



Development and synthetic application of the allylbis (silane) cyclization terminator
by Timothy Scott Kercher

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:

In order to advance the existing methodology of allylsilane-terminated cyclizations, a series of amino-allyl(bis)silanes was prepared for use as intermediates in route to cationic cyclizations terminated by the novel allyl(bis)silane nucleophile. This terminator was found to readily participate in the intramolecular trapping of activated imines and C-acylnitrilium ions providing highly substituted and functionally diverse pyrrolidines, piperidines and pyrrolines. These processes occurred not only in high chemical efficiency under mild conditions but with excellent levels of regioselectivity and substrate based stereocontrol.

As a result, this methodology was successfully applied to the stereoselective synthesis of biologically active isotropane alkaloids and the azapolycyclic core of the potent natural insecticide, stemofoline. These applications demonstrated the ability of the allyl(bis)silane terminator to engage in tandem silicon-directed cyclizations. Such reactivity was not possible with the silane terminators previously used by synthetic chemists.

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Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

April 1997

D378
K4537

APPROVAL

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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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To all of my wonderful family

ACKNOWLEDGMENTS

The successful completion of this dissertation was made possible only by the contributions of many individuals. First and foremost, Professor Livinghouse has always proven to be a valuable source of problem-solving ability, creativity and motivation all of which flow from his great enthusiasm for organic chemistry. His hard work and dedication is greatly appreciated and helped provide all of resources, tools and finances necessary for the execution of research in his labs. Thanks goes to Dr. Sears for performing all of the high resolution, mass analysis on the many compounds that were synthesized and also to Ray Larson for contributing his crystallography expertise. Additional gratitude is expressed to all of my fellow workers at Montana State University for their sharing of ideas, talents, resources and valuable time.

Many individuals outside of the world of chemistry contributed my well being during the course of this graduate work. My parents, James and Linda Kercher, were and will always be an inexhaustible source of love, patients and encouragement. I cannot possibly thank them enough for all they have done for me. Various outdoor activities with many friends will never be forgotten and represent time that was both enjoyed and appreciated. Special thanks and admiration goes to my family at the Bozeman Church of Christ who are always supplying encouragement, care and love for the benefit of others. Praise be to Almighty God our Father, by and through whom all things are possible, who created the beautiful lands of Montana.

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ABSTRACT

In order to advance the existing methodology of allylsilane-terminated cyclizations, a series of amino-allyl(bis)silanes was prepared for use as intermediates in route to cationic cyclizations terminated by the novel allyl(bis)silane nucleophile. This terminator was found to readily participate in the intramolecular trapping of activated imines and C-acylnitrilium ions providing highly substituted and functionally diverse pyrrolidines, piperidines and pyrrolines. These processes occurred not only in high chemical efficiency under mild conditions but with excellent levels of regioselectivity and substrate based stereocontrol.

As a result, this methodology was successfully applied to the stereoselective synthesis of biologically active isotropane alkaloids and the azapolycyclic core of the potent natural insecticide, stemofoline. These applications demonstrated the ability of the allyl(bis)silane terminator to engage in tandem silicon-directed cyclizations. Such reactivity was not possible with the silane terminators previously used by synthetic chemists.

INTRODUCTION

A vast proportion of the molecular targets of interest to the synthetic organic chemist such as natural products, pharmaceuticals and synthetic intermediates contain cyclic or polycyclic carbon frameworks. The degree of complexity of these cyclic arrays of atoms may range drastically. This becomes evident upon comparing menthol, a simple monocyclic terpene used as peppermint flavoring, to the formidable heptacyclic structure of the powerful poison, strychnine (Figure 1). It is therefore no surprise that carbon-carbon bond formation in an intramolecular fashion has been the crux of countless past and present research endeavors in the field of organic chemistry.

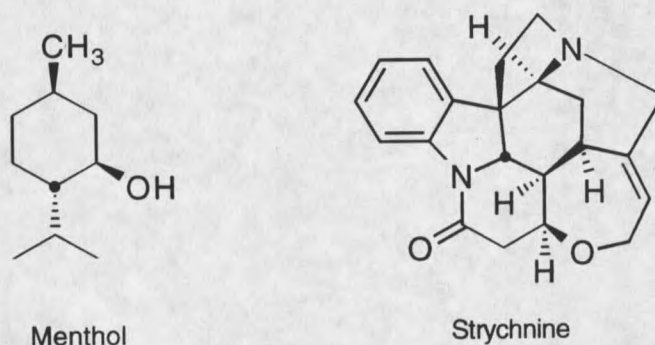
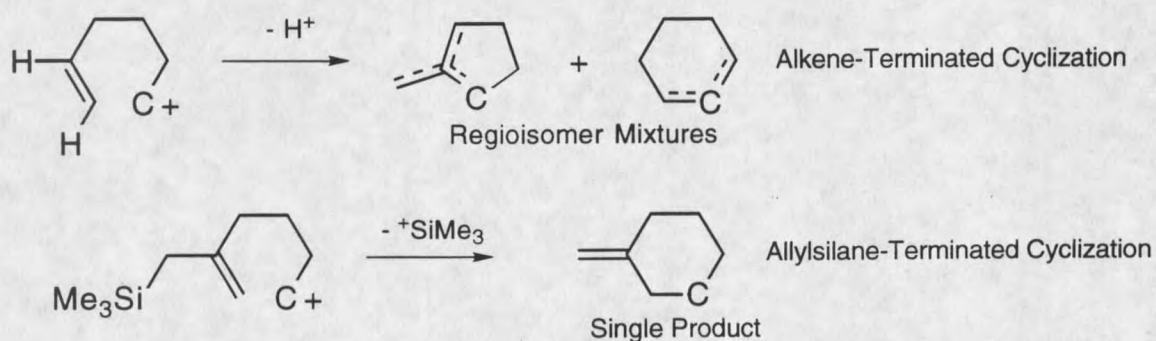


Figure 1. Well Known Cyclic Molecules

The classical method for formation of such important bonds has involved the intramolecular trapping of a reactive carbon electrophile, termed the initiator, by a suitably disposed nucleophilic carbon or terminator. From a standpoint of the terminator, alkenes and alkynes have been extensively applied by virtue of the nucleophilicity of their pi electron clouds. It has been demonstrated over the course of research involving alkene terminators that,

unless the cyclization substrate is carefully chosen, alkene-terminated cyclizations generally result in mixtures of products. This problem originates from lack of sufficient regiocontrol in both the ring formation and elimination steps of the cyclization reaction resulting in products of various ring size and position of unsaturation respectively. Competitive reactions such as alkyl and hydrogen shifts have also been shown to commonly occur, further complicating the product mixture. Fortunately, it eventually became realized that by using an alkene appended to a silane moiety, as in an allylsilane, these types of cationic cyclizations may be directed through a single reaction pathway giving rise to a single reaction product (Scheme 1).



Scheme 1

As a result of this observation that a strategically located silicon atom has a dramatic effect on the course of cationic cyclizations and electrophilic additions in general, a host of silicon terminators has evolved over the years (Figure 2). These nucleophiles are in constant use today in both the intramolecular and intermolecular formation of strategic bonds employing a broad spectrum of electrophiles. More specifically, the cationic cyclization

reaction has become a more versatile and efficient synthetic tool finding broad application in the synthesis of many types of cyclic molecules.

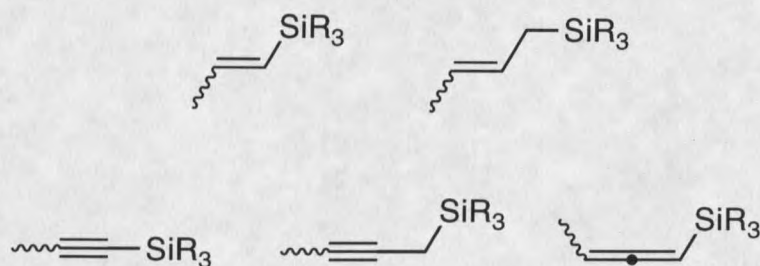


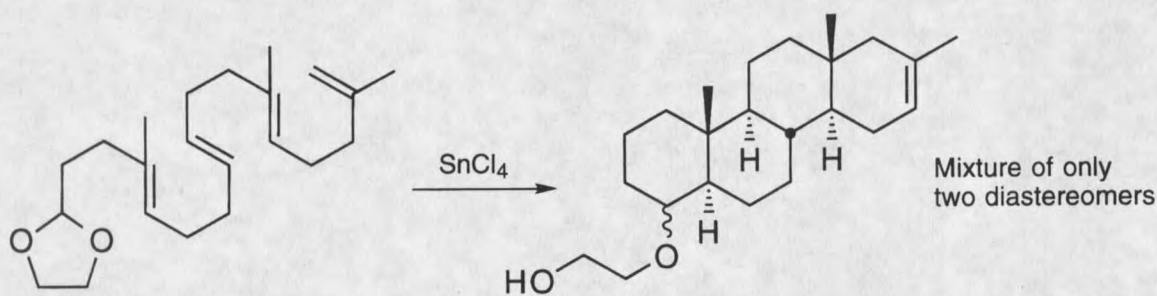
Figure 2. Silicon-Based Terminators

Despite the tremendous amount of development, there is still a strong motivation for continuing the evolution of silicon-directed cyclizations. The standards of modern synthetic chemistry demand not only regioselectivity but diastereo- and enantioselectivity from a reaction as well. Polyfunctionalization and sensitive groups in substrates also renders the need for terminators that engage under mild conditions. Ultimately, practical and concise syntheses of molecular targets of high topological complexity might be realized using silicon based terminators with the ability to direct not just a single cyclization but multi-cyclizations as well. Thus it became the goal of this research to develop a silane terminator that could potentially satisfy these criteria of today's synthetic methods. It was conceived that an allylbis(silane) terminator might meet this challenge and eventually be applicable to the synthesis of polycyclic alkaloids, particularly in the construction of the azatricyclic core of the alkaloid stemofoline (Figure 3).

