



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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APPROVAL

of a thesis submitted by

Timothy Scott Kercher

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.

4/22/97
Date

Tom Whor
Chairperson, Graduate Committee

Approved for the Major Department

April 24, 1997
Date

David M. Wiles
Head, Major Department

Approved for the College of Graduate Studies

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Date

P. Brown
Graduate Dean

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To all of my wonderful family

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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.

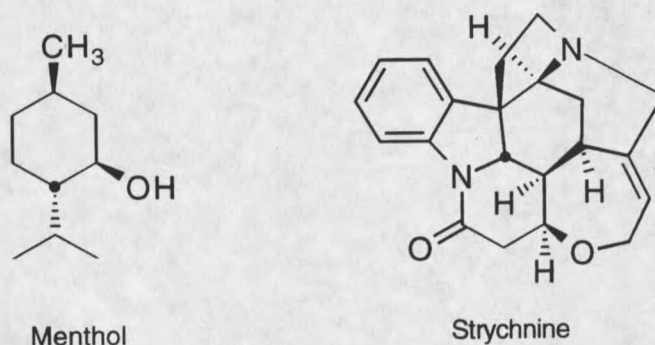
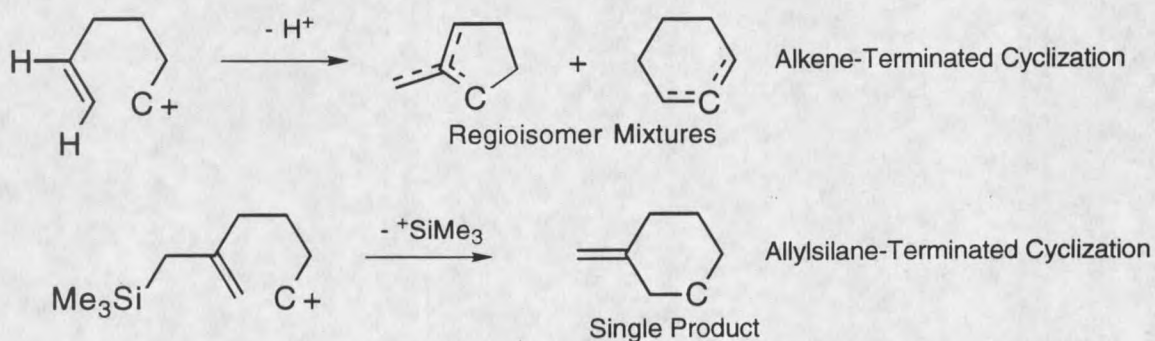


Figure 1. Well Known Cyclic Molecules

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.

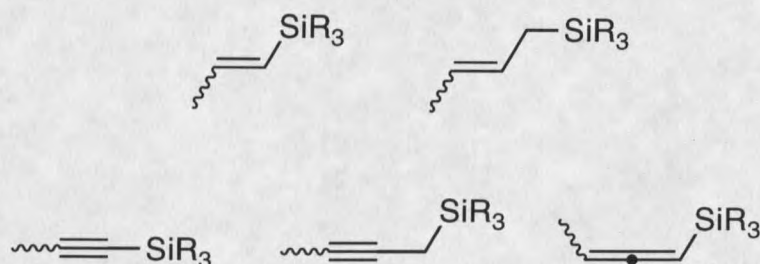


Figure 2. Silicon-Based Terminators

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).

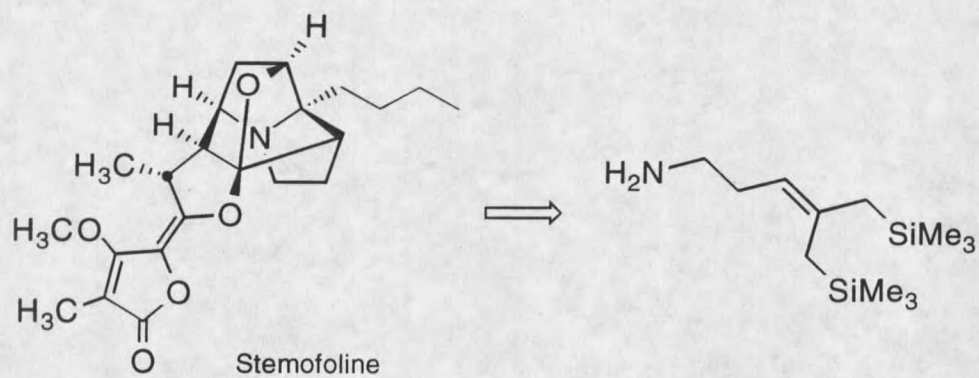
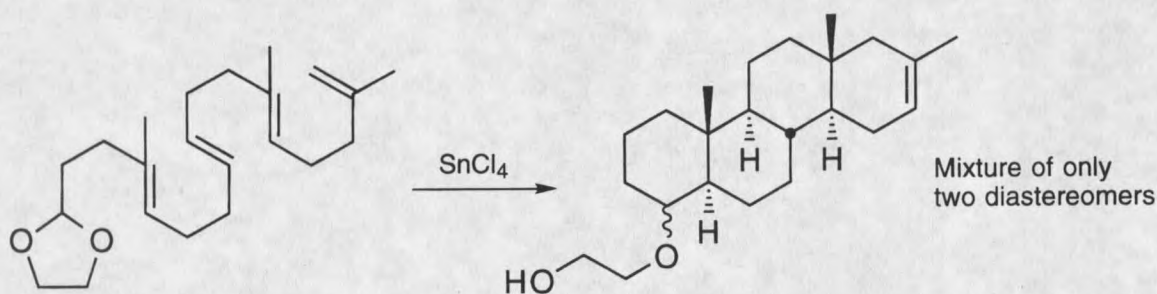


Figure 3. Stemofoline and the Allylbis(silane) Terminator

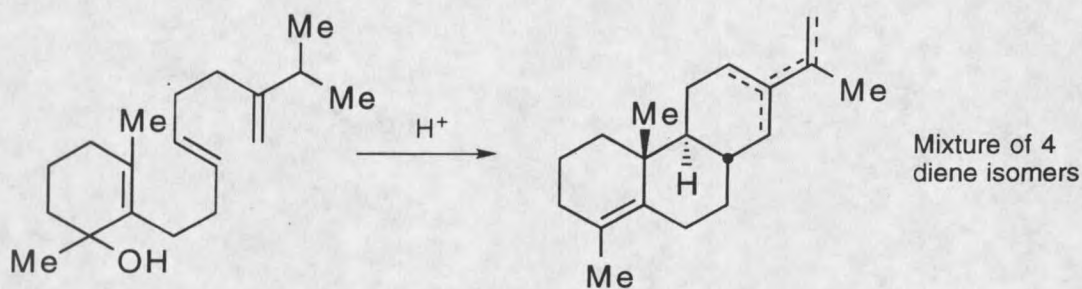
BACKGROUND

Origin of Allylsilane Cyclizations

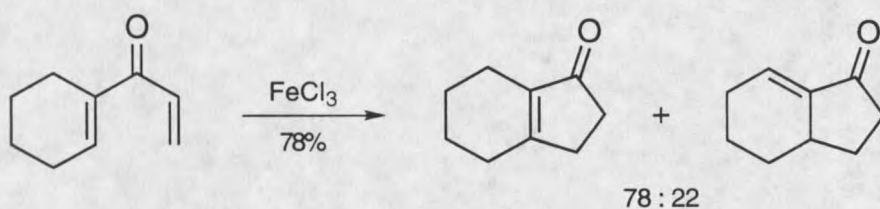
When confronting the task of constructing carbocyclic and heterocyclic systems by means of a cationic approach, chemists must carefully select appropriate functionality by which to successfully initiate and terminate the ring-forming process. In the past, the electrophilic addition of carbonium ions 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**

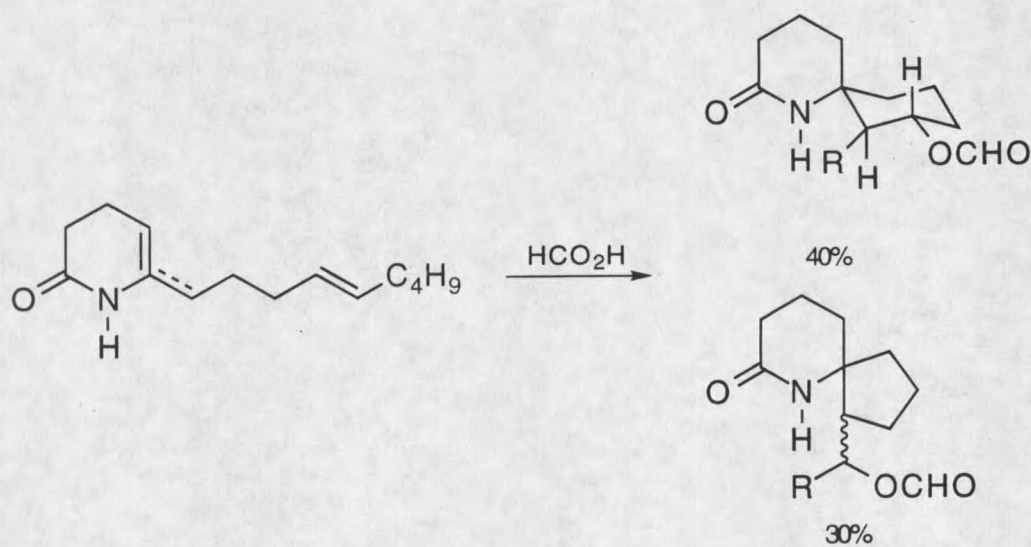
In contrast, Johnson and others have encountered alkene-terminated cyclizations that proceeded in an uncontrolled fashion. This is demonstrated by the polyene cyclization of Scheme 3 in which a mixture of four regiodifferent olefins was isolated.² Regiocontrol problems of this nature have also arisen 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

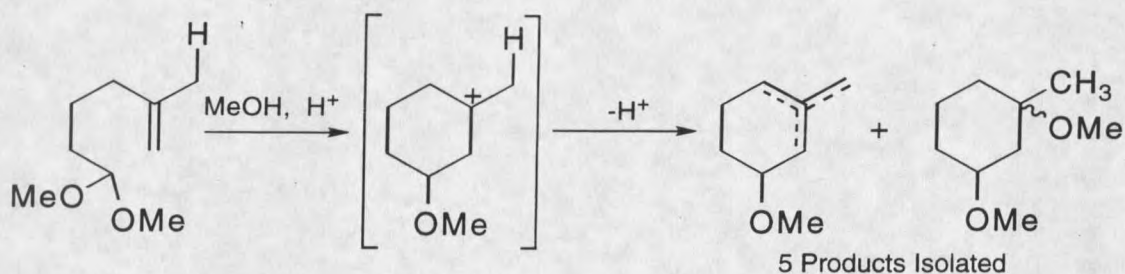


Scheme 5

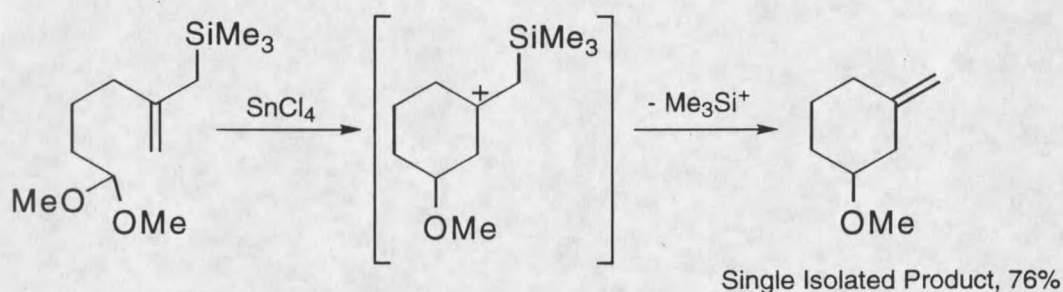
As previously mentioned, a second limitation with alkene-terminated additions is ambiguity in the initial bond formation. For instance, in Evan's formal synthesis of (+)-perhydrohistrionicotoxin,⁴ the key step involved an

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 SnCl_4 rather than the harsher Bronsted acidic medium needed to trigger Johnson's cyclization.

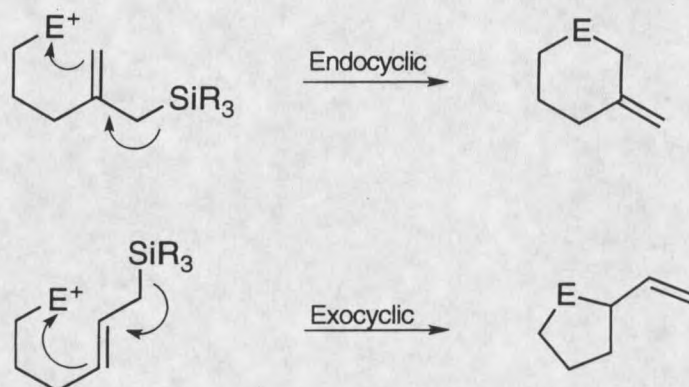


Scheme 6

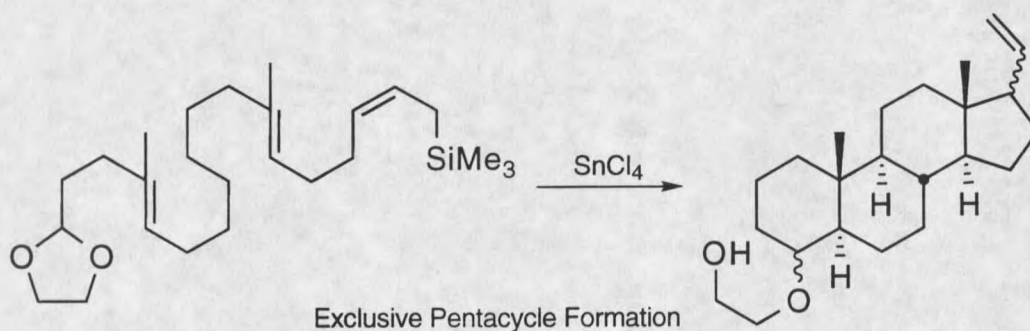


Scheme 7

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.

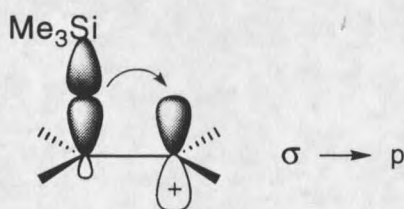
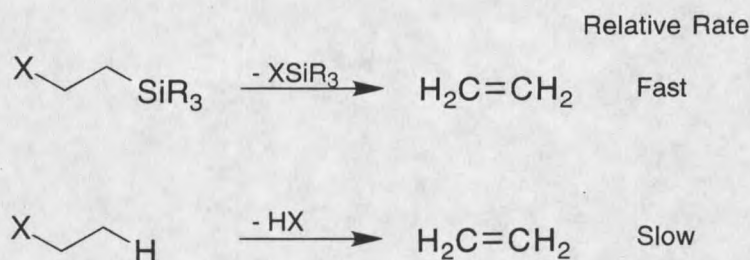


Figure 4. The β Effect

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.

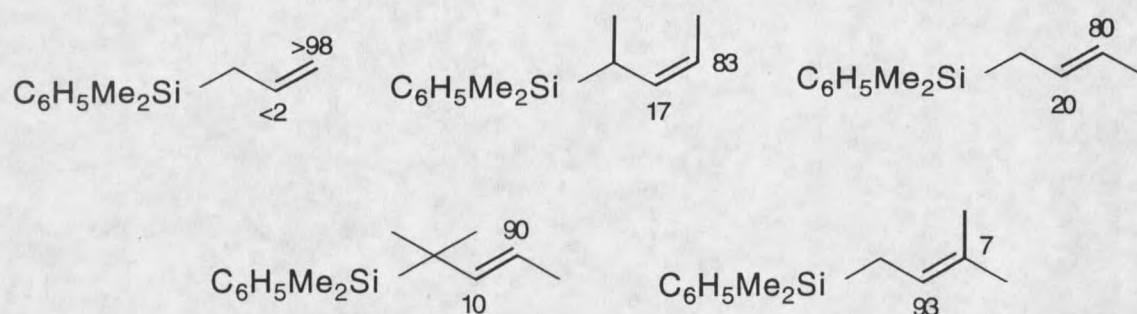
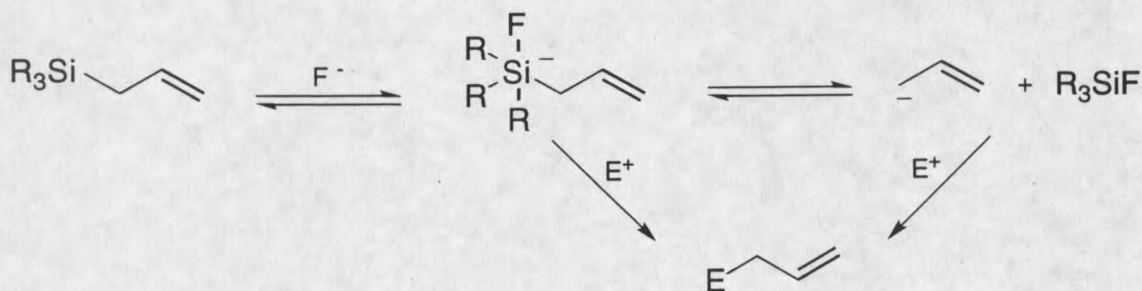


Figure 5. Sites of Boronation in Allylsilanes

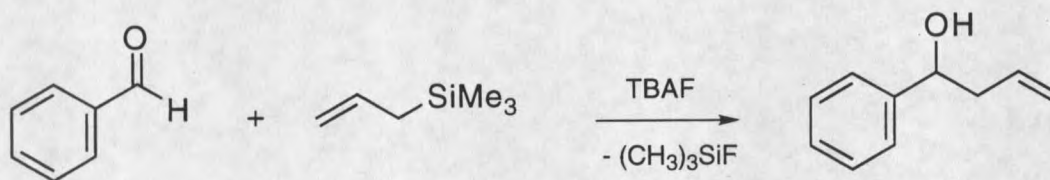
The issue of specific collapse of the initially formed silicon-stabilized carbocation is more simply addressed. By virtue of the strong hyperconjugation present in the β cation, the carbon-silicon bond is very polarized and weakened. Thus the β -silicon electrofuge is typically cleaved more rapidly than 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.

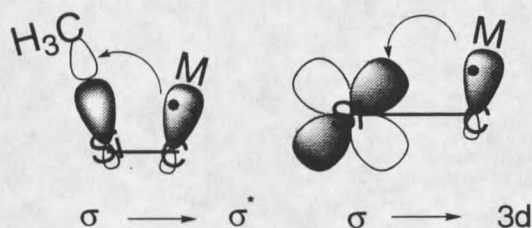


Figure 6. The α Effect

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).

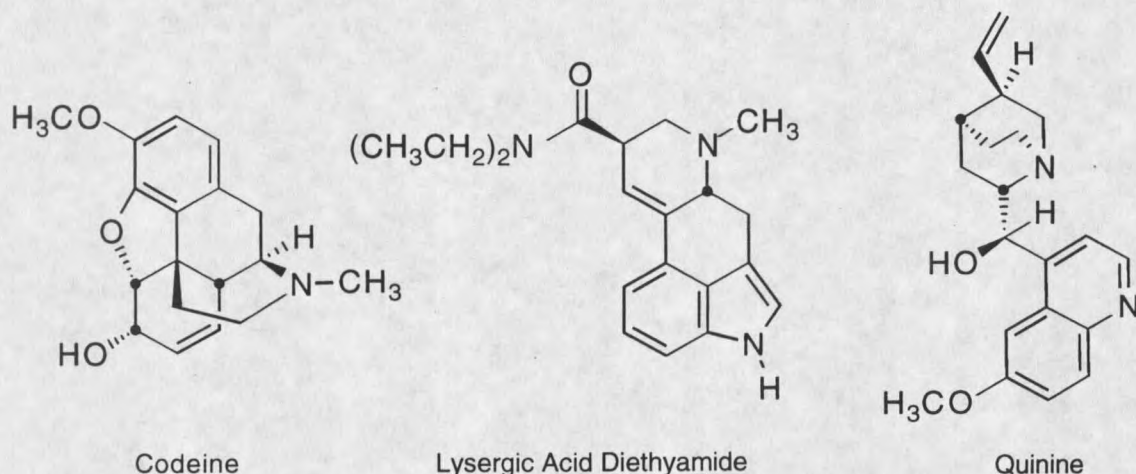


Figure 7. Biologically Active, Polycyclic Alkaloids

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.

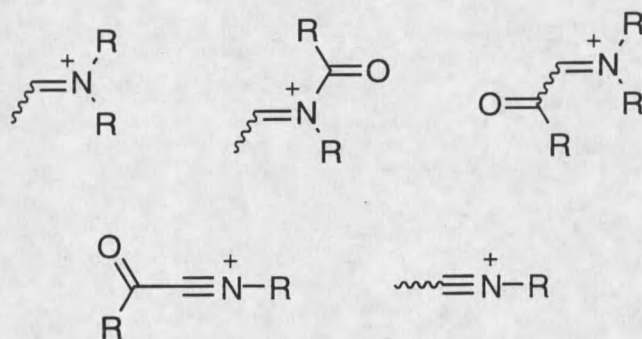
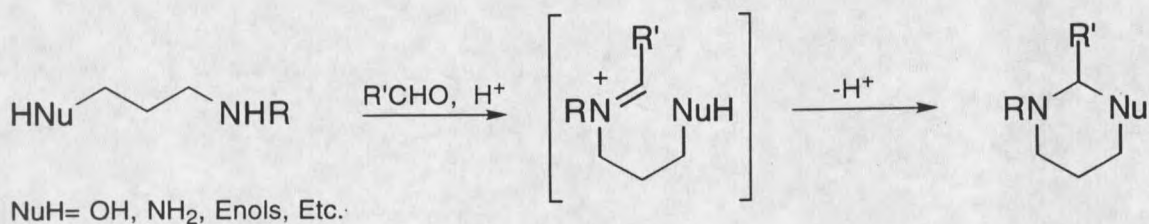


Figure 8. Nitrogenous Cationic Initiators

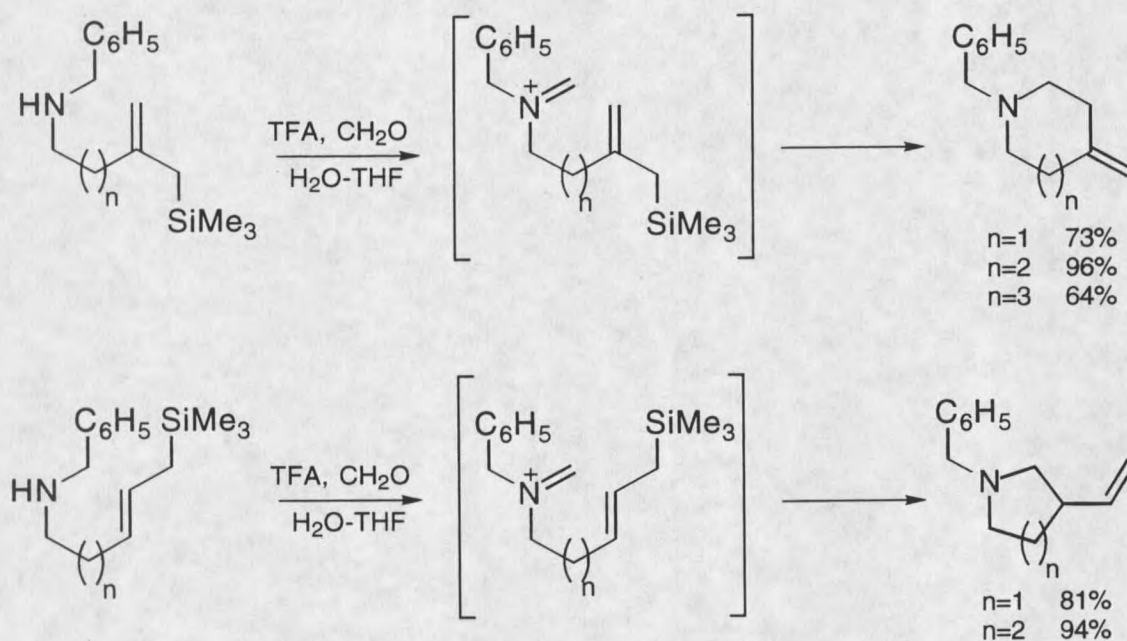
The classical application of iminium ions in cyclization reactions has been the Mannich cyclization.³¹ These reactions involve the use of heteroatom or enol nucleophiles and represent an important early method for the construction of nitrogen heterocycles (Scheme 14). Although Mannich cyclizations have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



Scheme 14

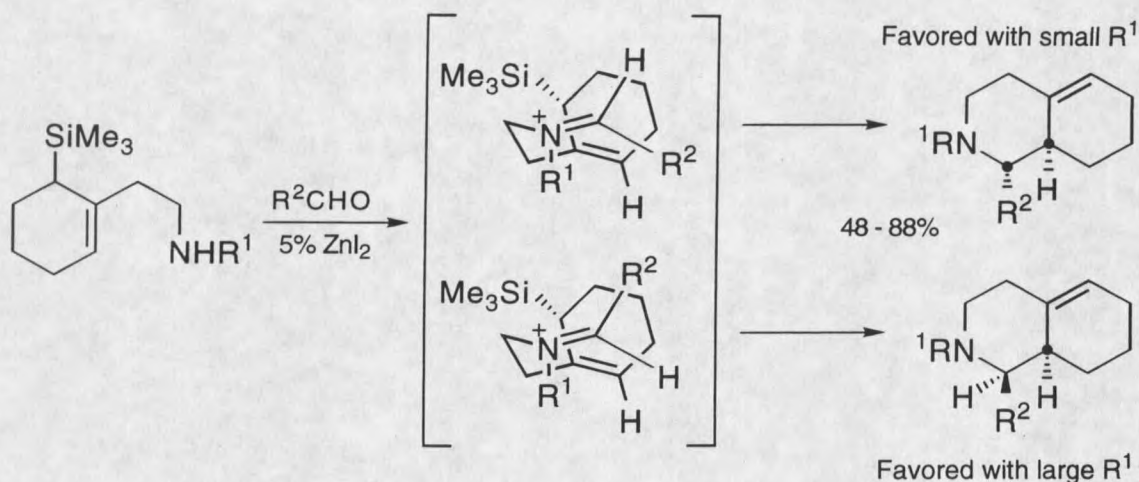
Ten years after the first allylsilane cyclization of Fleming, Grieco successfully utilized Mannich type conditions in the intramolecular capture of iminium ions by allylsilanes. In these reactions, allylsilane ammonium salts

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.



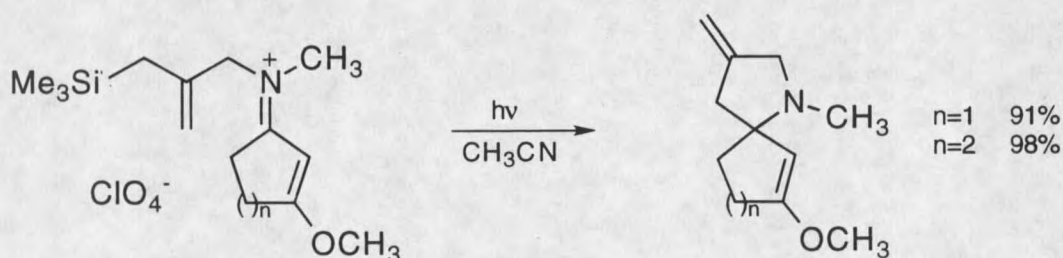
Scheme 15

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

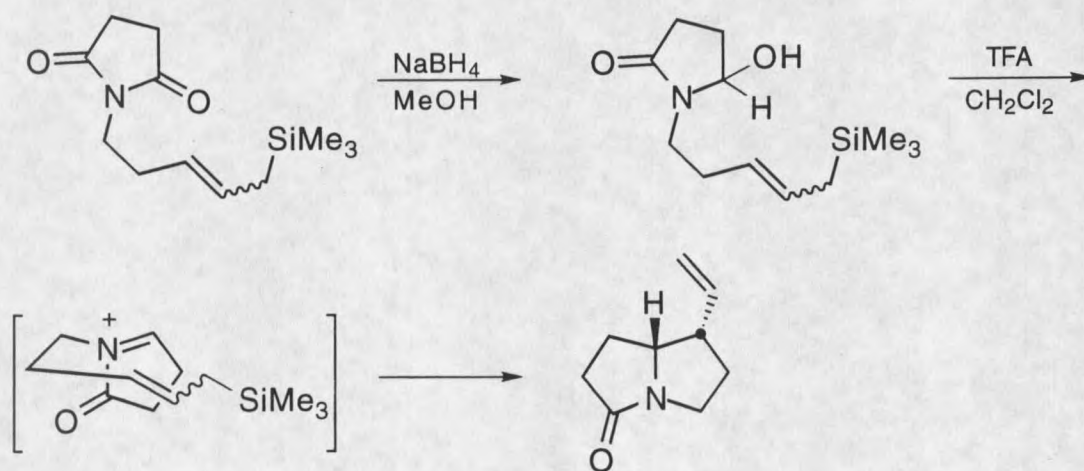
Although the most frequently employed, cationic routes such as Mannich type reactions are not the exclusive method for initiating iminium ion cyclizations. Thermally stable iminium salts such as conjugated perchlorate derivatives have been activated photochemically in order to promote the desilylative 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

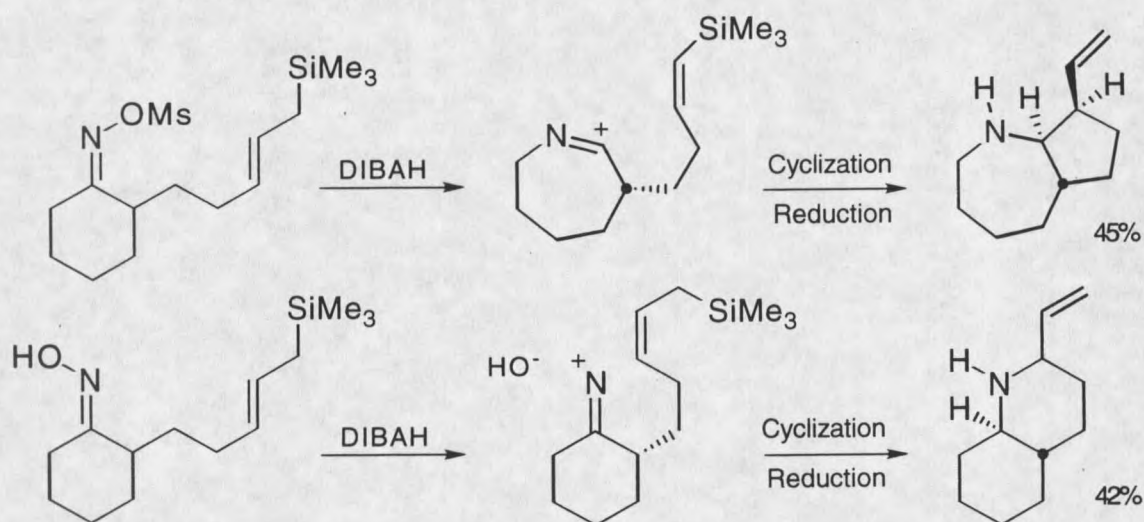
In contrast to iminium ions derived from basic allylsilane amines and aldehydes³², the N-acyliminium ion²⁸ has received considerably more use in allylsilane cyclizations. This is likely due to the numerous methods available for generation of such ions, the greater reactivity over iminium ions and the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



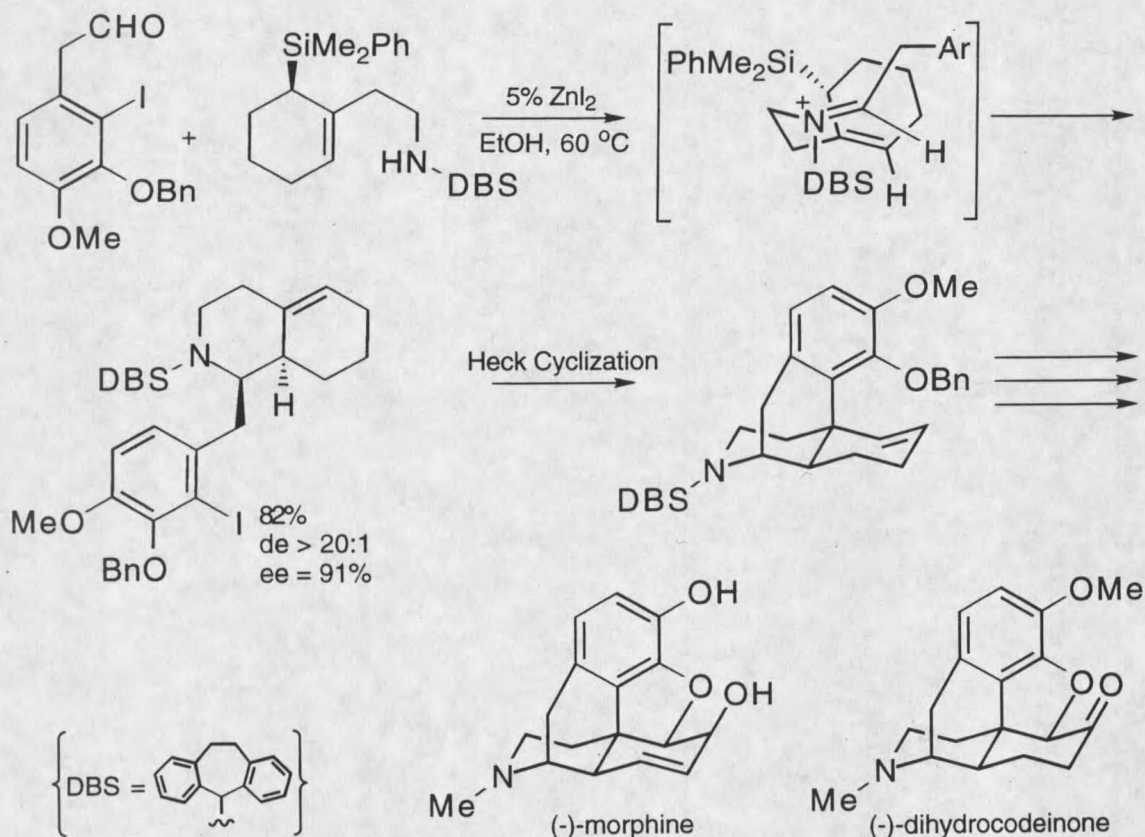
Scheme 19

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

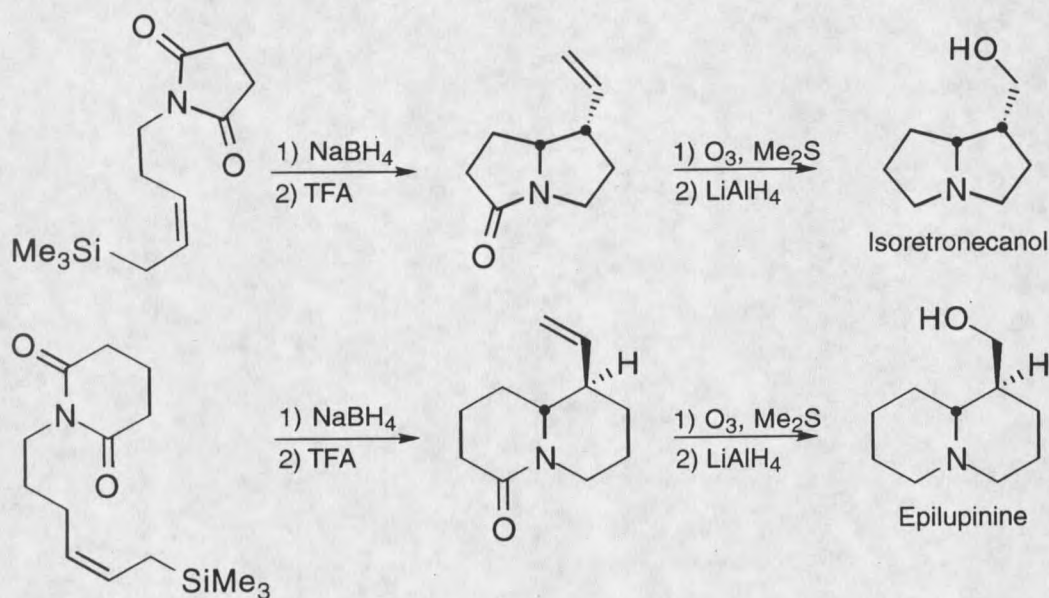
The successful total synthesis of a natural product offers the ultimate arena in which to test the applicability and practicality of reaction methodologies. In the past two decades the cyclizations of allylsilanes onto iminium ions such as those previously described have served as efficient key steps 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.



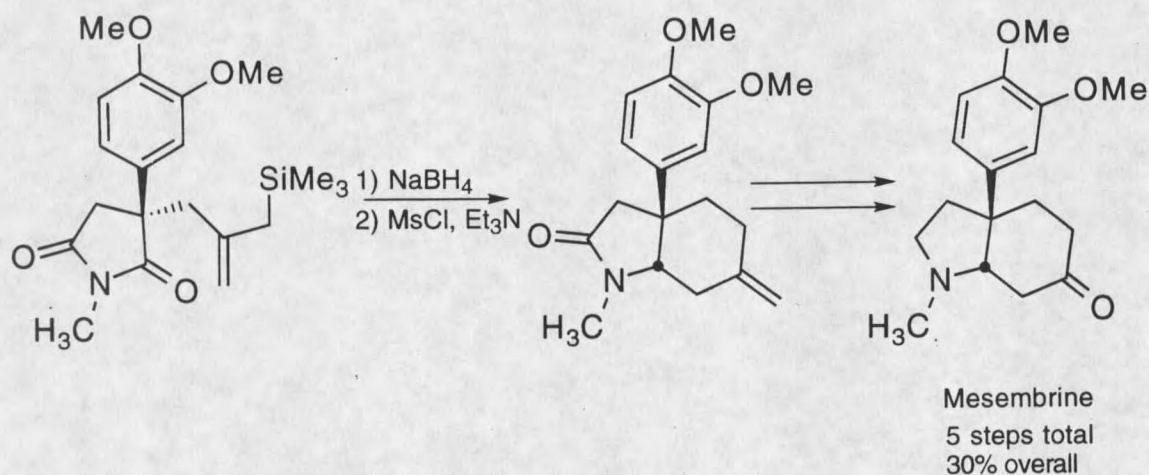
Scheme 20

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 Remuon 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



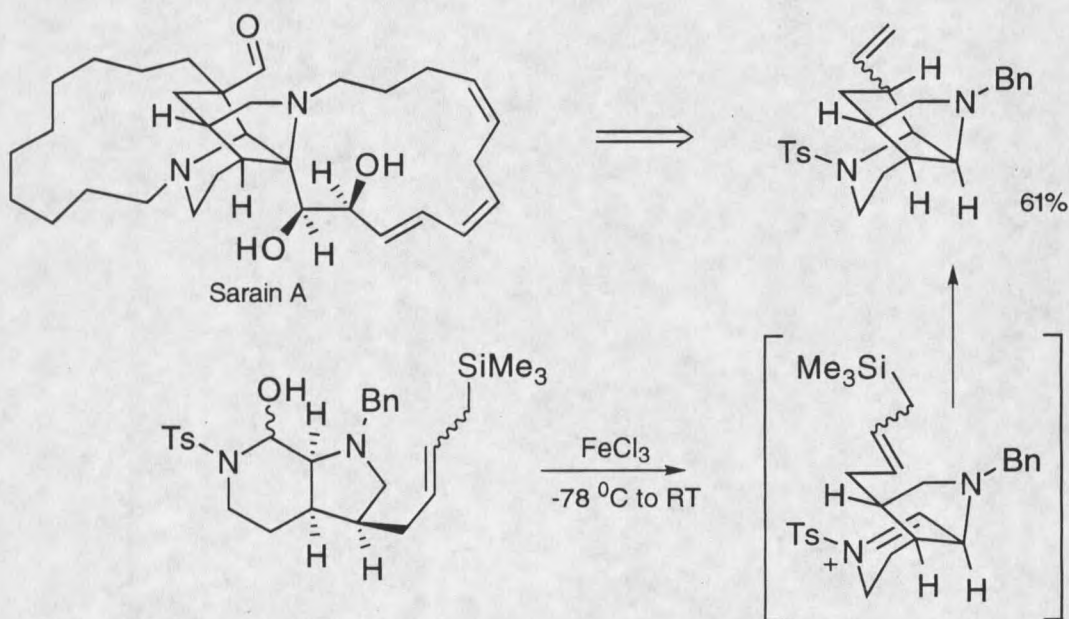
Scheme 21



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

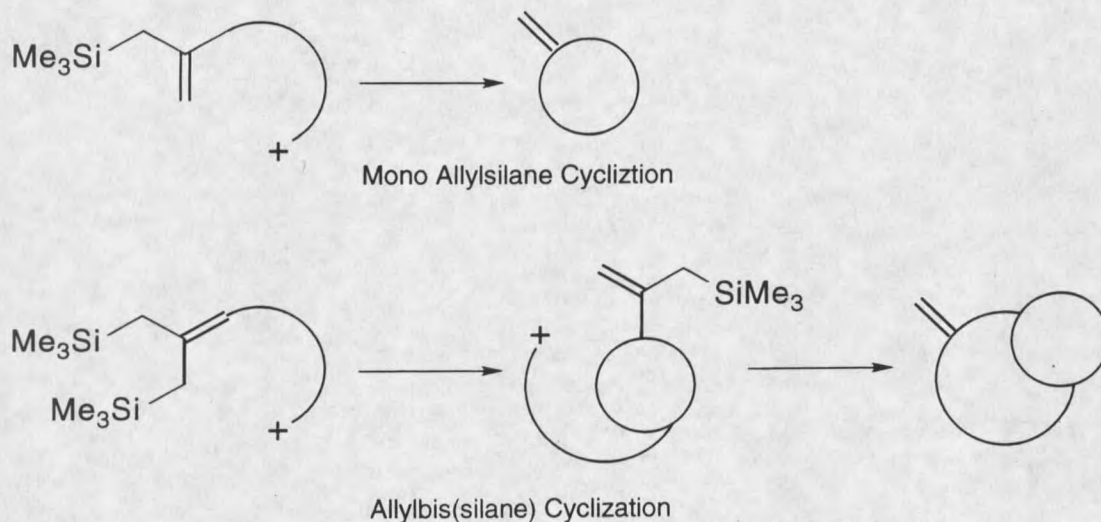
These are the most recent and efficient examples of the synthetic usefulness of allylsilane-terminated cyclizations from a standpoint of alkaloid synthesis, an area of high relevance to this dissertation. Clearly shown in all cases is the regiospecific nature of the cyclization processes and for the 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.

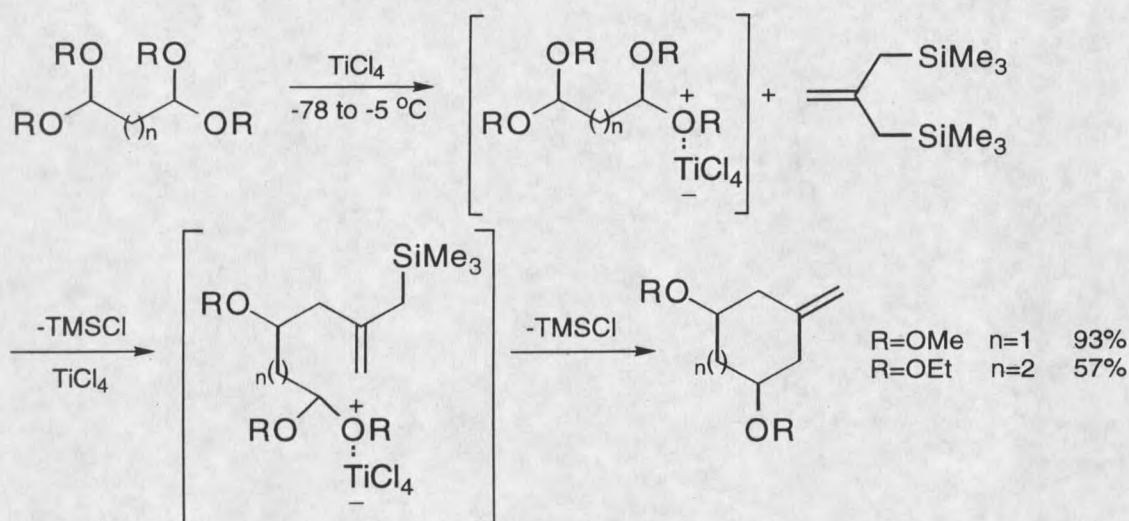
Electrophilic Additions to Allylbis(silanes)

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 TiCl₄ 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).

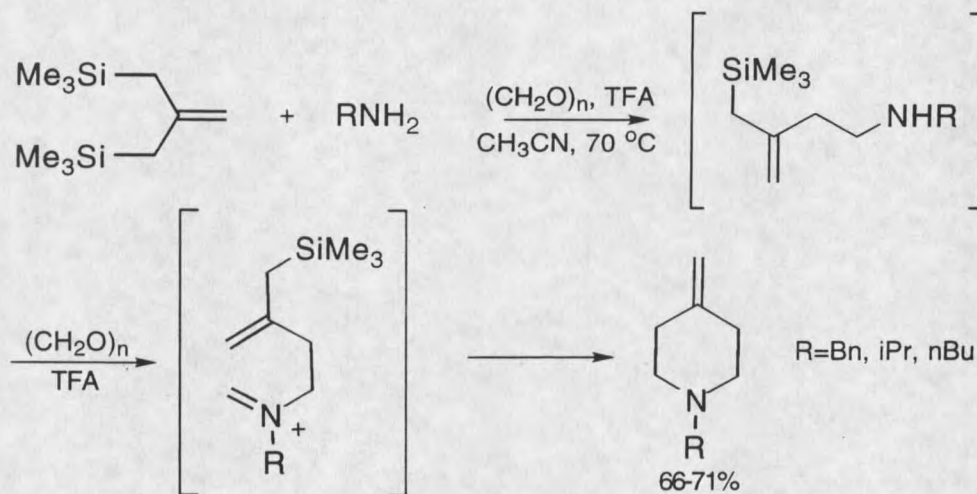


Scheme 25

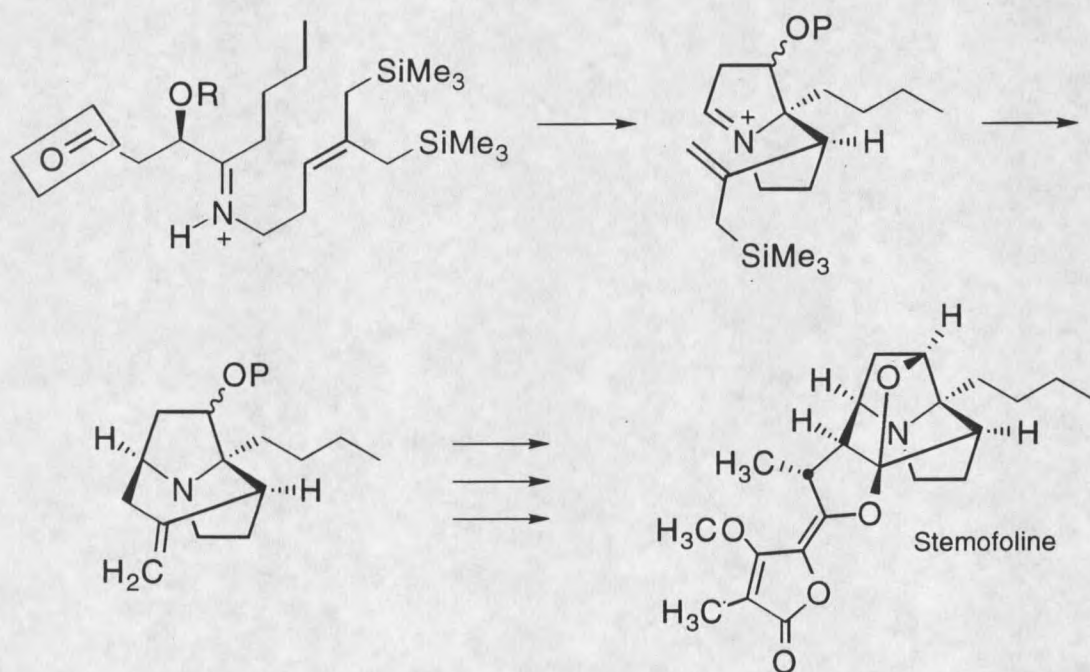
In an analogous reaction, the same allylbis(silane) nucleophile underwent a Mannich type addition-cyclization upon treatment with paraformaldehyde and primary amines in acidic media (Scheme 26).⁴⁰ Methylene substituted piperidines were obtained in good yield via a reaction pathway believed to involve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



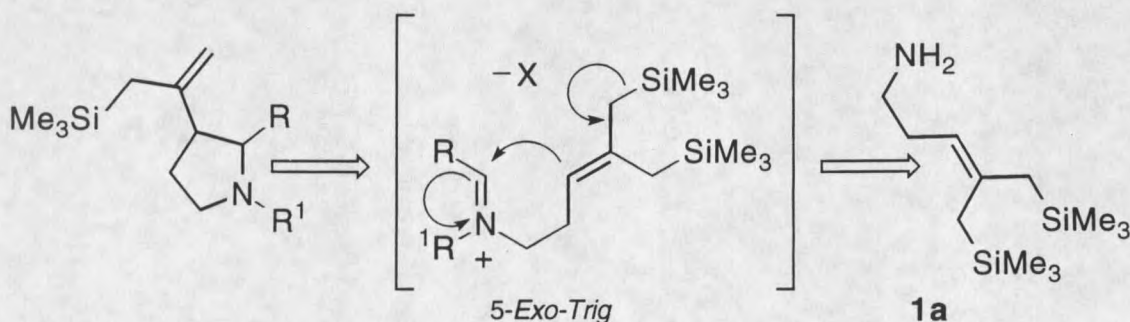
Scheme 27

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.

