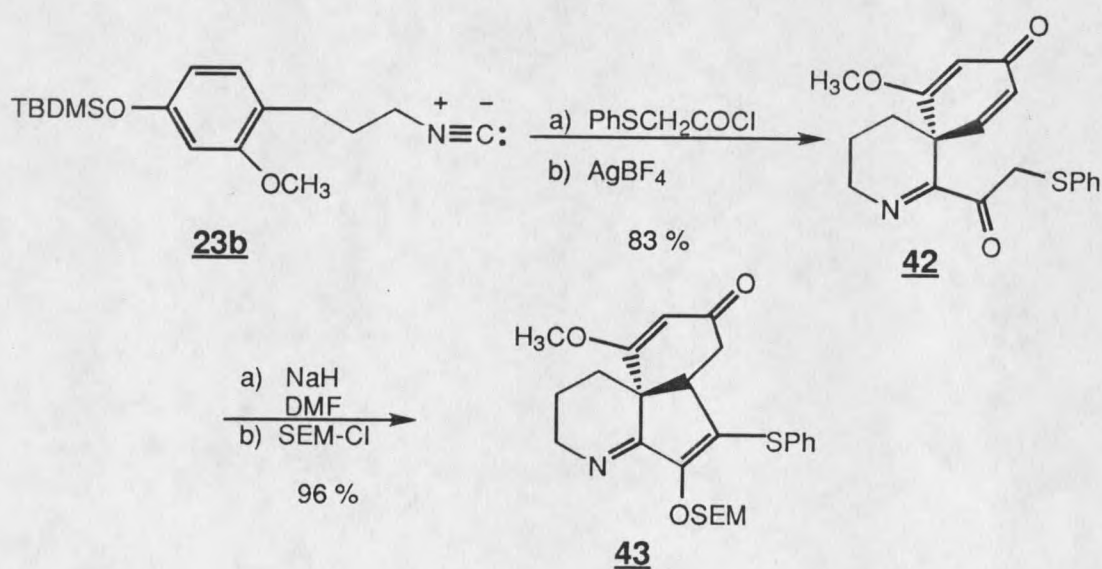
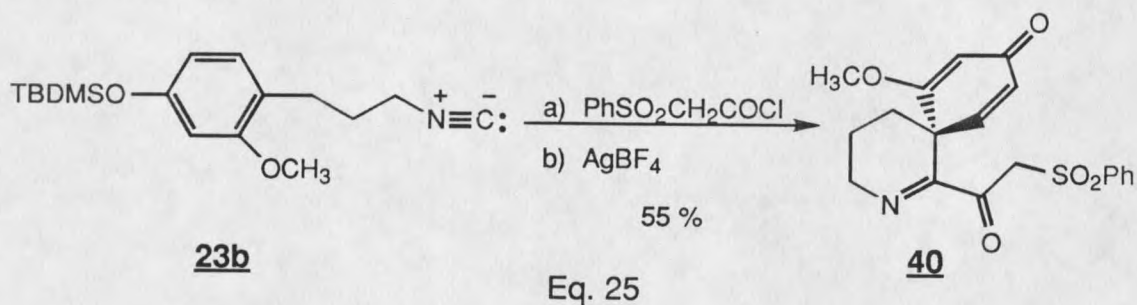
Bearing all of these negative results in mind, attention was turned to the formation of the B ring of the molecule. It was hoped that once this was formed, it would relieve some of the steric constraints of nucleophilic addition to the imine and perhaps at the same time change the electronic characteristics of this section of the molecule, making addition to the imine favorable. We then proceeded with the next step in our initial synthetic plan for this ring formation, however, it was soon discovered that these plans were flawed in that the desired radical cyclization did not occur, only reduction product was formed under the conditions used by Ishibashi³⁹ (Eq. 24). Further studies on this type



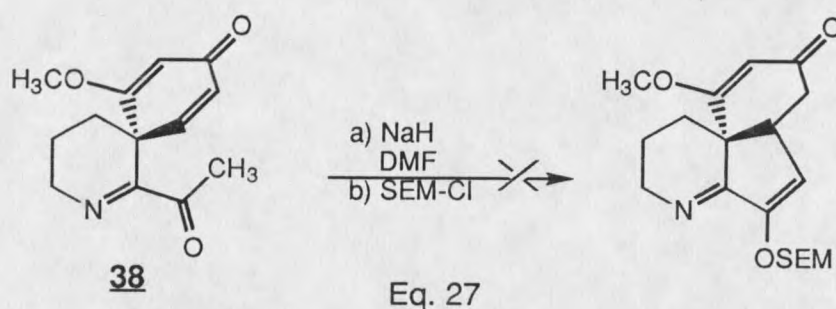
of ring closure were not carried out, instead, attempts to form the ring using conjugate addition methodology⁴⁶ were examined with the hope that the additional functionality required would come into service later in the synthesis.

It was thought that an ideal candidate for this first attempt at forming the tricycle would be spirocycle **40**. However it was found that the yields in forming

this spirocycle were unusually low (55 %) and spirocycle **42**, obtained in 83 % yield, was used in its stead (Eq. 25 and Eq. 26). Thus treatment of **42** with NaH in DMF at 0 °C and warming to 25 °C resulted in the desired tricycle upon quenching with AcOH. However, this compound readily decomposed. It was found, much to our pleasure, that quenching the intermediate with SEM-Cl at -78 °C resulted in the stable tricycle **43** in 96 % yield. In this step the enolate that was created after the cyclization was trapped, thus eliminating one more acidic position within the resulting tricycle.



An attempt was made to form this third ring from the spirocycle **38** containing an acetyl moiety, however, no cyclized product was observed (Eq. 27).



With tricycle **43** in hand, several of the same intermolecular nucleophilic additions were attempted which had been tried previously with the spirocycle **27**. Once again, none of these attempts were successful. However, due to the additional functionality within the molecule, we were ready to pursue several new plans for the formation of the conclusive ring. The first method tried was based on the use of Sml_2 as a coupling agent.⁴⁷ It was believed that if the imine of the tricycle could be alkylated with 1-iodo-propanetrifluoromethanesulfonate and then treated with 2 equivalents of Sml_2 , a single electron transfer (SET) from the Sml_2 would occur, resulting in reductive coupling of the iodide and the iminium salt (Scheme 22).