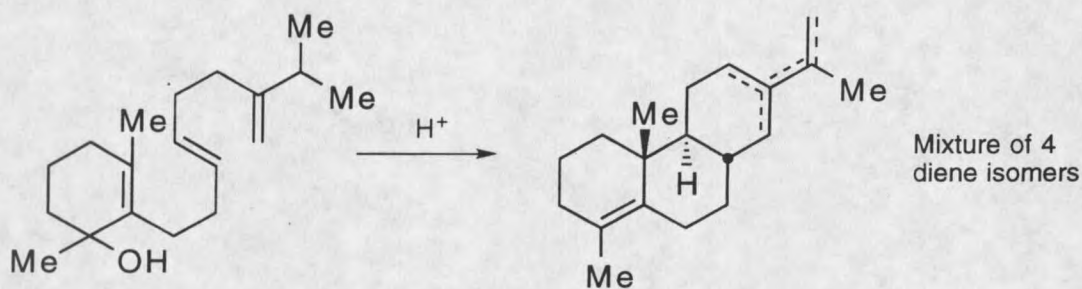
BACKGROUND

Origin of Allylsilane Cyclizations

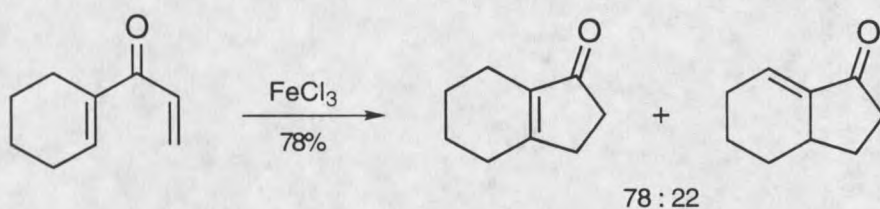
When confronting the task of constructing carbocyclic and heterocyclic systems by means of a cationic approach, chemists must carefully select appropriate functionality by which to successfully initiate and terminate the ring-forming process. In the past, the electrophilic addition of carbonium ions to alkene terminators has been a strategy of amazing success, but also severe limitations. No other work has illustrated the synthetic power of this method more than the pioneering polyene cyclizations of Johnson in which several carbon-carbon bonds are formed with regio- and diastereocontrol (Scheme 2).¹

**Scheme 2**

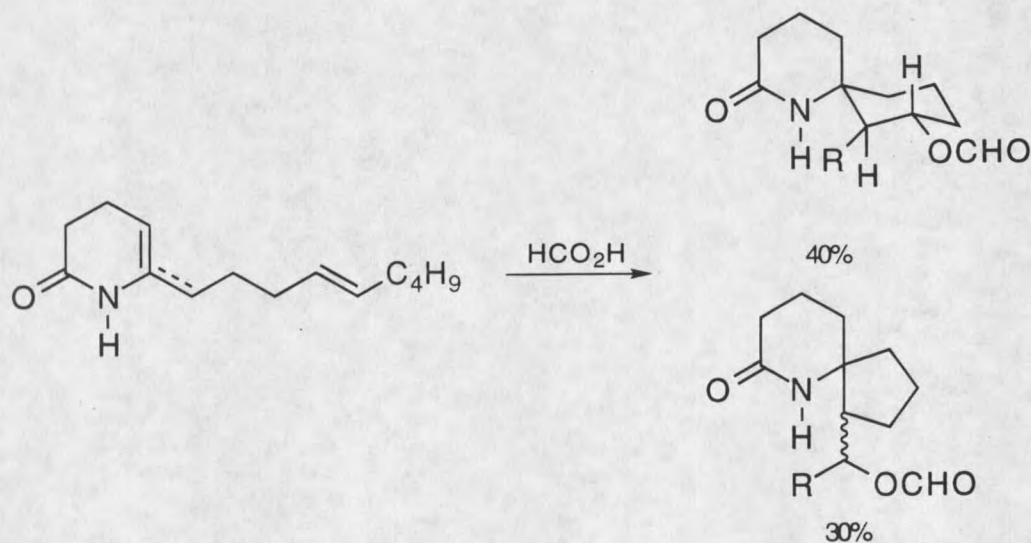
In contrast, Johnson and others have encountered alkene-terminated cyclizations that proceeded in an uncontrolled fashion. This is demonstrated by the polyene cyclization of Scheme 3 in which a mixture of four regiodifferent olefins was isolated.² Regiocontrol problems of this nature have also arisen in numerous related reactions such as Nazarov-type cyclizations³ (Scheme 4) and have severely attenuated this methodology from becoming broad in scope and general applicability despite some impressive examples existing.



Scheme 3



Scheme 4

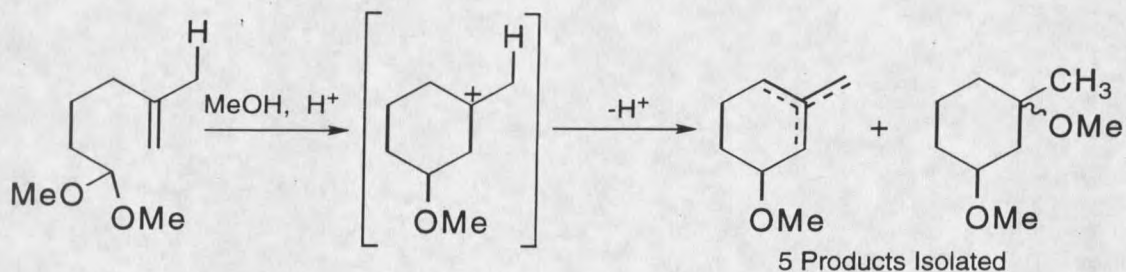


Scheme 5

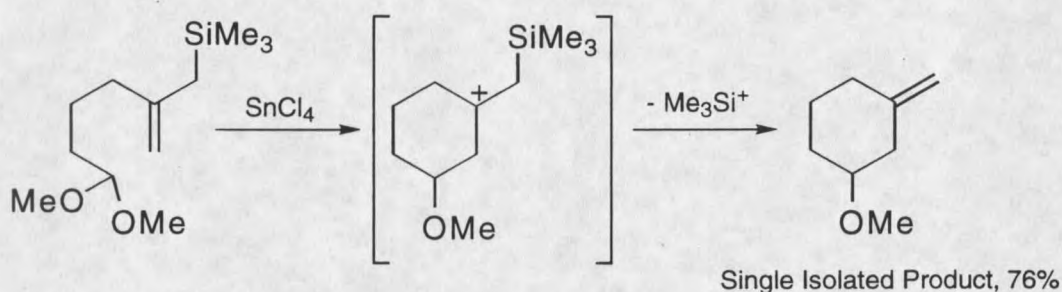
As previously mentioned, a second limitation with alkene-terminated additions is ambiguity in the initial bond formation. For instance, in Evan's formal synthesis of (+)-perhydrohistrionicotoxin,⁴ the key step involved an

acyliminium ion-alkene cyclization that produced almost equal proportions of both the desired six membered cycle and the unwanted five membered spirocycle (Scheme 5). Furthermore, the need for 0.1M formic acid as the solvent to promote this cyclization also presents limited applicability of the reaction to more sensitive substrates.

Fortunately in 1976, Ian Fleming found a means by which total control over alkene-terminated cyclizations could be obtained.⁵ Prior to this original work, the reactivity patterns of intermolecular additions of allyl and propargylic silanes⁶ were known to be regioselective. Fleming realized that such selectivity might also be achieved in the intramolecular mode of reaction. He decided to test this possibility on another troublesome system encountered by Johnson. In the Johnson protocol, a particular oxonium ion-initiated cyclization yielded not only all three possible olefins but products resulting from solvent capture of the carbonium ion as well (Scheme 6).⁷ Fleming circumvented this by inserting a trimethylsilyl group on the appropriate carbon atom of the starting material. The resulting allylsilane-terminated cyclization proceeded with regiospecificity to furnish exclusively the desired product in 76% yield (Scheme 7). Noteworthy is the fact that the cyclization could now be triggered by SnCl₄ rather than the harsher Bronsted acidic medium needed to trigger Johnson's cyclization.