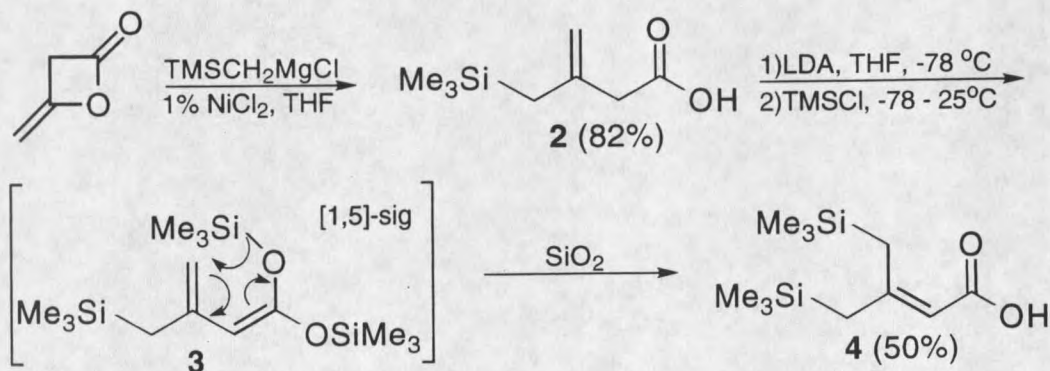
Cyclization of these substrates would, in theory, occur by way of a 5-*exo-trig* type process which is considered a favorable process when applying the classical rules for ring closure.⁴¹ Numerous accounts of 5-*exo-trig* cyclizations involving monoallylsilanes and iminium ions exist in the past literature.^{9, 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

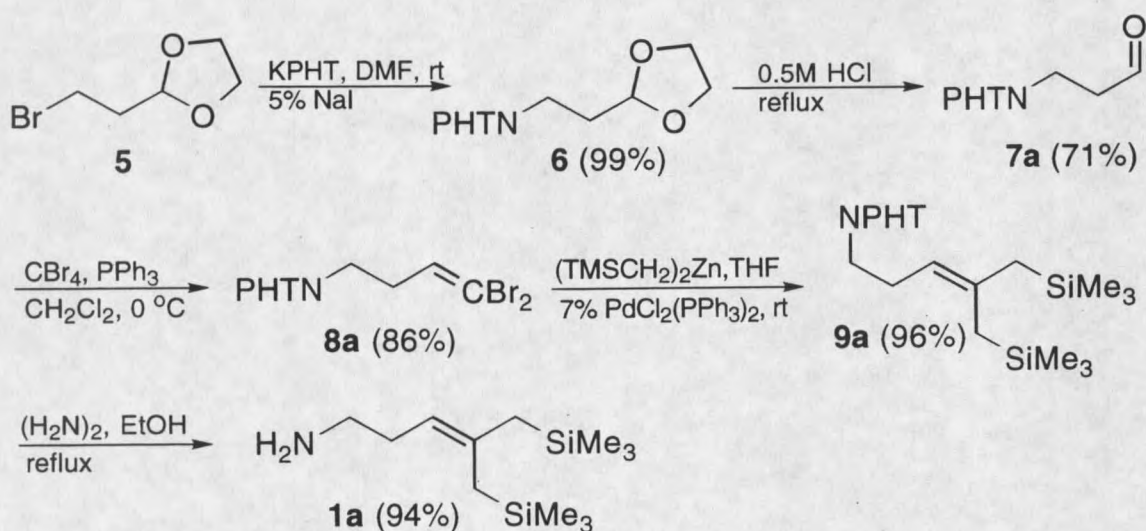
At the commencement of this work, there were no reported methods by which to synthesize the 2-propylidene-1,3-bis(silane) unit on a preparative scale.^{40, 42} After some experimentation, this goal was initially achieved using a reported 1,5 sigmatropic shift of silicon from oxygen to carbon.⁴³ Accordingly, diketene was selectively cleaved using $\text{TMSCH}_2\text{MgCl}$ in the presence of NiCl_2 (1 mol %) to afford butenoic acid **2** in 82% yield.⁴⁴ Treatment of **2** with excess LDA and TMSCl at -78°C followed by warming to room temperature furnished allylbis(silane) **4** in a maximum yield of 50% after purification and silyl ester cleavage on silica gel. In a fashion analogous to that reported, formation of **4** was believed to have occurred via a thermal 1,5 sigmatropic shift of an intermediate ketene silyl acetal upon warming of the reaction mixture to ambient temperature (Scheme 29).

Despite the success of the sigmatropic migration to form the allylbis(silane) unit, the low isolated yield of **4** and the large number of transformations required for conversion into amine **1a** prompted a search for a more efficient route. In addition, carboxylic acid **4** proved to be quite resistant towards reduction to the oxidation state appropriate for alteration into **1a**.



Scheme 29

A more straightforward and efficient synthetic route, centered around a palladium catalyzed, cross coupling reaction, was eventually developed for the synthesis of **1a** on a large scale. Known aldehyde **7a**⁴⁵ was economically prepared in 70% yield from commercially available bromo acetal **5** by substitution with potassium phthalimide followed by liberation of the carbonyl functionality with aqueous acid (Scheme 30). Olefination of the resulting aldehyde with the ylide derived from CBr_4 and PPh_3 ⁴⁶ provided dibromo alkene **8a** in 86% isolated yield.



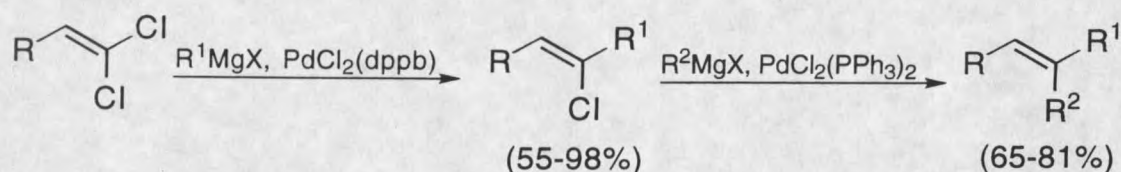
Scheme 30

Attachment of both trimethylsilylmethyl substituents to form phthalimide **9a** was readily achieved in one pot employing a variation of coupling conditions developed by Tamaou and Minato.⁴⁷ These chemists found that 1,1-dichloro-1-alkenes could be selectively mono alkylated by treatment with Grignard reagents in the presence of catalytic $\text{PdCl}_2(\text{dppb})$. Subsequent alkylation of the resulting 1-chloro-1-alkenes using $\text{PdCl}_2(\text{PPh}_3)_2$ as the

catalyst then provided unsymmetrical trisubstituted alkenes in good yield with complete regiocontrol (Scheme 31). From these results it was believed that subjecting the more reactive 1,1-dibromo-1-alkene **8a** to $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Me}_3\text{SiCH}_2\text{MgCl}$ should provide the desired dialkylation product **9a**.

During original experimentation with these conditions formation of the desired product was observed but byproducts originating from degradation of the phthalimide protecting group in **8a** allowed for only modest isolated yields. Fortunately, it was discovered that employing a mild organozinc reagent rather than the Grignard species permitted circumvention of this problem. Along these lines, exposure of **8a** to $(\text{TMSCH}_2)_2\text{Zn}$, prepared *in situ* from TMCH_2MgCl and zinc chloride, in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (7 mol %) provided the protected amine **9a** in 96% yield after purification on silica gel (Scheme 30). It was a surprising observation that none of the corresponding monoalkylated product was detected upon analyzing the products of this tandem cross coupling reaction.

Phthalimide deprotection of **9a** using standard conditions⁴⁸ occurred cleanly to afford the desired amine **1a** in 94% yield after neutral work up and bulb to bulb distillation. This synthetic scheme repeatedly proved to be very efficient on a preparative scale. Large scale runs employing as much as 20 grams of olefin **8a** in the coupling step produced the target amine in 78% overall from aldehyde **7a**. It is quite conceivable that longer chain homologues of amine **1a** could also be prepared in this fashion.

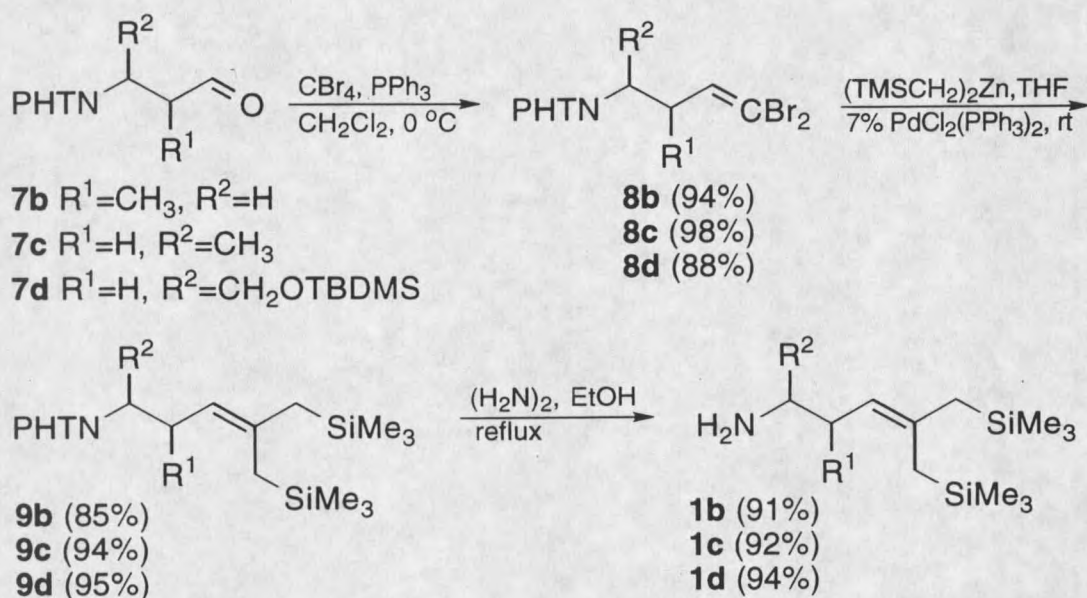


Scheme 31

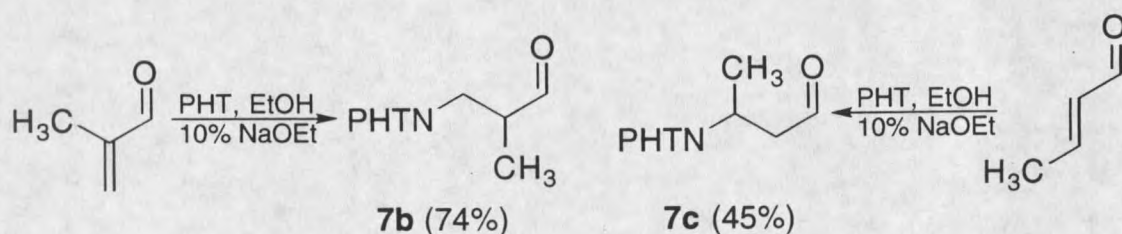
The above synthetic sequence was latter found to be quite flexible in that a series of substituted amino allylbis(silanes) was successfully synthesized by this method. These amines could theoretically give rise to trisubstituted pyrrolidines and related ring systems upon intramolecular cyclization onto iminium ions. More specifically, methyl and protected hydroxymethyl analogous of **1a** were selected for synthesis by virtue of their ease of preparation and relevance to substituent patterns found in natural alkaloids. Accordingly, amines **1b-d** were efficiently prepared from the appropriate aldehydes **7b-d** using conditions analogous to those applied to the synthesis of amine **1a** (Scheme 32).

For the methyl derivatives, starting aldehydes **7b** and **7c** were prepared by base catalyzed, conjugate addition of phthalimide to methacrolien and crotonaldehyde respectively (Scheme 33). The synthesis of the oxygenated aldehyde **7d** was more involved. Treatment of excess *cis*-1-4 butenediol with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) provided a mixture of the mono- and bis silylethers (85 : 15) which was oxidized with pyridinium chlorochromate (PCC) to afford the *trans* enone **10** in 49% overall yield after chromatographic separation of the bis(silyl)ether. Evidence for the *cis*-*trans* isomerization during exposure of the intermediate, mono alcohol to acidic PCC was provided by a large vinylic proton coupling constant of 15.5 Hz in the spectrum of enone **10**.

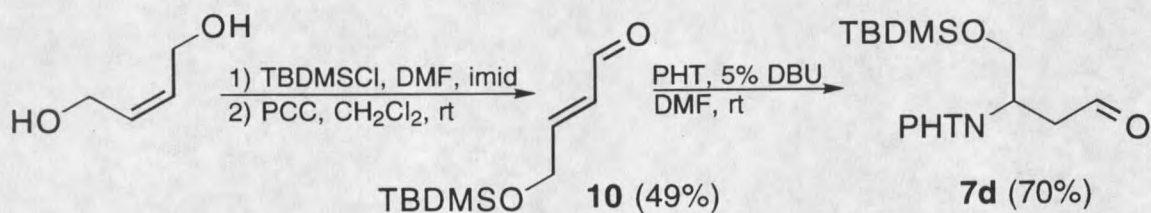
Base mediated addition of phthalimide to enone **10** furnished the required aldehyde **7d** in 70% yield (Scheme 34).



Scheme 32



Scheme 33

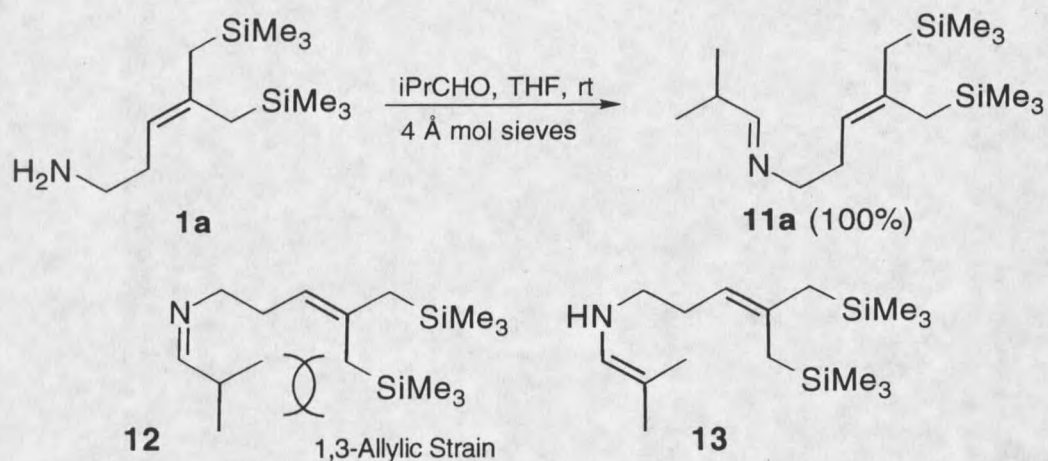


Scheme 34

2-Propylidene-1,3-bis(silane) Imine Cyclizations

With a reliable route to amino allylbis(silanes) having been established, prospective methods for generation of the cyclization initiator and execution of the subsequent cyclization were next examined. Along these lines, installation of an imine functionality was smoothly achieved by condensation of amine **1a** with isobutyraldehyde under mild conditions using 4 Å molecular sieves as a water trap. This provided imine **11a** in quantitative yield as a single geometrical isomer as indicated by NMR. The observed geometry of **11a** has been assigned as *E* configuration considering the preference for aldimines to adopt this thermodynamically stable, double bond geometry.⁴⁹ It is believed that the corresponding *Z* isomer **12** would suffer thermodynamically from allylic, nonbonded interactions (Scheme 35).

Furthermore, the enamine tautomer **13** of **11a** and all imines subsequently prepared under these conditions was not observed in the NMR spectra. Since tautomerization might induce self condensation and imines in general are prone to hydrolysis and decomposition, it was quite a pleasing realization that the preparation of imines from amine **1a**, and eventually **1b-d**, occurred cleanly with no additional purification required.



Scheme 35

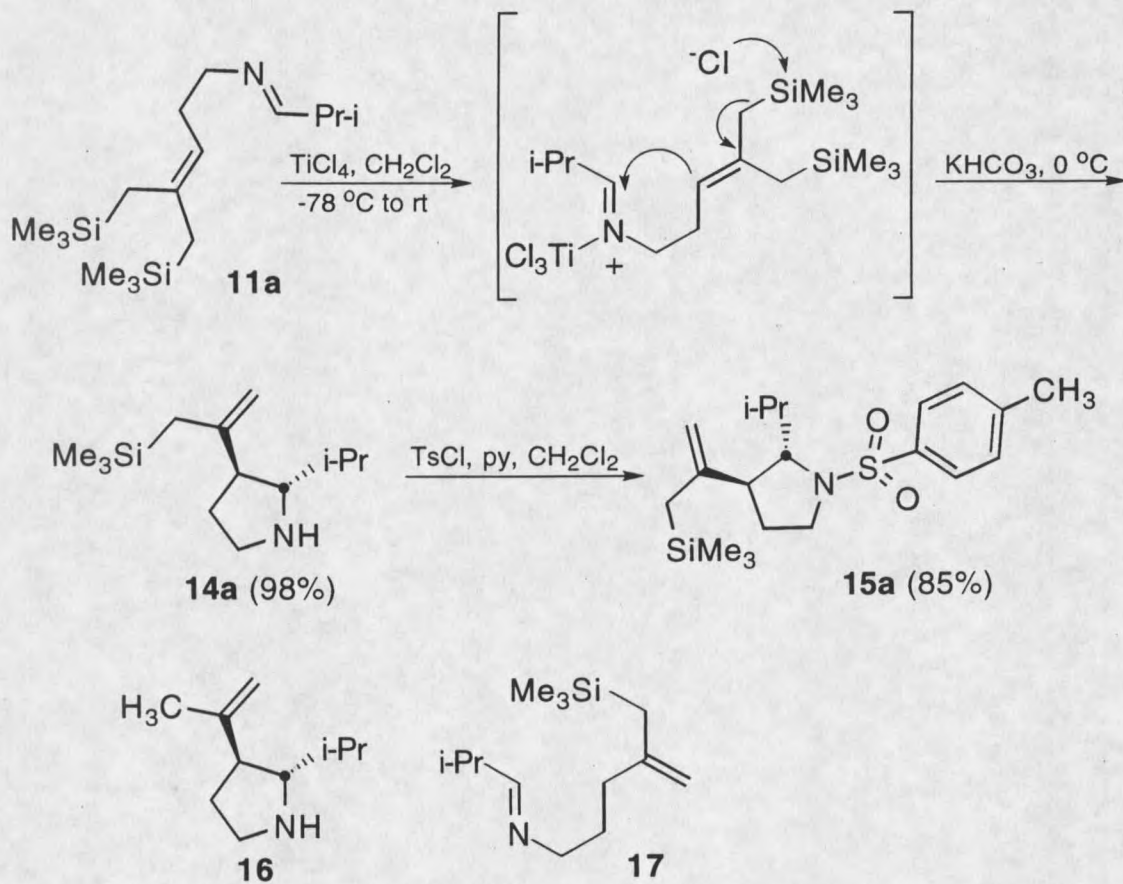
Conditions to promote cationic cyclization of imine **11a** were screened next. Initially, Bronsted acids such as trifluoroacetic acid (TFA), camphorsulfonic acid and $\text{Me}_2\text{O}\cdot\text{HBF}_4$ failed to provide either the desired cyclized product or isolable iminium salts upon exposure to imine **11a** as did trifluoroacetic anhydride and associated reagents. Alternative reagents that might promote an anionic cyclization such as tetrabutylammonium fluoride were not extensively screened as to avoid protodesilylation of the sensitive allylbis(silane) terminator. Data obtained from these fruitless cyclization attempts pointed to this unwanted desilylation reaction as the primary source of the problems associated with the use of Bronsted acids. Desilylation was believed to be occurring through intramolecular deprotonation of the alpha protons of the iminium ion of **11a** rather than directly from the protic reagents. In support of this theory, when amine **1a** was treated with TFA (0.95 equiv) in methanol at $-78\text{ }^\circ\text{C}$, the corresponding ammonium salt was found to be stable at room temperature with no products originating from protodesilylation being detected.

Attention was next focused on the use of lewis acids since it was discovered that Keck had successfully performed lewis acid promoted allylations of aldimines using mono allylstannanes.⁵⁰ With this in mind, imine **11a** was treated with a broad range of Lewis acids including SnCl_4 , $\text{Sn}(\text{OTf})_2$, and $\text{Cu}(\text{OTf})_2$ under a variety of conditions. In most cases examined, the result was the production of unwanted products, incomplete conversion of substrate or desilylation of the sensitive terminator.

It was ultimately discovered however that precomplexation of imine **11a** with 1.0 equivalent of TiCl_4 at $-78\text{ }^\circ\text{C}$ followed by slow warming to ambient temperature promoted complete cyclization to the desired pyrrolidine **14a** which was isolated as a single stereoisomer ($>50:1.0$ trans:cis) as indicated by high resolution NMR spectroscopy (Scheme 36). Careful quench of the reaction mixture using slow, inverse addition to cold KHCO_3 (aq) proved necessary as to avoid the production of the undesired pyrrolidine **16**. More over, desilylated imine **17** was not observed during analysis of the reaction products. Conversion of **14a** to the corresponding *N*-tosyl derivative **15a** allowed for optimal characterization of the cyclic product.

It was also observed that substoichiometric amounts (0.8-0.9 equiv) of TiCl_4 also promoted complete cyclization to **14a**. Catalytic amounts (15%) failed to induce any significant conversion however. Milder titanium-based Lewis acids like $\text{Ti}(\text{OiPr})\text{Cl}_3$ and $\text{Ti}(\text{OiPr})_2\text{Cl}_2$ did promote cyclization to afford pyrrolidine **14a** but extended reaction times were required to induce even modest conversions. Cyclization experiments performed using toluene or mixtures of toluene and CH_2Cl_2 as a solvent were found to be not as clean compared to pure CH_2Cl_2 . Another group IV metal complex was found to

promote efficient cyclization of **11a**. Using $(\text{Me}_2\text{S})_2\text{ZrCl}_4$ (1.1 equiv., CH_2Cl_2 , -78 °C to rt) resulted in pyrrolidine **14a** in 83% yield. The results using group IV lewis acids are summarized in Table 1.



Scheme 36

Table 1. Cyclization Results Using 11a and Group IV Lewis Acids

Group IV Lewis Acid	Equiv.	Time at rt from -78 °C (hrs.)	Yield of 14a (%)
TiCl ₄	1.00	2.0	98
TiCl ₄	0.90	2.0	98
TiCl ₄	0.15	11	~0
(Me ₂ S) ₂ ZrCl ₄	1.10	2.0	83
TiCl ₃ (OiPr)	1.00	2.0	26 (ca.)
TiCl ₃ (OiPr)	1.00	15	52 (ca.)
TiCl ₂ (OiPr) ₂	1.00	18	<20 (ca.)

The conditions developed for the preparation and cyclization of imine **11a** were found to be quite applicable to a broad range of alkyl and aryl imines.⁵¹ The results of this study are summarized in Table 2. The imines **11b-i** derived from simple aldehydes and amine **1a** were, as in the case of **11a**, cleanly prepared and all of these imines were found to be homogeneous with respect to imine configuration. For the reactive imine **11c**, preparation from acetaldehyde was best carried out at -10 °C employing short reaction times.

As shown in Table 2, pyrrolidines **14b-i** were synthesized in good to excellent yield after purification on Florisil or silica gel and in the case of **14a**, no such techniques were necessary. Crude samples of all pyrrolidines were treated with TsCl to afford the *N*-toluenesulfonyl derivatives **15a-i**. This was

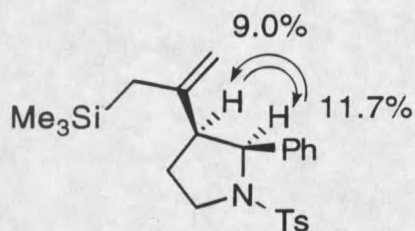
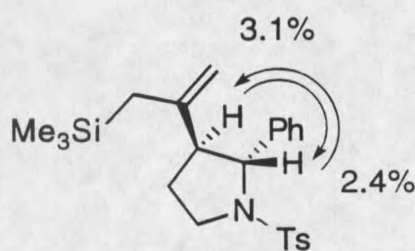
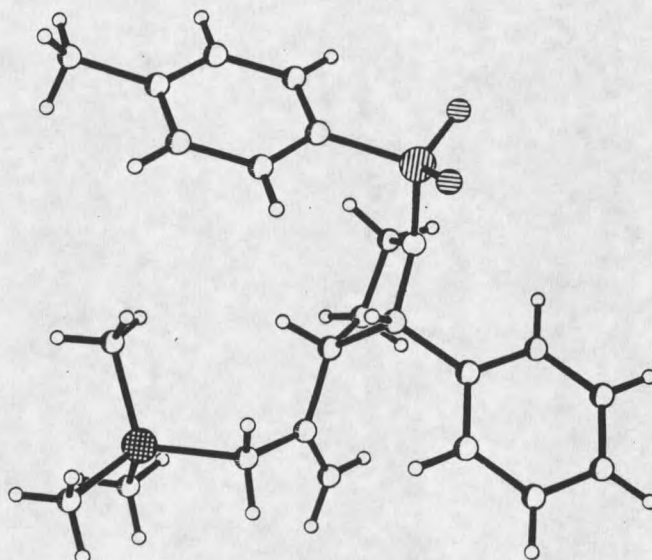
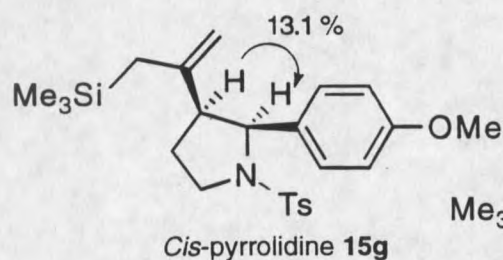
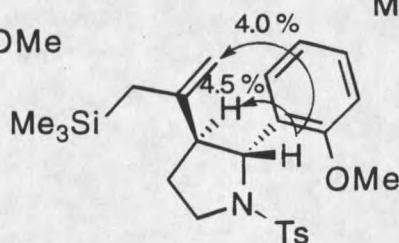
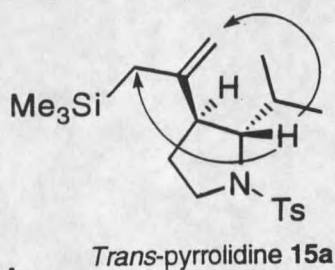
found advantageous for numerous reasons. Unlike the corresponding pyrrolidines **14a-i**, the NMR spectra of these derivatives clearly showed that the majority of the signals correlating to diastereotopic protons contained within the molecule were well defined and separated. This feature permitted thorough characterization, accurate analysis of diastereomer mixtures and also aided in NOE studies. The *N*-tosylates also proved to be more stable during storage than the basic pyrrolidines. Moreover, the crystalline properties of some of the derivatives allowed for separation of isomers and eventually single crystal X-ray analysis.

Table 2. Cyclization Results for Aldimines Derived From Amine 1a

Aldehyde (-R)	Imine	Pyrrolidine (% Yield)	<i>Trans</i> : <i>Cis</i>	N-Tosylate (% Yield)
-CH(CH) ₂	11a	14a (99)	> 50 : 1.0	15a (85)
-CH ₂ CH(CH) ₂	11b	14b (88)	> 50 : 1.0	15b (80)
-CH ₃	11c	14c (67)	34 : 1.0	15c (82)
	11d	14d (-)	> 50 : 1.0	15d (62)
	11e	14e (84)	14 : 1.0	15e (80)
	11f	14f (84)	1.0 : 7.3	15f (84)
	11g	14g (90)	1.0 : 3.4	15g (90)
	11h	14h (99)	1.0 : 1.7	15h (86)
	11i	14i (-)	1.0 : 5.0	15i (88)

The quantification of the diastereomer composition was achieved by integration of the expanded 300 MHz proton NMR spectra of the crude pyrrolidines and or isolated *N*-tosylates. The spectra of diastereomeric *N*-tosylates was quite resolved and enabled accurate determination of ratios. Subjecting the *N*-tosyl compounds to this analysis also eliminated ambiguity arising from trace or sometimes significant amounts of desilylated imine present in the crude pyrrolidines **14a-i**.

Determination of the relative configuration of the substituents at the C-2 and C-3 positions of the pyrrolidines was initially performed on the products obtained from the nonselective cyclization of imine **11h**. Specifically, fractional crystallization of the mixture of *N*-tosylates (**15h**) provided pure samples of the major and minor isomers which were analyzed individually by NOE spectroscopy after definitive assignments were made from homonuclear decoupling experiments. Irradiation of the C-3 methine proton (H^3) in the major *cis* isomer gave rise to a 11.7% signal enhancement at H^2 . Irradiation in the reverse direction produced a 9.0% enhancement at H^3 . Corresponding irradiation of the minor *trans* isomer resulted in much smaller, 2.4% and 3.1%, NOE signals respectively. Eventually, the structure of the major *cis* compound was conclusively elucidated by single crystal X-ray analysis (Figure 9). The relative stereochemical assignments for the remaining pyrrolidines **14a-g** and **14i** were derived from analogous NOE studies carried out on *N*-tosylates **15a-g** and **15i** and some of the diagnostic results are included in Figure 10.

*Cis*-pyrrolidine **15h***Trans*-pyrrolidine **15h***Cis*-pyrrolidine **15h****Figure 9. Elucidation of Structure for *Cis* and *Trans* 15h***Cis*-pyrrolidine **15g***Trans*-pyrrolidine **15d***Trans*-pyrrolidine **15a****Figure 10. Representative NOE Results for Pyrrolidines 15a-i**

One of the most attractive features of the allylbis(silane) aldimine cyclizations lies in the general high levels of substrate-based diastereocontrol.⁵² Most notable is the preference of alkyl substituted imines **1a-c** to undergo essentially a completely *trans*-selective mode of cyclization. Ratios in favor of the *trans* isomer were observed to be quite high (34-→50:1.0)

regardless of the size of the alkyl substituent although significant fluctuations in stereoselectivity were observed during runs performed on the acetaldehyde imine **11c**. The origin of such a high preference could be the result of the avoidance of nonbonded interactions in the transition state and it is conceivable that such steric interactions might outweigh any electronic effects. In order for products of *cis* configuration to form, a transition state possessing a potentially severe 1,2 steric interaction would develop along the course of bond formation (Figure 11). Alternatively, the diastereotopic transition state leading to the observed *trans* pyrrolidine products would avoid such a high energy interaction by rotation about the vinylic C-C bond of the terminator.

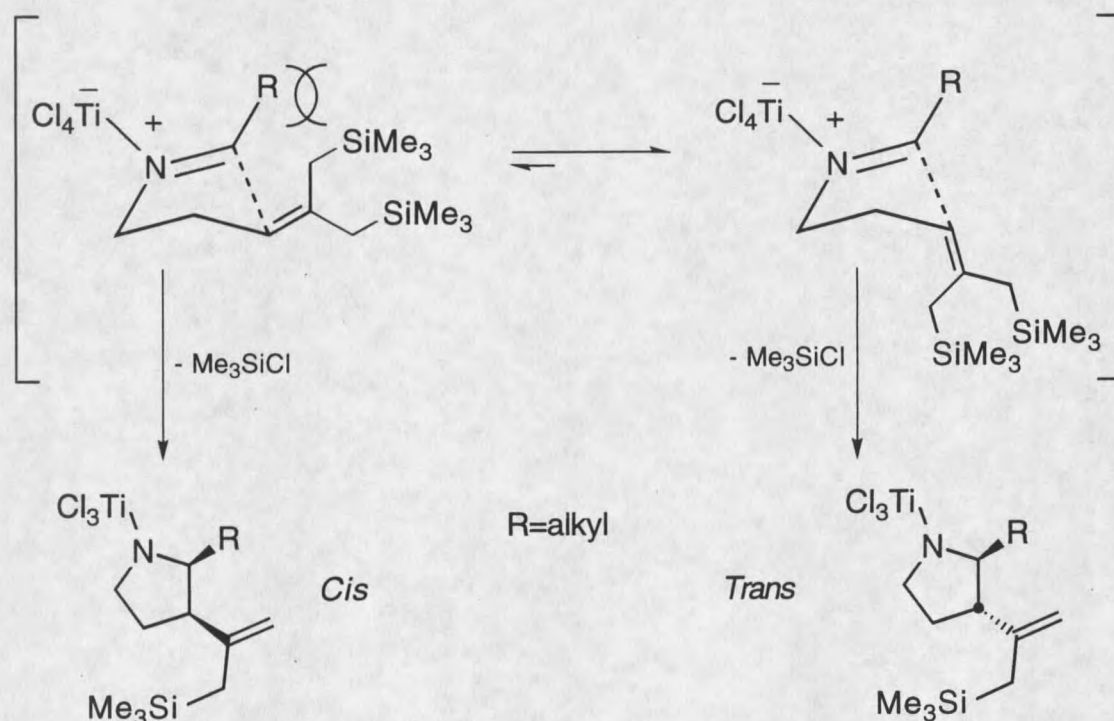


Figure 11. Transition States for Alkyl Imine Cyclizations

An interesting contrast to the high *trans* selectivity is apparent upon reviewing the cyclization data. Imines **11f-i** derived from aryl substituted

aldehydes were found to produce diastereomeric mixtures favoring the cis isomers but with lower overall selectivity than the trans selective cases. The reason for this reverse selectivity is currently unclear but could be attributed the ability of aryl groups to stabilize an adjacent cationic center. Such an influence exerted by these groups might readily promote *E-Z* isomerization of imine-titanium complexes possessing less pi bond character. As a result, the cationic transition state would contain rotational freedom around the C-N bond in addition to the allylic C-C bond of the terminator resulting in electronic influences, such as charge separation, to govern the structure of the transition state rather than steric effects.

Transition state models of cis orientation would seemingly benefit in lower energy by having less separation of charge relative to the alternative trans transition state required for formation of the corresponding trans isomers (Figure 12). Minimization of charge separation would be preferred in noncoordinating solvents such as CH₂Cl₂ and the magnitude of such a stabilization would be affected by solvent polarity.⁵³ For example, it was observed that only a slight increase in solvent polarity resulted in a significant change in the cis-trans ratio during the cyclization of conjugated imine **11f** as evident by a ratio of 1.7:1.0 in CHCl₃ compared to 7.3:1.0 in CH₂Cl₂. Unfortunately, solvents higher than CHCl₃ on the polarity scale were too reactive to consider for extending the study of this solvent effect although toluene/CH₂Cl₂ mixtures generally gave lower selectivities. It should be mentioned that the trans olefin geometry of the phenylethenyl substituent in **11f** was preserved during cyclization as indicated by a large vinylic coupling constant of 15.7 Hz in **14f**.⁵⁴ This verifies the two isomers under investigation were not merely isomeric at the olefin rather than at the stereogenic centers.

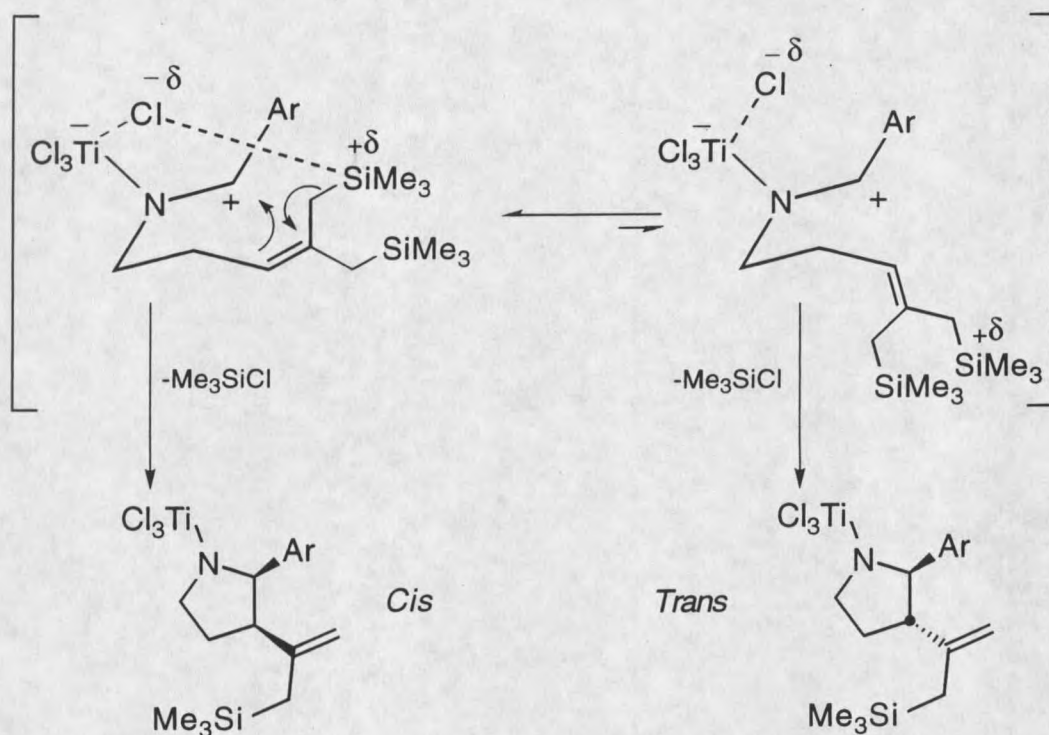


Figure 12. Transition States for Aryl Imine Cyclizations

It was found that complete trans stereocontrol could be achieved in the cyclization of certain aryl imines. When the 2-methoxy derivative **11d** was subjected to cyclization in place of the 4-methoxy analogue **11g**, complete trans selectivity was reestablished affording trans-pyrrolidine **14d**. This drastic reversal in the stereochemical outcome is most likely due to chelation by the titanium center to the ortho-disposed methoxy group in imine **11d**. Unlike the transition state for cyclization of imine **11g**, the corresponding transition state of this cyclization would be conformationally locked with respect to the imine geometry thus allowing the steric control elements promoting trans bond formation to dominate as in the alkyl substituted cases (Figure 13). Strong trans preference was also observed in the cyclization of the furanyl imine **11e** which would proceed by an analogous 5-membered chelate. The belief that chelation

does indeed play a role in the cyclization of these two imines (**11d** and **11e**) prompted us to use slightly modified conditions. Slow, reverse addition of imine substrate to a TiCl_4 solution at $-78\text{ }^\circ\text{C}$ was employed as to facilitate chelation and suppress coordination of two Lewis acid molecules to the imine.

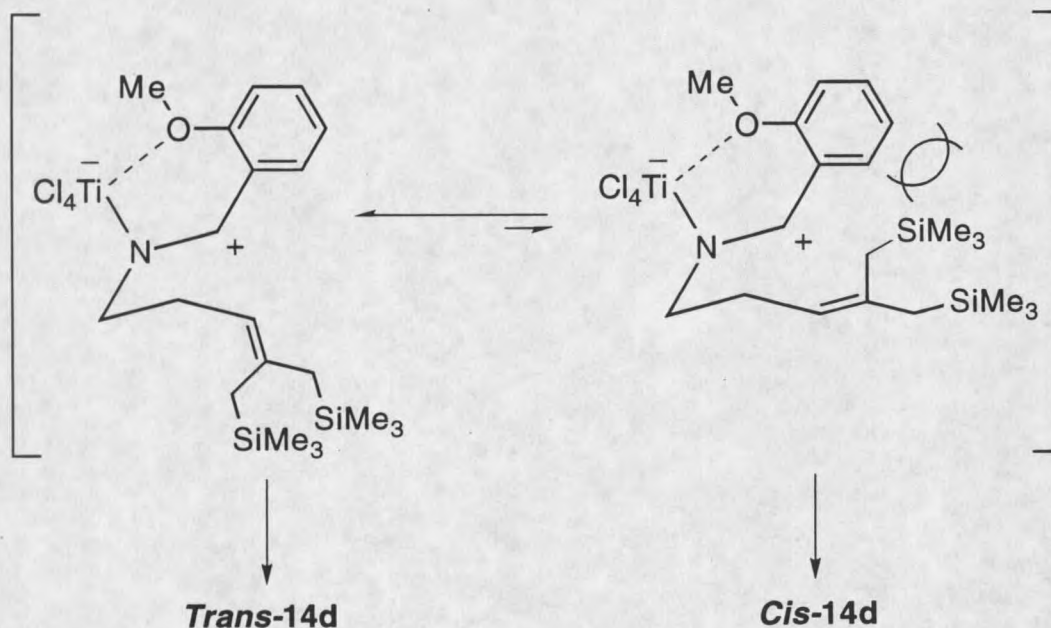


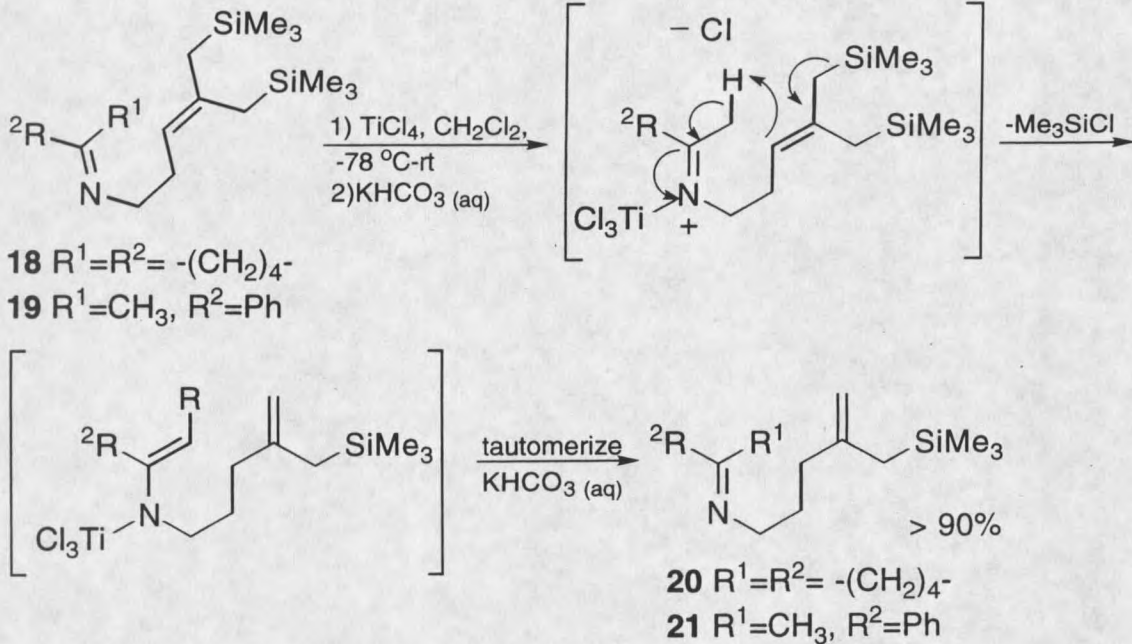
Figure 13. Chelated Diastereotopic Transition States

In addition to the high diastereoselectivity, these initial results draw other strengths with respect to synthetic utility of the cyclization reaction. First, the residual mono allylsilane unit is preserved during the course of reaction, work up and isolation of product. This permits the substituted pyrrolidines to be exploited by the vast amount of established mono allylsilane chemistry.^{6,9}

Secondly, the mono desilylative cyclization of allylbis(silane) imines occurred with complete regiochemical control. In all of the previously mentioned examples products arising from a competing 6-*exo* cyclization mode were not detected during product analysis. This is attributed to the β effect and

control elements previously discussed. For these cyclizations it could be postulated that a low energy pathway involving a β effect magnified by the presence of *two* silicon atoms adjacent to the developing cationic center might be in affect. At this moment however, there exists no experimental evidence to support this theory other than the fact that these cyclizations proceed under conditions more mild than those generally applied to mono allylsilane-iminium ion cyclizations.^{9,32,35} Furthermore, the 2-propylidene-1,3-bis(silane) nucleophile has shown a much stronger tendency to protodesilylation than the corresponding mono allylsilanes.

At this time, the scope of allylbis(silane) imine cyclization is generally limited to aldimine substrates. For example when cyclopentanone and acetophenone derived ketimines **18** and **19** were exposed to the general cyclization conditions, monodesilylated imines were obtained as the sole reaction products (Scheme 37). In these instances, cyclization rate was most likely depressed by the relative electron richness of ketimines relative to aldimines. As a result the reactive 2-propylidene-1,3-bis(silane) nucleophile could now, quit feasibly, kinetically act as a Bronsted base in an intramolecular fashion. The net result of such a mechanistic change would be a desilylative imine to enamine tautomerization. During the course of the reaction or during aqueous work up, reestablishment of the equilibrium favoring the imine tautomer would then afford the observed products **20** and **21**.



Scheme 37

Substrates containing the C-acyl imine unit also proved resistant towards desired cyclization. Imine **22**, prepared from 2,4-butanedione, afforded only mixtures of unwanted products under a variety of conditions screened to promote cyclization (Scheme 38). This problem was attributed to ambiguity at the two sites of electrophilicity present in the bifunctional C-acylimine.



Scheme 38

Stereoselective Synthesis of Trisubstituted Pyrrolidines

The successful cyclization of aldimines derived from unsubstituted amino-allylbis(silane) **1a** firmly established that the 2-propylidene-1,3-bis(silane) nucleophile could in fact fulfill the role as a cationic cyclization terminator.⁵¹ The high stereoselectivity of these cyclizations, especially for the alkyl substituted imines, motivated us to expand this methodology to the stereocontrolled formation of trisubstituted pyrrolidines. The efficient preparation of substituted amino allylbis(silanes) **1b-c** (Scheme 32) enabled us to pursue this endeavor.

Cyclization of imines derived from these amines could theoretically occur with control over the relative configuration of three newly-formed stereocenters. As eluded to previously, there are published, isolated examples of mono allylsilane-iminium ion cyclizations that proceeded with complete substrate based control in the course of forming two stereocenters.^{9,35-39} To our knowledge there are no reported examples of the diastereoselective creation of three new centers by such a cyclization.

Alkyl rather than aryl substituted aldehydes were chosen for the condensation with amines **1b-d** primarily for their high trans selectivity (34:1-50:1) when used in conjunction with amine **1a**. Transition states for cyclization of imines of amines **1b-d** should be quite sterically crowded rendering them quite sensitive to steric effects. It was initially predicted that the size of the alkyl substituent should have a significant impact on both the chemical yield and diastereoselection. With this in mind, isobutyraldehyde, isovaleryl aldehyde and acetaldehyde were implemented in order to provide a range of sterically diverse environments surrounding the electrophilic site of the corresponding

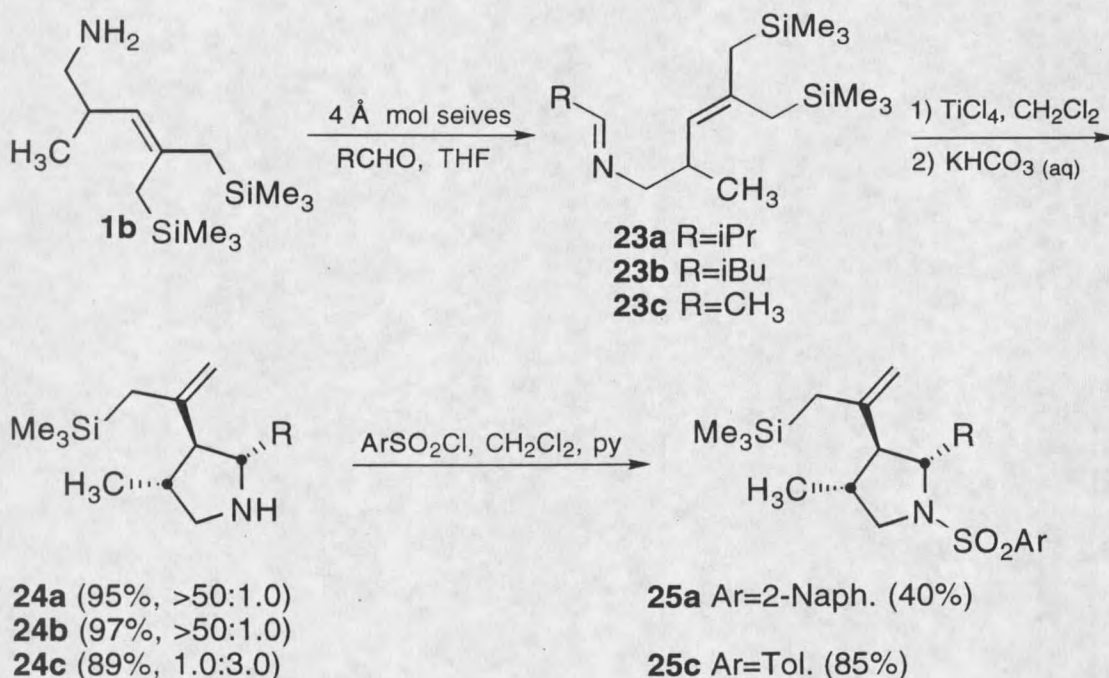
imines. The alkyl groups selected also have distinct and relatively simple signals in the NMR spectra which makes for easier analysis of products when considering that up to four diastereomers may form during cyclization.

Amine **1b** was initially used in the condensation-desilylative cyclization protocol. Condensation with isobutyraldehyde (4 Å mol. sieves, THF, rt.) provided imine **23a** in high yield (Scheme 39) which afforded trans pyrrolidine **24a** upon cyclization under the standard conditions (1 equiv. TiCl_4 , CH_2Cl_2 , -78 °C to rt.). This pyrrolidine was observed to be the sole product from this cyclization as indicated by both NMR and analysis by gas chromatography. Such a result is in good accord with the result obtained using amine **1a** and isobutyraldehyde (Table 2). Pyrrolidine **24a** was then converted to the 2-naphthalensulfonyl derivative **25a** for the purpose of NOE experiments. Similarly, when the less bulky isovaleryl aldehyde was used, trans pyrrolidine **24b** was also obtained in high yield as the only detected product.

When amine **1b** was condensed with acetaldehyde using the standard conditions, analysis of the products indicated that imine **23c** was not monomeric but had trimerized after isolation. As a result, condensations with acetaldehyde were executed at -10 °C using abbreviated reaction times. The imine was then isolated, immediately dissolved in CH_2Cl_2 , cooled to -78 °C and treated with TiCl_4 without delay in order to avoid polymerization.

Cyclization of the reactive imine **23c** and all acetaldehyde imines was carried out at -78 °C for one hour followed by 36 hours at -20 °C to achieve optimum yield and stereoselection. Despite these mild conditions, pyrrolidine **24c** was obtained as an inseparable mixture of diastereomers (2.0-4.0 : 1.0) albeit in good chemical yield. Interestingly, NOE experiments performed on *N*-tosylate

25c suggested that the structure of the major pyrrolidine is cis with regard to the C-2 and C-3 substituents.



Scheme 39

Evidence for the all trans configuration in pyrrolidines **24a-b** and the cis-trans configuration of **24c** was provided by NOE experiments performed on the corresponding *N*-tosyl or *N*-2-naphthalensulfonyl derivatives (**25a** and **25c**). The most diagnostic NOE enhancements are shown in Figure 14. As before, definitive assignments were based on a series of homonuclear decoupling experiments prior to NOE analysis. For the most selective cases (**24a-b**) trans configuration between the C-2 and C-3 substituents is believed to be the result steric effects similar to those governing the stereochemical outcome of imines **11a-c**. The avoidance of a severe 1,3-allylic strain is proposed to be the

driving force behind the trans orientation of the C-3 substituent and the C-4 methyl group (Figure 15).

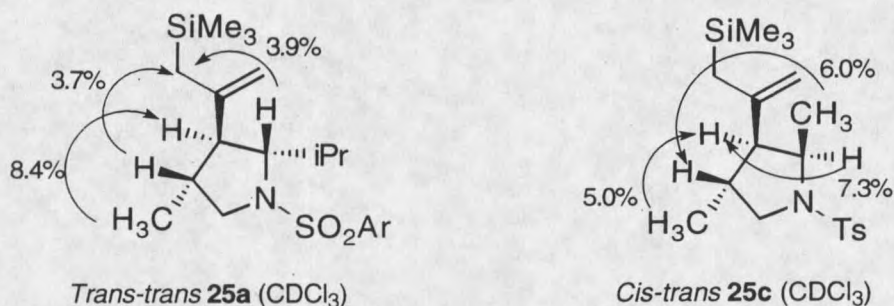


Figure 14. NOE Enhancements for 25a and 25c

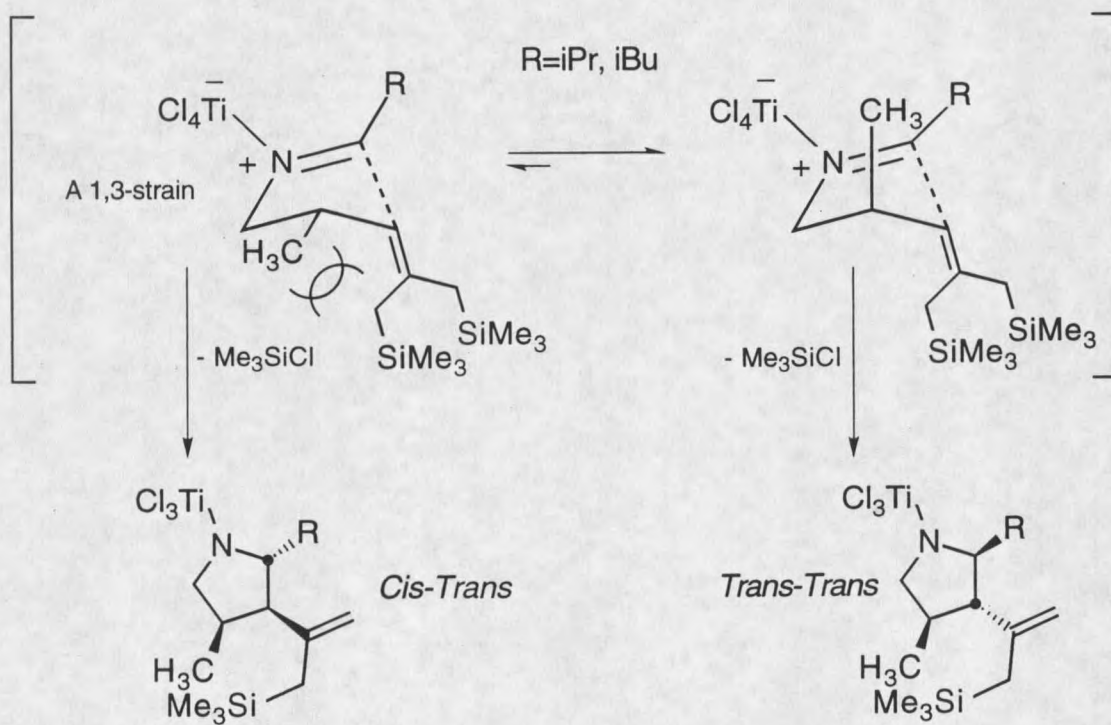
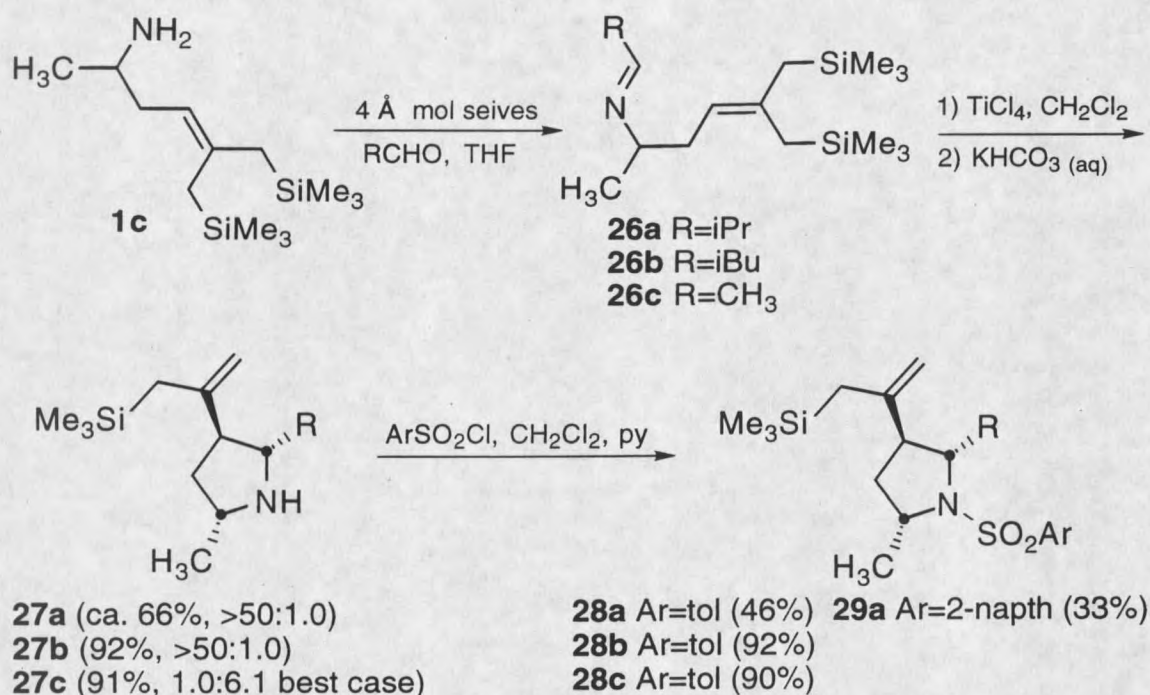


Figure 15. Transition State Models for 24a-b

This series of experiments was next performed using amine **1c** and conditions identical for the previous series involving **1b**. Of the three imines prepared from **1c**, only cyclization of the isovaleryl derived imine **26b** was

found to be efficient in chemical yield and trans diastereoselectivity (Scheme 40). Complete trans selection was also observed for the case of isopropyl substituted imine **26a** but with a severe decrease in yield. NMR analysis of the products obtained from cyclization of **26a** showed a 2.0:1.0 mixture of pyrrolidine **27a** and mono protodesilylated imine. Direct treatment of this mixture with TsCl secured the *N*-tosyl derivative **28a** in 46 % isolated yield from amine **1c**. This trans-trans pyrrolidine was found to be isomerically homogeneous by NMR. The proposed structure of the transition state responsible for the trans orientation of the C-3 and C-5 substituents is shown in Figure 16. The cis transition state would suffer from an allylic interaction that, although significant, would be of less magnitude than that governing the cyclization of imines from amine **1b** (Figure 15). Cyclization of acetaldehyde imine **26c** was carried out using the modified conditions developed for cyclization of **23c**. As with **23c** this imine cyclized in high yield but with modest selectivity. Diastereomer ratios were found to vary significantly from trial to trial and in the most selective run (6.1:1.0) NOE data pointed the major isomer having cis-trans structure (Figure 17).

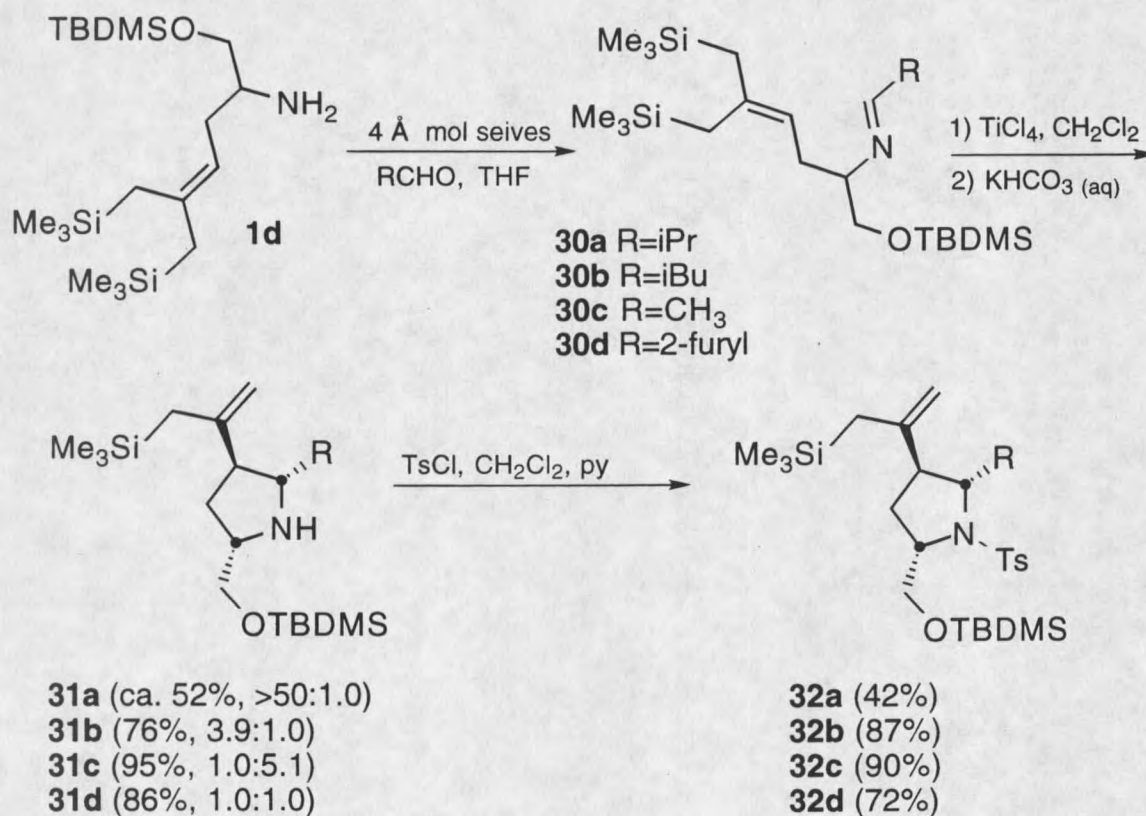


Scheme 40

Amine **1d** was hoped to provide the highest levels of substrate-based diastereocontrol since the large size of the TBDMS protecting group should induce more steric control over the transition state than the methyl substituent in imines originating from amines **1b-c**. The results of the cyclization of imines **30a-c** showed that this was not the case (Scheme 41). Isopropyl imine **30a** was found to undergo selective trans cyclization but an almost equal proportion of protodesilylated imine was also formed. Tosylation of this 1.3:1.0 mixture provided the pure trans derivative **32a** in 42% overall yield from amine **1d**.

Only modest levels of trans selectivity (4.7:1.0) were observed during the cyclization of imine **30b**. Surprisingly, NOE data pointed to the major pyrrolidine from cyclization of methyl imine **30c** as having an all trans structure. This result is inconsistent with the acetaldehyde imines originating from **1b** and

1c and serves to illustrate the random stereochemical nature observed in the cyclization of acetaldehyde imines. The aryl imine **30d** was subjected to cyclization but this resulted in even lower selectivities than the alkyl cases **30b-c**. The NOE data used to determine the structure of the pyrrolidines prepared from **1d** is also included in Figure 17. It should be mentioned that amounts of a third diastereomer could be detected in the product mixtures containing pyrrolidines **31b** and **31d**. Although the quantities were quite small, this observation does impose some limitation on the synthetic usefulness of cyclizations of imines derived from amine **1d**.



Scheme 41

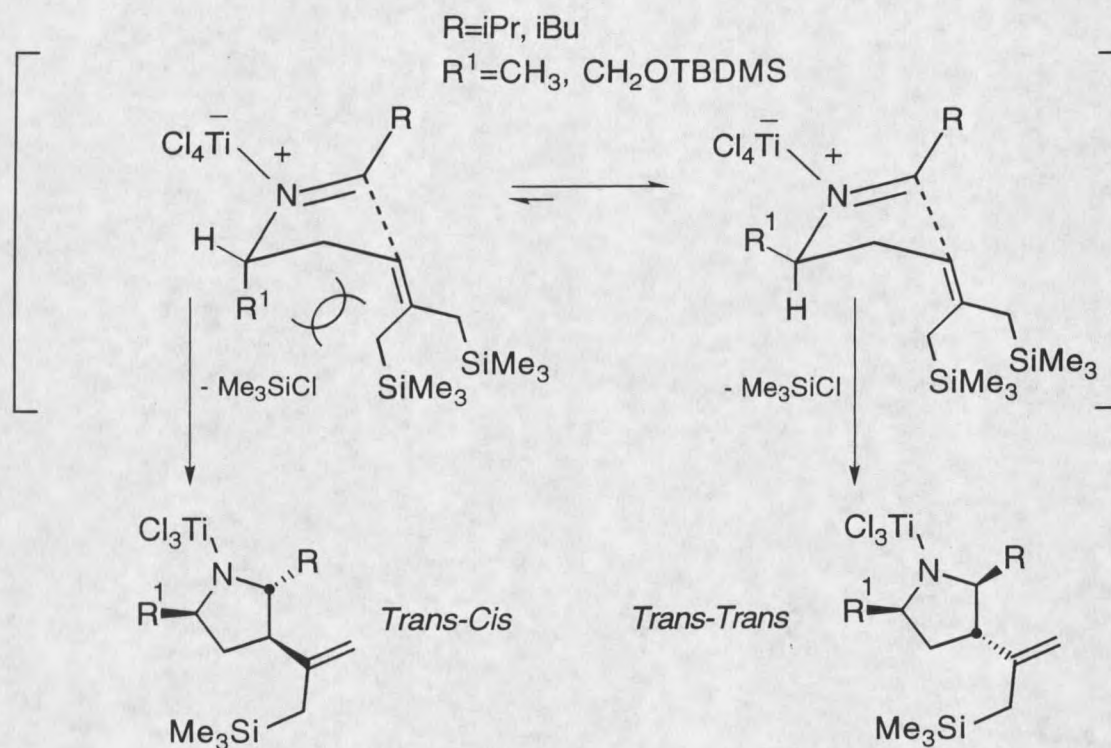


Figure 16. Transition States for Imines 26a-b and 30a-b

The results of this study concerning the stereoselective synthesis of trisubstituted pyrrolidines revealed several characteristics of the allylbis(silane) terminator. Foremost is the ability to form three new stereocenters in a stereocontrolled manner especially when alkyl groups of large steric size were employed on the starting aldehyde. Very high levels of all trans stereocontrol were obtained using isobutyraldehyde in conjunction with all three substituted amines (**1b-d**) and also employing isovaleryl aldehyde with amines **1b** and **1c**. The limit of general and consisted levels of diastereoselection was reached upon employing the smaller, more reactive imines derived from acetaldehyde and amines **1b-d**. These imines were found to undergo less selective cyclizations with significant fluctuation in the relative stereochemistry of the

resulting pyrrolidines. It is possible that rapid *E* to *Z* equilibration of the reactive acetaldehyde imines might be responsible for the stereochemical randomness of these cyclizations.

Regardless of stereoselectivity, the chemical yield of the trisubstituted pyrrolidines was generally quite high and in almost all cases, only one or two of the four possible diastereomers were detected. It is believed that this methodology might be quite applicable to the synthesis of stereodefined, pyrrolidine-based alkaloids. The remaining mono allylsilane substituent on the pyrrolidine ring should provide a versatile functional handle during synthesis of natural alkaloids.

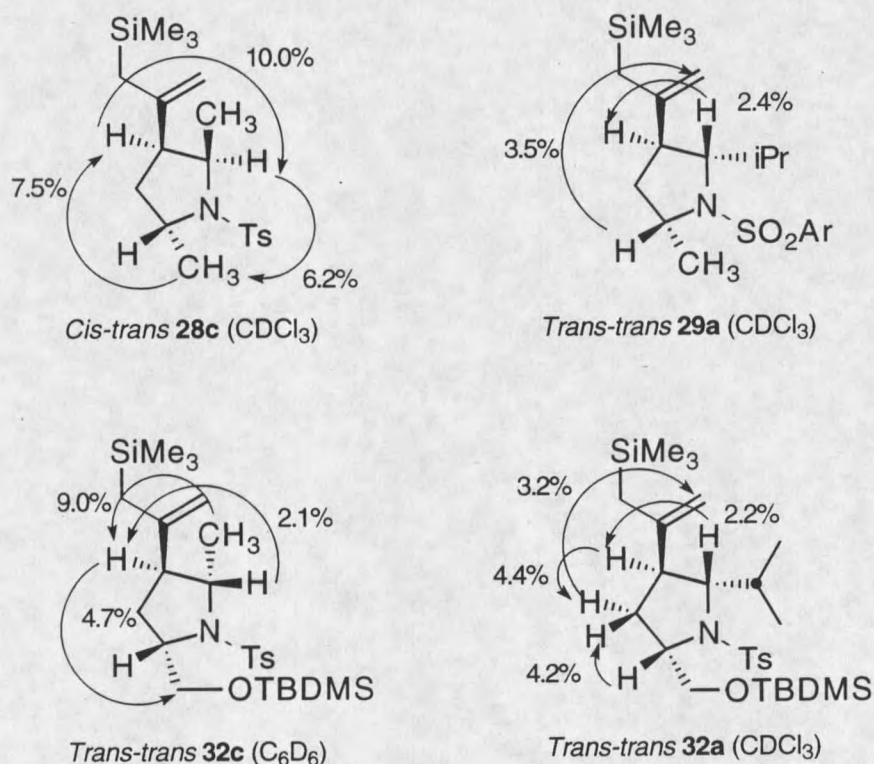


Figure 17. NOE Data for Pyrrolidines from Amines 1c and 1d

Cyclization of (S)-(-)-Ethyl Lactate-Derived Imines

In the 2-propylidene-1,3-bis(silane) imine cyclizations examined thus far, control over the relative stereochemistry was achieved between substituents contained within the pyrrolidine ring. In order to further probe the limits of diastereoselectivity, experiments were designed to see if these cyclizations could proceed with control of the orientation both endo and exo disposed stereocenters in the same cyclization. If successful, this transformation might be readily applied to the synthesis of stereodefined alkaloids. A pyrrolidine nucleus containing three adjacent stereocenters, two endo and one oxygenated exo center, is found in many pyrrolidine alkaloids⁵⁵, pyrrolizidine alkaloids like (-)-terneforicidine⁵⁶ and also in the tricyclic core of Stemofoline (Figure 18).

There are many examples of the stereoselective *intermolecular* additions of mono allylsilanes to SP^3 hybridized carbon electrophiles.^{6,9} Such reactions have been found to be governed by either coordination effects such as chelation control⁵⁷ or steric approach constraints⁵⁸ including Cram trajectories.⁵⁹ It was believed that these control devices might be applicable to the allylbis(silane) imine cyclizations in order to gain access to an additional, exocyclic stereocenter.

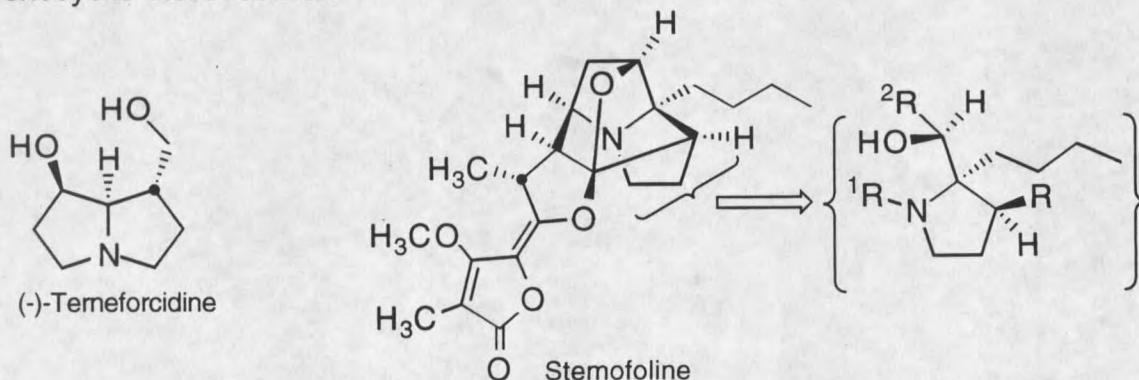
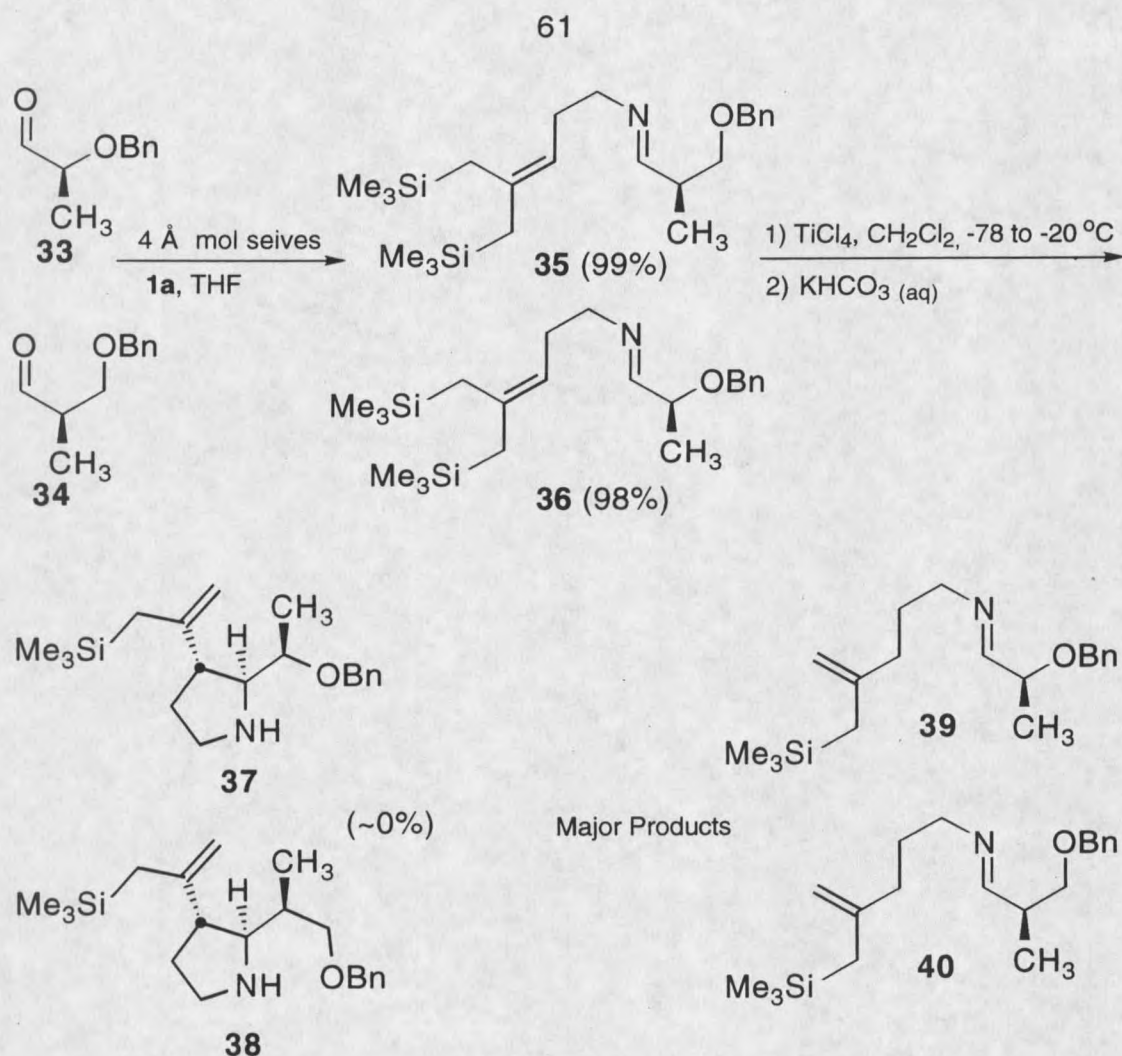


Figure 18. Naturally Occurring, Three Center Pyrrolidine Nuclei

Imines capable of chelation with Lewis acids were first synthesized and subjected to the cyclization conditions. The known, benzyl-protected aldehydes **33** and **34**, prepared from (*S*)-Ethyl lactate⁶⁰ and 2-methyl-2-propen-1-ol⁶¹ respectively, were condensed with amine **1a** over 24 hours to provide imines **35** and **36** (Scheme 42). Conditions employing TiCl_4 at low temperatures failed to produce any amounts of the desired pyrrolidines **37** and **38** via chelation control originating from five and six membered chelates respectively. In fact, no cyclic products were ever detected but rather unwanted imines **39** and **40** arising from protodesilylation of **33** and **34** were obtained as the major products. Successful cyclization was never realized even after extensive experimentation with conditions and various Lewis acids.

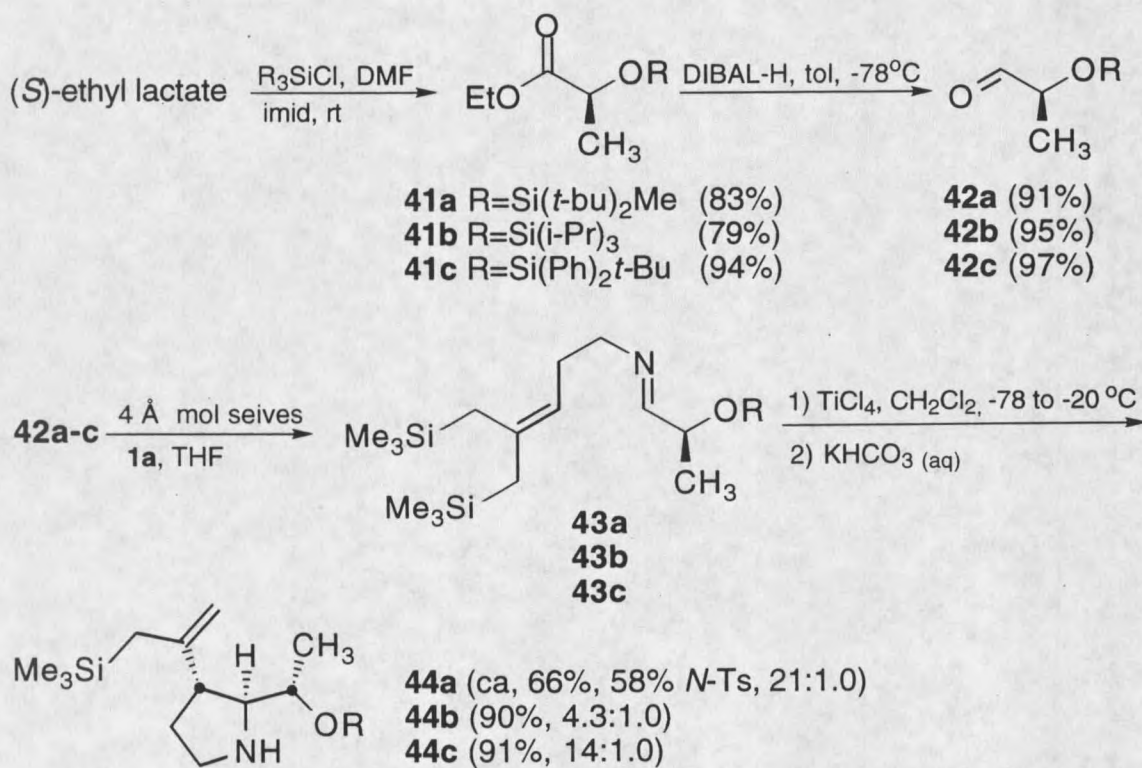


Scheme 42

Alcohol protecting groups not prone to coordination with Lewis acids were next installed on the cyclization precursors. Alcohols protected by bulky trialkyl silanes such as triisopropyl silane (TIPS) were reported by Eliel not to undergo coordination with cationic magnesium, aluminium or lithium reagents.⁶² These groups seemed to be ideal candidates for anti approach cyclizations terminated by the large 2-propylidene-1,3-bis(silane) nucleophile.

A series of silane protected hydroxy aldehydes were prepared with alkyl groups of varying size on the silicon atom. Silylation of the secondary alcohol

of (*S*)-ethyl lactate using standard conditions⁶³ provided the silyl ethers **41a-c** in good yield (Scheme 43). Partial reduction of the ester functional group to the aldehyde was then efficiently achieved using diisopropyl aluminum hydride (DIBAL-H) at low temperatures.⁶⁴ A trimethylsilyl analog was also prepared but was found to be quite sensitive to Si-O cleavage during the reduction step. Hence it was eliminated from the series of aldehydes. Room temperature condensation of the resulting aldehydes **42a-c** with amine **1a** occurred cleanly over 24 hours to furnish the corresponding imines **43a-c**.



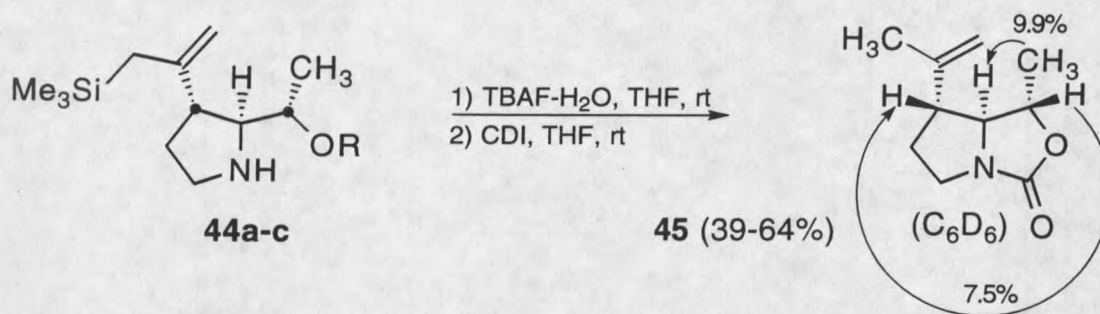
Scheme 43

Gratifyingly, treatment of the imines with TiCl₄ at -78 °C for one hour followed by 24 hours at -20 °C provided the anti-trans pyrrolidines **44a-c** in excellent yield after careful neutralization with KHCO₃ and purification on

Florisil (Scheme 43). More importantly, levels of diastereoselection were quite high with respect to a second isomer detected by NMR and GC in the crude product mixtures. The NMR spectrum of the products produced from TBDMS imine **43a** revealed a large amount of desilylated imine had also formed (ca. 34%). This could have possibly originated from some coordination of TiCl_4 to this relatively less bulky, TBDMS ether. The pyrrolidine **44a** was secured as the *N*-tosyl derivative in modest purified yield (58%) after direct treatment of the crude mixture with TsCl .

Elucidation of the relative stereochemistry of pyrrolidines **44a-c** was obtained from NOE analysis of the corresponding oxazolidinone derivatives.⁶⁵ Exhaustive desilylation of **44a-c** using tetrabutyl ammonium fluoride hydrate provided the crude amino alcohols which were immediately exposed to carbonyldiimidazole to afford oxazolidinone **45** (Scheme 44). The major oxazolidinones obtained from **44a-c** using this sequence were found to be identical with respect to spectrometric (^1H and ^{13}C NMR) and chromatographic (TLC) properties.

Most informative was a large transannular NOE effect (7.5%) observed between the C-3 methine hydrogen and the hydrogen located on the exocyclic methine. Simple models suggest that such a through space interaction between these protons is only possible if oxazolidinone **45** is in the anti-trans stereochemical configuration shown. The high diastereoselectivity of these cyclizations can be rationalized by a transition state involving a Cram type trajectory of the allylbis(silane) nucleophile in a conformation that also avoids non bonded interaction with the imine substituent (Figure 19).



Scheme 44

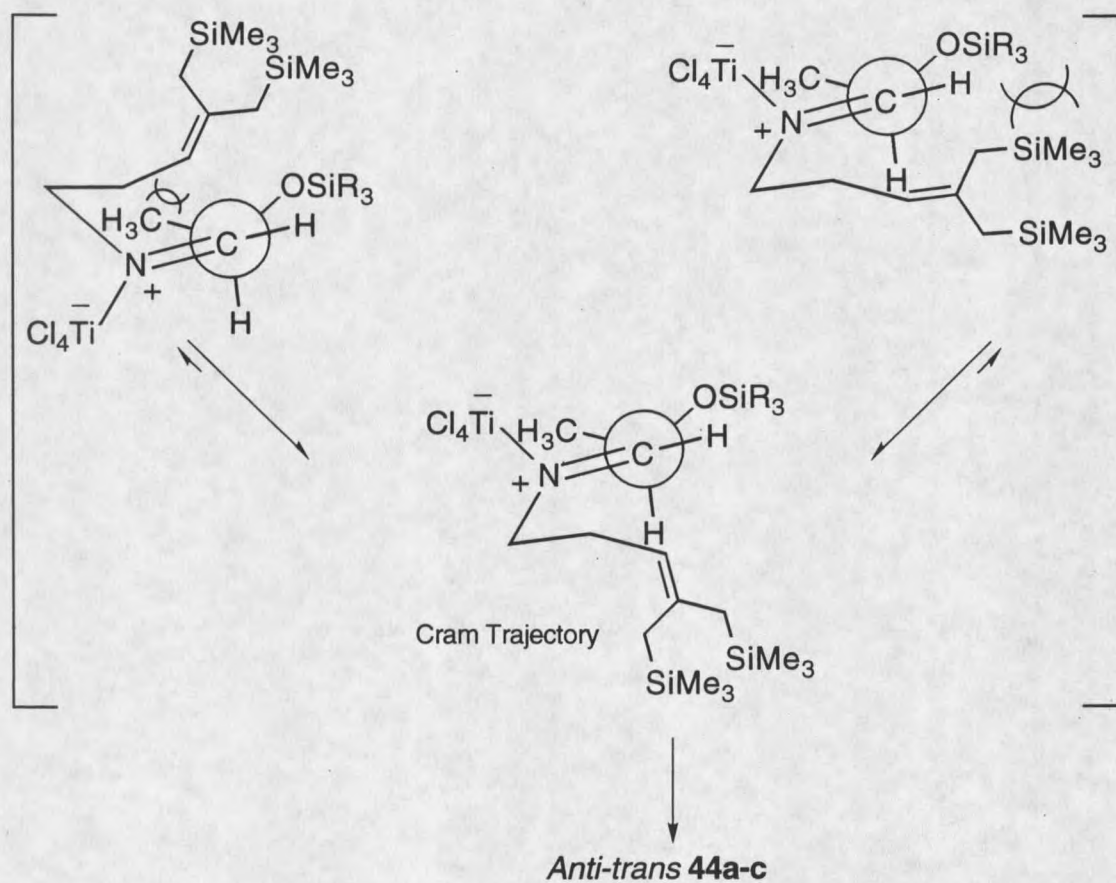


Figure 19. Diastereotopic Transition States for 44a-c.

2-Propylidene-1,3-bis(silane) C-Acylnitrilium Ion Cyclizations

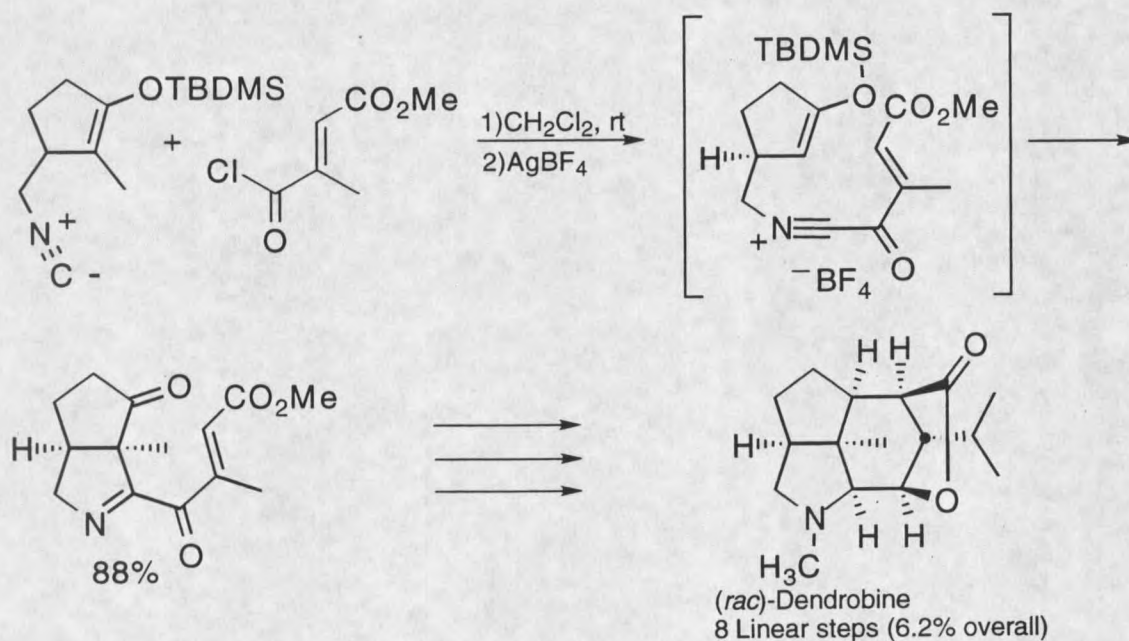
All of the cyclizations described thus far have involved the intramolecular coupling of the allylbis(silane) nucleophile with electron deficient imines. Before progressing towards application to the synthesis of alkaloids it was deemed advantageous to test the compatibility of this cyclization terminator with other types of initiators. The *C*-acylnitrilium ion (Figure 8) was immediately chosen as an alternative electrophile for numerous reasons. The structure of nitrilium cations provides additional functionality and reactivity which are brought about by the presence of a carbonyl group and an additional degree of unsaturation.

More importantly, this combination of initiator and silicon-based terminator has not been previously investigated and accounts of intramolecular addition of mono allylsilanes to *C*-acylnitrilium ions were unable to be found in the literature. The studies that were performed involved terminators other than allylsilanes and provided little insight into the diastereoselective nature of *C*-acylnitrilium ion cyclizations. As a result, this portion of the allylbis(silane) research would hopefully spawn advancements and reveal knowledge with respect to both the initiator and terminator elements of the reaction.

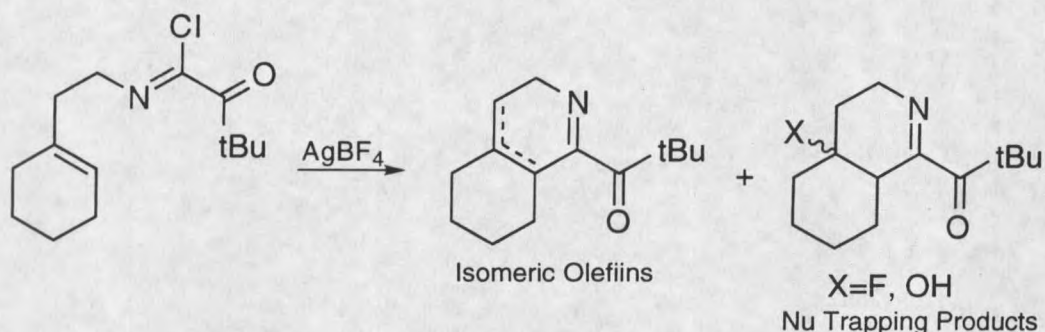
The majority of the research involving the generation and cyclization of *C*-acylnitrilium ions has come out of the Livinghouse research group. Work performed by previous group members has demonstrated that pi nucleophiles such as silyl enol ethers and arenes are suitable terminators for the cyclizations initiated by the acylnitrilium ion.^{30,66} Through this work an efficient and reliable method for the mild generation of *C*-acylnitrilium ions has been developed which involves the ionization of ketoimidoyl halides by silver (I) salts at low

temperatures. This protocol has culminated in a efficient synthesis of the sesquiterpene alkaloid dendrobine carried out by Cheol Lee in 1991 (Scheme 45).⁶⁷

Former coworker Dave Hughes has also shown that unactivated alkenes also efficiently add to keto imidolyl halides in the presence of silver salts to form fused, bridged and directly-connected bicyclic pyrrolines.⁶⁸ Although this served to demonstrate the reactivity associated *C*-acylnitrilium ions, lack of regioselectivity was observed in some cases (Scheme 46). Implementation of a suitable mono allylsilane was, surprisingly, not performed in an attempt to gain regiospecificity.

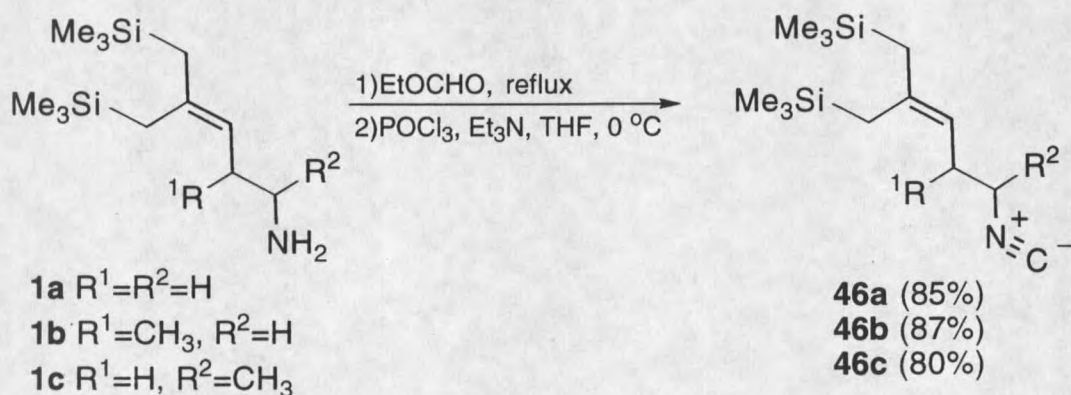


Scheme 45



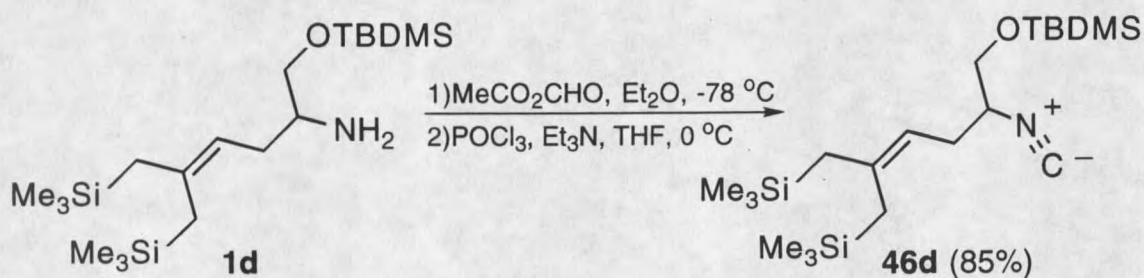
Scheme 46

This study commenced with the synthesis of requisite, isonitrile precursors from previously prepared amines **1a-d**. Following standard procedures for the preparation of isonitriles^{30,66-68}, *N*-formylation of amines **1a-c** was achieved by treatment with freshly neutralized and distilled ethyl formate at reflux to furnish the corresponding formamides. Dehydration of the crude formamides with POCl_3 in the presence of a triethyl amine buffer furnished the target isonitriles **46a-c** in good overall yield after purification on silica gel (Scheme 48). Fortunately, products resulting from electrophilic desilylation of the 2-propylidene-1,3-bis(silane) addend were not observed during the formylation-dehydration sequence.



Scheme 48

The sterically hindered amine **1d** failed to show significant signs of reactivity during exposure to refluxing EtO₂CHO. Higher temperatures incorporating n-butyl formate did promote complete amine to amide conversion but analysis of the isolated products also revealed that mono- and some di-protodesilylation of the sensitive 2-propylidene-1,3-bis(silane) terminator had occurred during the reaction. It is believed that the n-butanol liberated during formylation served as the proton source for this unwanted desilylation at elevated temperatures. In addition, the formation of the strong Si-O bond in the n-BuOSi(Me)₃ byproduct would provide thermodynamic momentum for a carbon to oxygen transfer of the trimethylsilane group. This problem was overcome by switching to the very reactive, acetic formic anhydride⁶⁹ to promote *N*-formylation of amine **1d**. Cold temperature treatment of **1a** with freshly prepared MeCO₂CHO (1.05 equiv.) resulted in total amine consumption after 30 minutes at -78 °C. Careful basic quench using NaHCO₃ and dehydration of the resulting crude formamide with POCl₃-Et₃N then provided isonitrile **46d** in 85% overall yield (Scheme 49).



Scheme 49

The alkylative cyclization of isonitrile **46a** was examined first. Addition of **46a** into a variety of simple and functionalized acid chlorides was found to occur cleanly at room temperature in CH₂Cl₂ to provide the intermediate

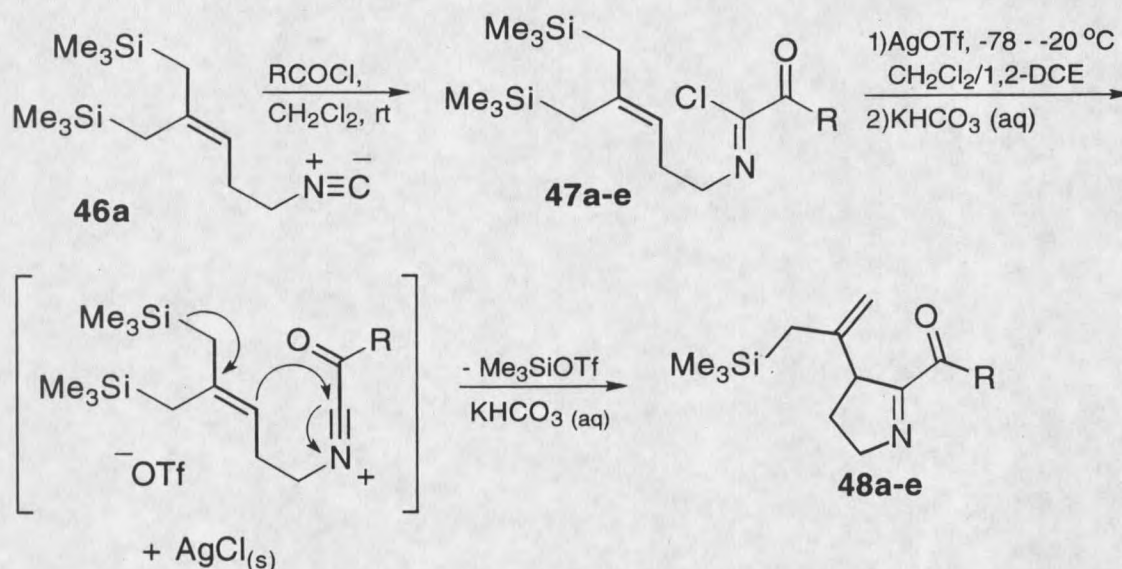
ketoimidoyl chlorides **47a-e** (Scheme 50). Experiments performed in an NMR tube showed that a reaction time of approximately 12 hours was optimal for complete isonitrile consumption in all cases examined. These NMR experiments also revealed that, in the worst cases, only trace amounts of protodesilylated materials were formed when freshly neutralized and distilled acid chlorides were employed. This eliminated a need for an amine buffer which could possibly interfere with the ensuing cyclization process.