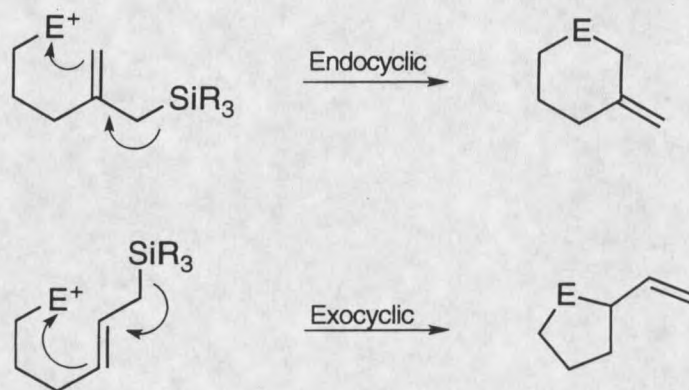


Scheme 6

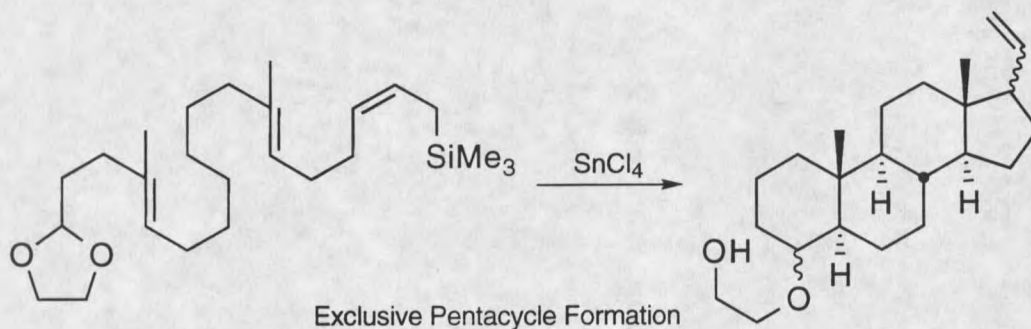


Scheme 7

This work eventually led to the realization that by merely altering the position of the silicon electrofuge, the chemist may select a mode of cyclization that furnishes the desired ring size and olefin location in a completely controlled fashion (Scheme 8). What followed the ground breaking work of Fleming was an immediate extension of the concept to numerous classes of carbonium ion cyclizations. Not surprisingly, an early application was in polyene cyclizations such as that shown in Scheme 9. Note that in contrast to the related reaction of Scheme 2, Johnson was now able to exclusively form five membered rings in these cascade cyclizations by merely adding a trialkyl silane in the appropriate position.⁸ Today this methodology is widely applied to a expansive range of electrophilic additions encompassing many permutations of electrophile type and silicon-based terminators (Figure 2).⁹



Scheme 8



Scheme 9

Mechanistic Features of Allylsilane Terminators

It is clear from the initial studies of Fleming and the volume of allylsilane methodology in general that the silicon atom has a powerful influence on both the alkene reactant and the intermediates formed during the course of the reaction. Hence, from a standpoint of synthetic utility, the significance is twofold. First, the alkene engages regioselectively to give a single addition product which results in the formation of only one of two possible ring sizes.

Secondly, the resulting carbocation eliminates regioselectively to give one olefin upon termination of the reaction.

The issue of regiocontrol in the initial bond forming process may be adequately summarized by the following generalization: allylsilanes will usually react in the manner that results in formation of a cation β to the silicon atom. This phenomenon has been labeled the β effect and is founded on the power of a silicon atom to stabilize an adjacent positive charge via overlap of the silicon-carbon σ bond with the vacant p orbital (Figure 4).¹⁰ The origins of such strong hyperconjugation lies in the polarizability of the silicon-carbon bond. The high electronegativity of carbon (2.35) relative to silicon (1.64) induces a stronger hyperconjugative effect than that capable of alkyl groups or hydrogens. The degree of stabilization is quite high. For instance the silylethyl cation is calculated to be 38 kcal mol⁻¹ more stable than the comparative ethyl cation.¹¹ Studies towards a quantitative determination of this β effect have been examined.¹² It is also believed that cations α to silicon are relatively destabilized, an influence that also undoubtedly contributes to the regioselective nature of allylsilanes.

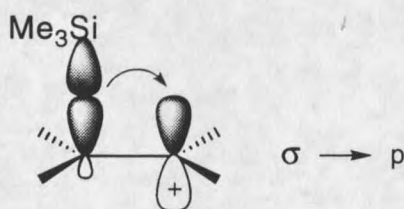
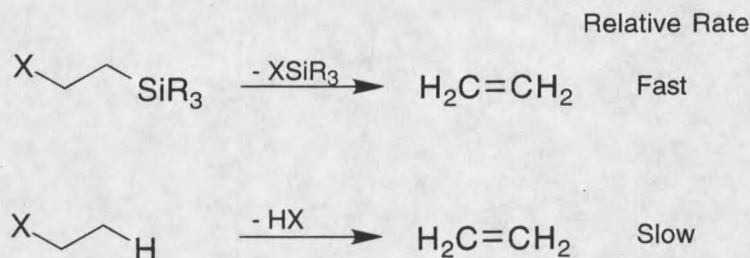


Figure 4. The β Effect

Historically, the consequences of the β effect were first observed in 1973 by Ushakov and Itenburg who discovered that eliminations of halogen alkylsilanes were particularly rapid (Scheme 10).¹³ Allylsilanes were observed

to undergo facile electrophilic attack as early as 1948 (Scheme 11).¹⁴ It was early findings such as these that initiated the development of intermolecular and eventually intramolecular application of allylsilanes and related terminators (Figure 2).^{6,9}



Scheme 10



Scheme 11

The tendency of the allylsilane terminator to regioselectively form β silylcations is believed to also be influenced from the reactant side of the reaction coordinate. There is evidence for ground state polarization of the reactive HOMO of the allylsilane. In the hydroboration of allylic silanes, a concerted process affected by ground state conditions more than product stability¹⁵, the boron resides predominately on the C-3 carbon of the silane (Figure 5).¹⁶ Other noncationic reactions, such as cycloadditions,¹⁷ show strong regioselectivity in the same sense. This data points to the C-3 carbon as the site of nucleophilicity of ground state allylsilanes. Nevertheless, regardless of ground state or thermodynamic considerations, the general rule of the β effect

usually predicts the regiochemical outcome of electrophilic additions to allylsilanes.

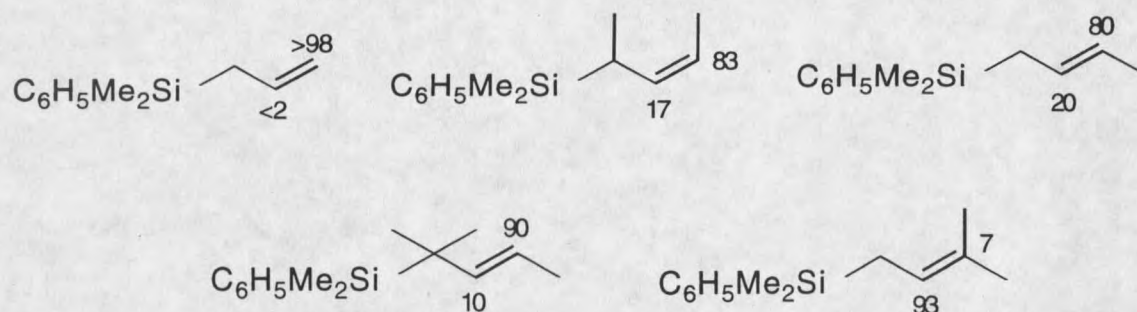
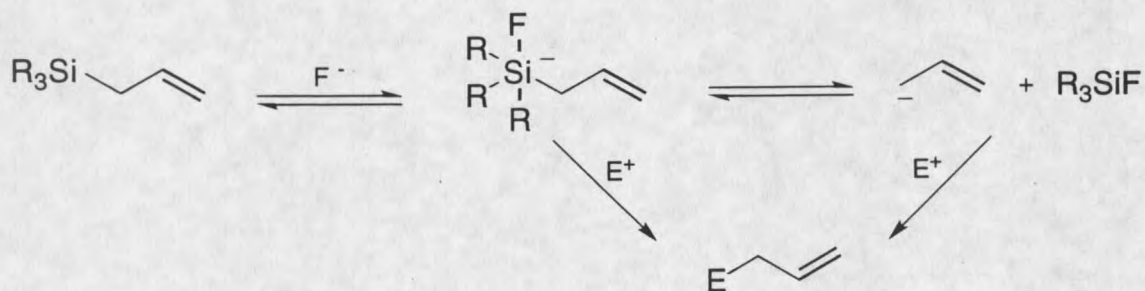