Not all of the acyl chlorides screened underwent clean addition with **46a**. When enones such as crotonyl chloride were used, the formation of large quantities of chlorotrimethylsilane and terminal olefin residues was observed while monitoring the reaction progress. It appears that functionalization of the isonitrile nucleophile was not chemoselective but rather the allylbis(silane) nucleophile also reacted with the unsaturated acyl chloride.

Immediate exposure of the crude ketoimidoyl chlorides **47a-e** to AgBF_4 in CH_2Cl_2 - $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1,2-DCE) at a temperature range of -78 to -65 °C did provide the desired Δ^1 -pyrrolines **48a-e** but in low isolated yields (<20-70%), (Table 3). During chromatographic purification of **48a-e**, significant amounts of acyclic, desilylated materials were also isolated. It is believed that formation of these byproducts had arisen from the presence of hydrofluoric acid in the stock solutions of AgBF_4 that were prepared.

Commercial AgOTf proved to be superior for inducing the ionization-cyclization sequence. This was carried out by treating a suspension of AgOTf in CH_2Cl_2 /1,2-DCE with a solution of the freshly prepared, crude ketoimidoyl chloride at -78 °C followed by stirring for 2-6 hours at -20 °C. Cautious neutralization of the cold reaction mixture was then performed with KHCO_3 . Cyclizations performed in this manner provided pyrrolines **48a-e** in far better

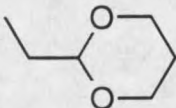
isolated yields than with AgBF_4 (Table 3) and these conditions became standard for all cyclizations involving isonitriles **26a-d**.⁷⁰

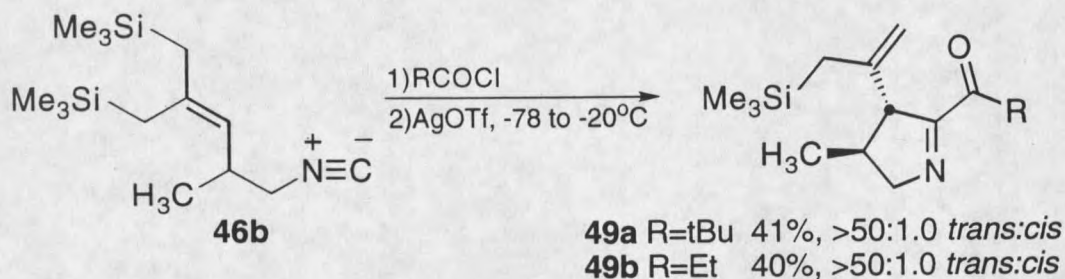


Scheme 50

The silver-mediated cyclization of ketoimidoyl chlorides derived from isonitrile **46b** were found to proceed with excellent levels of substrate based diastereocontrol⁵² (>50:1.0 NMR) in favor of the trans isomers **49a** and **49b** (Scheme 51). Isolated yields of these two pyrrolines were quite low in comparison to those obtained from isonitrile **46a**. The cyclization reactions were also carried out at -50 °C for 24 hours but no improvement in the yield of **49a** and **49b** was achieved. Functionalized acid chlorides were chosen not to be implemented in the cyclizations involving **46b** as a result of these low yields.

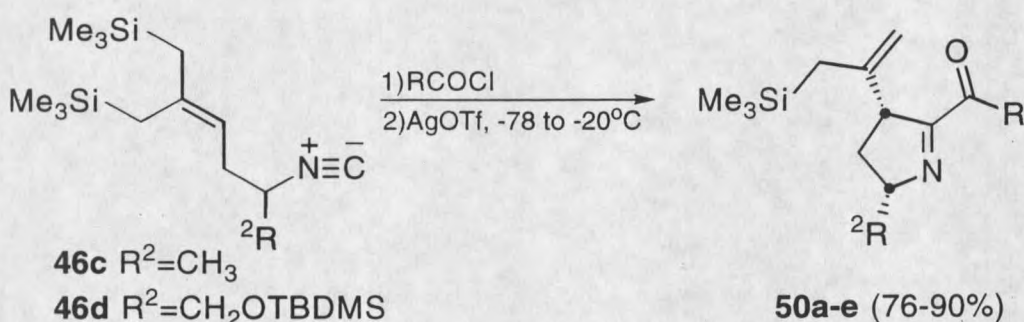
Table 3. Results for the Acylative Cyclization of Isonitrile 46a

Acylchloride (-R)	Δ^1 -Pyrroline	AgOTf	%Yield from 46a	AgBF ₄
-C(CH ₃) ₃	48a	82		70
-CH(CH ₃) ₂	48b	68		60
-CH ₂ CH(CH ₃) ₂	48c	77		27
-CH ₂ CH ₂ CH ₂ Cl	48d	61		<20
	48e	91		<20

**Scheme 51**

Cyclization of ketoimidoyl chlorides prepared from isonitriles **46c** and **46d** did occur with greater chemical efficiency (Scheme 52). Pyrrolines **50a-e** were prepared in good to excellent isolated yields but with lower diastereoselectivity in favor of the *cis* isomers (Table 4). As in the case of the

cyclizations involving **46b**, longer reaction times at lower temperatures failed to promote significant change in both yield and stereoselection. Fortunately, the major cis pyrrolidine isomers could be readily separated from the minor isomer by conventional chromatography on silica gel. This enabled synthetically useful quantities (47-65%) of pure cis pyrrolidines to be obtained from isonitriles **46c** and **46d**.

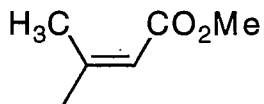


Scheme 52

As in the analysis of the pyrrolidine products obtained from the imine cyclizations, the relative stereochemistry of the substituted Δ^1 -pyrrolines **49a-b** and **50a-e** was elucidated by NOE spectroscopy. Several representative NOE enhancements are illustrated in Figure 20. For the cis pyrrolines, the observance of a large NOE interaction from the C-3 and C-5 methine hydrogens to the *same* proton on the centrally located, C-4 methylene was particularly diagnostic. In contrast to the cis isomers, the only significant NOE enhancements which were observed upon irradiation of the C-3 and C-5 methine protons of the minor trans isomers were to *different* protons on the central C-4 methylene.

The stereochemical outcome of the cyclizations involving isonitriles **46b-d** can be rationalized by transition state conformations that avoid non bonded

Table 4. Data for Acylative Cyclizations of Isonitriles 46c-d

Isonitrile ($-R^2$)	Acylchloride ($-R$)	Pyrroline	Yield (Isolated <i>Cis</i>)	<i>Cis:Trans</i>
46c	$-\text{C}(\text{CH}_3)_3$	50a	90 (65)	4.6 : 1.0
46c	$-\text{CH}_2\text{CH}_3$	50b	78 (49)	3.8 : 1.0
46d	$-\text{C}(\text{CH}_3)_3$	50c	87 (56)	2.6 : 1.0
46d	$-\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$	50d	77 (48)	4.5 : 1.0
46d		50e	76 (47)	3.0 : 1.0

interactions (Figure 21). The comparatively lower levels of 1,3 stereo induction observed in the cyclization of **46c** and **46d** could be the result of an allylic through space interaction that is less profound than in the cases involving high levels of 1,2 stereo induction (**49a** and **49b**). These transition states are conceivably quite analogous to those governing the trans selective imine cyclizations involving amines **1b-d** (Figures 15 and 16). Hence the comparatively lower selectivities observed in the acylnitrilium ion cyclizations could very well reflect the very reactive nature of the acylnitrilium ion initiator.

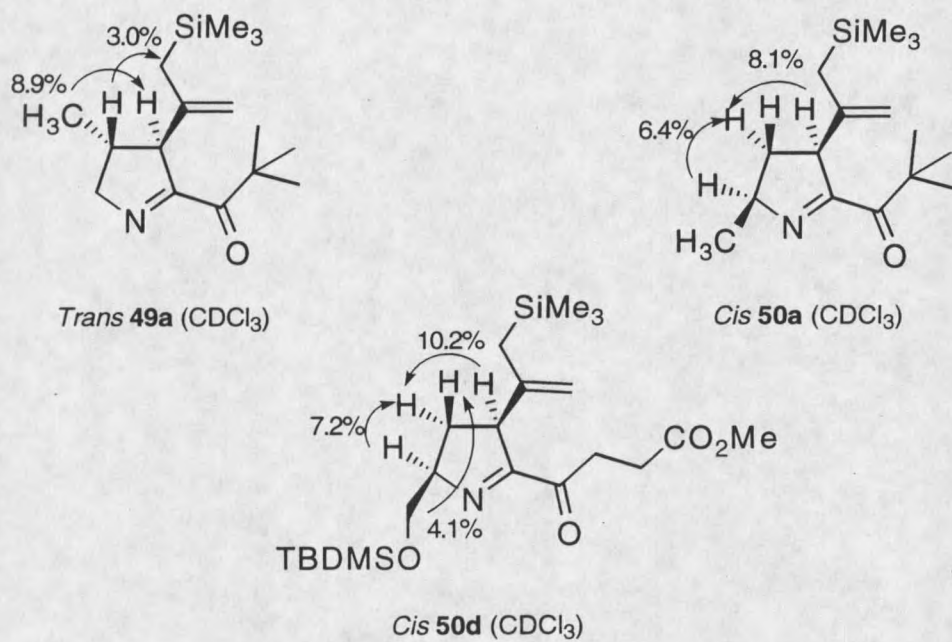


Figure 20. Diagnostic NOE Data for Substituted Pyrrolines

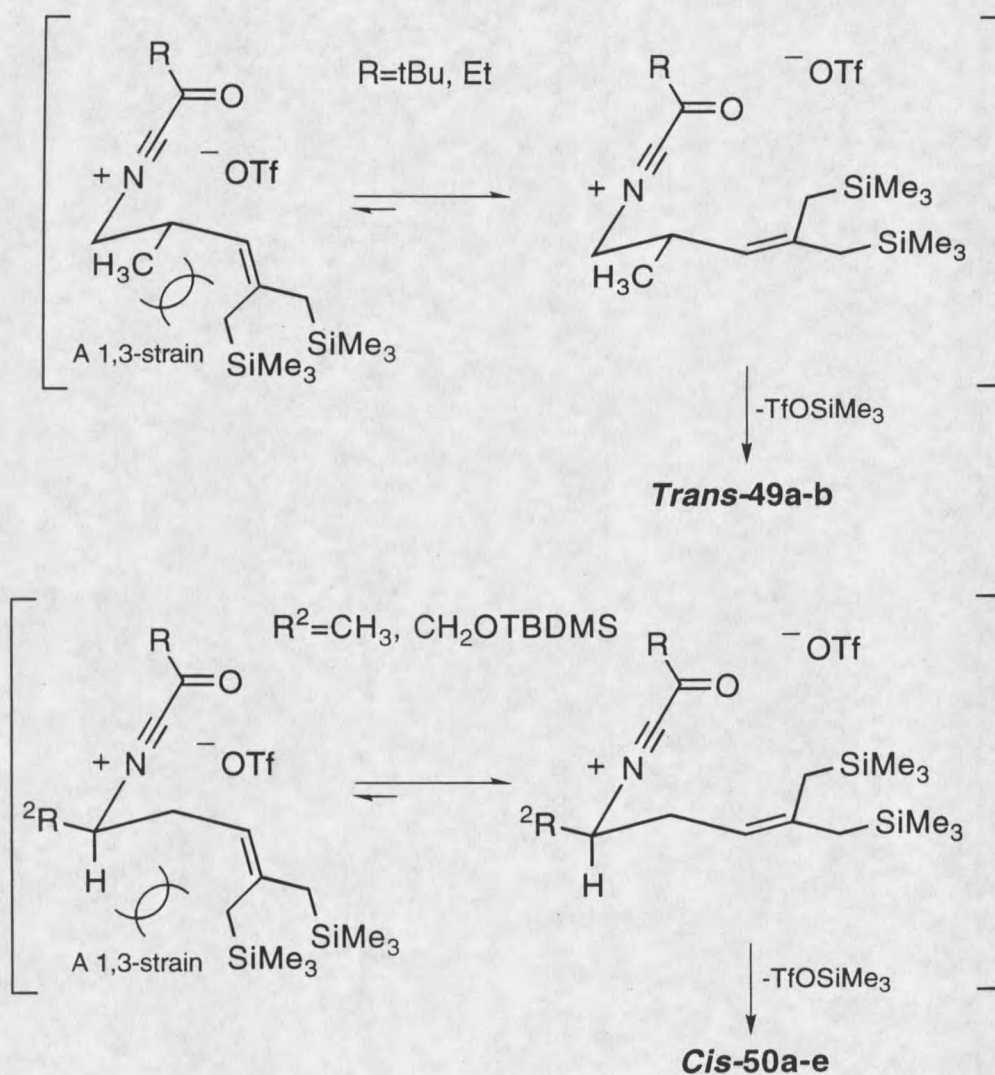
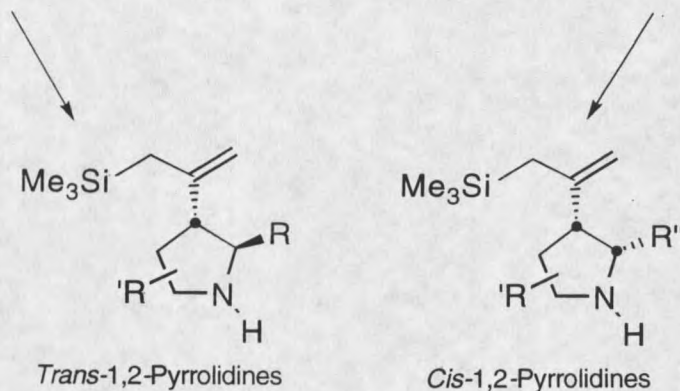


Figure 21. Diastereotopic Transition States for Cyclization of 46b-d

A sample of the Δ^1 -pyrrolines were transformed into saturated pyrrolidine analogs that have cis configuration at the C-2 and C-3 positions.⁷⁰ This was performed in order to demonstrate that this cyclization methodology could be used to synthesize pyrrolidines that stereochemically complement those prepared by the TiCl_4 -mediated cyclization of 2-propylidene-1,3-bis(silane) imines⁵¹ (Scheme 53).

Metallo Imine Cyclization

Acynitrilium Ion Cyclization-Reduction



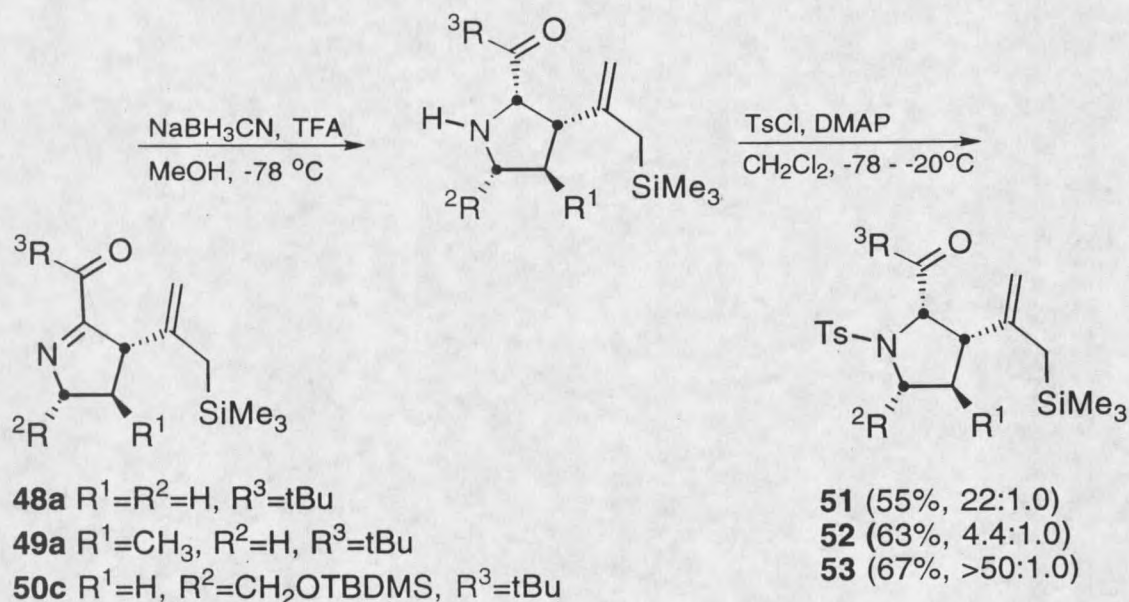
Scheme 53

It was discovered that this reduction could be readily accomplished by treatment of pyrrolines **48a**, **49a** and **50a** with excess NaBH_3CN and trifluoroacetic acid (1.05 equiv.) at $-78\text{ }^\circ\text{C}$ in methanol (Scheme 54). The resulting crude pyrrolidines were not purified but immediately subjected to *N*-tosylation under mild conditions (TsCl , DMAP, -78 to $-20\text{ }^\circ\text{C}$) to afford the sulfonamide derivatives **51-53**.

In this fashion, the basic pyrrolidines were safe guarded against epimerization at the labile C-2 stereocenter. Such epimerization has been observed in similar pyrrolidine systems by Overman upon exposure to silica gel.⁷¹ Derivatization also enabled the major isomer of **52** to be secured from the minor by fractional crystallization.

The reduction was observed to be quite stereoselective (22 to $>50 : 1$) for pyrrolines **48a** and **48c** which contain considerable facial bias around the region of unsaturation. As predicted, lower selectivities were realized during reduction of trans pyrroline **49a**. Evidence for the anti approach of hydride during the reduction of was provided by NOE experiments performed on *N*-

tosylates **51-53** after definitive assignments were made from homonuclear decoupling experiments. The results of the diagnostic NOE experiments are summarized in Figure 22 and are consistent with and, therefore, serve to support the initial stereochemical assignments of pyrrolines **49a-b** and **50a-e**.



Scheme 54

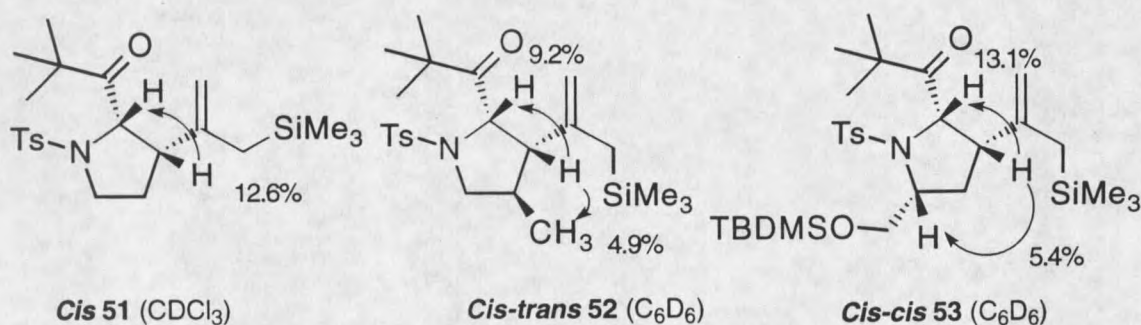
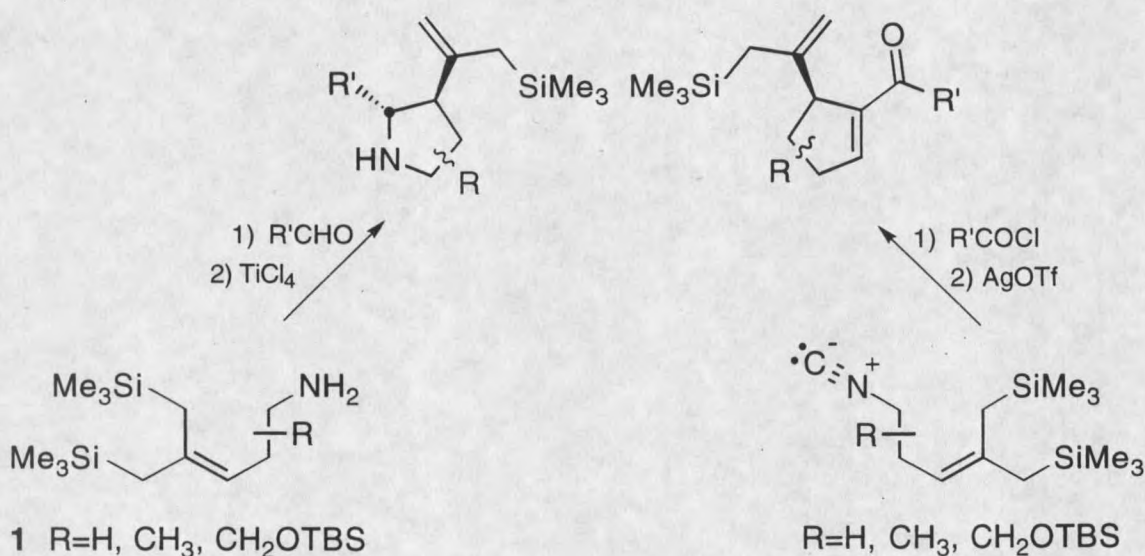


Figure 22. Diagnostic NOE Results for Pyrrolidines 51-53

Stereoselective Synthesis of Piperidines

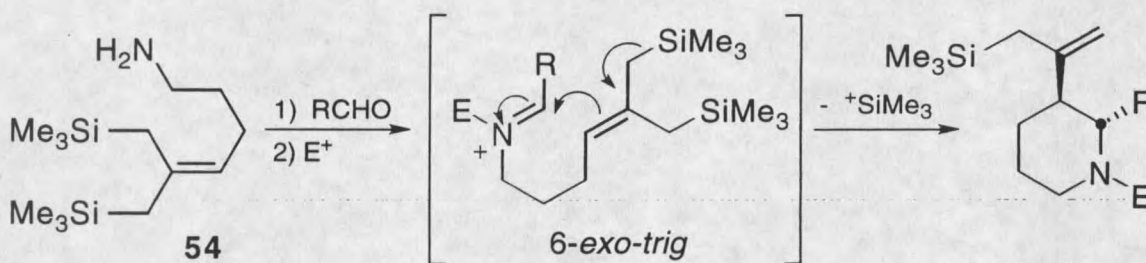
In the course of this research, the newly developed 2-propylidene-1,3-allylbis(silane) nucleophile has been found to be a highly reactive and functionalized cyclization terminator capable of directing intramolecular ring formation onto iminium ions⁵¹ and transient acylnitrilium ions⁷⁰ (Scheme 55). As a result, functionally diverse pyrrolidines and acyl pyrrolines were efficiently prepared in good chemical yield with not only complete regiochemical control but with high levels of substrate based diastereochemical control as well.



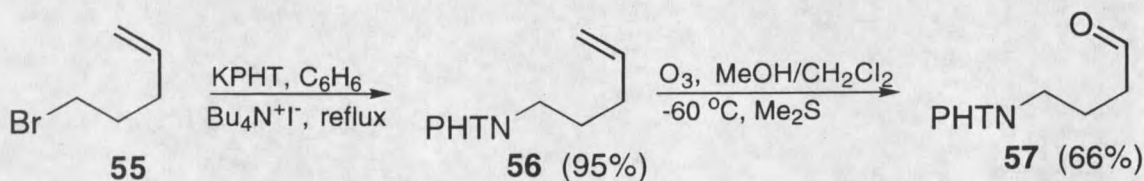
Scheme 55

With these results in mind, the testing of the ability of the allylbis(silane) terminator to direct the formation of six-membered azacycles via the intramolecular trapping of iminium ions was singled out as a worthy research endeavor. With an efficient synthesis of amino allylbis(silanes) of type **1** having already been devised, it was believed that the carbon chain homologue **54**

could be rapidly assembled (Scheme 56). This would allow quick access to the experimental investigation of a stereocontrolled piperidine synthesis that utilizes this cyclization terminator.



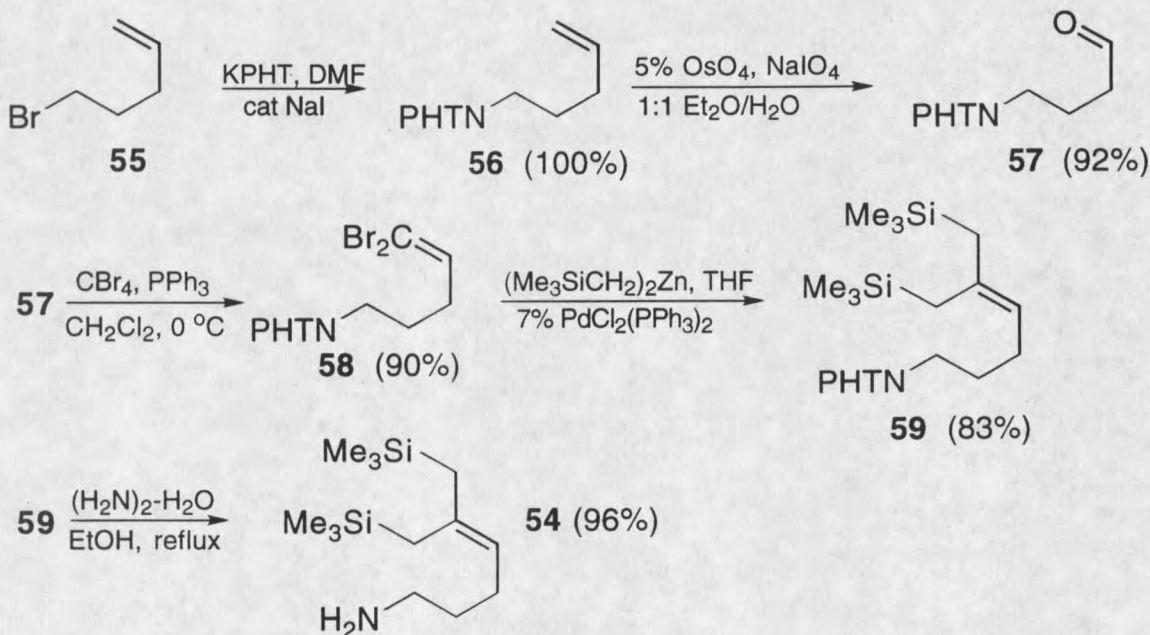
This study began with the synthesis of amino allylbis(silane) **54**. Since phthalimido aldehydes were found to be suitable precursors to amines of type **1**, known aldehyde **57** was initially prepared (Scheme 57). It was reported that **57** could be synthesized by phase transfer, phthalimide substitution of commercially available 5-bromo-1-pentene followed by oxidative cleavage of the carbon double bond with ozone.⁷² When this sequence was executed, it was found however that the crude aldehyde underwent unavoidable polymerization during purification after initial isolation from the ozonolysis reaction medium.



A more efficient method for the production of **57** was developed.

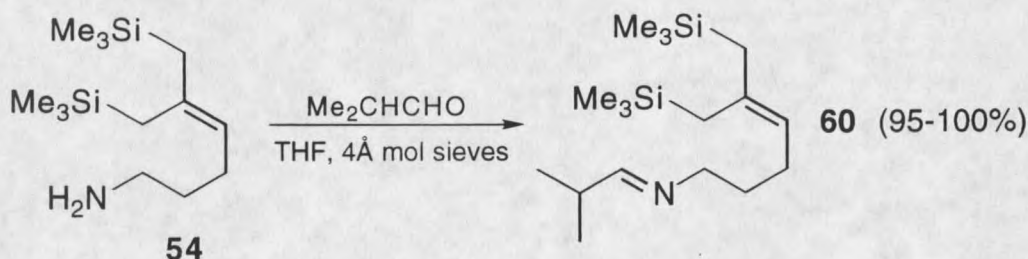
Treatment of bromo olefin **55** with KPHT in DMF containing a catalytic amount of NaI furnished phthalimide **56** in quantitative yield after purification. Rather than employing ozone, oxidative cleavage of the double bond in **56** was achieved with catalytic OsO₄ and NaIO₄ under biphasic conditions.⁷³ In this fashion pure aldehyde could be obtained in 92% purified yield without any polymerization being observed during isolation and purification (Scheme 58).

With large amounts of the starting aldehyde in hand, the previously developed dibromo olefination and tandem cross coupling procedures^{51,70} were implemented to provide the protected amine **59** in high purified yield. Hydrazine-mediated deprotection then secured the target amine in 96% yield after bulb to bulb distillation.



Scheme 58

Amine **54** was next subjected to the condensation- TiCl_4 mediated cyclization protocol. Condensation of **54** with isobutyraldehyde occurred cleanly to afford imine **60** in high yield (Scheme 59). It should be mentioned that a pure sample of imine **60** in CDCl_3 was observed to undergo complete decomposition after 48h at rt. and suggests thermal and or air instability of the compound. As a precaution, all cyclization experiments performed on imines prepared from amine **54** were executed without delay using immediately isolated imine.

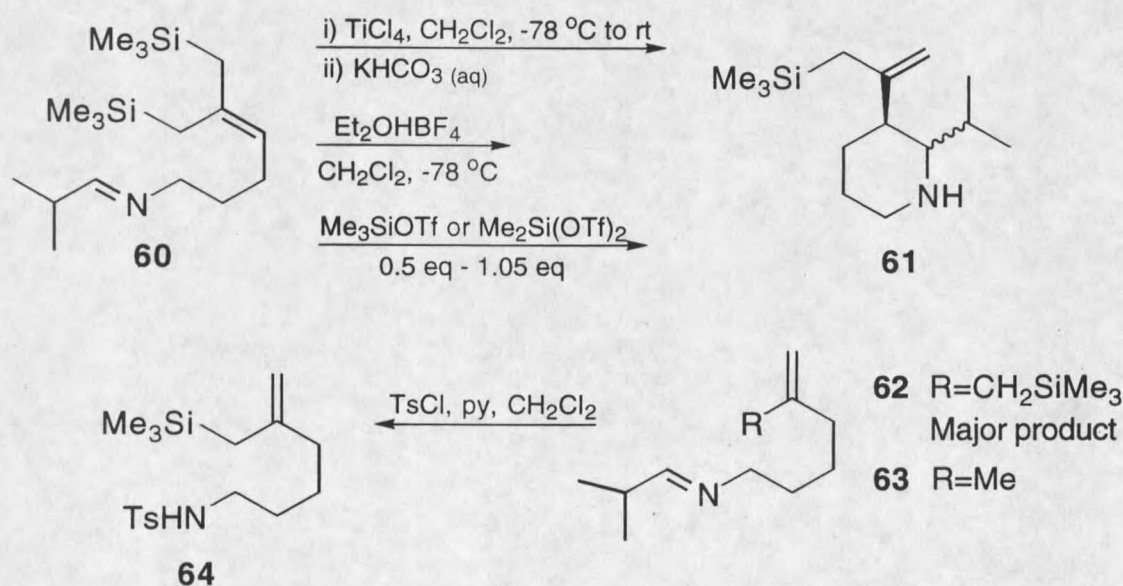


Scheme 59

Treatment of imine **60** with freshly purified TiCl_4 (1.00 equiv., CH_2Cl_2) at -78°C followed by slow warming to rt. and careful base quench did not result in isolation any of the desired piperidine **61** (Scheme 60). Rather, mixtures consisting primarily of desilylated imine **62** and small amounts of imine **63** were obtained. Verification of the major product was provided by the isolation of tosylamine **64** after treatment of the cyclization products with TsCl and pyridine.

Similar results were obtained using either TMSOTf or $\text{Me}_2\text{Si}(\text{OTf})_2$ in either stoichiometric or catalytic (0.5 equiv.) quantities. In these experiments acyclic desilylated materials were observed as the major products. Nitrophilic lewis acids such as $\text{Cu}(\text{OTf})_2$ also failed to induce cyclization. The undesired

imine **62** was also formed in high yield upon exposure of **60** to Bronsted acids such as TFA and Et_2OHBF_4 at low temperatures. Attempts to carry out alkylative or acylative cyclizations using either MeOTf , $\text{Et}_3\text{O}^+\text{BF}_4^-$, TFAA or CNBr also met with failure to produce any of the desired cyclic products. As a result of these initial experiments, alternative strategies for initiating cyclization of imines derived from **54** and alkyl aldehydes are currently under investigation.

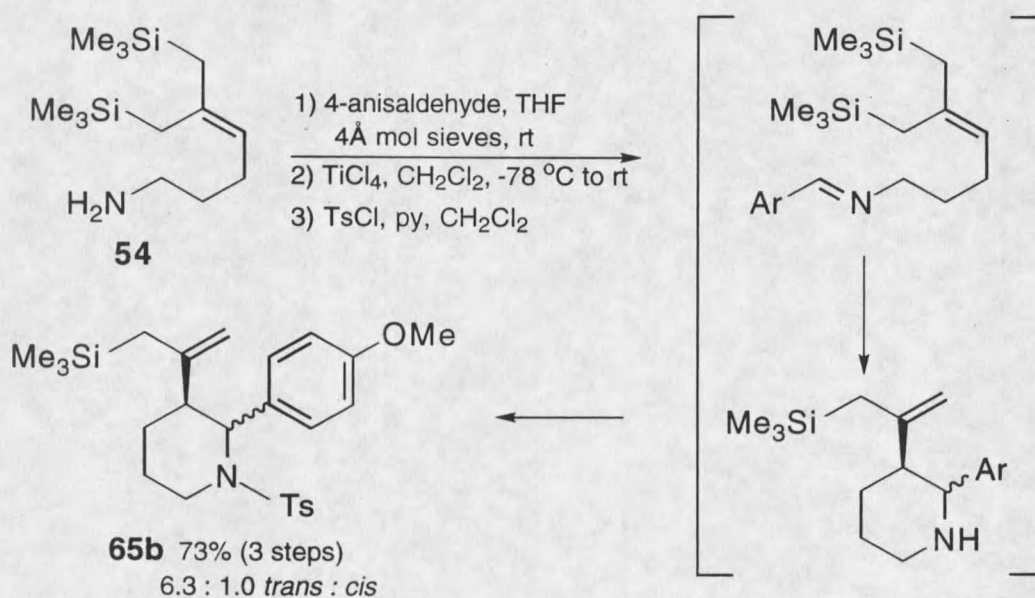


Scheme 60

Successful cyclizations were achieved upon employing imines derived from aryl aldehydes. For example, condensation of amine **54** with 4-anis aldehyde followed by exposure of the crude imine to TiCl_4 under standard conditions furnished a diastereomeric mixture of piperidines **65b** in 73% purified yield after treatment of the crude cycles with TsCl (Scheme 61).

NMR analysis of the crude *N*-tosylates indicated a 6.3 : 1.0 ratio of stereoisomers and the relative configuration of the C2 and C3 substituents in the major component was found to be *trans* as indicated by NOE experiments

performed on the individual isomers (Figure 23). Most informative was the observance of a large (12.4%) NOE enhancement between the C2 and C3 methine protons in the minor isomer compared to a significantly smaller enhancement (3.6%) observed in the major component. These NOE results, combined with the values previously obtained from NOE analysis of the *N*-tosyl pyrrolidines, permitted the major isomer to be confidently assigned as the *trans* stereoisomer.



Scheme 61

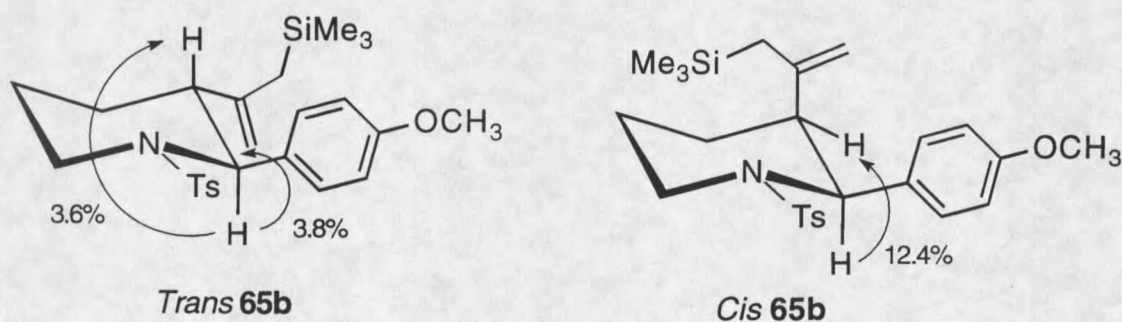


Figure 23. NOE Results for Cis and Trans Piperidine 65b.

This three step condensation-cyclization-tosylation sequence was found to occur efficiently with yields ranging from 42% to 83% when several aryl aldehydes of varying electronic properties were utilized (Table 5). Isolated yields of the purified tosyl derivatives **65a-d** as well as diastereoselection were found to be optimum when both the crude imine and cyclization products were carried through the synthetic sequence with minimal delay before the next step.

In nearly all cases examined, high levels of trans substrate-controlled stereoselectivity were observed as indicated by NOE enhancements of 3.5 to 4.6 % in the major stereoisomers. The preference for a trans configuration is thought to be the result of transition state structures that minimize steric, nonbonded interactions. Such transition states would most likely conform to a chair structure in which both substituents are aligned in an equatorial fashion (Figure 24).

This degree of stereoselection was found to be highest for the electron-deficient 4-nitrophenyl substrate (16:1.0) and lowest for the electron-rich 4-methoxyphenyl imine (6.3:1.0). This trend suggests an increased electronic influence on the transition state as the ability of the aryl group to stabilize a carbonium ion increases. Electronic effects such as minimization of charge separation would lead to a greater propensity to adopt a cis structure and would explain the observed increase in the formation of cis products as electronic donating properties of the aryl substituent increases. Additional evidence for this was observed in the case of piperidine **65a** derived from cinnamaldehyde. In this instance, a 2.3:1.0 preference for the cis diastereomer was observed and this is attributed to the high affinity for charge stabilization by the conjugated cinnamyl substituent relative to the aryl groups contained in **65b-d**.

Despite the unsuccessful cyclizations performed with alkyl imines of amine **54**, these results obtained with the aryl imines demonstrate the ability of the 2-propylidene-1,3-bis(silane) nucleophile to direct the formation of six membered azacycles. In all cases examined thus far, products arising from a competitive seven-membered cyclization were not detected. The high level of trans stereoselectivity found in these aryl imine cyclizations also complements the cis preference previously observed in the formation of piperidines from aryl imines.

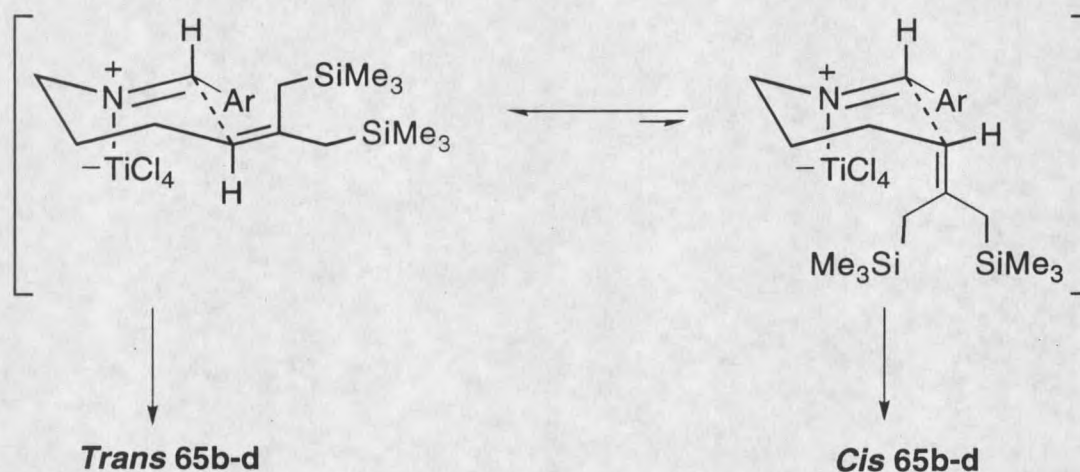
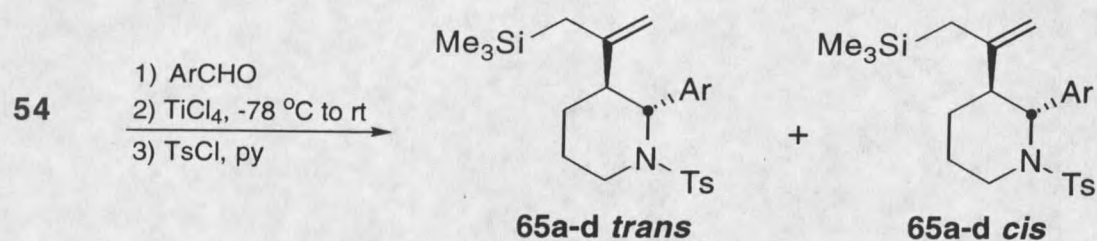


Figure 24. Diastereotopic Transition States for Piperidines 65b-d

Table 5. Cyclization Data for Aryl Imines Derived From Amine 54

Aldehyde (-Ar)	Piperidine NTs (% Yield, 3 steps)	<i>Trans</i> : <i>Cis</i>	C2H-C3H NOE (%)	
			Major	Minor
	65a (55)	1.0 : 2.3	11.6	4.5
	65b (73)	6.3 : 1.0	3.6	12.4
	65c (83)	9.5 : 1.0	4.6	--
	65d (42)	16.0 : 1.0	3.5	--

*Stereoselective Synthesis of Functionalized Isotropane Alkaloids
and Azabicyclononanes*

There exists in nature a class of alkaloids containing the azabicyclic octane ring system. Although quite structurally small and compact, these basic amines exhibit strong pharmacological and sometimes physiological properties when consumed by living beings. Most representative are the 2-azabicyclo-[3.2.1]-octanes which are commonly referred to as tropane alkaloids after the simplest member of this family tropine (Figure 25). Cocaine, a potent stimulant and anesthetic found in cocoa leaves, is also included in this family and is probably the most recognized. Tropine itself has biologically active properties as well.²⁵

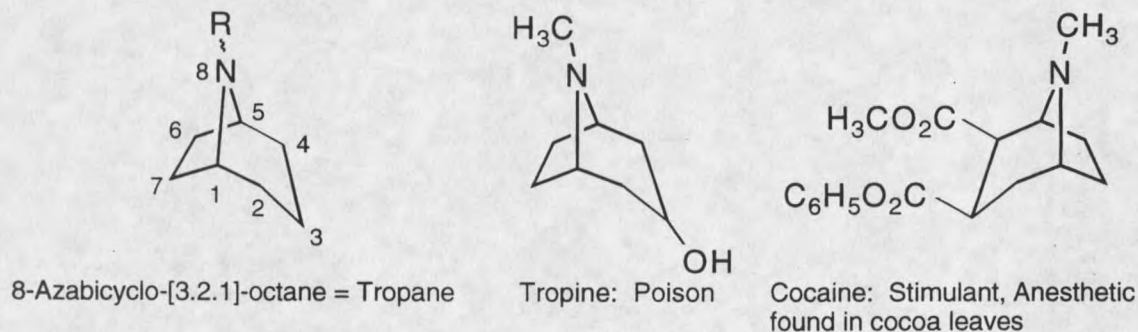


Figure 25. Tropane Alkaloids

Isomers of the tropane skeleton in which the nitrogen is located on the bridgehead are not, however, naturally abundant but do possess properties of interest to the pharmaceutical industry (Figure 26). Past clinical studies have shown that substituted 1-azabicyclo-[3.2.1]-octanes, sometimes called isotropanes, act as muscarinic antagonists in humans suffering from the effects of Alzheimer's disease.^{74,75} Such activity has been linked to stimulation of

neural transmission which is at very low levels in patients experiencing the senile dementia associated with this terrible disease. These studies point to the structure of the isotropane ligand as well as the appended functional group as having a severe influence on the magnitude of the biological activity.

Additional studies have indicated that substituted isotropanes also behave as antagonists of receptors found in the heart, central nervous system and gastrointestinal tract. Interestingly, the discovery of this biological activity was a result of screening synthetic azabicyclic octanes that were designed to mimic strained, high energy conformations of quinolizidine and indolizidine alkaloids.⁷⁶

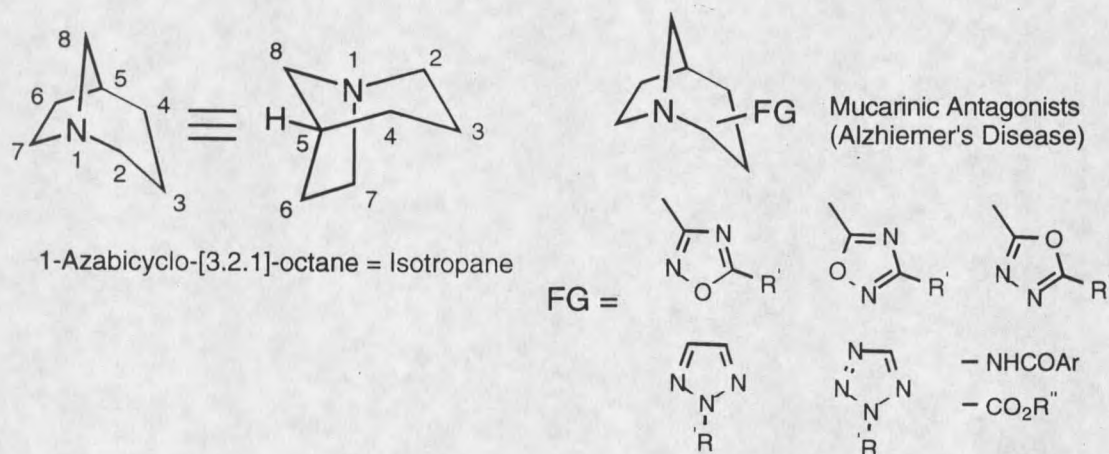
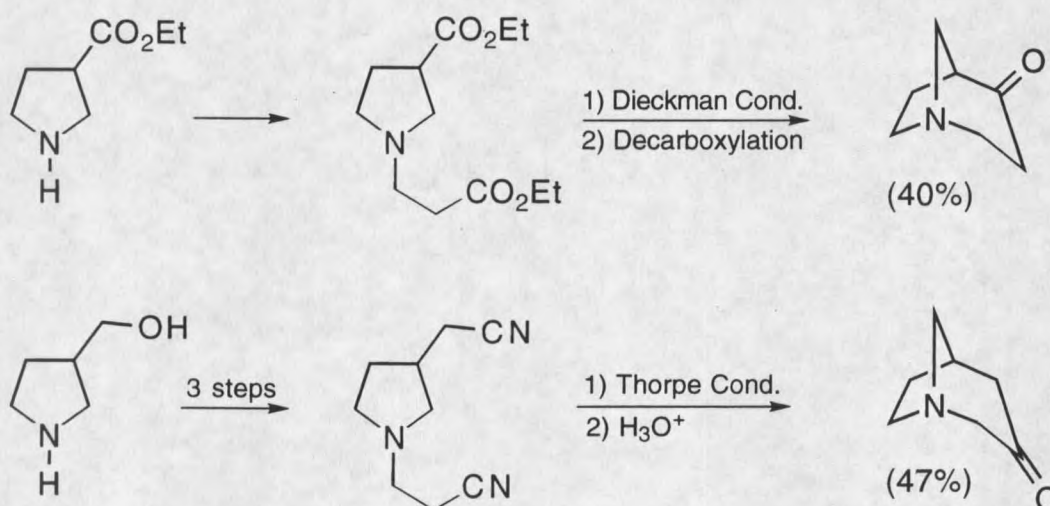


Figure 26. Isotropane Alkaloids

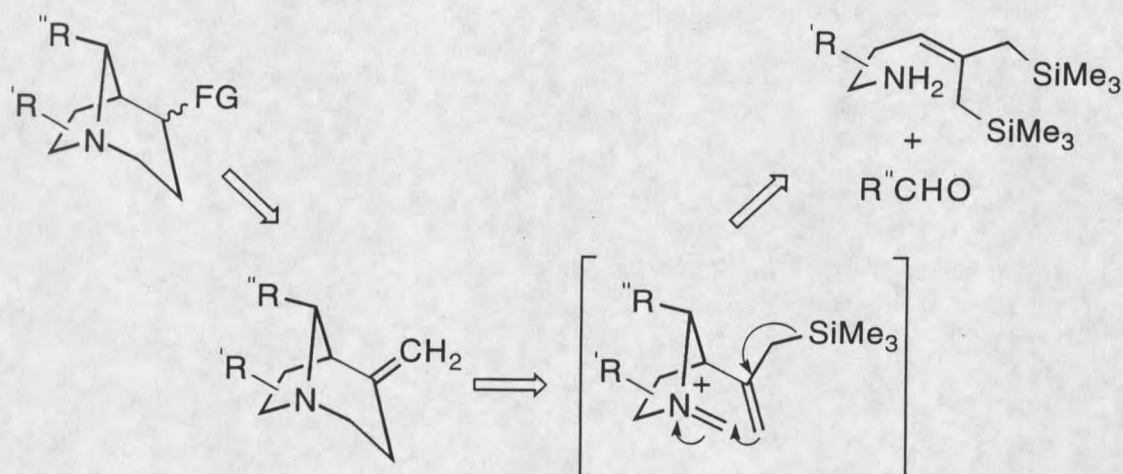
Past syntheses of the 1-azabicyclo-[3.2.1]-octane skeleton have been centered around more classical organic reactions such as Dieckman⁷⁷ and Thorpe⁷⁸ condensations (Scheme 62). Although these methods have proven reliable in obtaining modest yields of the target compound from readily available starting materials, they do not offer the flexibility required for the preparation of functionally diverse and multisubstituted isotropanes.