Figure 5. Sites of Boronation in Allylsilanes

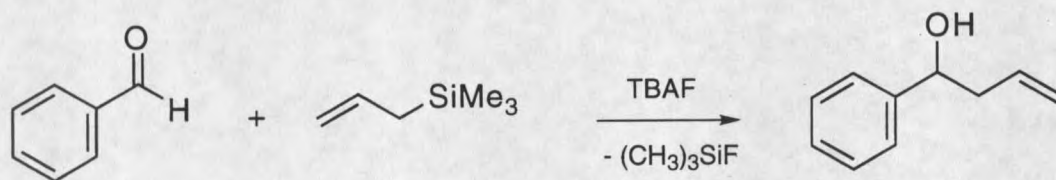
The issue of specific collapse of the initially formed silicon-stabilized carbocation is more simply addressed. By virtue of the strong hyperconjugation present in the β cation, the carbon-silicon bond is very polarized and weakened. Thus the β -silicon electrofuge is typically cleaved more rapidly than β hydrogens and also more rapidly than nucleophilic capture of the cation (Schemes 6 and 7). The relative thermodynamic stability of β silyl cations, unlike conventional primary and secondary carbocations, retards the termination against hydride shifts and Wagner Meerwein rearrangements. These features combined with the control devices focused on previously are the primary reasons behind the capacity of the allylsilane terminator to funnel a cyclization along a single reaction pathway in route to a single, predictable product.

This mechanistic analysis of the regioselectivity of the allylsilane is based on a pathway involving addition of a highly electron deficient atom to a neutral allylsilane receptor. There are however certain instances when a nucleophile may activate the allylsilane triggering an anionic pathway. The

most commonly applied nucleophilic catalyst is tetrabutyl ammonium fluoride (TBAF) which is a soluble source of fluoride anions. Fluoride anions rapidly attack allylic silanes, by virtue of the extremely strong silicon-fluorine bond (135 kcal/mol), to form pentavalent silicon anions which may also collapse into discrete allylanions (Scheme 12).¹⁸ It is uncertain as to which species is the reactive nucleophile but whether it be the electron rich pentavalent allylsilane or an actual allylanion, there is clearly an acceleration in the rate of addition. For example, the TBAF promoted addition of trimethylallylsilane to benzaldehyde proceeds without the usual lewis acid activation of the aldehyde (Scheme 13).¹⁹ Although the regioselectivity is generally lower for fluoride-initiated reactions, which suggests an ambiguous allylanion intermediate, this method does provide the chemist with alternative reaction conditions.



Scheme 12



Scheme 13

One final characteristic of silanes in general²⁰ should be revealed. This is the ability of a trialkylsilicon group to stabilize an adjacent negative charge, a phenomenon sometimes called the α effect. It is believed that such stabilization arises from either overlap between the σ orbital of the anion and the σ^* orbital of the C-Si bond or delocalization of the negative charge into the vacant, low energy 3d orbitals of the silicon atom (Figure 6).²¹ Although not a crucial point to the cationic cyclization itself, this feature has been exploited to assist in the synthesis of cyclization substrates. Silicon stabilized organometallic reagents such as Grignards, organozincs and cuprates²² have been applied to efficient syntheses of allylsilane substrates as have α silylvinyl anions generated by silicon directed hydroaluminations²³ or cuprate additions²⁴ to silyl acetylenes.

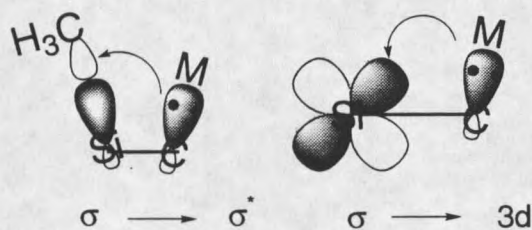


Figure 6. The α Effect

Allylsilane Terminated-Azacation Cyclizations

One of the fundamental goals of this research project was to exploit the useful chemistry of the allylsilane nucleophile in the synthesis of polycyclic alkaloids (Figure 3). Such nitrogenous compounds are one of the classes of natural products most frequently targeted for total synthesis. This is attributed to the strong pharmacological and physiological properties of many alkaloids which render them or derivatives of them potential candidates for

pharmaceutical use. As with most natural products and drugs, the majority of alkaloids are cyclic or polycyclic in structure.²⁵ Familiar examples include codeine, quinine, lysergic acid diethylamide (Figure 7) and strychnine (Figure 1).



Figure 7. Biologically Active, Polycyclic Alkaloids

When considering the synthesis of polycyclic alkaloids, allylsilane terminated cyclizations present an attractive means by which to construct strategic bonds²⁶ within the cyclic framework. If a cationic approach is to be applied, cyclization initiators which contain a nitrogen atom are obviously necessary. Proven well suitable for this role are iminium ions²⁷, their N-acyl²⁸ and C-acyl²⁹ variants as well as nitrilium ions³⁰ (Figure 8). By the location of the nitrogen adjacent to the cationic center, these initiators benefit from stability imparted by resonance. Hence, such nitrogen stabilized cations are relatively easier to generate and also are less prone to rearrangements and migrations than conventional carbonium ions. These features make iminium and related

ions practical choices for initiators when preparing nitrogen heterocycles by allylsilane-terminated cyclizations.

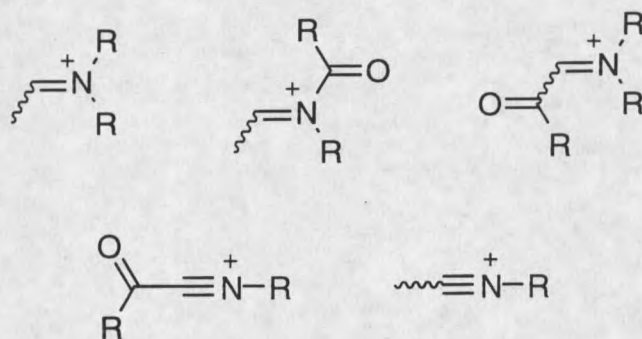
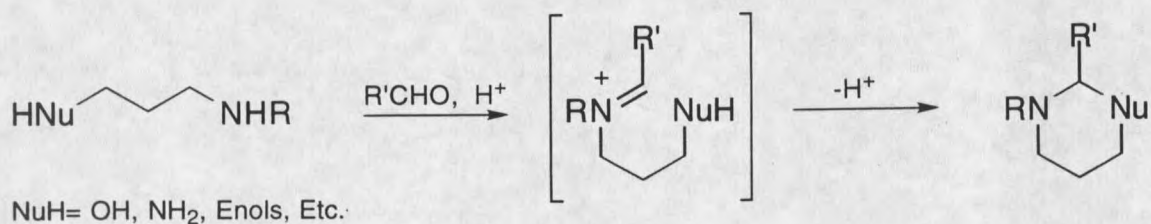


Figure 8. Nitrogenous Cationic Initiators

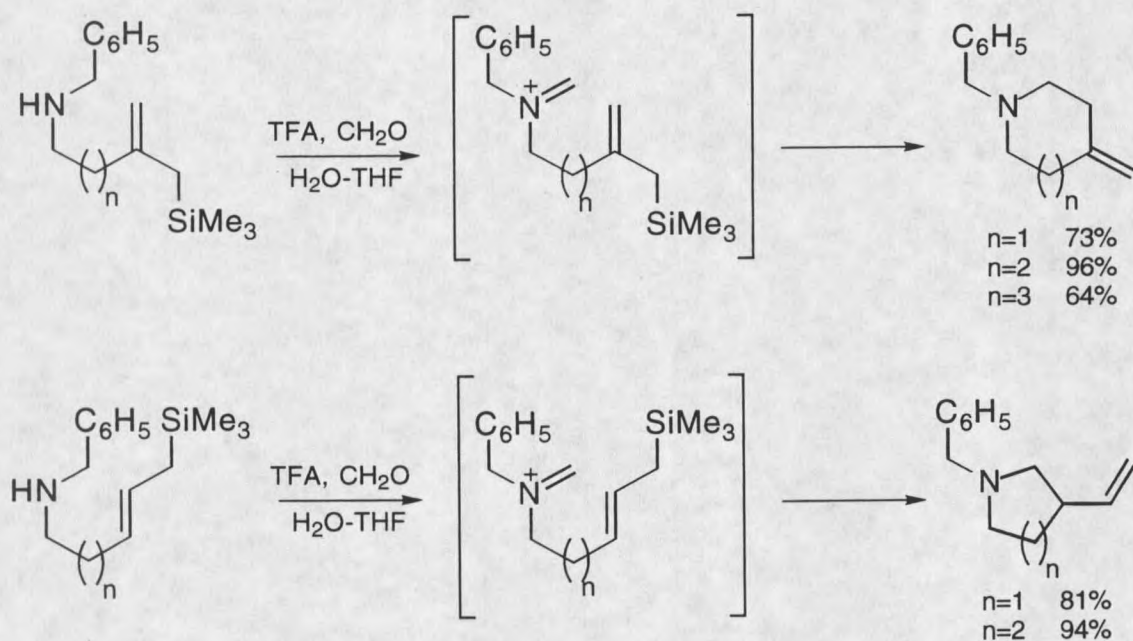
The classical application of iminium ions in cyclization reactions has been the Mannich cyclization.³¹ These reactions involve the use of heteroatom or enol nucleophiles and represent an important early method for the construction of nitrogen heterocycles (Scheme 14). Although Mannich cyclizations have been employed for over 70 years, the progression towards applying tethered allylsilanes did not occur until the mid 1980s.



Scheme 14

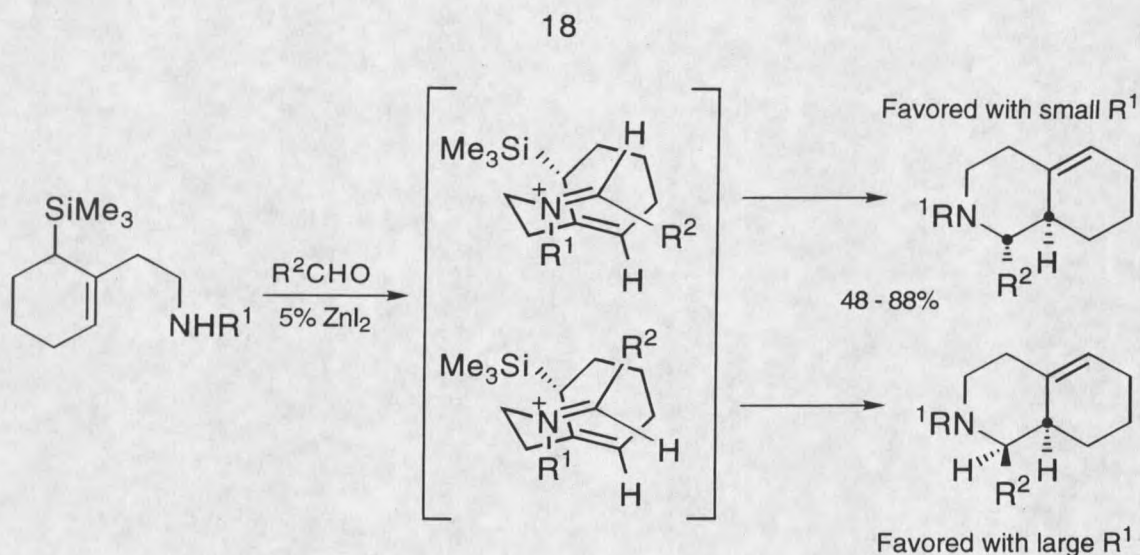
Ten years after the first allylsilane cyclization of Fleming, Grieco successfully utilized Mannich type conditions in the intramolecular capture of iminium ions by allylsilanes. In these reactions, allylsilane ammonium salts

were treated with aldehydes under aqueous conditions resulting in the regiocontrolled formation of not just five membered but six, seven and even eight membered heterocycles (Scheme 15).³² Moreover, despite the acidic Mannich type conditions used to generate the iminium ions, protodesilylation of the allylsilane was not a competitive process.



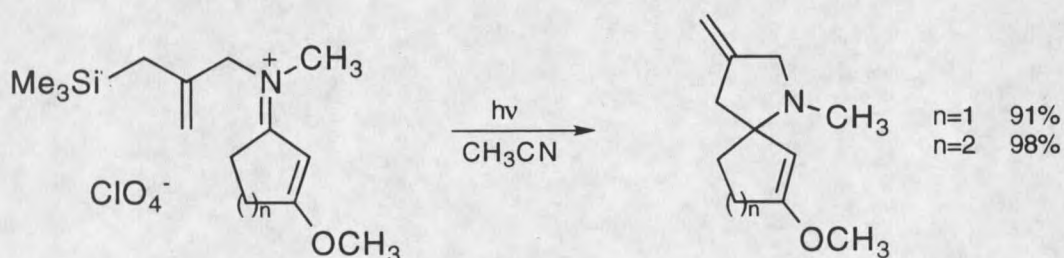
Scheme 15

More recently, Overman has extended this reaction to the stereocontrolled synthesis of *cis* and *trans* hydroquinolines³³, a structure found in many alkaloid subclasses. This flexible method presents the option of selectively forming either the *cis* or *trans* diastereomer by merely altering the steric size of the amine substituent (Scheme 16). The mild conditions (cat. ZnI₂) used in forming the requisite iminium ions provides additional attractiveness to this protocol.



Scheme 16

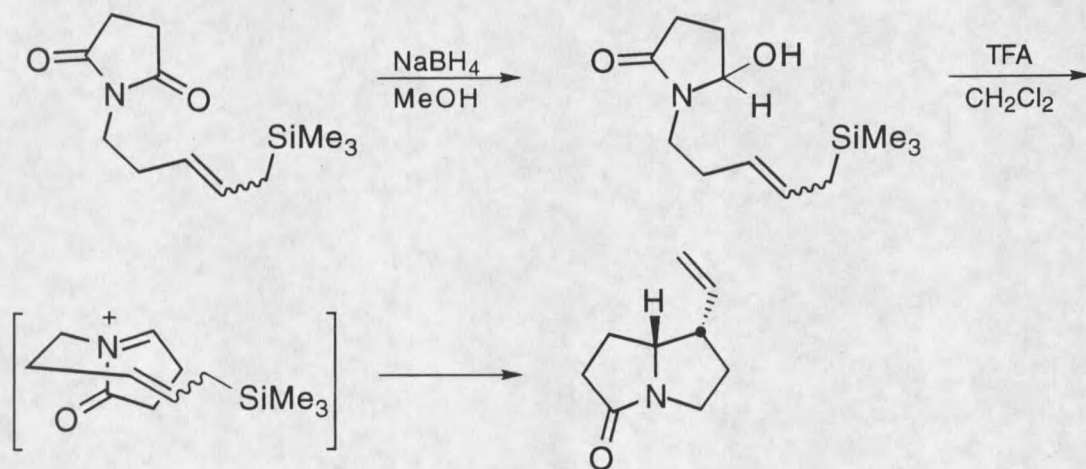
Although the most frequently employed, cationic routes such as Mannich type reactions are not the exclusive method for initiating iminium ion cyclizations. Thermally stable iminium salts such as conjugated perchlorate derivatives have been activated photochemically in order to promote the desilylative ring closure (Scheme 17). These novel photochemical cyclizations have been in large developed by Mariano³⁴ and provide alternative reaction conditions. Unfortunately, with the exception of the example in Scheme 17, the chemical yields are commonly low for such processes.



Scheme 17

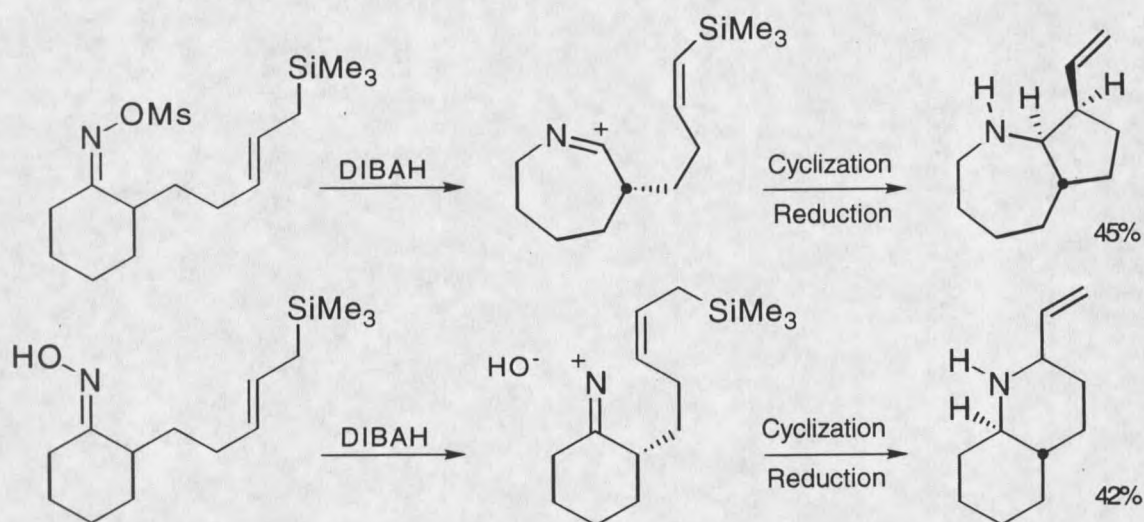
In contrast to iminium ions derived from basic allylsilane amines and aldehydes³², the N-acyliminium ion²⁸ has received considerably more use in allylsilane cyclizations. This is likely due to the numerous methods available for generation of such ions, the greater reactivity over iminium ions and the functionality value of the carbonyl substituent.