The clinical studies have also found that the relative stereochemical orientation of the substituents on the isotropane ligand strongly impacts the pharmacological activity of the entire molecule.⁷⁴⁻⁷⁶ Hence it was believed that the development of new methods by which to synthesize functionalized isotropanes in a stereocontrolled fashion would help contribute to the advancement of isotropanes as therapeutics.

It was rationalized that substituted isotropanes might be efficiently prepared by successive iminium ion cyclizations directed by the 2-propylidene-1,3-bis(silane) terminator (Scheme 63). The residual exocyclic olefin that would remain after this bicyclization could serve as a useful functional handle for the attachment of the groups required for biological activity. This could most likely be carried out using reliable alkene chemistry such as hydroboration-oxidation.



Scheme 62

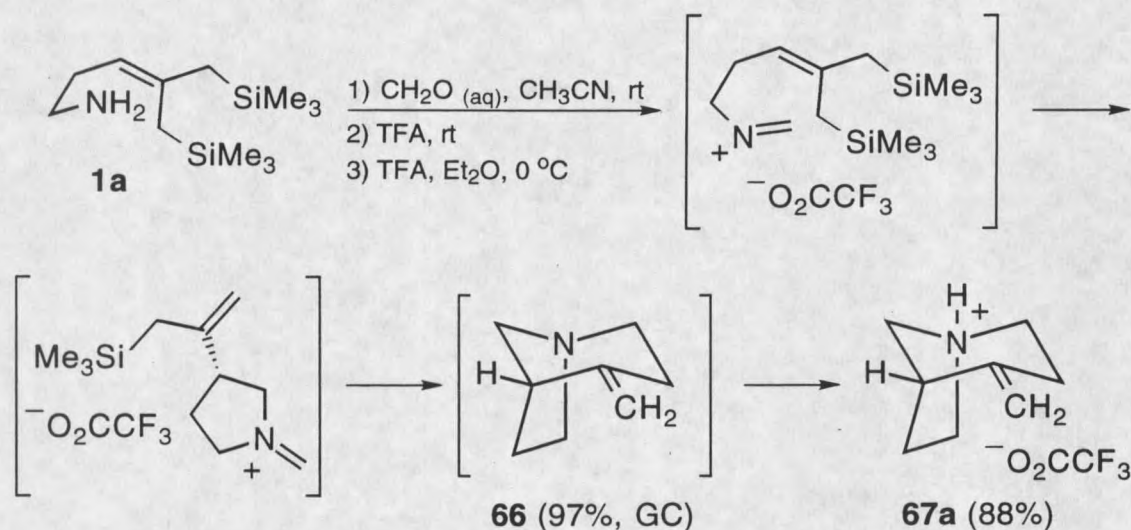


Scheme 63

Methods that might achieve a one pot, direct bicyclization of **1a** were screened first. After some experimentation, it was realized that treatment of **1a** with excess aqueous formaldehyde (4.0 equivalents) in acetonitrile followed by 1.00 equivalents of trifluoroacetic acid induced bicyclization to provide the corresponding isotropane **66** in 97% yield as indicated by gas chromatography analysis (Scheme 64). Mono cyclization products were not observed by GC or NMR after a reaction time of 4 to 8 hours at room temperature. This observation was not surprising since the nucleophilicity of the intermediate pyrrolidine would be quite high.

Initially, isolated yields of the volatile isotropane were not as high as thought possible considering the cleanness of the reaction as indicated by GC. As a result, the solution containing the crude isotropane was treated with TFA (1.00 equivalents) at 0 °C to provide the corresponding trifluoroacetate derivative **67a** in high yield upon purification. Trifluoroacetic acid was chosen for derivatization of the volatile isotropes because the corresponding amine salts possess a marked increased solubility in organic solvents, a less

hygroscopic nature and also unique NMR properties.⁷⁹ Isolation and purification of the corresponding hydrogen chloride salt of **66** proved to be more cumbersome and overall yields were diminished in comparison.

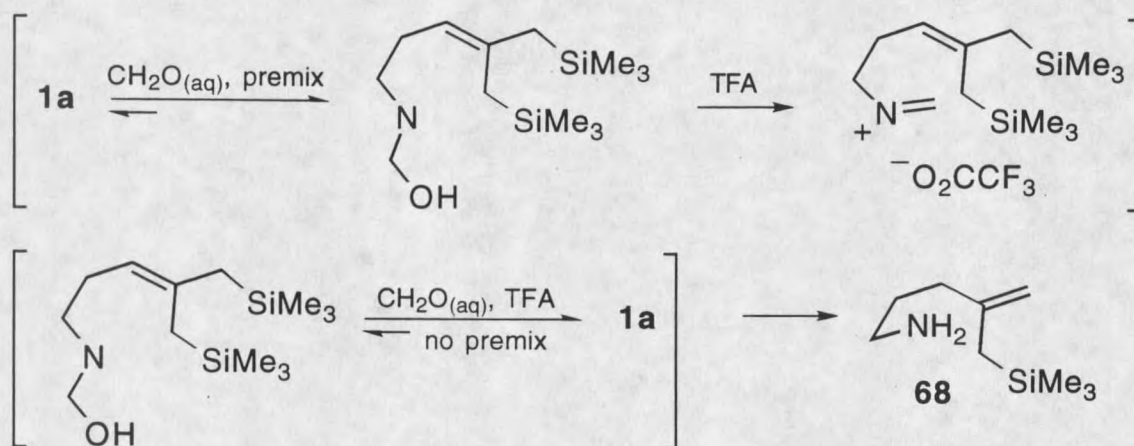


Scheme 64

Certain experimental details were discovered to be crucial for the successful bicyclization of amine **1a**. Initial trials using sequential addition of aqueous formaldehyde and TFA produced a mixture of isotropane **66** and the mono protodesilylated form of amine **1a**. Clean conversion was only achieved if a 1-2 hour time of premixing of the amine and CH_2O was carried out prior to addition of protic acid. This suggests that amine-amino alcohol equilibrium must first be completely established in order to avoid protonation of **1a** and subsequent formation of the unwanted amine **68** (Scheme 65).

The bicyclization reaction was also found to be sensitive to solvent polarity. Large amounts of desilylated amine **68** were detected upon employing solvents less polar than acetonitrile such as methylene chloride.

Presumably, media of high dielectric constants are more suitable for driving the highly charged reaction away from the amine substrate **1a**. Addition of water, provided by the use aqueous formaldehyde, seemed beneficial to the rate and yield of the reaction when compared to runs performed using paraformaldehyde in anhydrous CH₃CN. Additional experiments showed that 2,2,2-trifluoroethanol (TFE) could be used as an alternative solvent to acetonitrile but did not provide optimum yield and reaction cleanness.

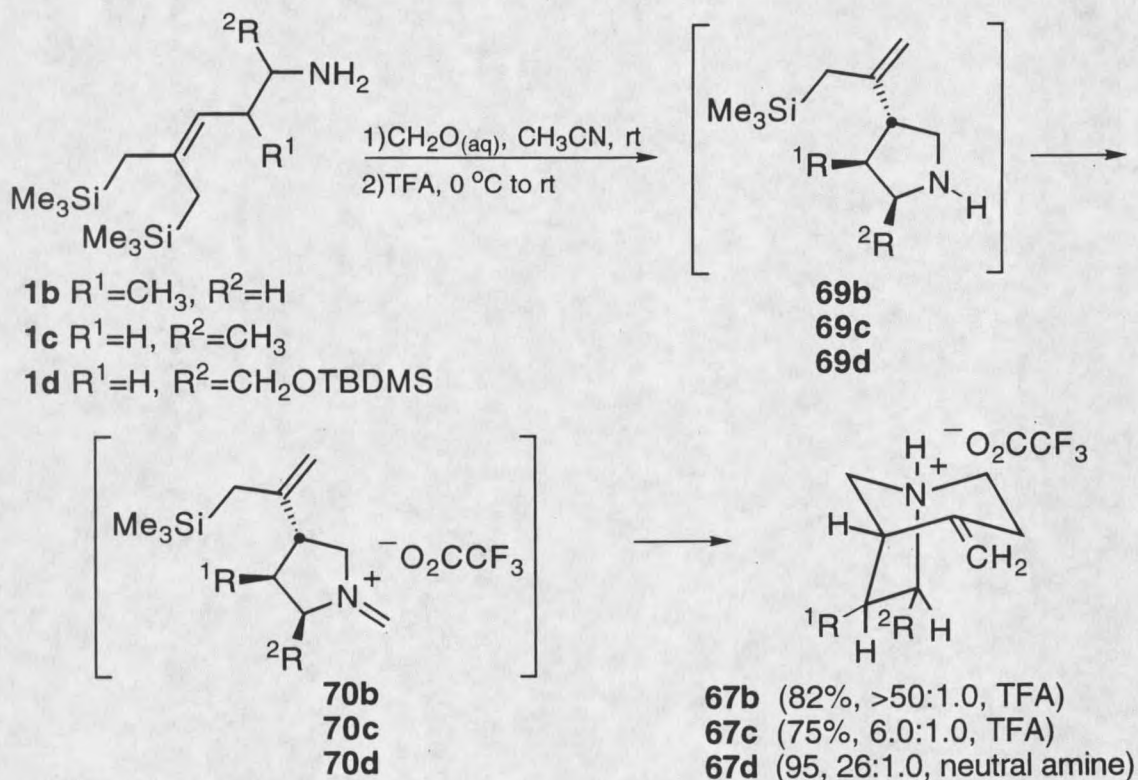


Scheme 65

Using the conditions developed for the bicyclization of amine **1a**, amines **1b-d** were successfully converted in good yield to the substituted isotropanes **67b-d** which, as before, were isolated as their TFA derivatives (Scheme 66). Such derivatization was unnecessary for the more massive OTBDMS product **67d** which could be readily isolated as the neutral amine in high yield after purification on Florisil.

Gratifyingly, relative stereochemistry was preserved with high diastereo fidelity (6.0->50:1.0) during the course of bicyclization as indicated by GC and NMR. For the example involving amine **1c**, a 6.0:1.0 mixture of epimers was

obtained and was resistant towards separation. Condition modifications such as lower temperatures and more polar solvents (TFE) failed to improve this ratio.



Scheme 66

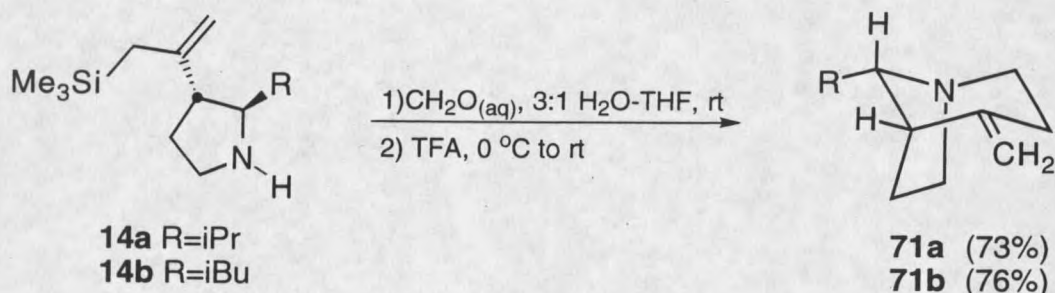
The relative stereochemical orientation of the C-6 substituent in **67b** and the C-7 substituents in **67c-d** was most likely established prior to the second desilylative cyclization. Trans configuration is believed to have been preferentially formed during the initial cyclization resulting in pyrrolidine intermediates **69b-d**. In an attempt to characterize these intermediates, the cyclizations were run using only 1.00 equivalents of formaldehyde. This produced equal mixtures of the azabicyclooctane and starting material thus

revealing the facility of the second condensation-cyclization. As in the trans selective, imine cyclizations involving amines **1b-c**, transition state structures governed by allylic through space interactions were thought to be the influence behind the eventual exo configuration of the substituents in isotropanes **69b-d**.

It was envisioned that the second desilylative cyclization of this tandem reaction proceeding by way of a cis pyrrolidine intermediate would be considerably impeded. Simple models suggest that in the cis isomers of iminium ions **70a-d** approach of the mono allylsilane nucleophile to the cationic center would be hindered by the substituents on the same face of the pyrrolidine. This serves to support trans pyrrolidines **69b-d** as intermediates en route to **67b-d**.

The CH₂O-TFA cyclization protocol was next used in conjunction with the metallo imine, monodesilylative cyclization methodology in order for the preparation of substituted isotropanes in a stepwise fashion. Trans pyrrolidines **14a** and **14b** were exposed to excess aqueous formaldehyde (2.00 equiv.) followed by TFA (1.05 equiv.) to provide the C-8 substituted isotropanes **71a** and **71b** in isomerically pure form (Scheme 67). Under these conditions, good yields were realized after purification on silica gel and without the need for TFA derivatization.

As in the previous, direct bicyclization reactions, solvent choice was important for obtaining maximum yield of isotropanes **71a-b**. After much experimentation with mixtures of polar solvents including H₂O, CH₃CN and TFE, a 3:1 water-tetrahydrofuran solvent system³² was found to be optimal with respect to yield, reaction rate, solubility and the suppression of unwanted byproducts. Although completely heterogeneous at the onset, the reaction mixtures in H₂O-THF achieved homogeneity upon the addition of TFA.



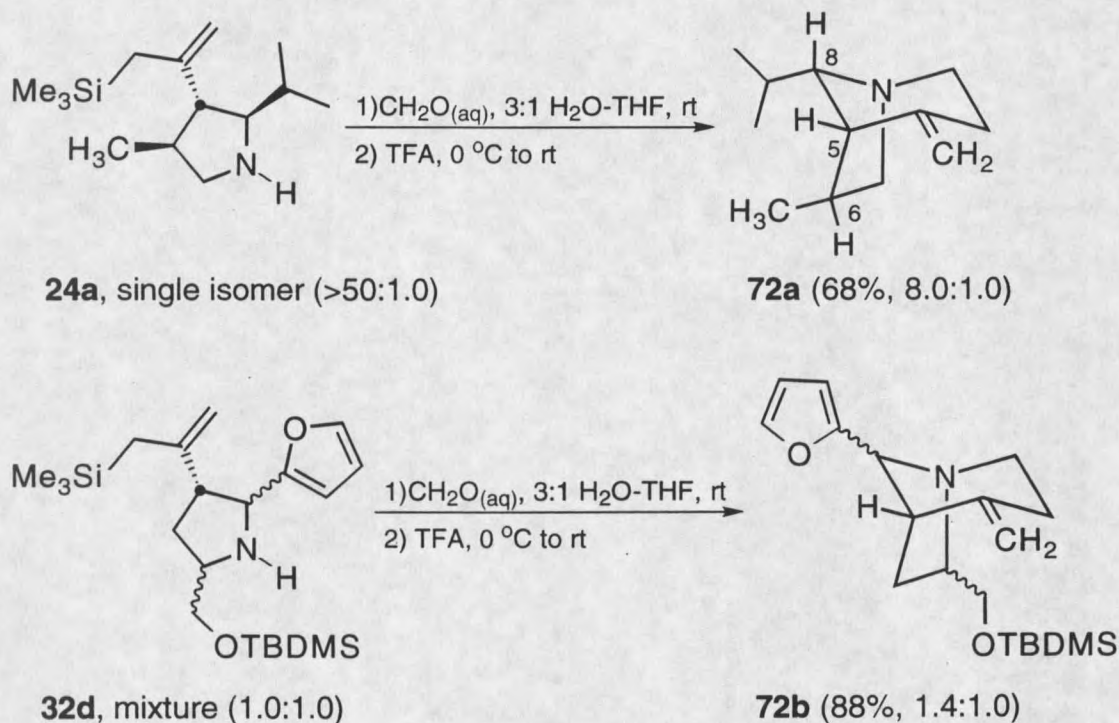
Scheme 67

A very interesting phenomenon was observed to take place when the trans pyrrolidine **24a** was exposed to these conditions. The expected isotropane **72a** was isolated in 68% yield but small quantities (ca 12%) of a second diastereomer were also detected even though the starting substrate **24a** was isomerically pure. This stereochemical scrambling also took place upon using the OTBDMS pyrrolidine **32d** (Scheme 68).

Evidence for the relative stereochemical disposition of **72a** was provided by the ^1H NMR spectrum after assignments were based on extensive homonuclear decoupling experiments. The spectrum revealed that the C-8 methine proton corresponded to only a doublet signal and the C-5 bridgehead methine proton appeared, surprisingly, as a singlet. Application of the Karplus correlation⁸⁰ strongly points to dihedral angles approaching 90° between the C-8, C-5 and C-6 protons. Simple molecular modeling points to the exo-exo structure illustrated for **58a** as the only one capable of three perpendicular, adjacent protons. Such an absence of coupling has been previously noted in work involving unsubstituted isotropanes.^{75, 76}

Further support came from HD experiments that identified the location of the C-8 methine doublet at 2.11 ppm. This is unusually up field for such a

proton considering normal deshielding effects. Thus it is believed that this proton lies over the shielding cone of the exocyclic olefin in **72a** in an axial (endo) not equatorial (exo) alignment.

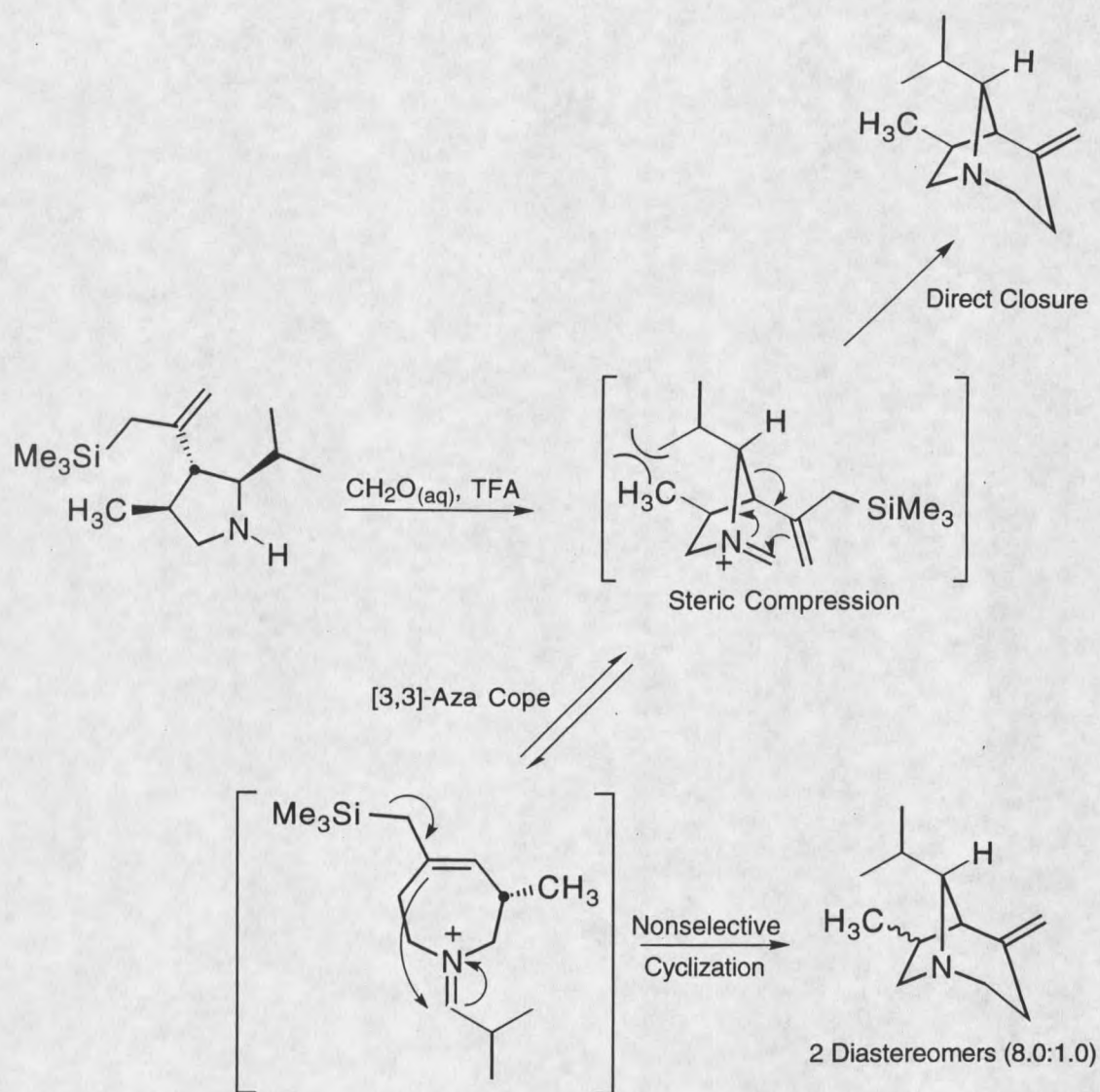


Scheme 68

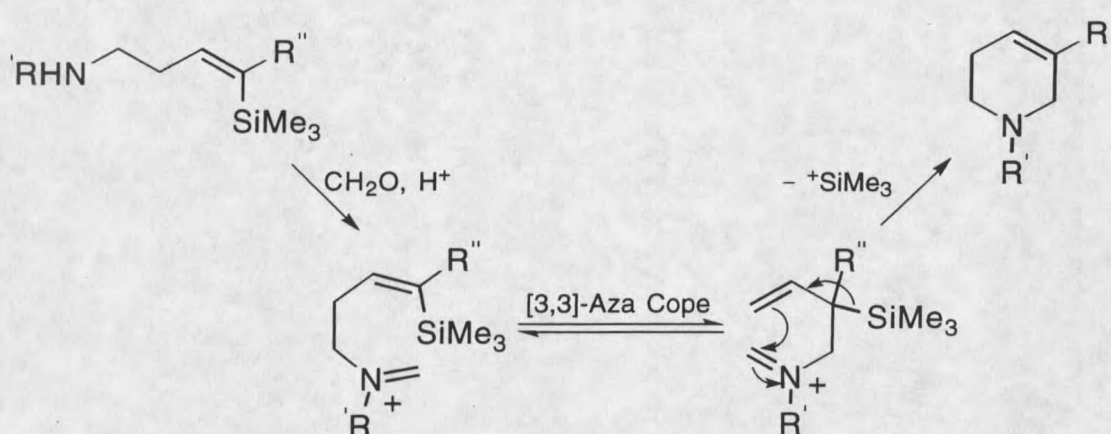
The stereochemical scrambling observed during the cyclization of **24a** and **32d** must have occurred in a pathway that permits the formation of two of the four possible diastereomers. It was conceived that a [3,3] sigmatropic aza cope rearrangement was in competition with direct desilylative ring closure for control over the fate of the initial iminium ion (Scheme 69). For the pyrrolidine substrates **24a** and **32d**, direct closure of the initial iminium ion would be expected to be a higher energy process than the alternative aza cope pathway. This increased energy would be a result of the development of steric

compression during approach of the allylsilane nucleophile to the hindered iminium ion. Conversely, transannular cyclization of the aza cope product could feasibly occur onto either diastereotopic face of the iminium ion resulting in the formation of two diastereomeric bicycles.

It is also conceivable that *E* to *Z* configurational interconversion about the iminium ion geometry could also give rise to additional diastereomeric products. If this was occurring, four diastereomeric products could potentially be generated. The observance of only two isomers in the cyclization of **24a** and **32d** suggests that this is not occurring. In support of the alternative aza cope pathway, Overman has also observed rapid sigmatropic rearrangements in numerous iminium ion reactions including systems that contain vinylsilane nucleophiles (Scheme 70).⁸¹



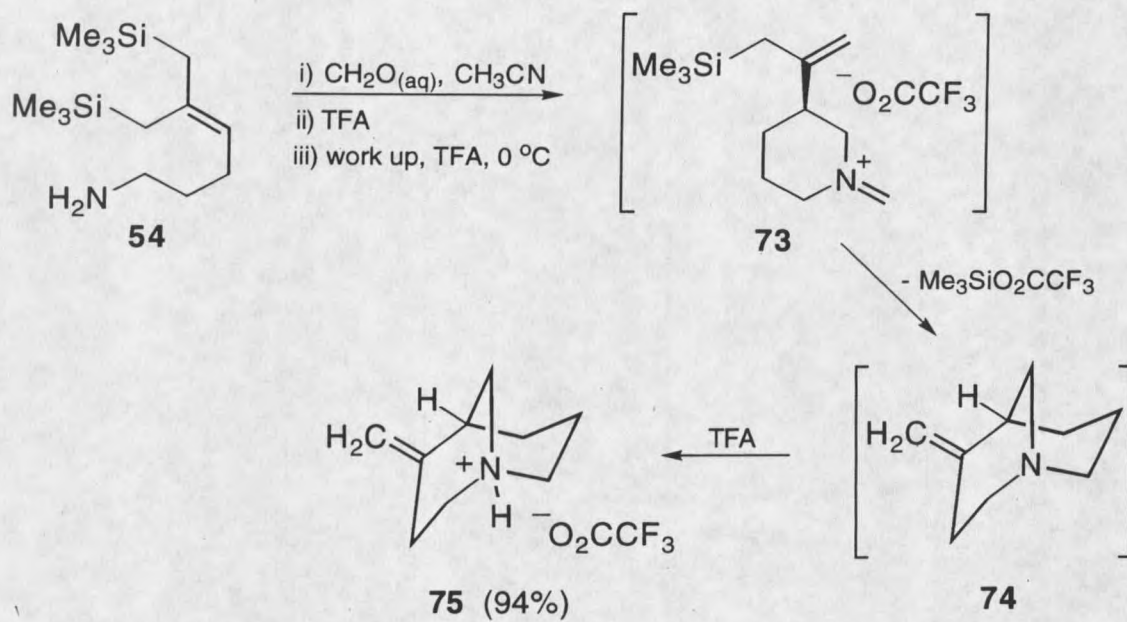
Scheme 69



Scheme 70

It was most gratifying to observe analogous bicyclization of amine **54** when exposed to the same conditions as those employed for the synthesis of **67a-d** from amines **1a-d**. For instance, premixing amine **54** and aqueous formaldehyde (4.00 equiv.) in CH_3CN for 2h followed by addition of TFA (1.05 equiv.) resulted in formation of 1-aza[3.3.1]bicyclononane **74** after an overnight period at room temperature (Scheme 71). The free amine could be isolated and purified in modest yield (59%) but, as in the case for the volatile isotropanes, superb purified yields of the corresponding TFA derivative were achieved upon treatment of the crude product solution with TFA (1.05 eq). In this fashion, amine salt **75** was obtained in 94% yield from amine **54**.

Even though this study brought forth intriguing mechanistic and spectrometric observations, it also revealed the ability of the 2-propylidene-1,3-bis(silane) terminator to prepare functionalized isotropane alkaloids and azabicyclononanes in an efficient and stereocontrolled manner. Flexibility was demonstrated by applying both a direct, bicyclization approach or stepwise cyclizations in the preparation of these potentially useful compounds.



Scheme 71

Synthesis of the Azatricyclic Core of Stemofoline

Since the late 1960s, Japanese natural product chemists have been isolating structurally intriguing alkaloids from the roots, stems and leaves of *stemonaceae* plants.^{82,83} These polycyclic alkaloids were found to contain numerous rings of various size and mode of connectivity. Interestingly, all of these alkaloids possess one or more γ -lactones joined to the core in either a fused, spiro or directly joined fashion (Figure 27).

In former days, extracts from the *stemonaceae* plants were utilized to eradicate zooparasites and agricultural pests on men and cattle. Even today the extracts are used as domestic insecticides for agricultural pests in localized regions of China. Of the *stemonaceae* alkaloids screened for biological activity, Stemofoline has been shown to possess the strongest insecticidal activity, especially against silkworm and related larvae, when administered orally.⁸³

Stemofoline is very unique in structure upon comparison to the other members of the *stemonaceae* family. For the majority, the natural assembly of rings is always in a fused, spiro or directly joined pattern. Stemofoline, however, is the only member that contains a bridged array of cyclic nuclei resulting in a very rigid and compact, cage-like structure. Although no evidence currently exists, this unique structure might be responsible for Stemofoline's potent insecticidal activity. Nevertheless, the combination of structural complexity and biological activity serves to make Stemofoline an attractive yet challenging target for total synthesis.

It was considered crucial that an efficient route to the azatricyclic core of Stemofoline be developed in order for total synthesis to eventually be realized. With this in mind, bridged pyrrolizidine **77** was selected as the key synthetic

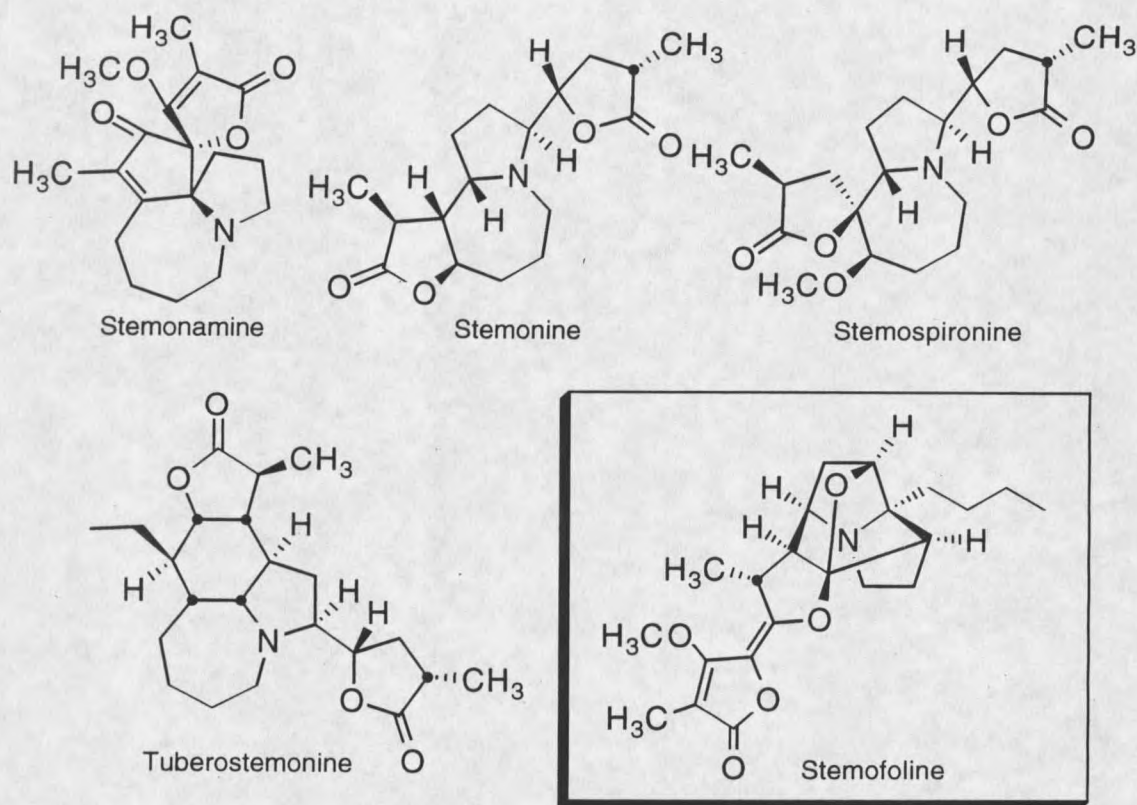
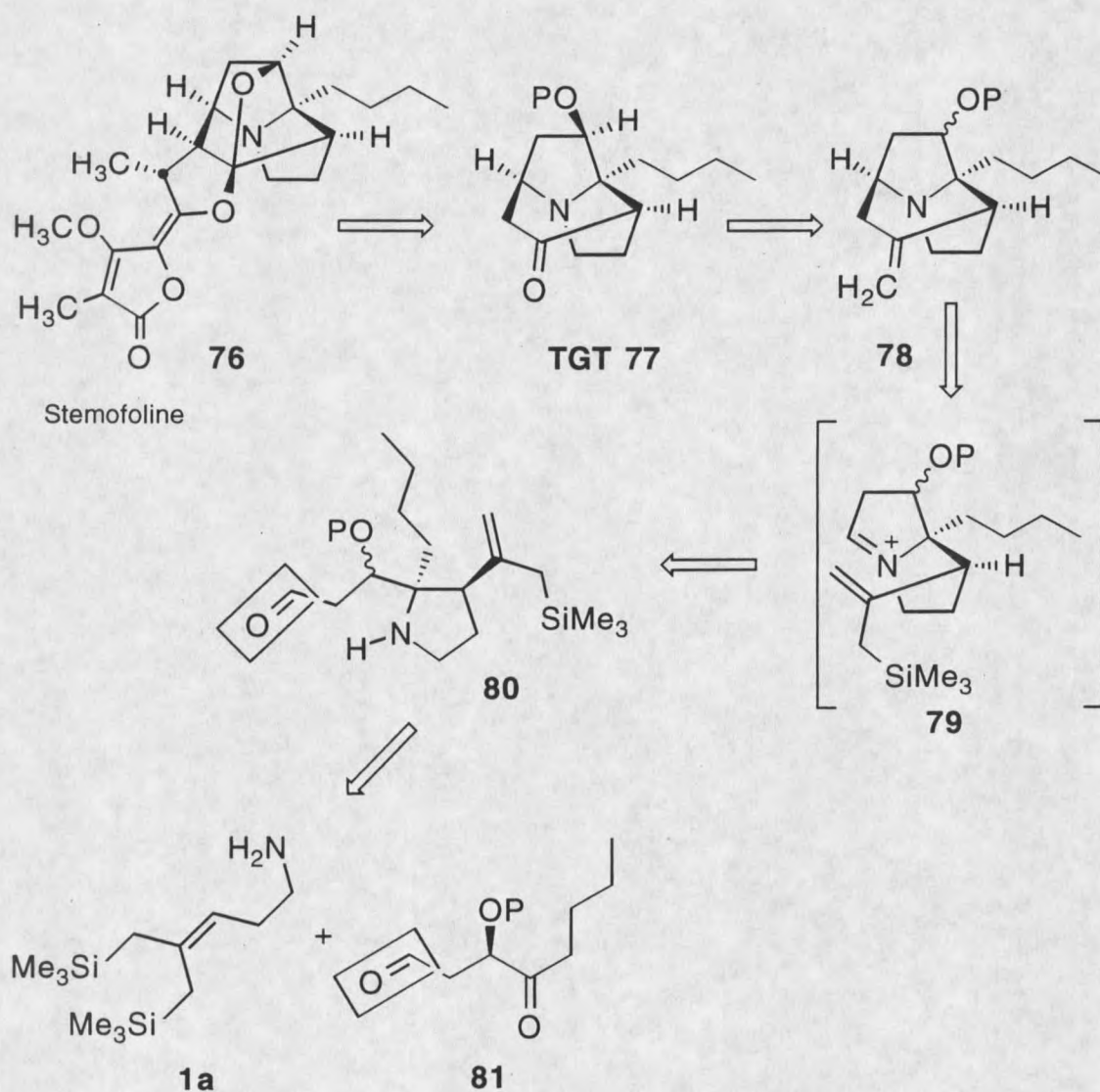


Figure 27. Representative *Stemonaceae* Alkaloids

target and the next goal for the application of the allylbis(silane) methodology (Scheme 72). The exocyclic double bond of viable precursor **78** would, upon oxidative cleavage, provide the ketone required for the eventual formation of the bridged ketal in the natural product **76**. In addition, the resulting ketone would also provide activated alkylation sites that might permit facile attachment of the butenolide segment to the parent core.

More importantly, the olefin in **78** is also the retron²⁶ for the exocyclic, allylsilane-iminium ion cyclization transform. Retrosynthetic cleavage of the Mannich type bond in **78** reveals iminium ion **79** as an appropriate intermediate which should be readily generated from pyrrolidine **80** upon unmasking of the aldehyde or related functionality. Pyrrolidine **80** correlates

nicely to a 2-propylidene-1,3-bis(silane) imine cyclization involving components **1a** and dicarbonyl compound **81**.

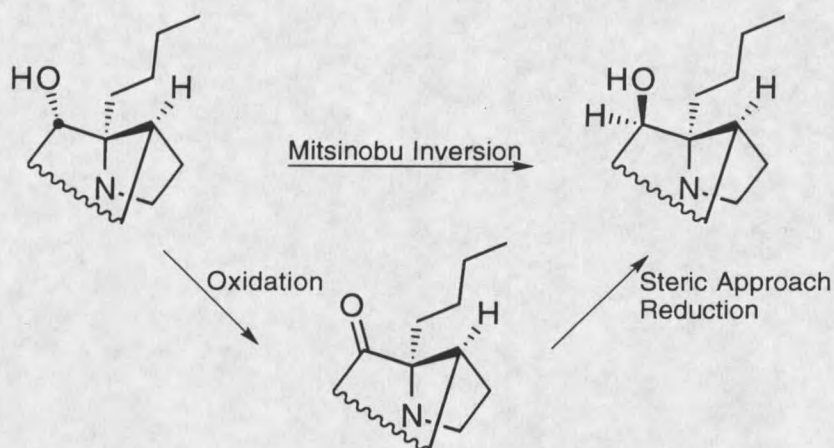


Scheme 72

From a stereochemical-based, retrosynthetic analysis of target **77**, the success of the above approach lies in the selective formation of a trans relationship between the butyl group and 1-(trimethylsilylmethyl)ethylidene

substituent in pyrrolidine **80**. Prediction of the stereochemical outcome of the initial allylbis(silane) imine cyclization was somewhat vague but the results from the cyclization of ethyl lactate derived imines (Scheme 43) do suggest that stereoselective formation of the contiguous stereocenters in **80** is feasible. Moreover, the facility of this ketimine cyclization involving components **1a** and **81** was also in question since previous attempts to efficiently cyclize imines derived from ketones met with unfavorable results. As a result, the key allylbis(silane) imine cyclization was believed to require strenuous experimentation in order to obtain proper stereochemistry and also avoid unwanted desilylation of the imine precursor.

The relative orientation of the protected alcohol function in **78-80** was of lesser concern. If the stereochemical relationship of this group proves to be opposite of that in the target compound **77**, it was believed that correct configuration could be established at numerous points along the synthetic sequence. This could most likely be accomplished by either Mitsunobu inversion⁸⁴ or an oxidation-stereoselective reduction sequence after removal of the alcohol protecting group (Scheme 73). Considering the results of the ethyl lactate imine cyclizations, an alignment of the protected alcohol opposite of that present in the target molecule was predicted. Hence application of the inversion techniques was anticipated.

**Scheme 73**

The feasibility of utilizing the 2-propylidene-1,3-bis(silane) terminator in the synthesis of target **77** was initially probed on a model system lacking the protected alcohol functionality. Ethyl levulinate was selected for condensation with amine **1a** since this ketoester contains both the electrophilic carbonyl and a suitably disposed, aldehyde surrogate capable of eventual conversion into an iminium ion analogous to ion **79**. The commercial availability and inexpensiveness of ethyl levulinate allowed for rapid screening of the key allylbis(silane) imine cyclization.

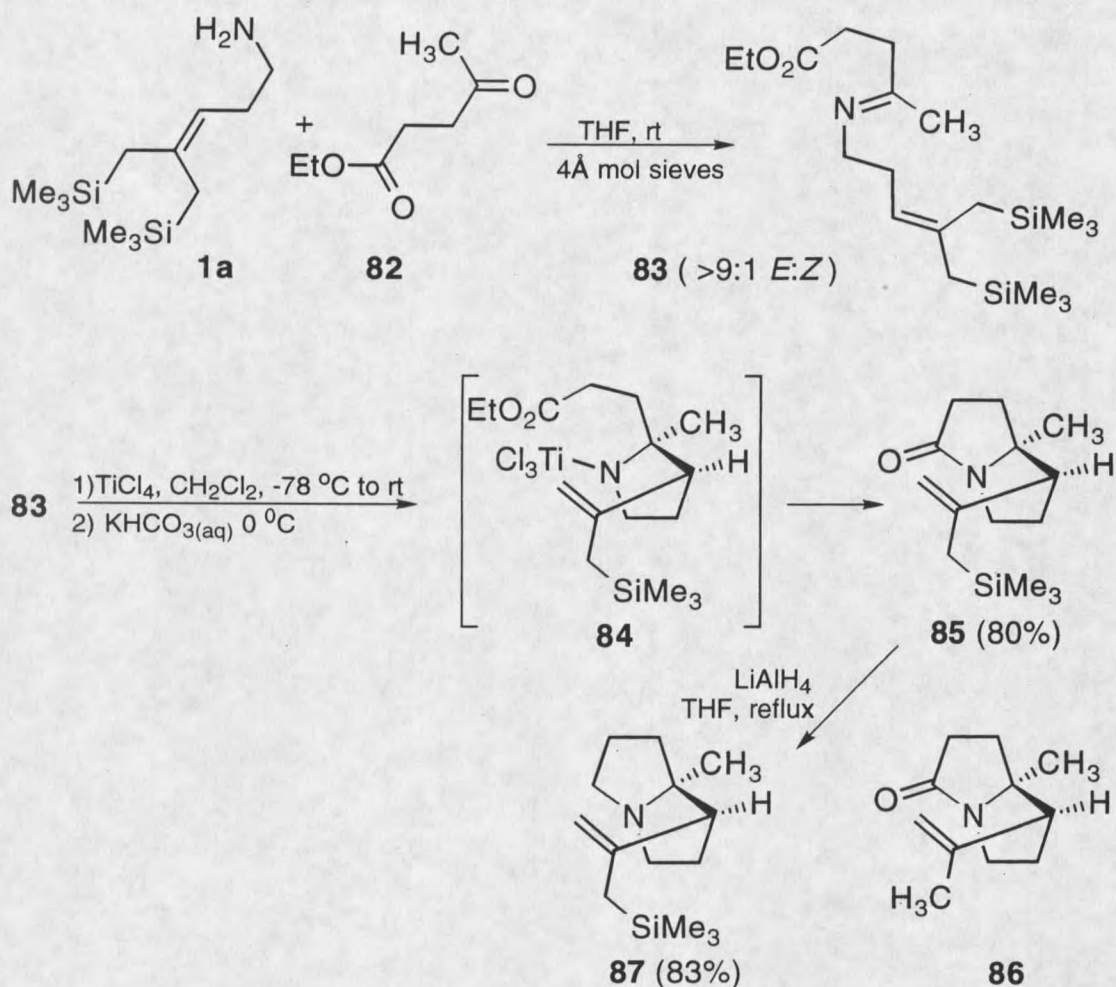
Using the standard conditions (4Å mol. sieves, THF, rt.), condensation of ethyl levulinate with amine **1a** over 24 hours afforded imine **83** (Scheme 74). Unlike the aldimines prepared via this method, NMR analysis of imine **83** showed the presence of a second compound in up to 10% composition which has been tentatively assigned as the *Z* isomer. The crude imine was then subjected to the standard cyclization protocol without delay.

It was an extremely pleasing observation that upon immediate exposure to TiCl_4 (1.0 equiv., CH_2Cl_2 , -78°C to rt.) imine **83** underwent cyclization and

intramolecular lactam closure to provide bicyclic lactam **85** which was isolated as a single diastereomer in 80% yield after purification on silica gel. Analysis of the crude reaction mixture showed no evidence for formation of the alternative stereoisomer of **85** but did reveal that some desilylation of the imine substrate had occurred during the course of the cyclization reaction. Once again the mode of reaction quench was crucial for high isolated yields. On a large scale run employing addition of base to the reaction mixture, desilylated product **86** was isolated in significant quantities. Slow inverse addition of the reaction solution to cold, aqueous KHCO_3 suppressed any formation of this undesired lactam.

Initial evidence for the desired stereochemical outcome of the bicyclization came from magnetic anisotropic effects observed in the proton NMR spectrum of **85**. The two olefinic protons showed a marked difference in chemical shift ($\Delta\text{ppm} = 0.23$) indicating that one of these two protons lies in close proximity to the shielding cones of the carbonyl group. Such an effect would most likely be of lesser magnitude in the alternative diastereomer. Removal of the influential carbonyl in **85** by exhaustive reduction (LiAlH_4 , THF, reflux) provide pyrrolizidine **87** and NMR analysis clearly showed a less pronounced anisotropic effect occurring in the olefinic proton signals ($\Delta\text{ppm} = 0.04$). These signals in amine **87** were also 0.26 ppm downfield relative to those in lactam **85** indicating relief from shielding had occurred upon reductive removal of the carbonyl group. More conclusive evidence for the stereochemical structure of **85** eventually came from cyclization into a bridged pyrrolizidine.

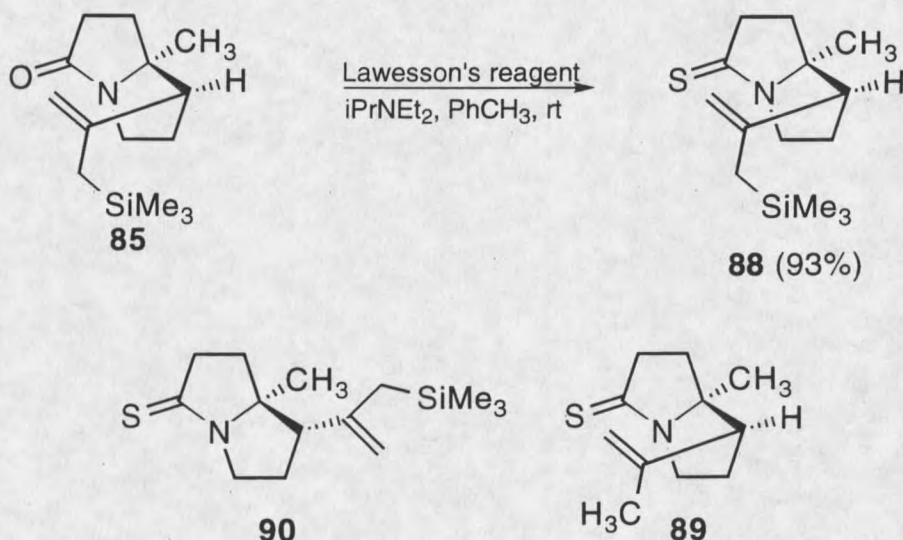
Oxygen to sulfur conversion was carried out on lactam **85** in order to gain access to the nucleophilic thiolactam. Along these lines, treatment of **85**



Scheme 74

with Lawesson's reagent⁸⁵ in the presence of an amine buffer (Et_2NiPr , PhCH_3 , rt.) furnished thio derivative **88** in high yield after purification (Scheme 75). It was discovered that in the absence of the buffer, mixtures of products comprised of **88**, desilylated thiolactam **89** and also a small amount (4%) of the epimer **90** were formed. These products must have arisen from protonation of the allylsilane unit in **88** by phosphoric acid present in the moisture-sensitive Lawesson's reagent. The NMR spectrum of **90** indicated no significant

anisotropic effects on the olefinic protons and helped to reinforce the stereochemical arguments proposed for lactam **85**.

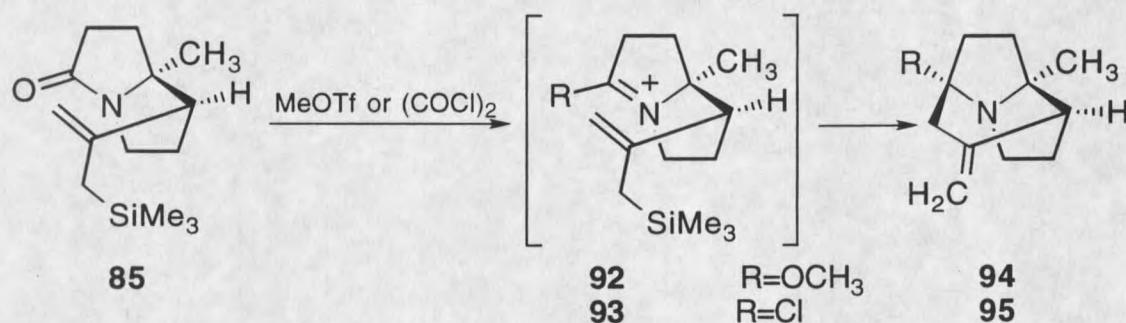


Scheme 75

Attention was next turned to executing the second allylsilane iminium ion cyclization. It was reported that amides could be partially reduced to amines and aldehydes⁸⁶ and also that lactams generate iminium ions upon partial reduction with DIBALH.⁶⁴ Unfortunately, attempts to partially reduce either lactam **85** or thiolactam **88** resulted in either no significant reaction or deprotonation to the corresponding enolate which tautomerized back to substrate upon work up. Coordination of some of the reducing agents (DIBALH, K-selectride, Red-Al, and Super hydride) to the nucleophilic sulfur and oxygen might have facilitated internal deprotonation rather than reduction.