The primary chemists behind the development of N-acyliminium ion-allylsilane additions which occurred in the mid 1980s were Speckamp and Hiemstra.³⁵ Scheme 18 depicts one of their earliest results. The synthetic power of this cyclization reaction lies not only in the high yields but the ability to form numerous ring sizes with complete regio- and stereocontrol regardless of the geometry of the allylsilane substituent. For the case illustrated, the observed diastereochemical outcome is thought to be the result of an equatorial alignment of the allylsilane unit in a chair-like transition state. Another important feature is the formation of requisite acyliminium intermediates from a cyclic imide by a partial reduction-elimination sequence. This simple procedure has become the method of choice in numerous total syntheses.



Scheme 18

To our knowledge, there has been only one account of an allylsilane-nitrilium ion cyclization and no examples of analogous C-acylnitrilium ion cyclizations. Schinzer has recently reported that nitrilium ions formed by way of a Beckman rearrangement are effectively trapped by tethered allylsilanes (Scheme 19).³⁶



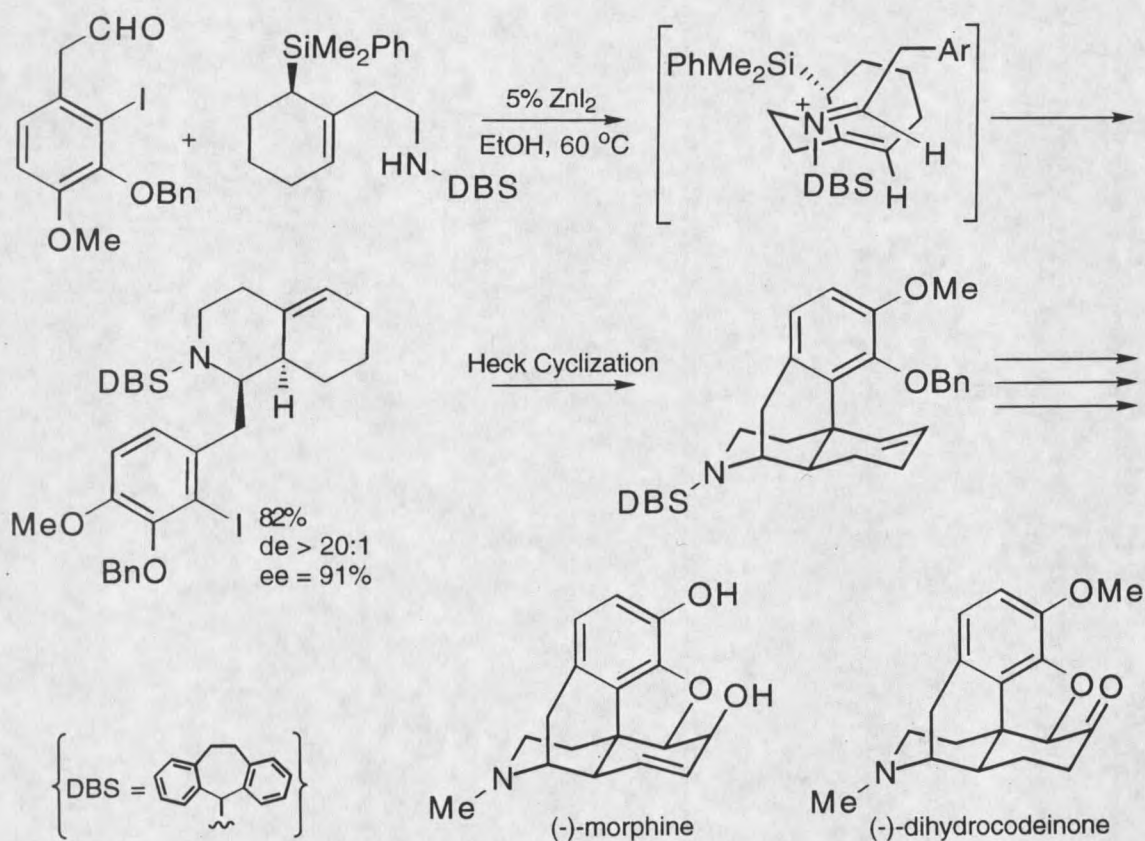
Scheme 19

Diisobutylaluminum hydride was used as a Lewis acid to promote the Beckman rearrangement and as a reductant of the intermediate bicyclic imine.

Interestingly, the reaction mode of the allylsilane terminator was found to be quite dependent on the configuration of the starting oxime. If the E isomer was employed, cyclization occurred onto the electron deficient nitrogen faster than the Beckman rearrangement. Such allylsilane reactivity was previously unprecedented.

Application to Total Synthesis of Alkaloids

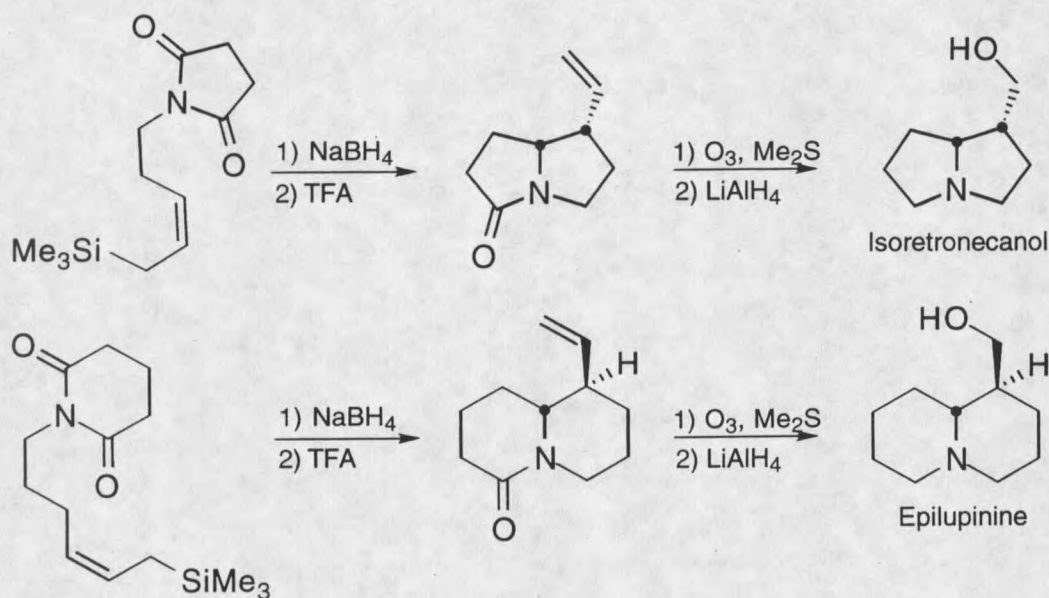
The successful total synthesis of a natural product offers the ultimate arena in which to test the applicability and practicality of reaction methodologies. In the past two decades the cyclizations of allylsilanes onto iminium ions such as those previously described have served as efficient key steps in several syntheses of polycyclic alkaloids. A premier example is the total synthesis of both antipodes of the opium alkaloids morphine and dihydrocodeinone executed by the Overman group in 1993 (Scheme 20).³⁷ In the synthetic sequence the central step involved application of the diastereoselective synthesis of cis and trans hydroisoquinolines previously developed by Overman (Scheme 16). In this instance the large DBS amine protecting group was used in the iminium ion-allylsilane cyclization to promote the trans configuration present in the natural target molecules. The process occurred with high diastereoselection (>20:1.0), high enantioselection (91% ee) and in high chemical yield (82%). An intramolecular Heck cyclization then furnished the common pentacyclic intermediate used to prepare both of these opiates. The absolute chirality of the products was introduced in the preparation of the requisite allylsilane amine by an enantioselective reduction. This was carried out in 96% ee and enabled the preparation both enantiomeric substrates whose absolute configuration was preserved with high stereofidelity throughout the key sequence.



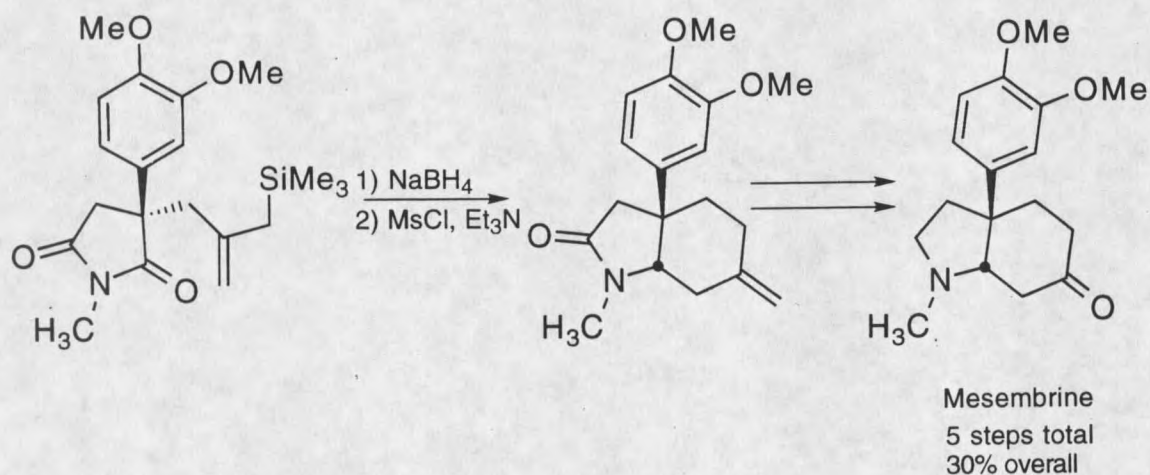
Scheme 20

The allylsilane - N-acyliminium ion cyclization protocol has been particularly successful in the synthesis of indolizidine, quinolizidine and pyrrolizidine alkaloids. Pertaining to the latter two classes, Speckamp and Hiemstra in 1985 exercised identical synthetic strategies for the stereoselective synthesis of both (\pm)-isoretronecanol and (\pm)-epilupinine (Scheme 21).³⁵ A similar but improved route was used by Gramain and Remuion in a very concise and efficient synthesis of the indolizidine alkaloid (\pm)-mesembrine (Scheme 22).³⁸ The synthetic series was carried out in five linear steps with an overall yield of 30%. Highlighting the scheme was the nonacidic medium (MsCl, Et₃N, CH₂Cl₂) in which the key allylsilane-acyliminium ion cyclization was executed

thus providing improved, milder conditions than those previously used by Speckamp and Hiemstra (trifluoroacetic or formic acid).³⁵



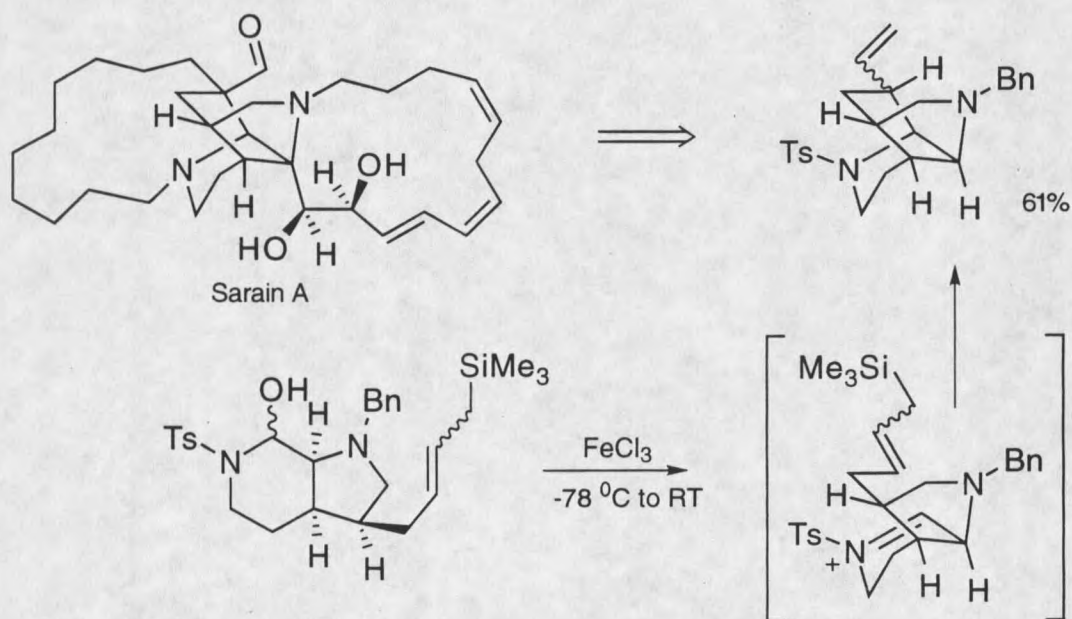
Scheme 21



Scheme 22

A final example illustrates the construction of polycyclic alkaloids possessing topological complexity. In 1993 progress was made towards the

synthesis of the unusual marine alkaloid sarain A. In this publication, Weinreb utilized a novel N-tosyliminium ion-allylsilane cyclization to complete the synthesis of the tricyclic nucleus of sarain A (Scheme 23).³⁹ Despite the key cyclization proceeding in 61% yield, this approach suffers from the long linear sequence of over ten steps used to prepare the bicyclic precursor. Nevertheless, the synthetic scheme does reveal the potential of allylsilanes to form strategic bonds in complex molecular systems.



Scheme 23

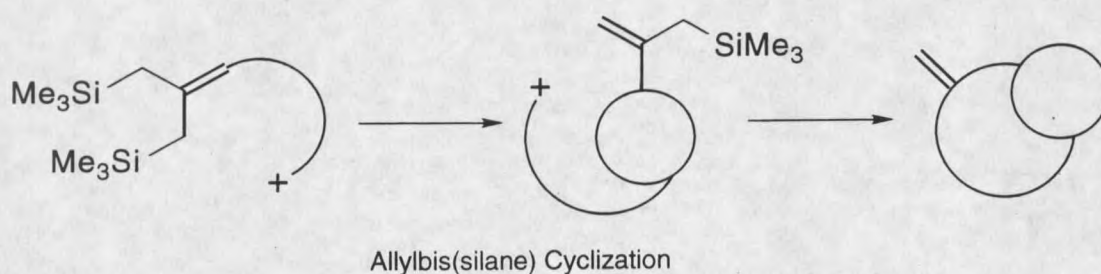
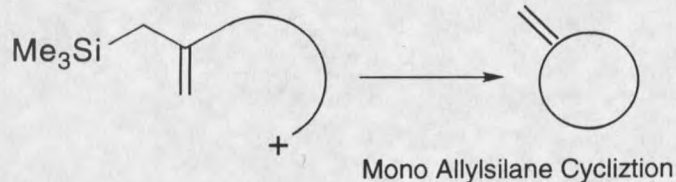
These are the most recent and efficient examples of the synthetic usefulness of allylsilane-terminated cyclizations from a standpoint of alkaloid synthesis, an area of high relevance to this dissertation. Clearly shown in all cases is the regioselective nature of the cyclization processes and for the most part, the diastereoselective capabilities as well. Such high levels of substrate-based diastereocontrol were able to be found only in isolated instances such as

these examples. Despite the past and ongoing research activity in this area, there still exists a need for achieving general and consistent levels of high diastereocontrol in the addition of allylsilanes and related pi-nucleophiles to carbon centered electrophiles.

Electrophilic Additions to Allylbis(silanes)

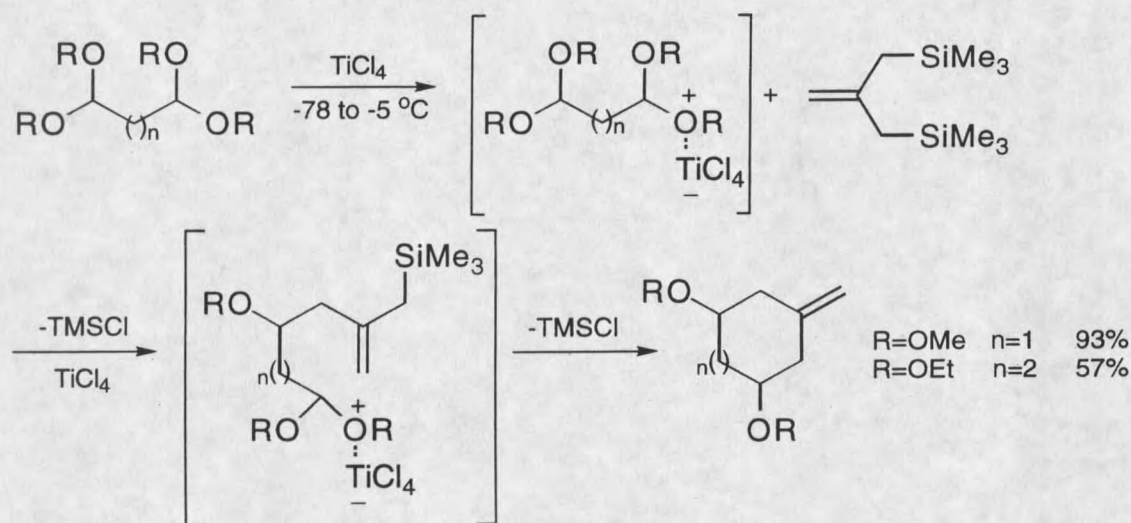
A fundamental limitation that lies within the silicon-based pi-nucleophiles currently available to the synthetic chemist is the attachment of a single electrofugal silane group. As a result, only one directed cyclization is possible. If sequential electrophilic additions are desired in a synthetic plan, those occurring after the initial silicon-controlled reaction would have to be carried out with a conventional pi-nucleophile and would be prone to the regiocontrol problems previously addressed.