Activation of lactam **85** towards reduction by *O*-alkylation prior to hydride addition was tried next.⁸⁷ Treatment with MeOTf did not result in clean

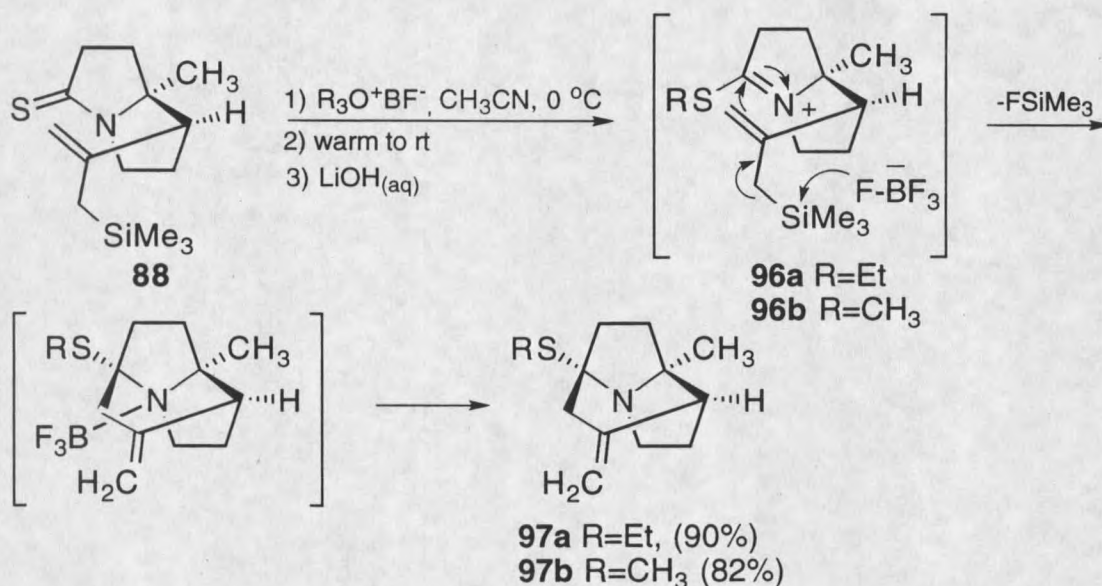
formation of the expected iminium ether **92** but, surprisingly, mixtures containing cyclized, bridged pyrrolizidine **94** were obtained (Scheme 76). Analogous results were realized during attempts to generate the corresponding Vilsmeier salt **93** by treatment of **85** with oxalyl chloride.⁸⁸ Both of the tricyclic compounds **94** and **95** were found to be too unstable for isolation and purification but their detection did indicate the propensity of the allylsilane nucleophile to engage in cyclization upon generation of even electron rich iminium ions in the bicyclic lactam. These results also provided additional evidence for the stereochemical configuration of lactam **85**.



Scheme 76

This observation that the allylsilane nucleophile readily closes onto iminium ions that are relatively electron rich prompted us to take advantage of this surprising reactivity in securing the desired bridged pyrrolizidine. After initial experimentation, it was found that treatment of the nucleophilic thiolactam **88** with either trimethyl- or triethyloxonium tetrafluoroborate, better known as Meerwein's reagents⁸⁹, resulted in clean alkylation at 0 °C as indicated by TLC to form the intermediate iminium salts **96a** and **96b** (Scheme 77). These salts could not be isolated but rather warming of the reaction mixture to ambient temperature then promoted thermal cyclization into the bridged pyrrolizidines

97a and **97b**. These thioaminals were obtained in high yield after purification on basic alumina and were found to be sufficiently stable during careful storage. Quench of this alkylation-cyclization reaction was best carried out using aqueous LiOH to ensure complete decomplexation of BF_3 from the basic nitrogen in **97a** and **97b**.

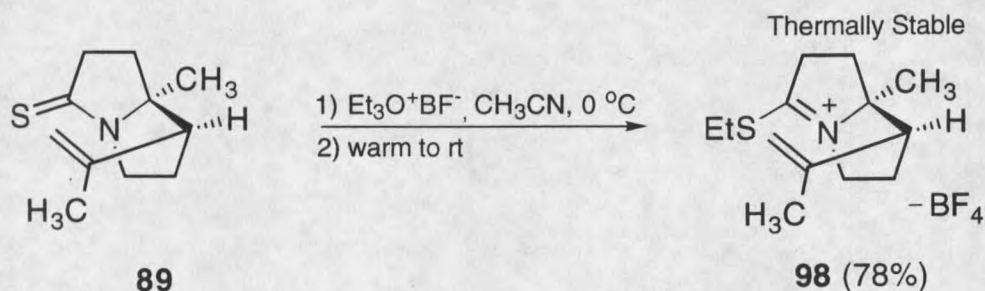


Scheme 77

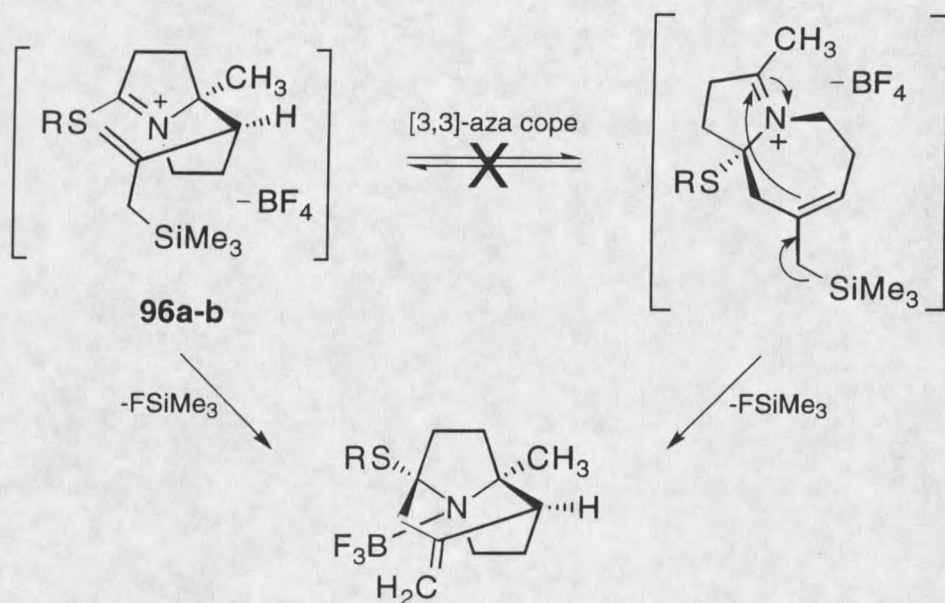
One of the keys to the success of this reaction was the ability of thiolactam to undergo complete alkylation at temperatures below those that promoted thermal cyclization. If this could not be carried out, competitive alkylation of the cyclized product would undoubtedly ruin this reaction sequence. Although this reaction could be performed in methylene chloride, the use of the more polar CH_3CN allowed for better yields and faster rate of cyclization. Fortunately, this nucleophilic solvent did not interfere with the initial alkylation step. Employing protic solvents such as TFE resulted in desilylation

of the allylsilane unit and also hydrolysis of the thio iminium ion to give only desilylated lactam upon isolation of products.

As stated before, the room temperature cyclization of the electron rich iminium ions **93** and **96a-b** was somewhat unexpected. It is believed that the preferred conformational position of the allylsilane nucleophile was ideal for bonding to the electrophilic carbon and resulted in a facile, kinetic ring closure. In addition, fluoride ion assistance provided by the BF_4^- counterion might have enhanced the rate of the desilylative ring closure. For sake of comparison, desilylated thiolactam **89** was exposed to Meerwein's reagent under identical conditions. No cyclized product was observed but rather iminium salt **98** was isolated in 78% yield (Scheme 78). More significantly, this salt was observed to be thermally stable even after months of storage under argon. This result not only exposed the reactive nature of silyl iminium salts **96a-b** but also suggests that a potential aza cope-transannular allylsilane cyclization pathway does not ensue from these iminium ions leading to the formation of the tricyclic thioaminals (Scheme 79).



Scheme 78

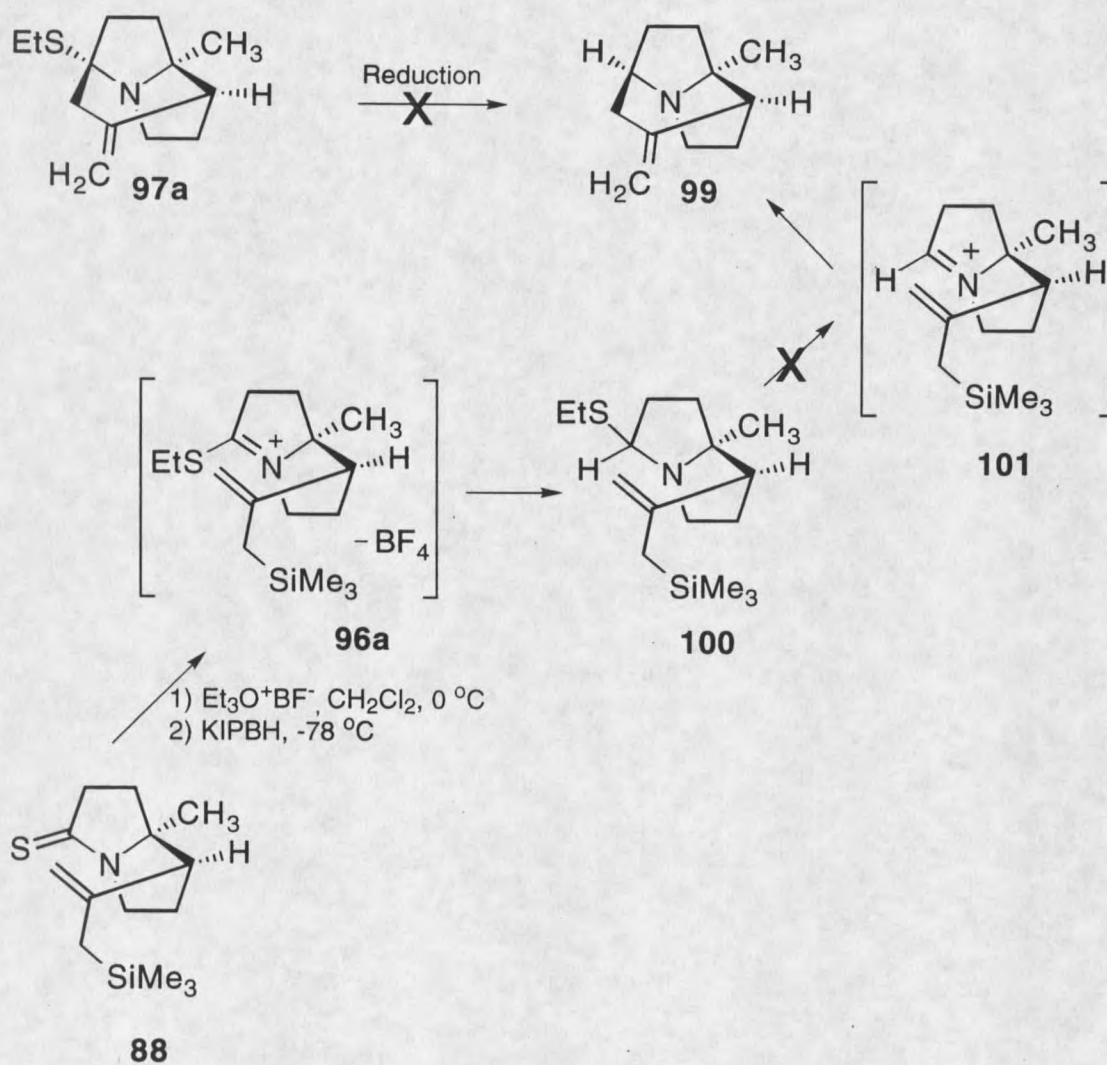


Scheme 79

In order for this sequence to be applicable towards the formation of the desired target **77** (Scheme 72), desulfurization of the bridged pyrrolizidine **97a** was required. This compound proved extremely resistant towards reductive desulfurization with either W-2 Raney Ni, or a variety reductions involving potassium and lithium metal dissolved in various media. Extensive investigation with this reduction failed to produce the desired compound **99** to any appreciable extent (Scheme 80).

As a result, the reduction was implemented at an earlier point in the synthetic sequence. Alkylation of **88** with Meerwien's reagent followed by cold temperature reduction of iminium salt **96a** afforded bicyclic thioaminal **100** (Scheme 80). Although more than one reducing agent promoted this partial reduction before cyclization could ensue, low temperatures ($-78\text{ }^{\circ}\text{C}$) and optimum yield were realized upon using potassium triisopropoxy borohydride (KIPBH).⁹⁰ All attempts to induce ionization of **100** and concomitant cyclization

of iminium ion **101** failed, generally resulting in only complex product mixtures. Ionization of **100** was attempted with numerous thiophilic reagents such as Lewis acids, mercury salts and silver salts. Even the extremely thiophilic reagent developed by Trost, $(\text{CH}_3)_2\text{S}-\text{SCH}_3+\text{BF}_4^-$ ⁹¹, failed to induce formation of the desired tricyclic amine **99**.

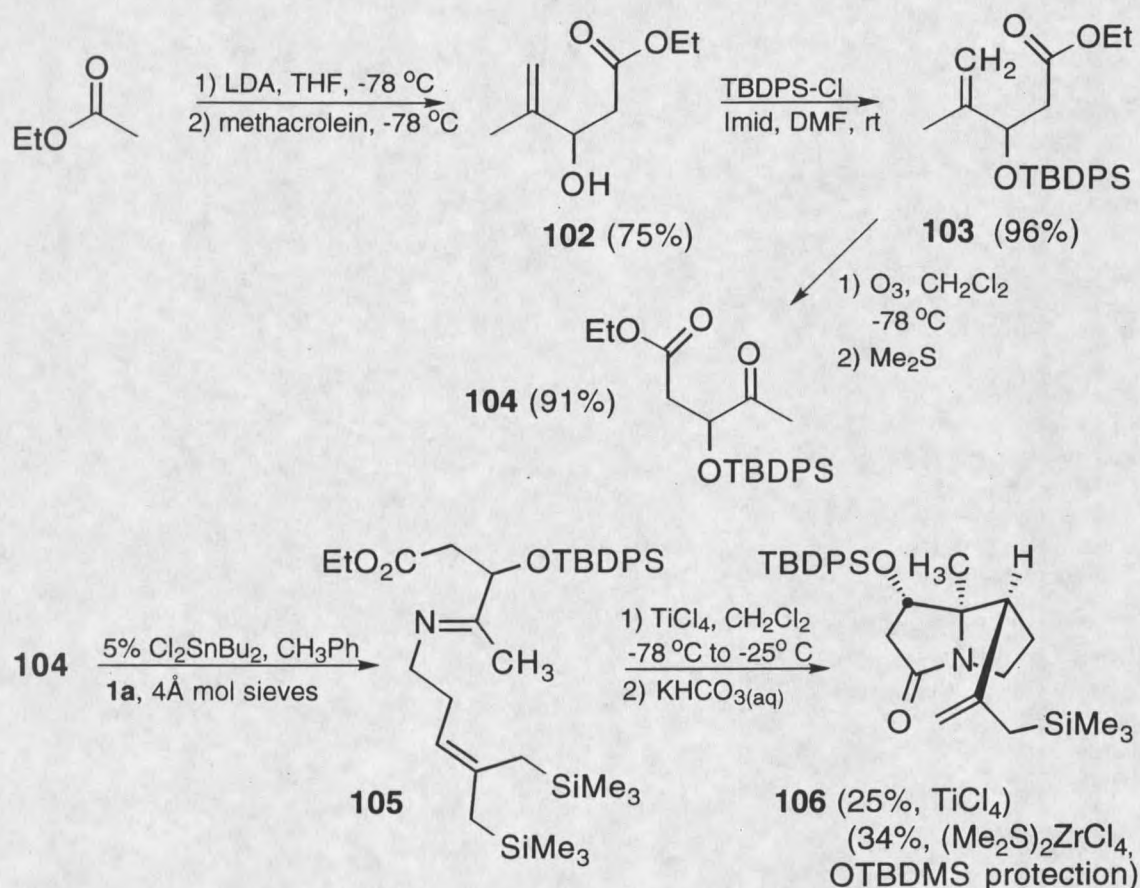


Scheme 80

Despite the inability to secure the desulfurized azatricycle, we were quite pleased in the ability of the allylbis(silane) terminator to rapidly construct the basic core of Stemofoline in a completely stereocontrolled manner. This stereoselectivity combined with the efficiency of the synthetic scheme, four steps from ethyl levulinate in 67 % overall yield, motivated us to test the feasibility of carrying out this sequence on substrates equipped with the required alcohol functionality.

An appropriate oxygenated ketoester was quickly prepared. Following known procedures⁹², aldol addition of ethyl acetate to methacrolien furnished adduct **102** in 75% yield (Scheme 81). Silylation of the alcohol with *tert*-butyldiphenylsilyl chloride furnished silyl ether **103** which was converted into ketoester **104** in 91% yield upon ozonolysis followed by reductive work up with Me₂S. Condensation of **104** with amine **1a** proceeded with low conversion to using the standard conditions (4Å mol. sieves). After testing several reagents to promote the condensation, high levels of conversion into imine **105** were obtained when catalytic amounts of water-stable Bu₃SnCl⁹³ were employed in the reaction. Exposure of **105** to TiCl₄ at low temperatures (-78 to -25 °C) resulted in the bicyclization product **106** but only in 25% isolated yield from amine **1a**. Despite the low yield, this lactam was obtained in stereochemically pure form and has been tentatively assigned the diastereomer shown based on spectral comparison to bicyclic lactam **85**. A slightly higher yield (34%) was obtained using (Me₂S)₂ZrCl₄ and the less hindered OTBDMS imine substrate. Strenuous experimentation with reaction conditions involving several permutations of different Lewis acids and solvents did not result in an increase in the yield of the bicyclization. Low temperature monitoring of the reaction indicated that desilylation of the imine substrate was the preferred mode of

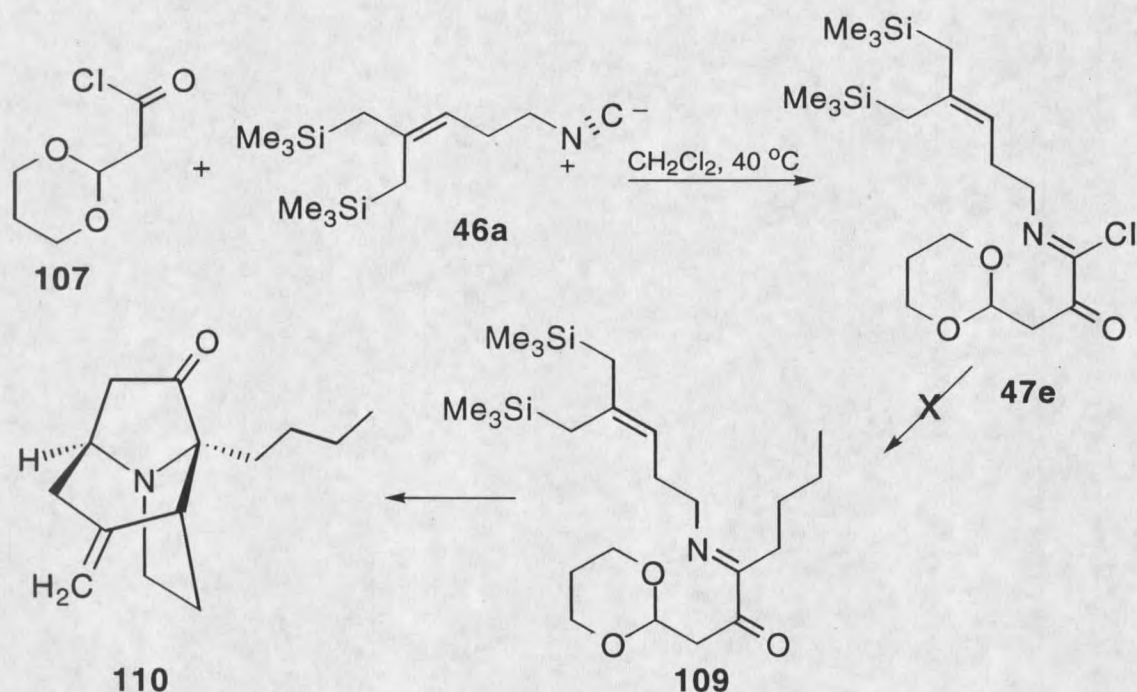
reaction and, in almost all cases examined, protodesilylated imines were isolated as the major products. These unfavorable results motivated us to seek a significantly different synthetic approach to the functionalized tricyclic core of Stemofoline using the allylbis(silane) terminator.



Scheme 81

A C-acyliminium ion-initiated, polycyclization sequence was conceived as a potentially rapid method to obtain the functionalized target molecule. It was believed that an appropriate C-acyliminium ion could be generated from imidoyl chloride **74e** via cuprate addition-elimination followed by activation by a suitable acid (Scheme 82). Unfortunately, reliable conditions could not be

found to produce imine **108** in good yield after extensive testing of various butyl cuprates under a host of conditions. Hence production of **110** by this tricyclization cascade was never able to be investigated.

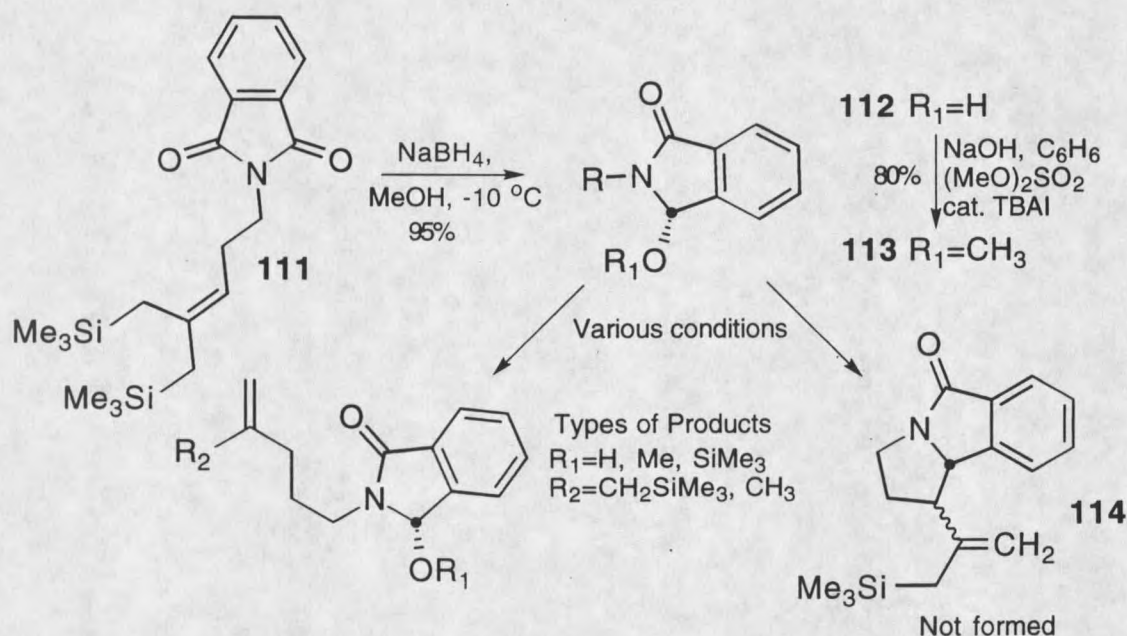


Scheme 82

In comparison to C-acyl iminium ions and conventional iminium ions, the N-acyl variants have received considerably more use in cyclizations terminated by allylsilanes. To our knowledge, there has been no account of such a cyclization employing an allyl(bis)silane as a terminator. With the synthesis of the Stemofoline core in mind, experiments were made in order to address the feasibility of this type of cyclization but, unfortunately, the results have been undesirable.

For example, previously prepared phthalimide **9a** was partially reduced via the procedure of Speckamp^{28,35} to furnish hydroxy lactam **111** in high yield

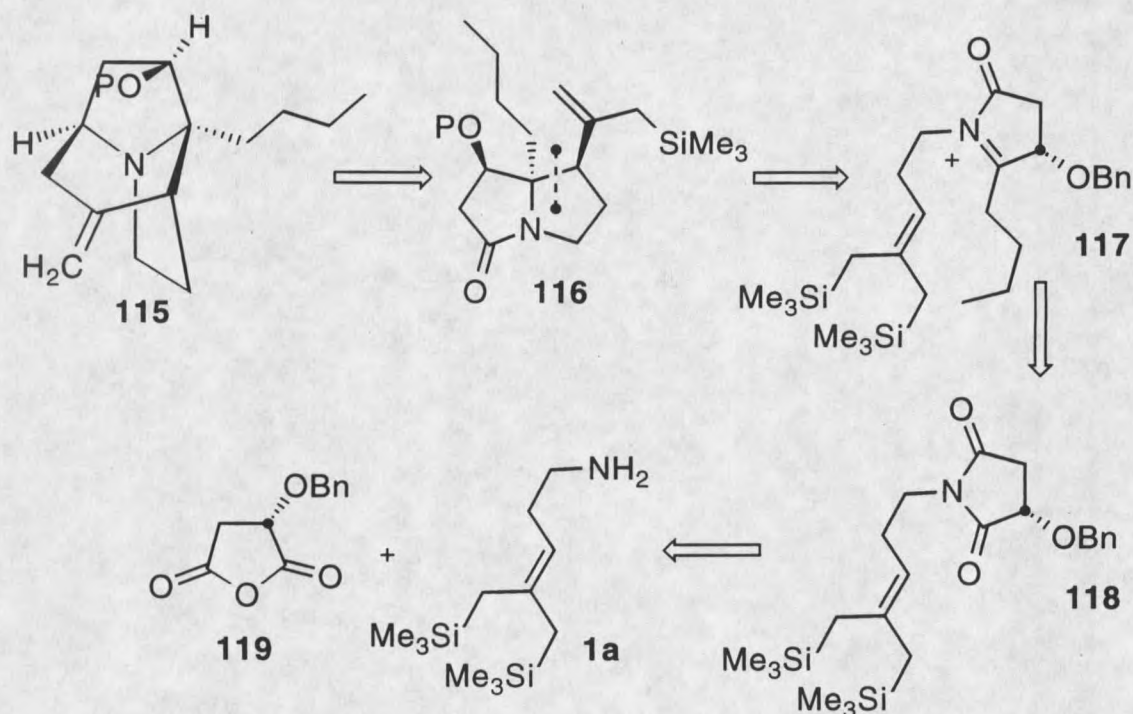
(Scheme 83). Alkylation under biphasic, phase transfer conditions provided the methoxy derivative **112** in 83% yield. Exposure of either **111** or **113** to conditions that should promote ionization-cyclization^{28,35,38} did not result in any detected formation of tricyclic lactam **114**. For this system, the high energy required to form an anti-aromatic iminium ion was believed to be the source of failure. As a result, lower energy pathways such as protodesilylative processes dominated.



Scheme 83

Nevertheless, it became realized that a more conventional N-acyliminium ion-allyl(bis)silane cyclization might be an attractive means by which to synthesis the Stemofoline target molecule. In this retrosynthetic analysis (Scheme 84), application of the alkylation-desilylative cyclization transform to the tricycle **115** reveals bicyclic lactam **116** as a plausible intermediate. Disconnection of the strategic Mannich-type bond in **116** furnishes acyliminium

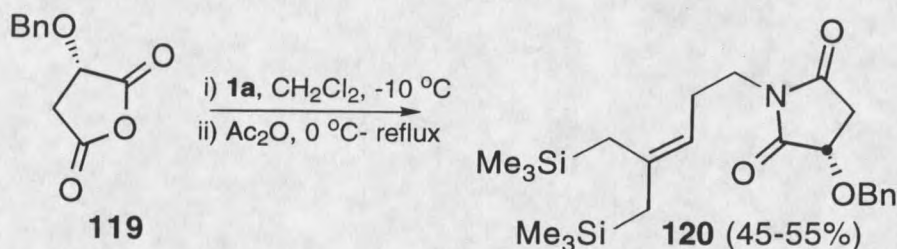
ion **117** which should be accessible from cyclic imide **118** through a Grignard addition-elimination sequence. Imide **118** maps nicely onto the previously prepared amine **1a** and the known, homochiral anhydride **119**.⁹⁴



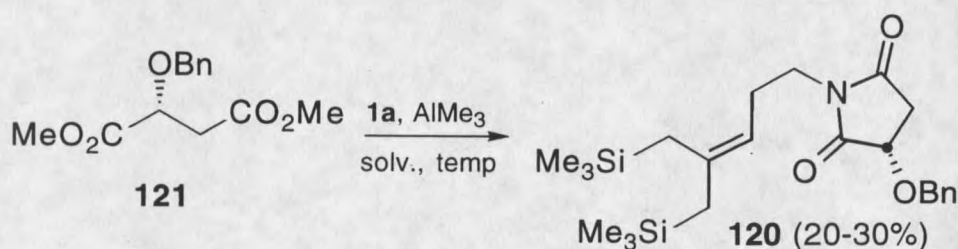
Scheme 83

Preparation of the imide **118** was carried out by nucleophilic opening of **119** by amino-allyl(bis)silane **1a** followed by immediate exposure of the intermediate acid-amide to acylation conditions (py, DMAP, Ac₂O), (Scheme 84). In this fashion a yield of 45-55% of the purified imide was realized. Decomposition of the sensitive 2-propylidene-1,3-bis(silane) addend was observed to be the major source of the low yield. Alternative methods to induce imide closure such as DCC, AcCl and TFAA under a variety of conditions also met with low yields and destruction of the 2-propylidene-1,3-bis(silane) unit. Using the Weinreb protocol⁹⁵, a more direct route starting from diester **120**⁹⁴

was investigated (Scheme 85). This however furnished low yields even after extensive screening of a broad range of reaction conditions in which solvent, temperature and amount of AlMe_3 were varied.



Scheme 84



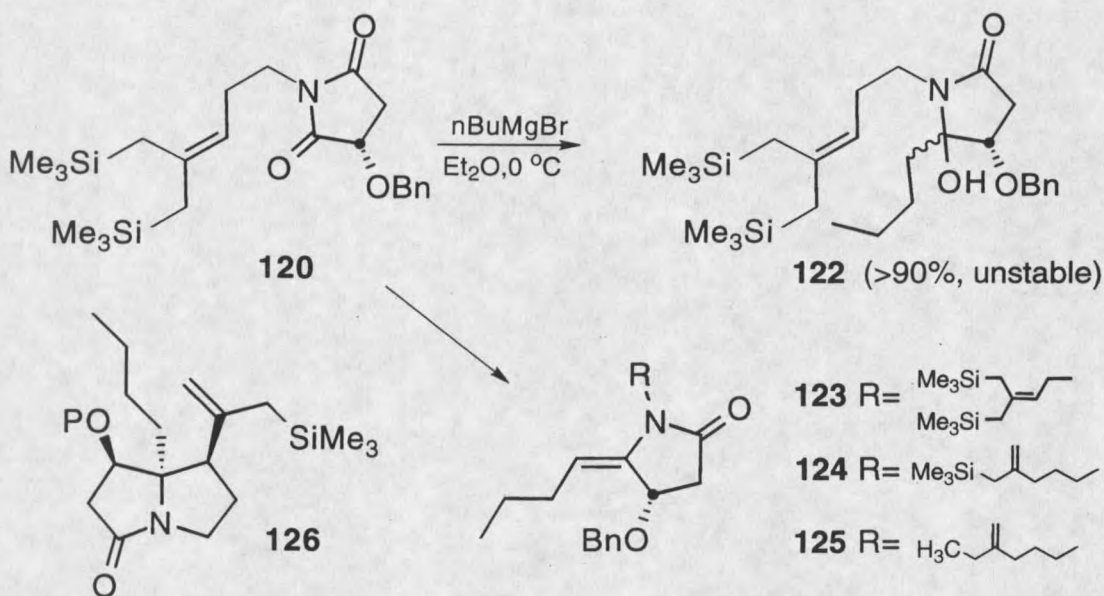
Scheme 85

With some quantities of the desired imide in hand, initial probing into the Grignard addition-cyclization sequence began. Treatment of **120** with nBuMgBr (1.1 equiv., Et_2O , 0°C , 0.5-1h) resulted in rapid consumption of substrate to provide the unstable hydroxylactam **122** in near quantitative crude yield upon protic quench ($\text{NH}_4\text{Cl(aq)}$) (Scheme 86). A second minor product could be detected (TLC) and has tentatively been assigned as a minor diastereomer based on ^1H NMR analysis.

Evidence for regioselective attack by the Grignard nucleophile to the more activated carbonyl was provided by the observance of a large chemical shift of the OBn-methine H in the ^1H NMR spectrum relative to the adjacent

methylene hydrogens upon introduction of the butyl group to the molecule. In addition, the reaction was found to proceed at very low temperatures ($-20\text{ }^{\circ}\text{C}$) but excess Grignard reagent and long reaction times (12h) were required. These results were encouraging since similar Grignard additions have been performed by both Speckamp⁹⁶ and Evans.⁴ In these instances, addition to cyclic imides lacking activating groups such as an OBn ether proceeded with low conversions even when long reaction times (20h, rt.) or heating were employed. The corresponding ring-opened products also complicated their product mixtures but was not observed in the preparation of **122**.

Development of conditions that might trigger the ionization-cyclization sequence was next undertaken. Activation of the hydroxylactam using a variety of reagents (TFAA, MsCl, TFA, $\text{Me}_2\text{Si}(\text{SMe})_2$) resulted in elimination products of type **123-125** frequently being isolated with no desired bicyclic lactam **126** detected (Scheme 87). The intermediate magnesium alkoxide upon treatment of **120** with $n\text{BuMgBr}$ was exposed to both MeI and TMSCl in the hope to afford more stable iminium ion precursors but little reactivity was observed (TLC) in these reactions. In addition, direct treatment of the alkoxide with TFAA or MsCl also produced enamides **123** and **124**. In fact, the hydroxylactam substrate was found to undergo decomposition after several hours at rt. in CDCl_3 to afford a mixture of products containing **124**. In all these instances, elimination was observed to have occurred exclusively in an *exo* fashion. This is somewhat surprising since Speckamp and others observed primarily *endo* elimination in related hydroxylactam systems.⁹⁶

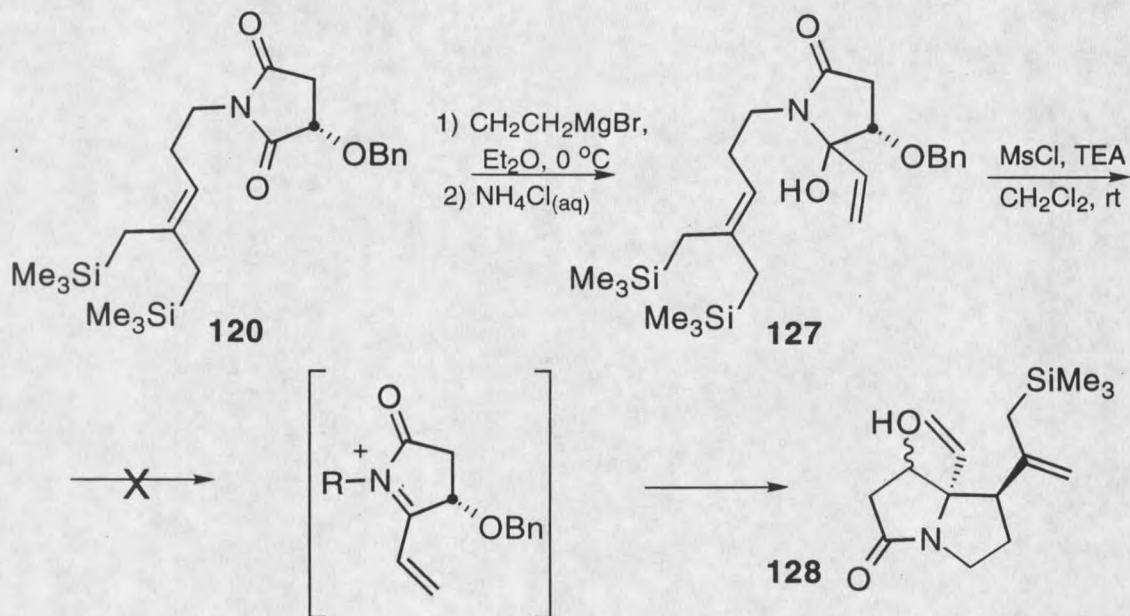


Scheme 87

With the strong tendency for hydroxylactam **122** and related derivatives to undergo facile exo elimination, it was hypothesized that removal of the relatively acidic protons on the butyl substituent prior to the critical cyclization might prevent this elimination. Such an alteration of the synthetic plan could theoretically be carried out by utilizing the vinyl Grignard reagent derived from *trans*-1-iodobutene in the formation of the requisite hydroxylactam. Hydrogenation of the double bond could most likely be induced later in the synthesis.

To quickly test this possibility, imide **120** was treated with ethenyl-magnesium bromide (1.2 eq, Et₂O, 0 °C) to cleanly provide hydroxylactam **127** in 95% yield with the ¹H NMR suggesting the presence of a small amount of a second diastereomer (Scheme 88). An initial attempt to induce ionization-cyclization using the mild and effective conditions of Gramian³⁸ (TEA 1.1 eq., MsCl 1.1 eq., CH₂Cl₂, rt.) resulted in complete consumption of **127**. None of

the desired bicycle **128** was isolated from the reaction mixture however. Two products that were isolated contained no TMS residues and were unable to be completely characterized. Further experimentation with this synthetic route was not performed.



Scheme 88

The *N*-acyliminium ion approach has not resulted in any production of the crucial Stemofoline intermediates. In practice, the synthetic scheme has been plagued by the high propensity of the cyclization precursors to undergo elimination rather than ionization-cyclization. In the only two accounts of *N*-acyliminium ion cyclizations proceeding by way of *tertiary* hydroxylactams, both Evans⁴ and Speckamp⁹⁶ exposed corresponding enamides to formic acid to induce *N*-acyliminium ion formation. Their results and the observations of this study suggest that, unlike secondary hydroxylactams^{35,38}, iminium ion formation from a tertiary hydroxylactam must proceed via protonation of the

enamide, not by direct ionization. The strongly acidic conditions required for such a transformation could easily render the 2-propylidene-1,3-bis(silane) terminator useless for cationic cyclizations originating from tertiary hydroxylactams.

To this date the properly functionalized, tricyclic core of Stemofoline has not been synthesized in acceptable yield via three different synthetic strategies involving tandem allylbis(silane)-iminium ion cyclizations. Nevertheless, the efficient synthesis of the unfunctionalized azatricyclic core from amine **1a** does illustrate the potential of the allylbis(silane) terminator to construct complex, stereodefined polycycles and the results of this study show that a synthetic approach to Stemofoline via this methodology is still a worth while research endeavor.

SUMMARY

In response to the synthetic limitations of the mono allylsilane nucleophile, an allylbis(silane) cyclization terminator was developed for use in the synthesis of cyclic alkaloids. Amines tethered to a 2-propylidene-1,3-bis(silane) nucleophile were efficiently prepared via a scheme involving a tandem, palladium catalyzed cross coupling reaction as the pivotal step. Under mild conditions, these amines were transformed into activated imines which underwent regiospecific and stereoselective cyclizations directed by the allylbis(silane) terminator. As a result, substituted pyrrolidines and piperidines bearing a mono allylsilane were synthesized in high yield and with good control over the relative configuration of the substituents. Additional cyclizations performed on imines derived from ethyl lactate proceeded with high levels of diastereocontrol between stereocenters disposed both within and outside of the cycle periphery.

This terminator was also found to engage in cyclizations onto transient C-acylnitrilium ions generated from isocyano-allyl(bis)silanes and acid chlorides. Using this reaction, functionally diverse acylpyrrolines were synthesized in good chemical yield with moderate to high levels of diastereocontrol as well as a set of pyrrolidines that stereochemically complemented those obtained from the imine cyclization protocol.

Iminium ion cyclizations directed by the 2-propylidene-1,3-bis(silane) terminator were successfully applied to the stereodefined synthesis of therapeutic alkaloids shown to combat the symptoms of Alzheimer's disease. Azabicyclooctane and azabicyclononane ligands were synthesized in high

yield by employing either tandem, one-pot bicyclizations or controlled, stepwise sequences thus revealing the synthetic flexibility of the terminator.

This feature culminated in a concise and efficient synthesis of the azatricyclic nucleus of the alkaloid Stemofoline. In this instance, the key step involved an imine cyclization-lactam closure bicyclization that proceeded with complete stereocontrol. Intermediates containing the functionality present in the natural product were also prepared by this reaction but in yields that did not permit completion of the total synthesis.

The results of this research project demonstrated the capability of an allylbis(silane) terminator to direct cyclizations in a regio- and stereocontrolled manner. Unlike the silicon-based nucleophiles previously developed, this terminator enabled the control of two cyclizations from the same nucleophilic olefin. From this work, it is quite conceivable that other bis(silanes) such as vinyl- and propargylbis(silanes) could be utilized and continue the advancement of silicon directed reactions.

EXPERIMENTAL

General Experimental Details

Physical Data: ^1H NMR and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, with a Bruker AC-300 spectrometer. ^1H NMR and ^{13}C NMR chemical shifts are reported as δ values in ppm relative to residual proton signals in CDCl_3 ($\delta = 7.24, 77.0$) or C_6D_6 ($\delta = 7.15, 128.7$). ^1H NMR coupling constants are reported in Hz and refer to real or apparent multiplicities indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); p (pentet); sx (sextet); br (broad); m (multiplet); app (apparent); dd (doublet of doublets); dt (doublet of triplets); etc.

Infrared spectra were recorded on a Bruker IFS 25 IR. Electron impact mass spectra (70 eV) were obtained with a Hewlett Packard 5970 series mass selective detector. High resolution mass spectra were recorded on a VG Instruments 70E-HF spectrometer. Melting points were obtained using a Mel-Temp II apparatus equipped with a Fluke 51 digital thermometer and are uncorrected.

Chromatography: Gas chromatographs were obtained using a Hewlett Packard 5890 Series II gas chromatograph equipped with a flame ionization detector and an Alltech Econocap SE-54 bonded phase column (15 m length, 0.54 mm id, and 0.25 μm film thickness). TLC was performed on plates supplied by Alltech Associates (K42-G) using one or more following visualization techniques:⁹⁷ UV illumination at 254 nm, KMnO_4 oxidation, anisaldehyde derivatization, exposure to phosphomolybdic acid or ammonium molybdate, exposure to iodine vapor or ninhydrin derivatization. Column chromatography

was performed according to the methods of Still⁹⁸ employing Merck Silica Gel 60, Aldrich Activity 1 basic alumina (150 mesh) or commercial Florisil (100-200 mesh). Solvent systems used for elution are reported as %volume/volume.

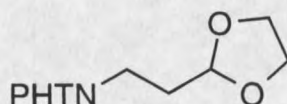
Chemical Materials, Reagents and Techniques: Tetrahydrofuran (THF), benzene, heptane and 1,2-dimethoxyethane (DME) were distilled from potassium and diethyl ether (Et_2O) was distilled from sodium-benzophenone. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5 . Toluene, acetonitrile (CH_3CN), dimethylformamide (DMF, dist. @ 15 torr), 1,2-dichloroethane (1,2-DCE), and commercially purchased amines were distilled from CaH_2 . Methanol (CH_3OH) was distilled from $\text{Mg}(\text{OCH}_3)_2$. Atmospheric pressure distillation of the above solvents and reagents and those mentioned hereafter was performed under an inert atmosphere of argon or nitrogen.

The molarities for alkylmagnesium halide and alkyl lithium reagents were established by titration with 2-butanol using 1,10-phenanthroline as an indicator. Total base concentration of these reagents was established by titration with standard potassium biphthalate solutions using a phenolphthalein indicator.

Unless otherwise noted, all reactions were carried out under an atmosphere of argon in flamed, oven-dried vessels of appropriate size and style equipped with magnetic stir bar and stir plate. Addition of reagents was carried out utilizing standard syringe-septum techniques. Unless stated otherwise, reagents were used as purchased from major chemical suppliers. Commercial alkyl halide reagents were purified by elution through Aldrich Activity 1 basic alumina (150 mesh) prior to use. Reduced pressure concentrations were performed with a Buchi RE 121 rotary evaporator.

Synthesis of Aminoallylbis(silanes)

General Information: Standard THF solutions of anhydrous zinc chloride were prepared by flame fusing commercial zinc chloride under high vacuum (< 250 μ torr) in a volumetric flask followed by dilution with dry THF. Commercial carbon tetrabromide was purified by elution through basic alumina (CH_2Cl_2 for elution) prior to use. $\text{PdCl}_2(\text{PPh}_3)_2$ was prepared from commercially purchased PdCl_2 using previously reported procedures.⁹⁹



2-(2-Phthalimidoethyl)-1,3-dioxolane (6). To a 250 mL, single-necked, round-bottomed flask containing a suspension of potassium phthalimide (25.6 g, 138 mmol) in DMF (100 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (20.0 g, 110 mmol) followed by anhydrous NaI (1.00 g, 6.67 mmol). The white suspension was vigorously stirred for 30h at 25 °C. The mixture was concentrated *in vacuo* and the resulting white solids were triturated with ethyl acetate (3 x 50 mL). The supernatant was filtered through a plug of silical gel with ethyl acetate for elution to give **6** (27.0 g, 99%) as a white solid upon evaporation of solvent: mp 117.2-118.0 °C (40% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.79 (dd, J = 5.4, 3.1 Hz, 2H, ArH), 7.66 (dd, J = 5.4, 3.1 Hz, 2H, ArH), 4.91 (t, J = 4.4 Hz, 1H, CH), 3.83 (m, 4H, $\text{CH}_2\text{O} \times 2$), 3.80 (t, J = 6.8 Hz, 2H, CH_2N), 2.03 (dt, J = 6.9, 4.4 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.15, 133.70, 132.26, 123.06, 102.58, 64.90, 33.12, 32.20; IR (KBr) 2948, 2885, 1766, 1694, 1612, 1398, 1372, 1125, 1063, 892, 728, 715 cm^{-1} .



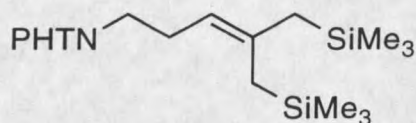
3-Phthalimidopropionaldehyde (7a). A 500 mL, single-necked, round-bottomed flask was charged with acetal **6** (10.0 g, 40.5 mmol) and degassed HCl (200 mL, 0.5 M). The reaction vessel was fitted with a condenser and the white suspension was heated at reflux for 1h during which vigorous stirring was maintained. The resulting homogeneous solution was cooled to room temperature during which a white precipitate formed. The mixture was placed in refrigeration (10 °C) overnight. The solid was collected on a fritted funnel, washed with cold H₂O (3 x 25 mL) and dried *in vacuo* to yield **7a** (5.84 g, 71%) as a white solid: mp 127.7-129.6 °C (90% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 9.77 (s, 1H, O=CH), 7.72 (m, 4H, ArH), 3.98 (t, J = 7.1 Hz, 2H, CH₂N), 2.82 (dt, J = 5.7, 1.2 Hz, 2H, CH₂); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 199.22, 167.87, 134.00, 131.92, 123.25, 42.25, 31.61; IR (KBr) 2948, 2925, 2848, 2742, 1767, 1698, 1612, 1470, 1441, 1403, 1369, 1136, 1031, 721, cm⁻¹.



1,1-Dibromo-4-phthalimido-1-butene (8a). To a 500 mL, three-necked, round-bottomed flask equipped with a 100 mL, addition funnel and a 50 mL, solid addition funnel was added CBr₄ (18.7 g, 56.4 mmol) and CH₂Cl₂ (85 mL). The resulting solution was cooled to 0 °C and PPh₃ (29.6 g, 113 mmol) dissolved in CH₂Cl₂ (50 mL) was added dropwise over 30 min. After stirring the resulting deep orange mixture for an additional 10 min at 0 °C, aldehyde **7a** (5.73 g, 28.2 mmol) was added over 30 min via the solid addition funnel. The dark burgundy mixture was stirred for 2h at 0 °C and then

concentrated *in vacuo*. Trituration of the solids (EtOAc, 3 x 100 mL) followed by Celite filtration of the supernatant liquid furnished the crude product as a white solid which was subjected to chromatography on silica gel (20% EtOAc / hexane elution) to afford **8a** (8.72 g, 86%) as a white crystalline solid: mp 114.2-115.3 °C (50% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.76 (m, 4H, ArH), 6.39 (t, J = 7.2 Hz, 1H, C=CH), 3.73 (t, J = 6.8 Hz, 2H, NCH_2), 2.44 (q, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 167.92, 134.46, 133.92, 131.91, 123.19, 91.44, 35.45, 32.19; IR (KBr) 3100, 3043, 3025, 2945, 1771, 1684, 1613, 1403, 1365, 1248, 1133, 988, 872, 805, 792, 722, 713, 625 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_9\text{NO}_2\text{Br}_2$ (M^+) 356.9000, found 356.8985.