An obvious advancement, particularly in the broad field of allylsilane chemistry, would be to efficiently prepare and utilize an allylbis(silane) nucleophile. Such an olefin could be apt to participate in tandem silicon-directed electrophilic additions. Ultimately, an allyl(bis)silane terminator could theoretically enable the efficient construction of polycyclic skeletons (Scheme 24). If used in conjunction with nitrogenous initiators, this concept might be ideally suited for the regio- and stereocontrolled synthesis of polycyclic alkaloids.



Scheme 24

At the onset of this research there were surprisingly no reported examples of cyclizations terminated by a 2-propylidene-1,3-bis(silane). In fact, prior to this dissertation there was only one account of this nucleophile used in electrophilic addition reactions. Recently, Guyot and Miginiac demonstrated that 2-trimethylsilyl allyltrimethylsilane could participate in tandem intermolecular-intramolecular additions to bifunctional electrophiles.⁴⁰ It was observed that exposure of this allylbis(silane) to bis-acetals in the presence of TiCl_4 resulted in the formation of methylene cycloalkanes. This process was proposed to occur by way of an initial intermolecular allylbis(silane)-oxonium ion addition followed by intramolecular capture of a second oxonium ion by the remaining mono allylsilane (Scheme 25).

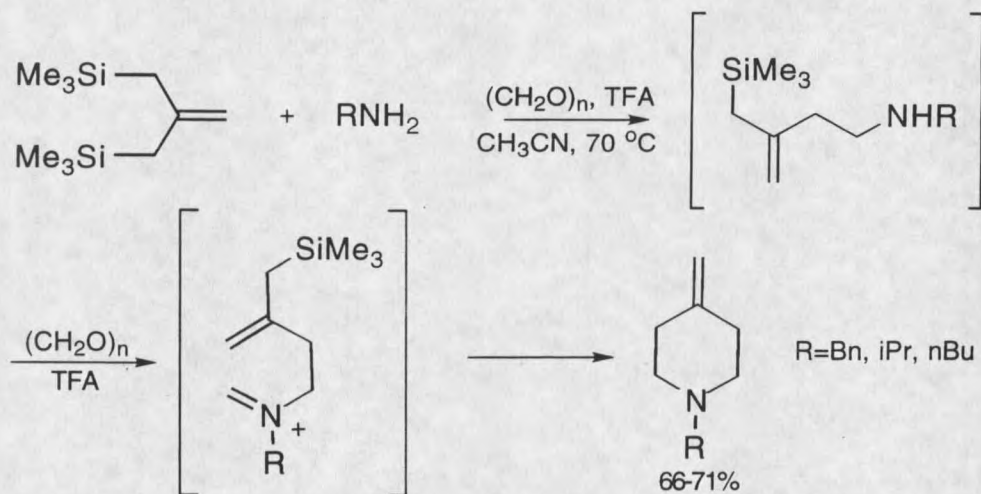


Scheme 25

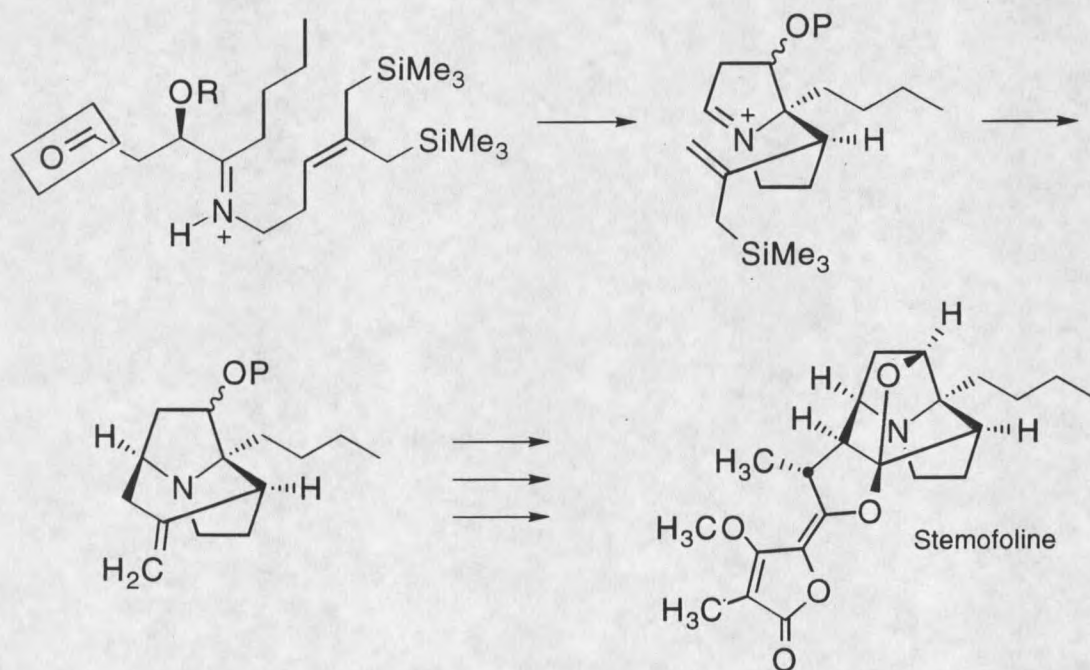
In an analogous reaction, the same allylbis(silane) nucleophile underwent a Mannich type addition-cyclization upon treatment with paraformaldehyde and primary amines in acidic media (Scheme 26).⁴⁰ Methylene substituted piperidines were obtained in good yield via a reaction pathway believed to involve initial intermolecular iminium ion capture followed by subsequent allylsilane cyclization onto a second iminium ion.

Even though these reactions of Guyot and Miginiac occur in good yield and constitute the first electrophilic additions to an allylbis(silane), the protocol was not expanded to the synthesis of more complex and useful systems. As a result the impetus for this doctoral research became twofold. First, the synthetic potential of allylbis(silane) nucleophile has been relatively uninvestigated. Hence it was deemed crucial to explore its role as a cyclization terminator capable of directing two intramolecular reactions. Secondly, stereoselective cyclizations onto iminium ions would provide an ideal area in which to apply this new silicon terminator. More explicitly, the aza tricyclic core

of the potent natural insecticide stemofoline might succumb to efficient total synthesis by utilizing tandem regio- and stereocontrolled cyclizations mediated by an allylbis(silane) (Scheme 27).



Scheme 26



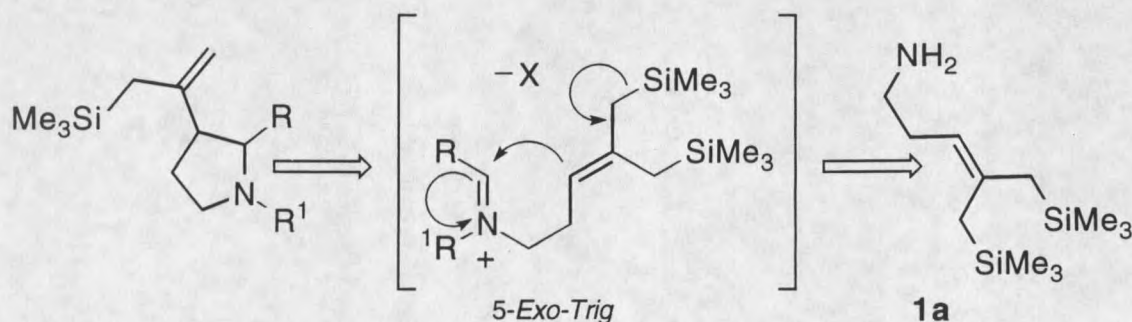
Scheme 27

RESULTS AND DISCUSSION

Synthesis of Aminoallylbis(silanes)

With the focus of this research directed towards the application of a newly developed allylbis(silane) terminator to the construction of cyclic alkaloids, amine **1a** was selected as an initial target for synthesis. It was believed that from this amine, a variety of iminium ion and related initiators could be readily prepared allowing for the proficiency of the allylbis(silane) to behave as a cyclization terminator to be examined (Scheme 28). These cyclization precursors bearing a chain length of five atoms from initiator to terminator would initially form the pyrrolidine ring system upon monocyclization. Such a nucleus is found in many classes of alkaloids including stemofoline.

Cyclization of these substrates would, in theory, occur by way of a 5-*exo-trig* type process which is considered a favorable process when applying the classical rules for ring closure.⁴¹ Numerous accounts of 5-*exo-trig* cyclizations involving monoallylsilanes and iminium ions exist in the past literature.^{9, 32,35} Hence, the feasibility of allylbis(silane) cyclizations originating from amine **1a** was established and a search for a synthetic route to **1a** began.



Scheme 28