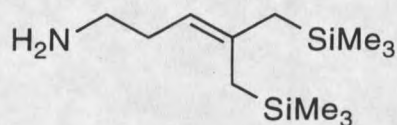
(Trimethylsilyl)methylmagnesium chloride. A 1.0 L, three-necked, round-bottomed flask equipped with a 100 mL, addition funnel and condenser was charged with magnesium powder (14.1 g, 578 mmol, 50 mesh) and THF (250 mL) followed by 1,2-dibromoethane (0.80 mL, 9.28 mmol). The magnesium suspension was stirred for 10 min and chloromethyltrimethylsilane (73.3 mL, 525 mmol) was added dropwise over 2h during which exotherms resulted in a gentle reflux of the reaction mixture. Following addition, the dark reaction mixture was stirred for 4h at rt and stirring was then stopped. The mixture was allowed to stand overnight after which the solution of the title Grignard reagent was transferred under argon into a storage bottle via cannula. Titration of aliquots using 2-butanol and 1,10-phenanthroline as an indicator showed the concentration to be 1.70 M in THF and the stock solution of the Grignard reagent was stored in refrigeration (10 °C) between useage.



5-Phthalimido-2-trimethylsilylmethyl-1-trimethylsilyl-2-

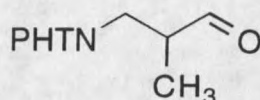
pentene (9a). To a 500 mL, three-necked, round-bottomed flask equipped with a 100 mL, addition funnel was added a solution of anhydrous ZnCl_2 (0.47 M in THF, 98.0 mL, 45.9 mmol) via syringe. The solution was cooled to 0 °C and a solution of $\text{TMSCH}_2\text{MgCl}$ (1.69 M in THF, 54.3 mL, 91.8 mmol) was added dropwise over 15 min via the addition funnel. The gray solution was stirred for 15 min at 0 °C and $\text{PdCl}_2(\text{PPh}_3)_2$ (1.50 g, 2.14 mmol, 7 mol%) was added in one portion. After stirring for 15 min at 25 °C, olefin **8a** (11.0 g, 30.6 mmol) in THF (60 mL) was added dropwise over 40 min via addition funnel to the black-brown reaction mixture. Stirring was continued at 25 °C for 7h whereupon the reaction mixture was poured into cold, saturated NH_4Cl (300 mL). Both phases were decanted into a separatory funnel and the organic phase was removed. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were washed with brine (2 x 200 mL), dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant liquid was filtered through a pad of Celite and concentrated. The crude product was purified by chromatography on silica gel (hexane - 5% EtOAc /hexane elution) to furnish the title compound (11.0 g, 96%) as a white solid: mp 57.9-58.8 °C (95% EtOH); ^1H NMR (300 MHz, CDCl_3) δ 7.71 (m, 4H, ArH), 4.76 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 3.61 (t, J = 7.5 Hz, 2H, NCH_2), 2.28 (q, J = 7.3 Hz, 2H, CH_2), 1.44 (s, 2H, SiCH_2), 1.36 (s, 2H, SiCH_2), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.12 (s, 9H $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.28, 138.15, 133.66, 132.34, 123.02, 114.55, 38.09, 29.61,

27.86, 23.85, -0.71, -1.28; IR (KBr) 3165, 2953, 2920, 2898, 1771, 1717, 1614, 1394, 1360, 1248, 1216, 1070, 1046, 854, 718 cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_2\text{Si}_2$ (M^+) 373.1893, found 373.1901.

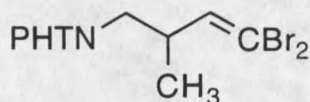


4-Trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (1a).

To a 250 mL, single-necked, round-bottomed flask containing a solution of phthalimide **9a** (15.3 g, 41.0 mmol) in degassed, absolute ethanol (115 mL) was added hydrazine monohydrate (4.0 mL, 82.5 mmol) dropwise over 2 min via a syringe. The flask was fitted with a condenser and the mixture was heated at reflux for 8h during which time a white solid precipitated. Upon cooling to ambient temperature, the solid was collected by filtration and washed thoroughly with hexane. The solvents were evaporated *in vacuo* and the residue was triturated with hexane. Filtration of the supernatant liquid followed by solvent removal *in vacuo* gave a cloudy oil which was purified by bulb to bulb distillation to furnish the title compound (9.58 g, 96%) as a clear, colorless oil: bp 40 °C, 50 μtorr ; ^1H NMR (300 MHz, CDCl_3) δ 4.71 (t, J = 6.8 Hz, 1H, $\text{C}=\text{CH}$), 2.61 (t, J = 6.8 Hz, 2H, NCH_2), 2.01 (q, J = 6.9 Hz, 2H, CH_2), 1.44 (s, 2H, CH_2Si), 1.37 (s, 2H, CH_2Si), 1.09 (s, 2H, NH_2), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.05 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 136.54, 116.61, 42.70, 33.20, 29.59, 23.85, -0.70, -1.16; IR (film) 3371, 3292, 3018, 2953, 2921, 2896, 1645, 1415, 1247, 1158, 1066, 837, 698, 624 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{29}\text{NSi}_2$ (M^+) 243.1839, found 243.1850.

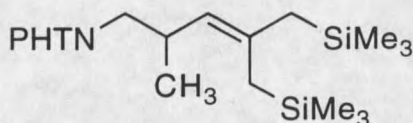


2-Methyl-3-phthalimidopropionaldehyde (7b). A 200 mL, three-necked, round-bottomed flask equipped with a 25 mL, addition funnel was charged with absolute EtOH (60 mL) and freshly cut sodium metal (230 mg, 10.0 mmol) was added. The mixture was stirred until complete consumption of the Na was observed (10 min). Phthalimide (17.6 g, 120 mmol) was added in one portion and the white suspension was stirred for 10 min. An ethanolic solution of freshly distilled methacrolein (8.27 mL, 100 mmol in 10 mL EtOH) was added dropwise over 20 min via the addition funnel and the mixture was stirred at 25 °C for 6h. The reaction mixture was treated with glacial acetic acid (2 mL), stirred for 5 min and filtered through a pad of Celite to produce a sticky white solid upon evaporation of solvent. The solid was dissolved in toluene (50 mL) and eluted through a silica gel plug (toluene for elution) to give **7b** (16.0 g, 74%) as a dry white powder upon pulverization: mp 83.8-85.3 °C (50% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 9.63 (d, J = 1.3 Hz, 1H, $\text{O}=\text{CH}$), 7.66 (m, 4H, ArH), 3.91 (dd, J = 14.1, 7.2 Hz, 1H, NCHH), 3.69 (dd, J = 14.1, 6.5 Hz, 1H, NCHH), 2.78 (dsx, J = 7.0, 1.3 Hz, 1H, CH), 1.05 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 201.89, 167.90, 133.88, 131.59, 123.09, 45.51, 37.90, 11.32; IR (KBr) 3099, 2975, 2939, 2881, 2758, 1774, 1694, 1611, 1464, 1435, 1398, 1357, 1041, 897, 721 cm^{-1} .



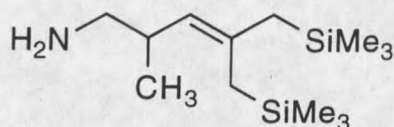
1,1-Dibromo-3-methyl-4-phthalimido-1-butene (8b). Utilizing the procedure used for the preparation of olefin **8a**, aldehyde **7b** (10.0 g, 46.0

mmol) was converted into the the title compound (15.3 g, 89%) which was isolated as a white, crystalline solid: mp 104.1-106.5 °C (20% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.73 (m, 4H, ArH), 6.22 (d, J = 9.7 Hz, 1H, C=CH), 3.58 (m, 2H, CH_2N), 2.97 (m, 1H, CH), 1.04 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.02, 140.53, 133.92, 131.92, 131.83, 123.20, 89.85, 41.69, 37.94, 16.61; IR (KBr) 3132, 2974, 2938, 1769, 1716, 1615, 1436, 1395, 1053, 720, 711, 626, cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{11}\text{Br}_2\text{NO}_2$ (M^+) 370.9156, found 370.9162.

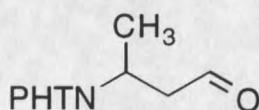


4-Methyl-5-phthalimido-2-trimethylsilylmethyl-1-trimethylsilyl-2-pentene (9b). The title compound was prepared employing the procedure used for the preparation of **9a**. From olefin **8b** (6.0 g, 16.1 mmol), phthalimide **9b** (5.32 g, 85%) was obtained as a white solid: mp 92.0-93.1 °C (95% EtOH); ^1H NMR (300MHz, CDCl_3) δ 7.73 (m, 4H, ArH), 4.61 (d, J = 9.4, Hz, 1H, C=CH), 3.47 (m, 2H, NCH_2), 1.63 (d, J = 13.4 Hz, 1H, CHHSi), 1.31 (app p, J = 13.4 Hz, 3H, CHHSi and CH_2Si), 0.90 (d, J = 6.6 Hz, 3H, CH_3), -0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.11 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.55, 136.77, 133.69, 132.23, 123.07, 122.07, 43.97, 32.12, 29.42, 23.60, 18.79, -0.69, -1.21; IR (KBr) 3099, 2981, 2949, 2890, 1766, 1707, 1613, 1396, 1381, 1251, 1073, 1046, 866, 729, cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_2\text{Si}_2$ (M^+) 387.2050, found 387.2043.

135

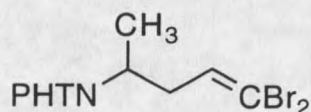


2-Methyl-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (1b). Using the procedure previously described for the preparation of **1a**, phthalimide **9b** (2.5 g, 6.45 mmol) was deprotected to yield amine **1b** (1.51 g, 91%) as clear colorless oil after bulb to bulb distillation: bp 70-73 °C, 50 μ torr; ^1H NMR (300 MHz, CDCl_3) δ 4.49 (d, J = 9.5 Hz, 1H, $\text{C}=\text{CH}$), 2.50 (dd, J = 12.1, 5.8 Hz, 1H, NCHH), 2.36 (dd, J = 12.2, 7.9 Hz, 1H, NCHH), 2.19 (m, 1H, CH), 1.62 (d, J = 13.5 Hz, 1H, CHHSi), 1.36 (ABq, Δv = 33.0 Hz, J = 13.5 Hz, 2H, CH_2Si), 1.29 (d, J = 13.5 Hz, 1H, CHHSi), 1.02 (s, 2H, NH_2), 0.85 (d, J = 6.4 Hz, 3H, CH_3), -0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.04 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 135.31, 124.01, 49.22, 36.55, 29.47, 23.86, 18.72, -0.69, -1.13; IR (film) 3380, 3301, 2954, 2924, 2897, 2869, 1644, 1455, 1416, 1248, 1159, 1068, 943, 867, 698, 624, cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{31}\text{NSi}_2$ (M^+) 257.1995, found 257.1987.

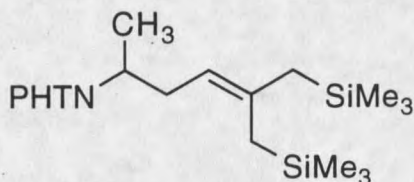


3-Phthalimidobutanal (7c). The preparation of **7c** was carried out as described for **7b** employing freshly distilled crotonaldehyde (16.6 mL, 200 mmol) and a reaction time of 24h at 25 °C to provide the title compound (19.7 g, 45%) as a white solid: mp 112.2-113.9 °C (50% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 9.66 (s, 1H, $\text{O}=\text{CH}$), 7.67 (m, 4H, ArH), 4.82 (app sx, J = 7.1 Hz, 1H, CH), 3.22 (dd, J = 18.0, 8.2 Hz, 1H, $\text{O}=\text{CHCHH}$), 2.94 (dd, J = 18.0, 6.2 Hz, 1H, $\text{O}=\text{CHCHH}$), 1.41 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 199.08, 167.80, 133.81, 131.69, 123.00, 47.17, 41.27, 18.63; IR

(KBr) 3044, 2986, 2926, 2867, 2755, 1771, 1699, 1611, 1472, 1395, 1360, 1333, 1305, 1145, 1134, 1031, 882, 720, cm^{-1} .

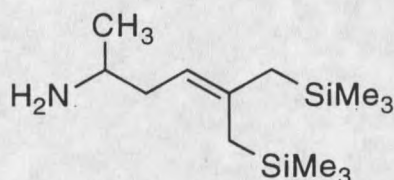


1,1-Dibromo-4-phthalimido-1-pentene (8c). The reaction of aldehyde **7c** (2.37 g, 10.9 mmol) with CBr_4 and PPh_3 was carried out as described previously for the preparation of **8a** to yield the title compound (4.00 g, 98%) as a white crystalline solid: mp 64.2-65.1 $^{\circ}\text{C}$ (20% EtOAc/hexanes); ^1H NMR (300MHz, CDCl_3) δ 7.71 (m, 4H, ArH), 6.30 (t, $J = 7.3$ Hz, 1H, $\text{C}=\text{CH}$), 4.41 (app sx, $J = 6.8$ Hz, 1H, NCH), 2.79 (app dt, $J = 15.6, 8.3$ Hz, 1H, $\text{CHHCH}=\text{C}$), 2.52 (app dt, $J = 15.0, 6.5$ Hz, 1H, $\text{CHHCH}=\text{C}$), 1.47 (d, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.00, 134.61, 133.85, 131.74, 123.07, 91.25, 45.55, 37.70, 18.19; IR (KBr) 3058, 2997, 2939, 2974, 1770, 1716, 1614, 1394, 1370, 1356, 1083, 1044, 795, 785, 717, cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{11}\text{Br}_2\text{NO}_2$ (M^+) 370.9156, found 370.9157.



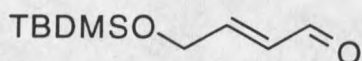
5-Phthalimido-2-trimethylsilylmethyl-1-trimethylsilyl-2-hexene (9c). Using the procedure described previously for the preparation of **9a**, dibromo olefin **8c** (15.0 g, 40.2 mmol) was converted into the title compound (14.6 g, 94%) which was isolated as a white crystalline solid: mp 68.9-70.2 $^{\circ}\text{C}$ (95% EtOH); ^1H NMR (300 MHz, CDCl_3) δ 7.69 (m, 4H, ArH), 4.67 (app t, $J = 7.0$ Hz, 1H, $\text{C}=\text{CH}$), 4.31 (m, 1H, NCH), 2.71 (dt, $J = 14.7, 8.8$ Hz, 1H, $\text{C}=\text{CHCHH}$),

2.31 (dt, $J = 14.7, 6.1$ Hz, 1H, C=CHCHH), 1.57 (d, $J = 13.3$ Hz, 1H, CHHSi), 1.42 (d, $J = 6.9$ Hz, 3H, CH₃), 1.28 (ABq, $\Delta\nu = 29.3$ Hz, $J = 13.3$ Hz, 2H, CH₂Si), 1.26 (d, $J = 13.3$ Hz, 1H, C=CHHSi), -0.02 (s, 9H, (CH₃)₃Si), -0.26 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 168.42, 137.92, 133.57, 132.24, 122.89, 115.31, 47.82, 33.36, 29.58, 24.02, 18.45, -0.63, -1.45; IR (KBr) 2970, 2952, 2894, 1767, 1696, 1614, 1467, 1394, 1374, 1165, 1077, 1169, 848, 722 cm⁻¹; HRMS calcd for C₂₁H₃₃NO₂Si₂ (M⁺) 387.2050, found 387.2049.



5-Trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (1c).

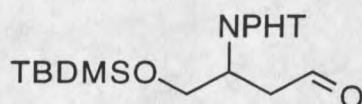
Employing the procedure for the preparation of **1a**, phthalimide **9c** (14.6 g, 37.7 mmol) was converted into the title amine (8.93 g, 92%) which was isolated as a clear colorless oil after bulb to bulb distillation: bp 65-75 °C, 50 μ torr; ¹H NMR (300 MHz, CDCl₃) δ 4.77 (t, $J = 7.2$ Hz, 1H, C=CH), 2.82 (app sx, $J = 6.3$ Hz, 1H, CH), 1.89 (app t, $J = 7.4$ Hz, 2H, CH₂), 1.45 (ABq, $\Delta\nu = 33.3$ Hz, $J = 13.3$ Hz, 2H, CH₂Si), 1.38 (s, 2H, CH₂Si), 1.16 (s, 2H, NH₂), 1.01 (d, $J = 6.2$ Hz, 3H, CH₃), -0.02 (s, 9H, (CH₃)₃Si), -0.03 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 136.73, 116.43, 47.74, 39.55, 29.67, 23.93, 23.51, -0.65, -1.08; IR (film) 3365, 3289, 2955, 2923, 2896, 1645, 1453, 1412, 1248, 1156, 1056, 1066, 833, 699, 624 cm⁻¹; HRMS calcd for C₁₂H₂₈NSi₂ (M⁺-CH₃) 242.1760, found 242.1760.



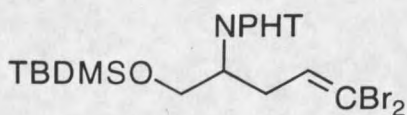
***E*-4-*Tert*-butyldimethylsilyloxy-2-butene-1-one (10).** To a 500 mL, single-necked, round-bottomed flask containing a vigorously stirred solution of *cis*-2-butene-1,4-diol (33.0 mL, 0.40 mol) and imidazole (27.2 g, 0.40 mol) in DMF (200 mL) was added a solution of *tert*-butyldimethylsilyl chloride (30.1 g, 0.20 mol) in DMF (40 mL) dropwise over 1.5h via a 100 mL, addition funnel. Stirring was continued for 6h and the reaction mixture was slowly poured into cold brine (700 mL). The aqueous mixture was extracted with three portions of hexane (250 mL) and the combined extracts were washed twice with brine (300 mL), dried over Na₂SO₄ and filtered through a pad of silica gel (Et₂O for elution). Removal of the solvents *in vacuo* furnished a mixture (85:15 by NMR) of the mono and bis *tert*-butyldimethylsilyl ethers which was used in the next step without further purification.

A 500 mL, single-necked, round-bottomed flask containing a solution of the *tert*-butyldimethylsilyl ethers in CH₂Cl₂ (200 mL) was cooled to 0 °C and pyridinium chlorochromate (43.1g, 0.20 mmol) was added in one portion during which time vigorous stirring of the reaction mixture was maintained. The mixture was stirred at 0 °C for 0.5h then at room temperature for 2h. The black reaction mixture was diluted with pentane (200 mL), filtered through a pad of silica gel (Et₂O for elution) and concentrated *in vacuo*. The residue was subjected to chromatography on silica gel (5% EtOAc/hexane for elution) to furnish the title enone (19.8 g, 49% from *cis*-butene-1,4-diol) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 9.57 (d, *J* = 8.0 Hz, 1H, O=CH), 6.85 (dt, *J* = 15.5, 3.3 Hz, 1H, HC=CH), 6.37, (ddt, *J* = 15.5, 8.0, 2.3 Hz, 1H, HC=CH), 4.42 (dd, *J* = 3.1, 2.0 Hz, 2H, OCH₂), 0.88 (s, 9H, (CH₃)₃CSi), 0.06 (s, 6H, (CH₃)₂Si); ¹³C

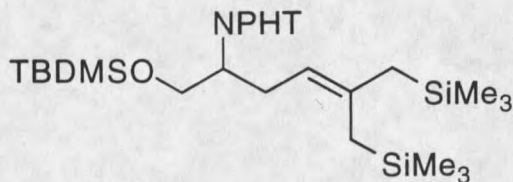
NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 193.12, 156.11, 130.65, 62.25, 25.79, 18.30, -5.47.



4-Tert-butyldimethylsilyloxy-3-phthalimidobutanal (7d). To a 100 mL, single-necked, round-bottomed flask containing a solution of enone **10** (5.00 g, 25.0 mmol) in DMF (50 mL) was sequentially added phthalimide (4.41g, 30.0 mmol) in one portion and DBU (374 μL , 2.50 mmol). The resulting homogeneous reaction mixture was stirred for 2h at rt and was then poured into H_2O (100 mL). The aqueous mixture was extracted with three portions of Et_2O (40 mL) and the combined extracts were dried (MgSO_4), filtered and concentrated. Purification of the residue by silica gel chromatography (10% EtOAc /hexane for elution) furnished the title aldehyde (6.00 g, 70%) as a colorless viscous material which solidified upon cold storage: ^1H NMR (300 MHz, CDCl_3) δ 9.73 (s, 1H, $\text{O}=\text{CH}$), 7.80-7.24 (m, 4H, ArH), 4.86 (dp, $J = 7.5, 2.2$ Hz, 1H, NCH), 3.86 (dd, $J = 7.7, 3.2$ Hz, 2H, SiOCH_2), 3.22 (ddd, $J = 17.8, 8.3, 1.3$ Hz, 1H, CHH), 2.99 (ddd, $J = 17.9, 6.1, 1.0$ Hz, 1H, CHH), 0.75 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), -0.02 (s, 3H, CH_3Si), -0.07 (s, 3H, SiCH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 198.92, 168.16, 133.99, 131.79, 123.19, 62.30, 47.53, 42.89, 25.61, 17.96, -5.58, -5.64; IR (film) 3062, 2942, 2857, 1774, 1701, 1613, 1470, 1366, 1228, 1115, 1036, 835, 779, 721, cm^{-1} .

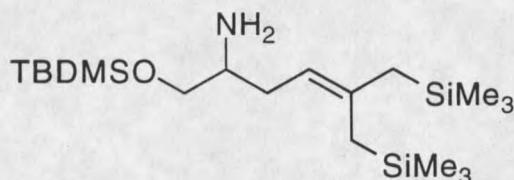


5-*Tert*-butyldimethylsilyloxy-1,1-dibromo-4-phthalimido-1-pentene (8d). Following the procedure outlined for the preparation of **8a**, aldehyde **7d** (5.20 g, 15.0 mmol) was converted into the title compound. In this instance, the crude product was isolated by pentane trituration of the residue obtained after concentration of the reaction mixture. The pentane solution was filtered through Celite (pentane for elution), concentrated and the crude product was purified by chromatography on silica gel (5% EtOAc/hexane for elution) to furnish the title compound (6.64 g, 88%) as a white wax: mp 39.2-49.8 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.82-7.68 (m, 4H, ArH), 6.35 (t, $J = 7.1$ Hz, 1H, C=CH), 4.41 (m, 1H, NCH), 3.99 (dd, $J = 10.0, 8.3$ Hz, 1H, SiOCHH), 3.86 (dd, $J = 10.0, 6.7$ Hz, 1H, SiOCHH), 2.79 (ddd, $J = 17.0, 9.6, 7.5$ Hz, 1H, CHH) 2.57 (ddd, $J = 15.4, 6.9, 5.5$ Hz, 1H, CHH), 0.73 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), -0.02 (s, 3H, CH_3Si), -0.09 (s, 3H, SiCH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.35, 134.36, 133.97, 131.83, 123.18, 91.35, 62.25, 52.00, 32.70, 25.60, 17.90, -5.52, -5.61; IR (film) 3030, 2942, 2857, 1776, 1706, 1614, 1469, 1372, 1258, 1113, 838, 780, 721 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{Br}_2\text{NO}_3\text{Si}$ (M^+) 500.9970, found 500.9968.



1-*Tert*-butyldimethylsilyloxy-2-phthalimido-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexene (9d). Using dibromo olefin **8d** (5.03 g, 10.0 mmol) in the procedure described for the preparation of **9a**

produced the title compound (4.90 g, 95%) which was obtained as a colorless, viscous gel: ^1H NMR (300 MHz, CDCl_3), δ 7.79-7.64 (m, 4H, ArH), 4.69 (t, J = 7.0 Hz, 1H, C=CH), 4.34 (m, 1H, NCH), 4.01 (t, J = 9.9 Hz, 1H, SiOCHH), 3.81 (dd, J = 9.9, 5.5 Hz, 1H, SiOCHH), 2.65 (ddd, J = 17.9, 9.0, 5.9 Hz, 1H, CHH), 2.37 (dt, J = 14.8, 6.4 Hz, 1H, CHH), 1.57 (d, J = 13.3 Hz, 1H, SiCHH), 1.35 (d, J = 13.4 Hz, 1H, SiCHH), 1.26 (dd, J = 13.5, 3.5 Hz, 2H, SiCH₂), 0.73 (s, 9H, (CH₃)₃CSi), -0.01, (s, 9H, (CH₃)₃Si), -0.03 (s, 3H, (CH₃)₃CSiCH₃), -0.01 (s, 3H, (CH₃)₃CSiCH₃), -0.25 (s, 9H, Si(CH₃)₃); ^{13}C NMR (75MHz, CDCl_3 , ^1H decoupled) δ 168.69, 138.15, 133.60, 132.20, 122.88, 114.49, 62.70, 54.32, 29.62, 28.07, 25.65, 24.03, 17.97, -0.64, -1.44, -5.57; IR (film) 3060, 2953, 2857, 1776, 1716, 1645, 1614, 1470, 1372, 1248, 1111, 836, 777, 720 cm^{-1} ; HRMS calcd for $\text{C}_{27}\text{H}_{47}\text{NO}_3\text{Si}_3$ (M^+) 517.2864, found 517.2845.

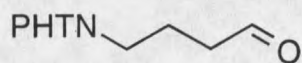


1-Tert-butyldimethylsilyloxy-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (1d). The procedure used for the preparation of amine **1a** was followed employing phthalimide **9d** (4.66 g, 9.00 mmol), hydrazine monohydrate (1.75 mL, 36.0 mmol) and a reaction time of 24h at reflux. In this instance, the crude isolated product was purified by elution through a plug of silica gel (Et_2O for elution) to yield the title compound (3.28 g, 94%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.77 (t, J = 7.3 Hz, 1H, C=CH), 3.55 (dd, J = 9.7, 4.1 Hz, 1H, SiOCHH), 3.33 (dd, J = 9.6, 7.1 Hz, 1H, SiOCHH), 2.77 (p, J = 6.8 Hz, 1H, NCH), 1.95 (m, 2H, CH₂) 1.46 (dd, J = 20.3,

13.4 Hz, 2H, SiCH₂), 1.39 (s, 2H, SiCH₂), 1.29 (br s, 2H, NH₂), 0.87 (s, 9H, (CH₃)₃CSi), 0.02 (s, 6H, (CH₃)₃CSi(CH₃)₂), -0.01 (s, 9H, (CH₃)₃Si), -0.02 (s, 9H, Si(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 137.06 115.75, 67.99, 53.73, 33.42, 29.69, 25.49, 23.95, 18.29, -0.64, -1.05, -5.34; IR (film) 3382, 2954, 2857, 1645, 1470, 1248, 1096, 837, 775, 699, cm⁻¹; HRMS calcd for C₁₉H₄₆NOSi₃ (HM⁺) 388.2887, found 388.2881.

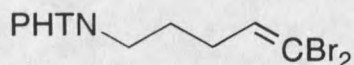


5-Phthalimido-1-pentene (56). To 200 mL, single-necked, round-bottomed flask containing a vigorously stirred suspension of potassium phthalimide (11.6 g, 62.6 mmol) in DMF (50 mL) was added 5-bromo-1-pentene (5.92 mL, 50.0 mmol) followed by anhydrous NaI (375 mg, 2.50 mmol). The white suspension was stirred for 18h at 25 °C. The mixture was poured into half-saturated, aqueous NaCl (100 mL) and the aqueous mixture was extracted with Et₂O (3 x 50 mL). The combined extracts were washed with brine (100 mL), dried over anhydrous MgSO₄ and filtered through a plug of silica gel (Et₂O for elution). The resulting solution was concentrated *in vacuo* to afford 5-phthalimido-1-pentene⁷² (11.0 g, 100%) as a white solid.

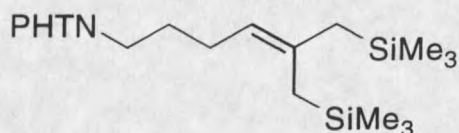


4-Phthalimidobutanal (57). To a 250 mL, single-necked, round-bottomed flask containing a biphasic mixture of alkene **56** (4.30 g, 20.0 mmol) in 1:1 Et₂O/H₂O (100 mL) was added OsO₄ (254 mg, 1.00 mmol) in one portion and the resulting dark brown mixture was stirred for 10 min. Sodium periodate (9.41g, 44.0 mmol) was added over 40 min via a solid addition funnel during

which time mild exotherms were observed. Following the addition, the reaction mixture was stirred vigorously for 2h and the organic layer was separated. The remaining aqueous phase was extracted with Et₂O (2 x 25 mL) and the combined organic fractions were washed with brine (2 x 30 mL), dried over anhydrous MgSO₄ and filtered. Silica gel (5 mL) was added to the solution, the mixture was concentrated and the resulting tan colored, silica gel support was loaded on top of a column of silica gel. The column was eluted with Et₂O to afford the known, title compound⁷² (4.00 g, 92%) as a white solid upon removal of solvent *in vacuo*.

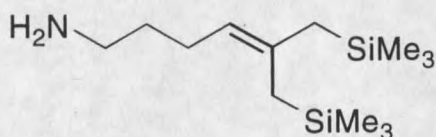


1,1-Dibromo-5-phthalimido-1-pentene (58). Utilizing the general procedure described for the preparation of olefin **8a**, aldehyde **57** (3.95 g, 18.2 mmol) was converted into the title compound (6.09 g, 90%) which was obtained as a white crystalline solid after purification of the crude product by silica gel chromatography (toluene then 10% EtOAc/hexanes for elution): mp 115.3-117.0 °C (20% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.82 (m, 2H, ArH), 7.71 (m, 2H, ArH), 6.42 (t, J = 7.2 Hz, 1H, C=CH), 3.70 (t, J = 7.1 Hz, 2H, CH₂N), 2.15 (q, J = 7.3 Hz, 2H, CH₂C=C), 1.81 (t, J = 7.2 Hz, 2H, CH₂); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 168.22, 137.06, 133.94, 131.99, 123.21, 89.84, 37.17, 30.33, 26.56; IR (film) 3065, 3030, 2968, 2932, 1771, 1714, 1614, 1465, 1438, 1398, 1335, 1227, 1070, 1039, 894, 832, 783, 723 cm⁻¹; HRMS calcd for C₁₃H₁₁Br₂NO₂ (M⁺) 370.9156, found 370.9150.



6-Phthalimido-2-trimethylsilylmethyl-1-trimethylsilyl-2-hexene

(59). The title compound was prepared employing the general coupling procedure used for the preparation of **9a**. From olefin **58** (7.00 g, 18.8 mmol), phthalimide **59** (5.79 g, 83%) was obtained as a white solid after purification of the crude material by silica gel chromatography (hexanes - 1% EtOAc/hexanes for elution): mp 65.3-66.4 °C (95% EtOH); ^1H NMR (300 MHz, CDCl_3) δ 7.81 (m, 2H, ArH), 7.67 (m, 2H, ArH), 4.79 (t, $J = 7.0$ Hz, 1H, $\text{C}=\text{CH}$), 3.65 (t, $J = 7.6$ Hz, 2H, NCH_2), 1.94 (q, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{C}=\text{C}$), 1.65 (p, $J = 7.7$ Hz, 2H, CH_2), 1.42 (s, 2H, CH_2Si), 1.36 (s, 2H, CH_2Si), -0.02 (s, 18H, $\text{Si}(\text{CH}_3)_3 \times 2$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 168.13, 135.26, 133.63, 132.14, 122.95, 117.97, 37.78, 29.33, 29.13, 26.09, 23.66, -0.76, -1.19; IR (film) 2949, 2888, 1771, 1717, 1615, 1398, 1373, 1245, 1039, 1046, 949, 837, 720 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_2\text{Si}_2$ (M^+) 387.2050, found 387.2045.



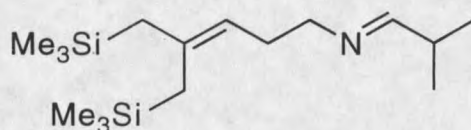
5-Trimethylsilylmethyl-6-trimethylsilyl-4-hexen-1-amine (54).

Using the procedure previously described for the deprotection of phthalimide **9a**, phthalimide **59** (5.00 g, 12.9 mmol) was deprotected to yield amine **54** (3.18 g, 96%) as clear colorless oil after bulb to bulb distillation: bp 61-67 °C, 250 μtorr ; ^1H NMR (300 MHz, CDCl_3) δ 4.76 (t, $J = 7.0$ Hz, 1H, $\text{C}=\text{CH}$), 2.66 (t, $J = 7.2$ Hz, 2H, NCH_2), 1.91 (q, $J = 7.2$ Hz, 2H, $\text{CH}_2\text{C}=\text{C}$), 1.43 (p, $J = 7.3$ Hz, 2H, CH_2), 1.42 (s, 2H, CH_2Si), 1.36 (s, 2H, CH_2Si), 1.05 (s, 2H, NH_2), 0.00 (s, 9H,

(CH₃)₃Si), -0.03 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 134.35, 119.06, 41.95, 34.49, 29.29, 25.94, 23.62, -0.74, -1.21; IR (film) 3377, 3300, 3018, 2953, 2921, 2849, 1645, 1412, 1247, 1158, 1068, 847, 698, 624, cm⁻¹; HRMS calcd for C₁₃H₃₁NSi₂ (M⁺) 257.1995, found 257.1990.

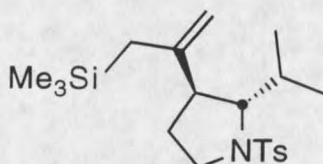
2-Propylidene-1,3-bis(silane) Imine Cyclizations

General Information: Titanium tetrachloride was distilled under an atmosphere of nitrogen and was stored as a stock solution in toluene (1.0 M) under an argon atmosphere. All aldehydes were provided by commercial suppliers and were distilled under argon prior to use. Molecular sieves (4 Å) were activated by flame drying under high vacuum.



N-(2-methylpropylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11a). The following serves as a general experimental procedure used for the preparation of imines. To a 10 mL, single-necked, round-bottomed flask containing a solution of amine **1a** (300 mg, 1.23 mmol) in THF (3.5 mL) was added activated 4Å molecular sieves (700 mg) followed by freshly distilled isobutyraldehyde (134 μ L, 1.48 mmol) and the solution was stirred for 12h at rt. The reaction mixture was diluted with Et₂O (3 mL) and filtered through a Celite pad. Evaporation of solvents and excess aldehyde *in vacuo* afforded imine **11a** (364 mg, 99%) as a colorless oil which was used immediately in the next step: ¹H NMR (300 MHz, CDCl₃) δ 7.47 (d, J = 5.0 Hz, 1H, N=CH), 4.73 (t, J = 7.0 Hz, 1H, C=CH), 3.28 (t, J = 7.4 Hz, 2H, NCH₂), 2.38 (m, 1H, CH(CH₃)₂), 2.17 (q, J = 7.3 Hz, 2H, CH₂), 1.45 (s, 2H, CH₂Si), 1.36 (s, 2H, CH₂Si), 1.04 (d, J = 6.9 Hz, 6H, (CH₃)₂CH), 0.00 (s, 9H, (CH₃)₃Si), -0.04 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 169.30, 135.69, 116.68, 61.84, 33.92, 30.46, 29.48, 23.91, 19.38, -0.65, -1.14;

IR (film) 2956, 2894, 2829, 1669, 1646, 1464, 1247, 1156, 1064, 854, 698, 624 cm^{-1} .



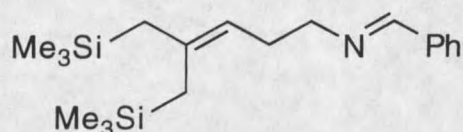
Trans-N-tosyl-2-isopropyl-3-[(3-trimethylsilyl)isopropenyl]

pyrrolidine (15a). The following represents the general experimental procedure used for the preparation of pyrrolidines from the corresponding imines. A 25 mL, single-necked, round-bottomed flask containing a solution of freshly prepared imine **11a** (364 mg, 1.22 mmol) in CH_2Cl_2 (8 mL) was cooled to -78°C and treated dropwise over 2 min with TiCl_4 (1.22 mL, 1.22 mmol of a 1.0 M toluene solution) via syringe. The resulting deep orange solution was allowed to gradually warm to room temperature (2-3h) after which stirring was maintained for an additional 2h. The reaction mixture was transferred dropwise via cannula into vigorously stirred, saturated aqueous KHCO_3 (16 mL) at 0°C and the biphasic mixture was stirred for 30 min at rt. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were then dried with Na_2SO_4 . The residual oil was dissolved in pentane (10 mL), filtered through a Celite pad and concentrated to furnish pyrrolidine **14a** (272 mg, 98%) as a colorless oil with no additional purification required: ^1H NMR (300 MHz, CDCl_3) δ 4.64 (s, 1H, $\text{C}=\text{CHH}$), 4.56 (s, 1H, $\text{C}=\text{CHH}$), 3.44 (br s, 1H, NH), 2.94 (t, $J = 6.9\text{Hz}$, 2H, CH_2N), 2.80 (dd, $J = 6.9, 6.0\text{ Hz}$, 1H, CHN), 2.27 (q, $J = 7.5\text{ Hz}$, 1H, $\text{CHC}=\text{C}$), 1.92 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.66 (m, 2H, CH_2), 1.49 (s, 2H, CH_2Si), 0.92 (d, $J = 7.5\text{ Hz}$, 3H,

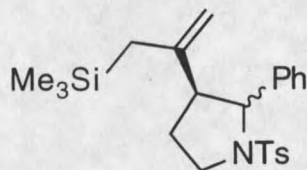
CH_3CHCH_3), 0.90 (d, $J = 7.5$ Hz, CH_3CHCH_3), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 149.20, 107.29, 68.75, 50.12, 45.75, 33.09, 31.17, 25.73, 20.80, 18.02, -1.06; IR (film) 3312, 3077, 2955, 2896, 1629, 1467, 1418, 1383, 1365, 1248, 1161, 852 cm^{-1} .

For purposes of complete and accurate characterization as well as NOE analysis, the pyrrolidine was converted to the corresponding *N*-tosylate **15a**. A 5.0 mL, single-necked, round-bottomed flask containing a solution of pyrrolidine **14a** (100 mg, 0.44 mmol) and pyridine (108 μL , 1.32 mmol) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and TsCl (105 mg, 0.55 mmol) was added in one portion. The mixture was stirred at 0 °C for 2h followed by an additional 2h at rt. Distilled H_2O (2.0 mL) was added and the biphasic mixture was stirred vigorously for 1h. The organic layer was removed and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and the residue was eluted through a silica gel plug (5% EtOAc / hexane) to afford the purified *N*-tosylate **15a** (142 mg, 85%) as a colorless, viscous oil: ^1H NMR (300 MHz, C_6D_6) δ 7.82 (d, $J = 8.1$ Hz, 2H, ArH), 6.83 (d, $J = 7.7$ Hz, 2H, ArH), 4.32 (s, 1H, C=CHH), 4.25 (s, 1H, C=CHH), 3.74 (t, $J = 4.4$ Hz, 1H, CHN), 3.43 (dt, $J = 10.7, 6.8$ Hz, 1H, NCHH), 3.21 (dt, $J = 10.7, 6.8$ Hz, 1H, NCHH), 2.50 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.34 (app q, $J = 6.4$ Hz, 1H, $\text{CHC}=\text{C}$), 1.95 (s, 3H, ArCH_3), 1.46 (m, 1H, CHH), 1.25 (d, $J = 14.3$ Hz, 1H, CHHSi), 1.19 (m, 1H, CHH), 1.07 (d, $J = 14.3$ Hz, 1H, CHHSi), 1.00 (d, $J = 7.0$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$), -0.07 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 147.20, 142.98, 135.60, 129.33, 127.61, 107.88, 68.77, 48.72, 47.45, 33.01, 30.40, 24.75, 21.34, 19.40, 17.08, -1.29; IR (film) 3084, 3029,

2958, 2892, 2875, 1632, 1599, 1466, 1347, 1248, 1159, 1096, 1004, 853, 662 cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{33}\text{NO}_2\text{SSi}$ (M^+) 379.2001, found 379.1986.



***N*-Benzylidene-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11h).** The procedure previously described for the preparation of imine **11a** was followed using benzaldehyde (126 μL , 1.24 mmol) and amine **1a** (250 mg, 1.03 mmol) resulting in the title compound (329 mg, 96%) which was obtained as a clear, colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 8.24 (s, 1H, $\text{N}=\text{CH}$), 7.70 (m, 2H, ArH), 7.38 (m, 3H, ArH), 4.80 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 3.57 (dt, J = 7.4, 1.0 Hz, 2H, CH_2N), 2.31 (q, J = 7.3 Hz, 2H, CH_2), 1.48 (s, 2H, CH_2Si), 1.38 (s, 2H, CH_2Si), 0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.05 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 160.63, 136.50, 136.04, 130.33, 128.48, 128.06, 116.57, 62.31, 30.48, 29.53, 23.93, -0.65, -1.18; IR (film) 3063, 3026, 2953, 2895, 2832, 1647, 1450, 1310, 1156, 1063, 852, 753, 694, 624 cm^{-1} .



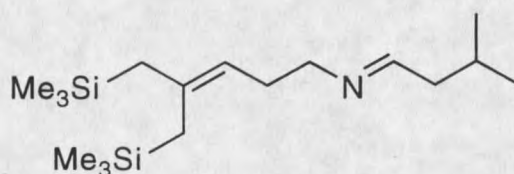
***Cis* and *trans*-*N*-tosyl-2-phenyl-3-[(3-trimethylsilyl)isopropenyl]pyrrolidine (15h_{cis}, 15h_{trans}).** Using imine **11h** (260 mg, 0.78 mmol) in the general cyclization procedure described for the preparation of **15a**, an inseparable mixture of pyrrolidines **14h_{cis}** and **14h_{trans}** (201 mg,

99%, 1.7 : 1.0 by NMR) was obtained as a colorless oil. Treatment of the mixture with TsCl as previously described furnished the purified, title *N*-tosylates (276 mg, 86%, 1.7 : 1.0 by NMR) as a viscous, colorless oil. A pure sample of the *cis* isomer was obtained via fractional crystallization (hexane) of the mixture and crystals suitable for X-ray analysis were recovered from recrystallization (10% Et₂O / hexane):

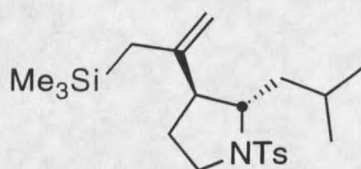
***Cis-N*-tosyl-2-phenyl-3-[(3-trimethylsilyl)isopropenyl]-pyrrolidine (15h_{*cis*}).** mp 107.2-109.3; ¹H NMR (300 MHz, C₆D₆) δ 7.68 (d, J = 8.2 Hz, 2H, SO₂ArH), 7.06 (m, 5H, ArH), 6.74 (d, J = 8.1 Hz, 2H, SO₂ArH), 5.15 (d, J = 7.6 Hz, 1H, NCH), 4.28 (s, 1H, C=CHH), 4.09 (s, 1H, C=CHH), 3.52 (app t, J = 9.0 Hz, 1H, NCHH), 3.31 (ddd, J = 10.6, 10.6, 6.7 Hz, 1H, NCHH), 2.26 (ddd, J = 13.1, 6.4, 6.4 Hz, 1H, CHC=C), 1.89 (s, 3H, ArCH₃), 1.74 (m, 1H, CHH), 1.28 (dd, J = 12.1, 6.0 Hz, 1H, CHH), 1.18 (ABq, Δv = 41.6 Hz, J = 13.7 Hz, 2H, CH₂ Si), -0.18 (s, 9H, (CH₃)₃ Si); ¹³C NMR (75 MHz, CDCl₃ ¹H decoupled) δ 143.08, 142.32, 139.10, 135.54, 129.37, 127.51, 127.45, 126.99, 109.70, 65.07, 51.70, 47.54, 27.18, 26.53, 21.36, -1.56; IR (film) 3086, 3063, 3031, 2953, 2889, 1636, 1599, 1495, 1454, 1346, 1248, 1160, 1097, 1015, 841, 736, 703, 666 cm⁻¹; HRMS calcd for C₂₃H₃₁NO₂SSi (M⁺) 413.1845, found 413.1857.

***Trans-N*-tosyl-2-phenyl-3-[(3-trimethylsilyl)isopropenyl]-pyrrolidine (15h_{*trans*}).** ¹H NMR (300 MHz, C₆D₆) δ 7.68 (d, J = 8.1, 2H, SO₂ArH), 7.31 (d, J = 7.1 Hz, 2H, ArH), 7.11 (m, 3H, ArH), 6.76 (d, J = 8.1 Hz, 2H, SO₂ArH), 4.80 (d, J = 6.1 Hz, 1H, NCH), 4.46 (s, 2H, C=CH₂), 3.70 (ddd, J = 12.4, 7.3, 5.1 Hz, 1H, NCHH), 3.35 (ddd, J = 14.1, 7.7, 6.8 Hz, 1H, NCHH), 2.38 (dd, J = 13.9, 6.5 Hz, 1H, CHC=C), 1.90 (s, 3H, ArCH₃), 1.44 (app sx, J =

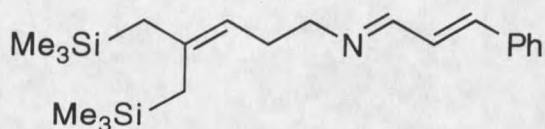
5.8 Hz, 1H, *CHH*), 1.29 (m, 1H, *CHH*), 1.25 (d, $J = 13.0$ Hz, 1H, *CHHSi*), 1.04 (d, $J = 13.8$ Hz, 1H, *CHHSi*), -0.18 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 145.44, 142.77, 139.11, 135.93, 128.24, 128.12, 127.41, 127.01, 126.42, 108.26, 67.70, 56.88, 48.69, 30.02, 25.46, 21.34, -1.45; IR (film) 3086, 3063, 3030, 2953, 2924, 2893, 1634, 1599, 1495, 1455, 1350, 1248, 1162, 1097, 1014, 851, 699, 663 cm^{-1} .



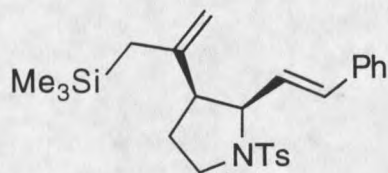
***N*-(3-Methylbutylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11b).** The general procedure used for the preparation of imine **11a** was followed using amine **1a** (300 mg, 1.23 mmol) and isovaleraldehyde (160 μL , 1.48 mmol) to afford the title imine (367 mg, 96%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.58 (t, $J = 4.8$ Hz, 1H, $\text{N}=\text{CH}$), 4.72 (t, $J = 7.0$ Hz, 1H, $\text{C}=\text{CH}$), 3.28 (t, $J = 7.4$ Hz, 2H, CH_2N), 2.17 (q, $J = 7.3$ Hz, 2H, CH_2), 2.08 (t, $J = 6.0$ Hz, 2H, $\text{N}=\text{CHCH}_2$), 1.85 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.43 (s, 2H, CH_2Si), 1.34 (s, 2H, CH_2Si), 0.90 (d, $J = 6.8$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 163.99, 135.73, 116.64, 62.01, 44.72, 30.48, 29.47, 26.31, 23.85, 22.47, -0.69, -1.18; IR (film) 2955, 2896, 2829, 1670, 1647, 1465, 1248, 1156, 1064, 854, 698, 624 cm^{-1} .



Trans-N-tosyl-2-isobutyl-3-[(3-trimethylsilyl)isopropenyl]-pyrrolidine (15b). The general procedure used for the preparation of **15a** was followed using imine **11b** (200 mg, 0.64 mmol) to furnish pyrrolidine **14b** (135 mg, 88%) as a viscous oil after chromatography on silica gel (5% MeOH / CH₂Cl₂). From a crude sample of pyrrolidine **14b** (108 mg, 0.45 mmol), the title *N*-tosylate was obtained as a thick, colorless oil (141 mg, 80%): ¹H NMR (300 MHz, C₆D₆) δ 7.80 (d, *J* = 8.2 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.2 Hz, 2H, Ar*H*), 4.29 (s, 1H, C=CH*H*), 4.17 (s, 1H, CH*H*), 3.76 (app p, *J* = 4.4 Hz, 1H, CH*N*), 3.35 (dt, *J* = 10.6, 6.4 Hz, 1H, CH*HN*), 3.22 (dt, *J* = 10.6, 6.4 Hz, 1H, CH*HN*), 2.13 (dd, *J* = 10.9, 6.3 Hz, 1H, CHC=C), 1.96 (m, 1H, CH*H*), 1.93 (s, 3H, CH₃Ar), 1.84 (m, 1H, CH(CH₃)₂), 1.45 (m, 2H, CH₂CH(CH₃)₂), 1.23 (d, *J* = 14.0 Hz, 1H, CHHSi), 1.13 (m, 1H, CH*H*), 1.04 (d, *J* = 6.5 Hz, 3H, CH₃CHCH₃), 1.00 (d, *J* = 6.6 Hz, 3H, CH₃CHCH₃), 0.96 (d, *J* = 14.6 Hz, CHHSi), -0.12 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, C₆D₆, ¹H decoupled) δ 146.89, 142.67, 137.15, 129.55, 127.66, 108.31, 62.26, 53.26, 48.05, 47.16, 29.89, 25.60, 24.74, 23.72, 22.47, 21.09, -1.25; IR (film) 3085, 3030, 2955, 2896, 2870, 1632, 1575, 1467, 1454, 1347, 1248, 1160, 1096, 1005, 847, 816, 662 cm⁻¹; HRMS calcd for C₂₁H₃₅NO₂SSi (M⁺) 393.2158, found 393.2143.

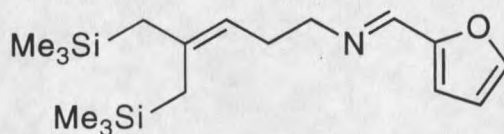


***N*-(*E*-3-Phenyl-2-propenylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11f).** Using *trans*-cinnamaldehyde (86 μL , 0.68 mmol), amine **1a** (150 mg, 0.62 mmol) and a reaction time of 24h in the general procedure used for the preparation of imine **11a**, imine **11f** (101 mg, 100%) was obtained as a thick, golden oil. In this case, excess aldehyde was removed via exposure of the crude product to high vacuum (<250 μtorr , rt, 2-3 h): ^1H NMR (300 MHz, CDCl_3) δ 7.99 (t, J = 1.2 Hz, 1H, $\text{N}=\text{CH}$), 6.89-7.47 (m, 7H, ArH and $\text{ArCH}=\text{CH}$), 4.79 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 3.48 (t, J = 7.4 Hz, 2H, NCH_2), 2.29 (q, J = 7.3 Hz, 2H, CH_2), 1.49 (s, 2H SiCH_2), 1.40 (s, 2H, CH_2Si), 0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 162.35, 141.22, 136.16, 135.93, 128.96, 128.76, 128.37, 127.17, 116.37, 62.07, 30.45, 29.52, 23.92, -0.67, -1.15; IR (film) 3083, 3061, 3027, 2953, 2895, 2831, 1637, 1621, 1449, 1412, 1247, 1151, 1063, 975, 853, 748, 690 cm^{-1} .



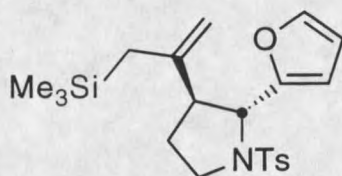
***Cis*-*N*-tosyl-2-(*E*-2-phenylethenyl)-3-[(3-trimethylsilyl)isopropenyl]pyrrolidine (15f).** Utilizing imine **11f** (221 mg, 0.62 mmol) in the procedure described for the preparation of **15a**, pyrrolidines **14f** *cis* and *trans* (153 mg, 86%) were obtained as a viscous oil upon purification of the crude product by filtration through a silica gel plug (CH_2Cl_2 - 5% MeOH /

CH_2Cl_2 for elution). A crude sample of the inseparable pyrrolidines (100 mg, 0.35 mmol) was converted to a *cis-trans* mixture of the corresponding, purified *N*-tosyl derivatives (129 mg, 84%, 8.0 : 1.0 by NMR) which was obtained as a viscous, colorless oil. A pure sample the title compound **15f** was secured from the diastereomer mixture by fractional crystallization (light petroleum ether): mp 113.9 - 116.4°C; ^1H NMR (300 MHz, C_6D_6) δ 7.83 (d, J = 8.1 Hz, 2H, SO_2ArH), 7.14 (m, 5H, ArH), 6.86 (d, J = 15.7 Hz, 1H, $\text{ArCH}=\text{C}$), 6.79 (d, J = 8.0 Hz, 2H, SO_2ArH), 5.93 (dd, J = 15.6, 6.2 Hz, 1H, $\text{ArC}=\text{CH}$), 4.72 (t, J = 6.6 Hz, 1H, NCH), 4.52 (s, 1H, $\text{C}=\text{CHH}$), 4.44 (s, 1H, $\text{C}=\text{CHH}$), 3.44 (app t, J = 8.9 Hz, 1H, NCHH), 3.21 (dt, J = 10.2, 6.8 Hz, 1H, NCHH), 2.13 (ddd, J = 12.5, 6.1, 6.1 Hz, 1H, $\text{CHC}=\text{C}$), 1.89 (s, 3H, CH_3Ar), 1.65 (m, 1H, CHH), 1.42 (d, J = 13.7 Hz, 1H, SiCHH), 1.33 (app p, J = 5.9 Hz, 1H, CHH), 1.19 (d, J = 13.7 Hz, 1H, SiCHH), -0.14 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 143.18, 143.00, 136.88, 135.88, 132.31, 129.53, 128.34, 127.49, 127.41, 126.59, 125.76, 109.32, 62.67, 49.80, 47.10, 26.93, 26.68, 21.36, -1.44; IR (KBr) 3084, 3025, 2952, 2873, 1631, 1598, 1495, 1341, 1335, 1246, 1163, 1097, 1044, 855, 696, 666 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_2\text{SSi}$ (M^+) 439.2001, found 439.1993.



***N*-[(2-Furyl)methylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11e).** Amine **1a** (100 mg, 0.41 mmol) and 2-furaldehyde (41 μL , 0.49 mmol) were used following the general procedure described for the preparation of imine **11a** to yield the title imine

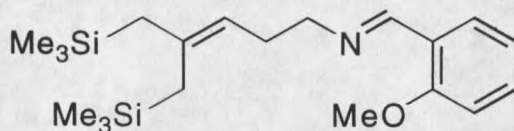
(132 mg, 100%) as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 8.04 (s, 1H, $\text{N}=\text{CH}$), 7.47 (s, 1H, $\text{C}=\text{CHO}$), 6.68 (d, $J = 3.3$ Hz, 1H, $\text{HC}=\text{CO}$), 6.43 (dd, $J = 3.5$, 1.7 Hz, 1H, $\text{HC}=\text{CHO}$), 4.76 (t, $J = 7.1$ Hz, 1H, $\text{C}=\text{CH}$), 3.52 (t, $J = 7.4$ Hz, 2H, CH_2N), 2.31 (q, $J = 7.3$ Hz, 2H, CH_2), 1.46 (s, 2H, CH_2Si), 1.37 (s, 2H, CH_2Si), 0.00 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 151.82, 149.31, 144.36, 136.25, 116.28, 113.17, 111.40, 62.35, 30.41, 29.49, 23.88, -0.70, -1.24; IR (film) 3125, 2954, 2895, 2828, 1646, 1485, 1247, 1155, 1014, 853, 744, 698, 624 cm^{-1} .



Trans-N-tosyl-2-furyl-3-[(3-trimethylsilyl)isopropenyl]-

pyrrolidine (15e). A 10 mL, single-necked, round-bottomed flask containing a solution of TiCl_4 (360 μL , 0.39 mmol of a 1.1 M toluene solution) in CH_2Cl_2 (3.0 mL) was cooled to -78°C and imine **11e** (125 mg, 0.39 mmol) in CH_2Cl_2 (400 μL) was added dropwise over 45 min via a gas tight syringe. The resulting deep orange reaction mixture was allowed to reach ambient temperature gradually (2-3h) and stirring was continued for 24h. The reaction mixture was quenched and the product was isolated in the manner described in the general procedure. Elution of the crude product through a plug of Florisil (CH_2Cl_2 for elution) furnished pyrrolidine **14e** (82 mg, 84%) as a light orange oil. A crude sample of pyrrolidine **14e** (80 mg, 0.32 mmol) was converted into the title *N*-tosyl derivative (103 mg, 80%) as described in the general procedure used for **15a**. The title compound was obtained as a viscous, colorless oil: ^1H NMR

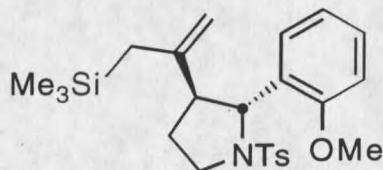
(300 MHz, C_6D_6) δ 7.62 (d, J = 8.3 Hz, 2H, ArH), 6.93 (d, J = 1.7 Hz, 1H, OCH=C), 6.77 (d, J = 8.2 Hz, 2H, ArH), 6.26 (d, J = 3.2 Hz, 1H, CH=CO), 6.00 (dd, J = 3.1, 1.9 Hz, 1H, OCH=CH), 4.94 (d, J = 5.4 Hz, 1H, NCH), 4.51 (s, 1H, C=CHH), 4.44 (s, 1H, C=CHH), 3.63 (ddd, J = 12.9, 7.2, 5.9 Hz, 1H, NCHH), 3.63 (dt, J = 9.8, 6.9 Hz, 1H, NCHH), 2.77 (app q, J = 6.5 Hz, 1H, CHC=C), 1.91 (s, 3H, ArCH₃), 1.73 (dq, J = 12.5, 6.6 Hz, H₂, 1H, CHH), 1.41 (dq, J = 12.5, 7.2 Hz, 1H, CHH), 1.30 (d, J = 13.7 Hz, 1H, CHHSi), 1.16 (d, J = 13.9 Hz, 1H, CHHSi), -0.12 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, C_6D_6 , ¹H decoupled) δ 154.96, 146.07, 142.47, 141.76, 137.67, 129.39, 127.68, 110.52, 108.38, 107.97, 61.35, 52.43, 47.98, 30.21, 25.71, 21.09, -1.42; IR (film) 3125, 3079, 3029, 2953, 2894, 1632, 1599, 1348, 1248, 1161, 1098, 1011, 852, 733, 663 cm⁻¹; HRMS calcd for C₂₁H₂₉NO₃SSi (M⁺) 403.1637, found 403.1639.



N-(2-Methoxybenzylidene)-4-trimethylsilylmethyl-5-

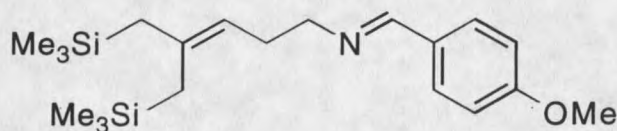
trimethylsilyl-3-penten-1-amine (11d). Using *o*-anisaldehyde (118 μ L, 0.98 mmol) and amine **1a** (200 mg, 0.82 mmol) in the general procedure described for the preparation of **11a** yielded the title imine (299 mg, 100%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 8.68 (s, 1H, N=CH), 7.92 (dd, J = 7.6, 1.6 Hz, 1H, ArH), 7.33 (dt, J = 8.0, 1.7 Hz, 1H, ArH), 6.95 (t, J = 7.5 Hz, 1H, ArH), 6.86 (d, J = 7.3 Hz, 1H, ArH), 4.82 (t, J = 7.1 Hz, 1H, C=CH), 3.83 (s, 3H, ArOCH₃), 3.57 (t, J = 7.4 Hz, 2H, CH₂N), 2.30 (q, J = 7.3 Hz, 2H, CH₂), 1.49 (s, 2H, CH₂Si), 1.38 (s, 2H, CH₂Si), 0.02 (s, 9H, (CH₃)₃Si), -0.04 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 158.65, 156.57, 135.78,

131.45, 127.34, 125.01, 120.73, 116.72, 110.93, 62.55, 55.41, 30.64, 29.48, 23.87, -0.67, -1.23; IR (film) 3085, 2998, 2953, 2893, 2836, 1639, 1601, 1487, 1465, 1439, 1373, 1298, 1286, 1248, 1159, 1047, 1029, 853, 754, 698, 624 cm^{-1} .

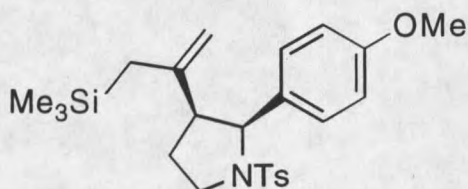


Trans-N-tosyl-2-(2-methoxyphenyl)-[(3-trimethylsilyl)isopropenyl]pyrrolidine (15d). Using the procedure described for the preparation of **15e**, imine **11d** (216 mg, 0.60 mmol) was converted into a mixture of the corresponding pyrrolidine and the monoprotodesilylated isomer (182 mg, 100%, ca. 1.5 : 1.0 by NMR). Direct treatment of the crude mixture with TsCl in the manner previously described for **15a** yielded the title *N*-tosyl pyrrolidine (164 mg, 62% overall from amine **1a**) as a viscous, colorless oil. A portion of this sample was crystallized from 10% Et₂O/hexane to furnish colorless crystals: mp 85.5 - 88.4 °C; ¹H NMR (300 MHz, C₆D₆) δ 7.75 (d, J = 8.0 Hz, 2H, SO₂ArH), 7.46 (d, J = 7.3 Hz, 1H, ArH), 7.07 (t, J = 7.6 Hz, 1H, ArH), 6.86 (t, J = 7.5 Hz, 1H, ArH), 6.78 (d, J = 8.1 Hz, 2H, SO₂ArH), 6.49 (d, J = 8.1 Hz, 1H, ArH), 5.38 (d, J = 3.3 Hz, 1H, CHN), 4.35 (s, 1H, C=CHH), 4.33 (s, 1H, C=CHH), 3.56 (app t, J = 5.8 Hz, 2H, NCH₂), 3.30 (s, 3H, ArOCH₃), 2.45 (ddd, J = 3.1, 6.2, 3.1 Hz, 1H, CHC=C), 1.92 (s, 3H, SO₂ArCH₃), 1.70 (dq, J = 12.6, 7.2 Hz, 1H, CHH), 1.59 (d, J = 13.6 Hz, 1H, CHHSi), 1.41 (dq, J = 12.0, 5.3 Hz, 1H, CHH), 1.18 (d, J = 13.7 Hz, 1H, CHHSi), -0.12 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, C₆D₆, ¹H decoupled) δ 156.47, 146.56, 142.36, 137.57, 132.11, 129.27,

128.54, 128.32, 128.05, 120.79, 110.64, 107.48, 63.33, 54.83, 54.04, 48.18, 28.80, 25.58, 21.10, -1.43; IR (film) 3098, 3080, 3030, 2998, 2973, 2948, 2890, 2845, 1630, 1598, 1489, 1344, 1247, 1159, 1096, 1023, 853, 763, 665 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{33}\text{NO}_3\text{SSi}$ (M^+) 443.1950, found 443.1930.

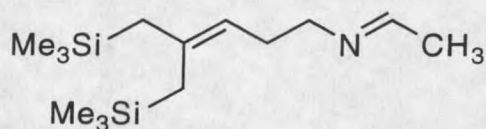


***N*-(4-Methoxybenzylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11g).** Using the general procedure for the preparation of aldimine **11a**, amine **1a** (100 mg, 0.41 mmol) and 4-anisaldehyde (55 μL , 0.45 mmol) were converted into the title imine (146 mg, 98%) which was isolated as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (s, 1H, $\text{N}=\text{CH}$), 7.63 (d, $J = 8.7$ Hz, 2H, ArH), 6.89 (d, $J = 8.8$ Hz, 2H, ArH), 4.79 (t, $J = 7.2$ Hz, 1H, $\text{C}=\text{CH}$), 3.81 (s, 3H, ArOCH_3), 3.52 (t, $J = 7.4$ Hz, 2H, NCH_2), 2.29 (q, $J = 7.3$ Hz, 2H, CH_2), 1.47 (s, 2H, SiCH_2), 1.37 (s, 2H, SiCH_2), 0.01 (s, 9H, $\text{Si}(\text{CH}_3)_3$), -0.06 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 161.47, 159.93, 135.90, 131.92, 129.55, 116.69, 113.92, 62.21, 55.29, 30.59, 29.51, 23.90, -0.65, -1.18; IR (film) 3004, 2953, 2896, 2836, 1647, 1607, 1579, 1512, 1307, 1248, 1165, 1036, 853, 699, 625 cm^{-1} .

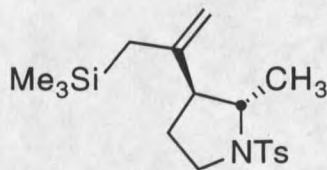


***Cis*-N-tosyl-2-(4-methoxyphenyl)-3-[(3-trimethylsilyl)isopropenyl]pyrrolidine (15g).** Imine **11g** (134 mg, 0.37 mmol) was used

in the general cyclization procedure used for **15a** with an extended reaction time of 8h after the reaction mixture reached room temperature. This produced a mixture of diastereomeric pyrrolidines (96 mg, 90 %, 3.4:1.0 by NMR) as a thick, colorless oil after purification by elution through a Florisil column (CH_2Cl_2 -10% MeOH/ CH_2Cl_2 for elution). The mixture of pyrrolidines (75 mg, 0.26 mmol) was converted into a mixture of the corresponding *N*-tosyl derivatives (103 mg, 90%, 3.3:1.0 by NMR) which was obtained as a viscous colorless oil upon chromatography on silica gel (5% EtOAc/hexane for elution). Fractional crystallization of the mixture (light petroleum ether) furnished a pure sample of the major isomer **15g** as small white needles: mp 109.4-110.5 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.59 (d, J = 8.1 Hz, 2H, ArH), 7.22 (d, J = 8.1 Hz, 2H, ArH), 6.95 (d, J = 8.6 Hz, 2H, ArH), 6.69 (d, J = 8.6 Hz, 2H, ArH), 4.91 (d, J = 7.5 Hz, 1H, NCH), 4.33 (s, 1H, C=CHH), 4.18 (s, 1H, C=CHH), 3.74 (s, 3H, ArOCH₃), 3.68 (t, J = 8.9 Hz, 1H, NCHH), 3.36 (ddd, J = 17.1, 10.1, 6.8 Hz, 1H, NCHH), 2.38 (s, 3H, SO₂ArCH₃), 2.34 (app q, J = 6.8 Hz, 1H, C=CCH), 2.06 (m, 1H, CHH), 1.77 (dq, J = 12.1, 6.2 Hz, 1H, CHH), 1.40 (d, J = 13.6 Hz, 1H, SiCHH), 1.22 (d, J = 13.6 Hz, 1H, SiCHH), -0.12 (s, 9H, Si(CH₃)₃); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 158.64, 142.99, 142.50, 135.65, 131.41, 129.35, 128.64, 127.31, 112.94, 109.69, 64.60, 55.11, 51.64, 47.47, 27.17, 26.58, 21.36, -1.53; IR (film) 3084, 3064, 3031, 2953, 2836, 1635, 1612, 1598, 1513, 1464, 1349, 1304, 1290, 1248, 1162, 1098, 1037, 851, 664 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{33}\text{NO}_3\text{SSi}$ (M^+) 443.1950, found 443.1943.

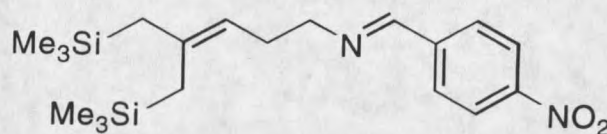


***N*-Ethylidene-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (11c).** The title imine was characterized via a NMR tube experiment. A flame dried NMR tube was cooled under a stream of argon and charged with amine **1a** (20 mg, .082 mmol) and CDCl_3 (350 μL). The tube was flushed with argon, fitted with a rubber septum and the solution was cooled to 0 °C. Acetaldehyde (8.0 μL , 0.14 mmol) was added via a cold syringe. The resulting cloudy mixture was kept at 0 °C for 1h, allowed to reach room temperature and was immediately analyzed. The ^1H and ^{13}C NMR spectra showed the presence of a single imine product (~100%): ^1H NMR (300 MHz, CDCl_3) δ 7.62 (q, J = 4.8 Hz, 1H, $\text{HC}=\text{N}$), 4.69 (t, J = 7.0Hz, 1H, $\text{C}=\text{CH}$), 3.26 (t, J = 7.4 Hz, 2H, CH_2N), 2.15 (q, J = 9.5 Hz, 2H, CH_2), 1.89 (d, J = 4.6 Hz, 3H, CH_3), 1.42 (s, 2H, CH_2Si), 1.34 (s, 2H, CH_2Si), -0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 160.23, 135.87, 116.49, 61.72, 30.20, 29.44, 23.85, 21.99, -0.72, -1.22.



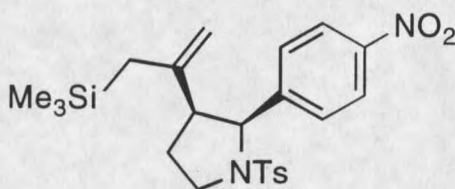
***Trans*-N-tosyl-2-methyl-[(3-trimethylsilyl)isopropenyl]-pyrrolidine (15c).** A 10 mL, single-necked, round-bottomed flask containing a solution of amine **1a** (200 mg, 0.82 mmol) in CH_2Cl_2 (4 mL) and 4 Å molecular sieves (400 mg) was cooled to -10 °C and acetaldehyde (50 μL , 0.90 mmol, *freshly distilled*) was added dropwise over 1 min via a gas-tight syringe.

The mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for 1h and quickly filtered through a Celite pad. The resulting solution of imine **11c** was diluted with CH_2Cl_2 (2 mL), cooled to $-78\text{ }^{\circ}\text{C}$ without delay and TiCl_4 (820 μL , 0.82 mmol of a 1.0 M toluene stock solution) was added dropwise. The resulting deep orange solution was gradually warmed to rt (2-3h) and stirred for an additional 2h. Reaction quench and product isolation was carried out as described in the preparation of **15a** to afford pyrrolidine **14c** (106 mg, 65%) as a colorless oil after purification of the crude product via filtration through a plug of Florisil (CH_2Cl_2 - 5% MeOH/ CH_2Cl_2 for elution). A sample of crude **14c** (100 mg, 0.51 mmol) was treated with TsCl as described previously to furnish the purified title compound (147 mg, 82%) as a viscous, colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 7.75 (d, J = 8.2 Hz, 2H, ArH), 6.84 (d, J = 8.2 Hz, 2H, ArH), 4.38 (d, J = 0.9 Hz, 1H, C=CHH), 4.29 (s, 1H, C=CHH), 3.51 (t, J = 6.4 Hz, 1H, NCH), 3.42 (ddd, J = 14.9, 8.7, 6.2 Hz, 1H, NCHH), 3.19 (ddd, J = 11.3, 7.5, 3.1 Hz, 1H, NCHH), 1.97 (app q, J = 6.8 Hz, 1H, CHC=C), 1.93 (s, 3H, CH_3Ar), 1.46 (d, J = 6.2 Hz, 3H, CH_3), 1.34 (m, 1H, CHH), 1.12 (d, J = 13.8 Hz, 1H, SiCHH), 0.97 (m, 1H, CHH), 0.91 (d, J = 13.9 Hz, 1H, SiCHH), -0.14 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, C_6D_6 , ^1H decoupled) δ 146.11, 142.75, 136.79, 129.60, 127.81, 108.62, 59.90, 55.79, 48.48, 30.20, 24.32, 22.33, 21.10, -1.27; IR (film) 3080, 3029, 2955, 2928, 2895, 1632, 1598, 1452, 1346, 1248, 1163, 1093, 854, 816, 737, 658 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_2\text{SSi}$ (M^+) 351.1688, found 351.1670.



***N*-(4-Nitrobenzylidene)-4-trimethylsilylmethyl-5-trimethylsilyl-**

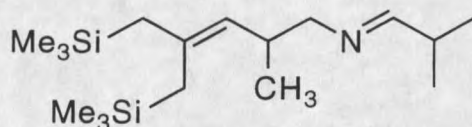
3-penten-1-amine (11i). Using the general procedure outlined for the preparation of imine **11a**, amine **1a** (150 mg, 0.62 mmol) and 4-nitrobenzaldehyde (98 mg, 0.65 mmol) were converted into the title imine which was isolated as a viscous, colorless oil and was used immediately in the next step: ^1H NMR (300 MHz, CDCl_3) δ 8.31 (s, 1H, $\text{N}=\text{CH}$), 8.24 (d, $J = 8.8$ Hz, 2H, ArH), 7.86 (d, $J = 8.8$ Hz, 2H, ArH), 4.77 (t, $J = 7.1$ Hz, 1H, $\text{C}=\text{CH}$), 3.63 (t, $J = 7.0$ Hz, 2H, NCH_2), 2.33 (q, $J = 7.1$ Hz, 2H, CH_2), 1.46 (s, 2H, SiCH_2), 1.37 (s, 2H, SiCH_2), 0.02 (s, 9H, $\text{Si}(\text{CH}_3)_3$), -0.07 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 158.31, 148.81, 141.82, 136.52, 128.64, 123.76, 115.94, 62.49, 30.09, 29.44, 23.88, -0.71, -1.25; IR (film) 3061, 2954, 2895, 2844, 1646, 1603, 1525, 1413, 1345, 1247, 1156, 1107, 1065, 1014, 837, 769, 748, 691, 625 cm^{-1} .



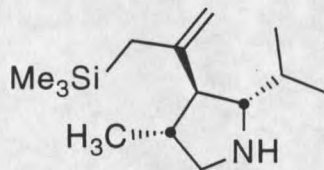
***Cis*-N-tosyl-2-(4-nitrophenyl)-3-[(3-trimethylsilyl)isopropenyl]-**

pyrrolidine (15i). Imine **11i** was used in the general cyclization procedure outlined for the preparation of **15a** to afford a mixture of diastereomeric pyrrolidines. The crude mixture was directly exposed to TsCl as outlined in the general procedure for **15a** to provide an inseparable mixture of the title compound and the minor *trans* isomer (5.0:1.0 by NMR, 250 mg, 88% from **1a**)

as a white solid after purification by chromatography on silica gel (5%-10% EtOAc/hexanes for elution): mp 140.2-143.7 °C; ^1H NMR (300 MHz, C_6D_6) δ 7.94 (d, J = 8.8 Hz, 2H, ArH), 7.75 (d, J = 8.1 Hz, 2H, ArH), 6.97 (d, J = 8.3 Hz, 2H, ArH), 6.88 (d, J = 8.0 Hz, 2H, ArH), 5.09 (d, J = 7.9 Hz, 1H, NCH), 4.25 (s, 1H, C=CHH), 4.00 (s, 1H, C=CHH), 3.56 (t, J = 8.5 Hz, 1H, NCHH), 3.24 (ddd, J = 17.3, 10.7, 6.6 Hz, 1H, NCHH), 2.24 (ddd, J = 12.9, 7.1, 7.1, Hz, 1H, C=CCH), 2.01 (s, 3H, SO_2ArCH_3), 1.60 (m, 1H, CHH), 1.30 (m, 1H, CHH), 1.24 (d, J = 13.6 Hz, 1H, SiCHH), 1.08 (d, J = 13.5 Hz, 1H, SiCHH), -0.12 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 147.02, 143.83, 141.50, 134.46, 129.70, 128.28, 127.28, 123.52, 122.71, 110.23, 64.27, 51.73, 47.78, 27.43, 26.45, 21.42, -1.65; IR (film) 3083, 3064, 2953, 2892, 1635, 1599, 1520, 1494, 1418, 1344, 1304, 1247, 1161, 1107, 1050, 1011, 845, 772, 754, 667 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{SSi}$ (M^+) 458.1696, found 458.1702.

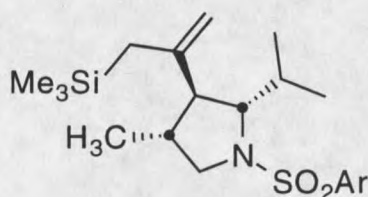
Synthesis of Trisubstituted Pyrrolidines

***N*-(2-Methylpropylidene)-2-methyl-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (23a).** The general procedure used to prepare imine **11a** was followed using amine **1b** (650 mg, 2.52 mmol) and isobutyraldehyde (275 μ L, 3.02 mmol) to yield the title imine (790 mg, 100%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.40 (d, J = 5.2 Hz, 1H, $\text{N}=\text{CH}$), 4.55 (d, J = 9.5 Hz, 1H, $\text{C}=\text{CH}$), 3.31 (dd, J = 11.1, 5.4 Hz, 1H, NCHH), 2.97 (dd, J = 11.0, 8.2 Hz, 1H, NCHH), 2.52 (m, 1H, CH_3CH), 2.38 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.58 (d, J = 13.5 Hz, 1H, CHHSi), 1.33 (ABq, $\Delta\nu$ = 20.8 Hz, J = 13.2 Hz, 2H, CH_2Si), 1.32 (d, J = 13.5 Hz, 1H, CHHSi), 1.03 (dd, J = 6.8, 1.4 Hz, 6H, $(\text{CH}_3)_2\text{CH}$), 0.83 (d, J = 6.6 Hz, 3H, CH_3CH), -0.00 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.04 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 169.54, 133.96, 124.14, 68.23, 33.95, 33.90, 29.24, 23.75, 19.43, 19.01, -0.65, -1.11; IR (film) 2956, 2926, 2895, 2820, 1673, 1645, 1456, 1417, 1366, 1247, 1156, 1065, 853. 698, cm^{-1} .



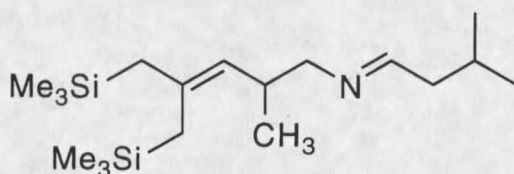
(2 α ,3 β ,4 α)-4-Methyl-3-[(3-trimethylsilyl)isopropenyl]-2-isopropylpyrrolidine (24a). Employing imine **23a** (790 mg, 2.53 mmol) in the general procedure used for the preparation of **14a**, the title pyrrolidine (595

mg, 98%) was obtained as the sole reaction product (NMR) in the form of a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.71 (d, $J = 1.7$ Hz, 1H, $\text{C}=\text{CHH}$), 4.61 (d, $J = 0.9$ Hz, 1H, $\text{C}=\text{CHH}$), 3.06 (dd, $J = 10.4, 7.2$ Hz, 1H, NCHH), 2.83 (dd, $J = 8.2, 5.1$ Hz, 1H, NCH), 2.44 (dd, $J = 10.4, 8.1$ Hz, 1H, NCHH), 2.12 (br s, 1H, NH), 1.96 (m, 1H, NCH_2CH), 1.84 (t, 8.5 Hz, 1H, $\text{CHC}=\text{C}$), 1.65 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.42 (s, 2H, CH_2Si), 0.92 (d, $J = 3.3$ Hz, 3H, CH_3CHCH_3), 0.90 (d, $J = 3.8$ Hz, CH_3CHCH_3), 0.87 (d, $J = 6.7$ Hz, 3H, CH_3), 0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 145.92, 111.35, 67.98, 59.91, 52.58, 38.53, 30.89, 21.72, 20.28, 17.77, 16.77, -0.84; IR (film) 3312, 3077, 2955, 1628, 1463, 1417, 1379, 1288, 1248, 1163, 844, 692, cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{29}\text{NSi}$ (M^+) 239.2069, found 239.2120.



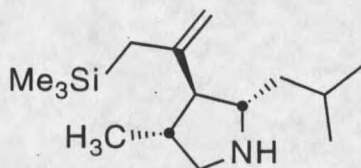
(2 α ,3 β ,4 α)-*N*-(2-Naphthalenesulfonyl)-4-methyl-3-[(3-trimethylsilyl)isopropenyl]-2-isopropylpyrrolidine (25a). For the purpose of NOE studies, pyrrolidine **24a** was converted into the corresponding *N*-(2-naphthalenesulfonyl) derivative. A 5.0 mL, single-necked, round-bottomed flask was charged with **24a** (100 mg, 0.42 mmol), pyridine (100 μL , 1.25 mmol) and CH_2Cl_2 (1.5 mL). The solution was cooled to 0 $^\circ\text{C}$ and 2-naphthalene-sulfonyl chloride (114 mg, 0.50 mmol) was added in one portion. After stirring for 10 min, the mixture was brought to ambient temperature and stirred for 10h. The resulting red mixture was treated with H_2O (2 mL) and the biphasic mixture was stirred for 1h. The organic layer was combined with three CH_2Cl_2 extracts

of the aqueous layer and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was subjected to chromatography on silica gel (5% EtOAc/ hexane) to give the title compound (72 mg, 40%) as a gelatinous, colorless material: ^1H NMR (300 MHz, CDCl_3) δ 8.41 (s, 1H, ArH), 7.93 (d, J = 8.8 Hz, 2H, ArH), 7.73 (m, 4H, ArH), 4.63 (s, 1H, C=CHH), 4.54 (s, 1H, C=CHH), 3.87 (dd, J = 12.2, 7.1 Hz, 1H, NCHH), 3.65 (dd, J = 8.1, 3.7 Hz, 1H, NCH), 2.80 (app t, J = 11.8 Hz, 1H, NCHH), 2.28 (m, 1H, CH(CH₃)₂), 2.11 (dd, J = 10.5, 8.6 Hz, 1H, CHC=C), 1.27 (m, 1H, CHCH₃), 1.26 (d, J = 15.0 Hz, 1H, SiCHH), 1.24 (d, J = 5.0 Hz, 3H, CH₃CHCH₃), 1.02 (d, J = 12.9 Hz, 3H, CH₃CHCH₃), 0.71 (d, J = 6.3 Hz, 3H, CH₃), 0.56 (d, J = 15.2 Hz, 1H, SiCHH), -0.91 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 145.04, 136.49, 134.67, 132.22, 129.26, 129.14, 128.56, 127.86, 127.53, 122.93, 113.15, 67.49, 59.16, 56.43, 36.76, 33.34, 19.46, 18.54, 17.48, 14.65, -1.17; IR (film) 3079, 3058, 2958, 2925, 2860, 1628, 1591, 1504, 1463, 1344, 1249, 1162, 1132, 1074, 1003, 912, 858, 734, 660 cm^{-1} .



***N*-(3-Methylbutylidene)-2-methyl-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (23b).** The general procedure used for the preparation of imine **11a** was carried out using amine **1b** (100 mg, 0.39 mmol) and isovaleraldehyde (50 μL , 0.47 mmol) to provide the title imine (126 mg, 100%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.55 (t, J = 5.3 Hz, 1H, N=CH), 4.57 (d, J = 9.5 Hz, 1H, C=CH), 3.35 (dd, J = 11.2, 5.1 Hz, 1H, NCHH), 2.99 (dd, J = 11.0, 8.6 Hz, 1H, NCHH), 2.54 (m, 1H, CHCH₃), 2.10 (t, J

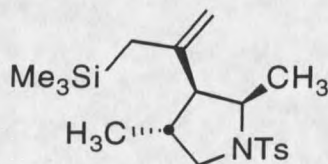
= 6.1 Hz, 2H, N=CHCH₂), 1.87 (m, 1H, (CH₃)₂CH), 1.57 (d, J = 13.4 Hz, 1H, SiCHH), 1.34 (d, J = 13.0 Hz, 1H, SiCHH), 1.34 (dd, J = 20.6, 13.3 Hz, 2H, SiCH₂), 0.93 (d, J = 6.7 Hz, 6H, (CH₃)₂CH), 0.85 (d, J = 6.7 Hz, 3H, CH₃CH), 0.00 (s, 9H, (CH₃)₃Si), -0.03 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 164.42, 134.05, 124.08, 68.52, 44.76, 33.95, 29.27, 26.44, 23.76, 22.55, 19.12, -0.65, -1.11; IR (film) 2955, 2822, 1670, 1646, 1458, 1419, 1368, 1247, 1157, 1065, 951, 837, 769, 698 cm⁻¹.



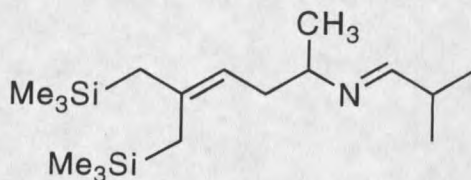
(2 α ,3 β ,4 α)-4-Methyl-3-[(3-trimethylsilyl)isopropenyl]-2-

isobutylpyrrolidine (24b). Employing imine **23b** (123 mg, 0.38 mmol) in the general procedure used for the preparation of pyrrolidine **14a** resulted in the title compound (93 mg, 97%) as the sole reaction product (NMR) which was obtained as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.68 (d, J = 1.6 Hz, 1H, C=CHH), 4.62 (d, J = 1.5 Hz, 1H, C=CHH), 3.08 (dd, J = 10.5, 7.9 Hz, 1H, NCHH), 2.95 (dt, J = 9.2, 3.5 Hz, 1H, NCH), 2.52 (dd, J = 10.6, 7.6 Hz, 1H, NCHH), 1.99 (m, 1H, CH₃CH), 1.67 (m, 1H, (CH₃)₂CH), 1.65 (br s, 1H, NH), 1.58 (t, J = 8.9 Hz, 1H, C=CCH), 1.43 (s, 2H, SiCH₂), 1.24 (m, 2H, CH₂CH(CH₃)₂), 0.94 (d, J = 6.7 Hz, 3H, CH₃), 0.85 (dd, J = 11.6, 6.5 Hz, 6H, (CH₃)₂CH), 0.01 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 147.05, 109.26, 64.15, 61.64, 53.72, 45.48, 39.48, 26.03, 23.93, 23.46, 21.78, 18.04, -0.78; IR (film) 3280, 3079, 2954, 2869, 1627, 1467, 1418, 1374, 1248,

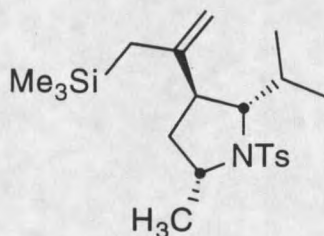
1164, 848, 692 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{31}\text{NSi}$ (M^+) 253.2226, found 253.2219.



(2 α ,3 α ,4 β)-N-Tosyl-4-methyl-3-[(3-trimethylsilyl)isopropenyl]-2-methylpyrrolidine (25c). Employing amine **1b** (100 mg, 0.39 mmol) in the procedure outlined for the preparation of **28c**, a mixture of pyrrolidine **24c** and a minor diastereomer (80 mg, 97% from **1b**, ave 3.0:1.0 by NMR) was obtained as a colorless oil. Complete characterization was achieved by conversion of the mixture (79 mg, 0.38 mmol) to the corresponding *N*-tosylates using the method previously described for **15a**. The inseparable title compound and the minor isomer (115 mg, 83%, ave 3.0:1.0 by NMR) were secured as a viscous, colorless material: ^1H NMR (300 MHz, CDCl_3) δ 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.30 (d, J = 8.1 Hz, 2H, ArH), 4.70 (s, 1H, C=CHH), 4.50 (s, 1H, C=CHH), 3.90 (p, J = 7.0 Hz, 1H, NCHCH₃), 3.58 (dd, J = 9.3, 7.4 Hz, 1H, NCHH), 2.67 (t, J = 9.7 Hz, 1H, NCHH), 2.40 (s, 3H, ArCH₃), 2.30 (m, 1H, CH₃CH), 1.58 (t, J = 11.5 Hz, 1H, C=CCH), 1.56 (d, J = 13.5 Hz, 1H, SiCHH), 1.11 (d, J = 13.5 Hz, 1H, SiCHH), 0.99 (d, J = 6.5 Hz, 3H, CH₃), 0.86 (d, J = 6.3 Hz, 3H, CH₃), -0.14 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 143.16, 141.97, 129.53, 127.45, 127.38, 109.11, 65.28, 57.90, 54.86, 32.39, 27.51, 21.39, 18.33, 15.63, -1.40; IR (film) 3083, 3029, 2956, 2874, 1634, 1598, 1455, 1343, 1248, 1157, 1096, 1042, 852, cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_2\text{SSi}$ (M^+) 365.1845, found 365.1845.

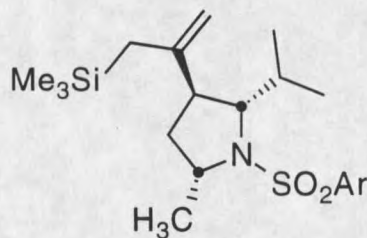


***N*-(2-Methylpropylidene)-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (26a).** The general procedure for the preparation of aldimine **11a** was employed using amine **1c** (130 mg, 0.50 mmol) and isobutyraldehyde (55 μ L, 0.61 mmol) to afford the title imine (155 mg, 99%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.42 (d, J = 5.6 Hz, 1H, $\text{N}=\text{CH}$), 4.68 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 2.94 (sx, J = 6.5 Hz, 1H, NCH), 2.37 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.05 (m, 2H, CH_2), 1.43 (ABq, $\Delta\nu$ = 32.0 Hz, J = 13.4 Hz, 2H, CH_2Si), 1.35 (d, J = 3.6 Hz, 2H, CH_2Si), 1.09 (d, J = 6.3 Hz, 3H, CH_3CHN), 1.02 (d, J = 6.8 Hz, 6H, $(\text{CH}_3)_2\text{CH}$), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.05 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 167.23, 135.60, 116.53, 66.91, 37.27, 33.86, 29.51, 24.01, 22.21, 19.63, -0.62, -1.09; IR (film) 2958, 2928, 2896, 2832, 1668, 1371, 1248, 1156, 1064, 852, 699, 624 cm^{-1} .



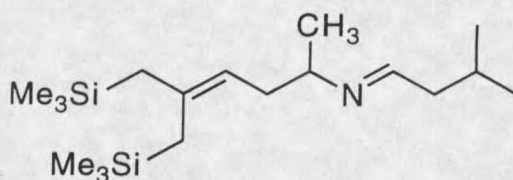
(2 α ,3 β ,5 α)-*N*-Tosyl-5-methyl-3-[(trimethylsilyl)isopropenyl]-2-isopropylpyrrolidine (28a). Employing freshly prepared imine **26a** (483 mg, 1.55 mmol) in the general cyclization procedure used for **14a**, a crude mixture (404 mg, 100%, 2.0:1.0 by NMR) of the corresponding pyrrolidine **27a** and the monoprodesilylated imine isomer was obtained. A 10 mL, single-

necked, round-bottomed flask was charged with the crude mixture, CH_2Cl_2 (4.0 mL) and pyridine (400 μL , 4.64 mmol). To the solution was added TsCl (370 mg, 1.94 mmol) in one portion and the mixture was stirred for 7h at 25 $^\circ\text{C}$. Water (4.0 mL) was added and the biphasic mixture stirred for an additional 1h. The organic layer was removed, combined with three CH_2Cl_2 extractions of the aqueous layer and dried over Na_2SO_4 . After removal of solvent *in vacuo*, the residue was chromatographed on silica gel (1% EtOAc/hexane - 5% EtOAc/hexane) to yield the title *N*-tosylpyrrolidine (280 mg, 46% from amine **1c**) as a viscous colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.66 (d, J = 8.0 Hz, 2H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 4.09 (s, 1H, C=CHH), 4.05 (s, 1H, C=CHH), 3.71 (app sx, J = 6.6 Hz, 1H, CH_3CHN), 3.47 (app t, J = 4.7 Hz, 1H, NCH), 2.38 (s, 3H, ArCH₃), 2.15 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.55 (m, 2H, CH_2), 1.32 (d, J = 6.3 Hz, 3H, CH_3), 1.15 (ABq, $\Delta\nu$ = 28.2 Hz, J = 13.9 Hz, 2H, CH_2Si), 0.96 (app t, J = 6.0 Hz, 6H, $(\text{CH}_3)_2\text{CH}$), -0.11 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 146.70, 142.94, 135.40, 129.19, 127.89, 107.98, 71.10, 56.47, 45.75, 38.01, 33.28, 24.82, 22.92, 21.41, 20.09, 17.68, -1.29; IR (film) 3098, 3029, 2958, 2895, 2870, 1633, 1599, 1464, 1343, 1249, 1162, 1093, 1022, 852, 733, 622 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{35}\text{NO}_2\text{SSi}$ (M^+) 393.2158, found 393.2153.

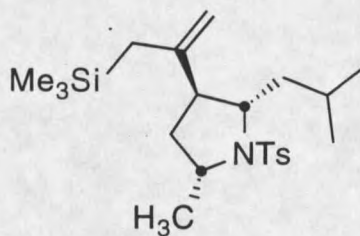


(2 α ,3 β ,5 α)-*N*-(2-Naphthalenesulfonyl)-5-methyl-3-[(3-trimethylsilyl)isopropenyl]-2-isopropylpyrrolidine (29a). The title

compound was prepared for the purpose of NOE studies. A 5.0 mL, single-necked, round-bottomed flask was charged with the crude pyrrolidine **27a** (141 mg, 0.59 mmol), CH_2Cl_2 (2.0 mL) and pyridine (200 μL , 2.5 mmol). DMAP (100 mg, 0.82 mmol) and 2-naphthalenesulfonylchloride (175 mg, 0.77 mmol) were sequentially added and the reaction mixture was stirred for 18h at 25 $^\circ\text{C}$. The mixture was treated with H_2O (2.0 mL) and the biphasic mixture was stirred for an additional 2h. The organic phase was removed, combined with three CH_2Cl_2 extracts of the aqueous phase and dried (Na_2SO_4). The solvent was removed *in vacuo* and silica gel chromatography (5% EtOAc/hexane) of the residue afforded the title compound (84 mg, 33%) as a gelatinous colorless material: ^1H NMR (300 MHz, CDCl_3) δ 8.35 (s, 1H, ArH), 7.90 (m, 4H, ArH), 7.59 (m, 2H, ArH), 3.98 (s, 1H, C=CHH), 3.81 (app sx J = 6.7 Hz, 1H, CH_3CHN), 3.73 (s, 1H, C=CHH), 3.62 (app t, J = 4.7 Hz, 1H, NCH), 2.36 (ddd, J = 7.8, 4.5, 4.5 Hz, 1H, $\text{CHC}=\text{C}$), 2.16 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.61 (m, 2H, CH_2), 1.38 (d, J = 6.5 Hz, 3H, CH_3), 1.16 (d, J = 13.8 Hz, 1H, CHHSi), 1.03 (d, J = 7.2 Hz, 3H, CH_3CHCH_3), 1.01 (d, J = 7.0 Hz, 3H, CH_3CHCH_3), 0.98 (d, J = 13.0 Hz, 1H, CHHSi), -0.02, (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 146.47, 135.53, 134.78, 132.22, 129.12, 128.89, 128.63, 128.41, 127.79, 127.26, 123.68, 107.79, 71.48, 56.61, 45.89, 37.92, 33.53, 24.86, 23.09, 20.21, 17.99, -1.39; IR (film) 3078, 3057, 2959, 2926, 2859, 1633, 1598, 1464, 1340, 1248, 1161, 1132, 1057, 1019, 971, 791, 693, 660, 645, 618, cm^{-1} .

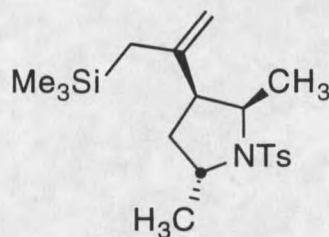


***N*-(3-Methylbutylidene)-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (26b).** The general procedure used for the preparation of imine **11a** was carried out using amine **1c** (200 mg, 0.78 mmol) and isovaleraldehyde (100 μ L, 0.93 mmol) to provide the title imine (249 mg, 98%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.57 (t, J = 5.4 Hz, 1H, $\text{N}=\text{CH}$), 4.68 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 2.97 (sx, J = 6.5 Hz, 1H, NCH), 2.07 (m, 4H, $\text{C}=\text{CCH}_2$ and $\text{N}=\text{CCH}_2$), 1.84 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.42 (ABq, $\Delta\nu$ = 24.3 Hz, J = 13.4 Hz, 2H, SiCH_2), 1.34 (s, 2H, SiCH_2), 1.10 (d, J = 6.3 Hz, 3H, CH_3CH), 0.91 (dd, J = 6.6, 3.1 Hz, 6H, $(\text{CH}_3)_2\text{CH}$), -0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.05 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 161.83, 135.75, 116.49, 67.24, 44.57, 37.32, 29.54, 26.44, 23.98, 22.49, 22.38, 22.23, -0.63, -1.10; IR (film) 2955, 2832, 1668, 1646, 1464, 1418, 1368, 1247, 1157, 1065, 838, 699 cm^{-1} .



(2 α ,3 β ,5 α)-*N*-Tosyl-5-methyl-3-[(3-trimethylsilyl)isopropenyl]-2-isobutylpyrrolidine (28b). Using imine **26b** (100 mg, 0.31 mmol) in the general procedure outlined for the preparation of **14a** furnished pyrrolidine **27b** (73 mg, 95%) as a colorless oil. For complete characterization, the pyrrolidine was converted into the title *N*-tosylate (110 mg, 92%) which was

obtained as a colorless, viscous oil using the method previously described for **15a**: ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, J = 8.2, 2H, ArH), 7.25 (d, J = 7.7 Hz, 2H, ArH), 4.28 (s, 1H, C=CHH), 4.22 (s, 1H, C=CHH), 3.83 (sx, J = 5.9 Hz, 1H, NCHCH₃), 3.57 (ddd, J = 13.6, 9.2, 4.6, Hz, 1H, NCH), 2.39 (s, 3H, ArCH₃), 2.38 (m, 1H, C=CCH), 1.76 (m, 2H, CHH and (CH₃)₂CH), 1.50 (m, 3H, CHH and CH₂CH(CH₃)₂), 1.30 (d, J = 6.3 Hz, 3H, CH₃CH), 1.23 (d, J = 14.2 Hz, 1H, SiCHH), 1.02 (d, J = 14.1 Hz, 1H, SiCHH), 0.93 (dd, J = 6.2, 3.9 Hz, 6H, (CH₃)₂CH), -0.10 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 146.00, 142.92, 136.03, 129.34, 127.65, 108.45, 63.36, 556.47, 51.41, 48.50, 37.64, 25.15, 24.48, 23.70, 23.47, 22.09, 21.41, -1.29; IR (film) 3083, 3029, 2956, 2870, 1632, 1598, 1461, 1347, 1249, 1163, 1091, 1009, 853, 663 cm^{-1} ; HRMS calcd for C₂₂H₃₇NO₂SSi (M⁺) 407.2314, found 407.2314.

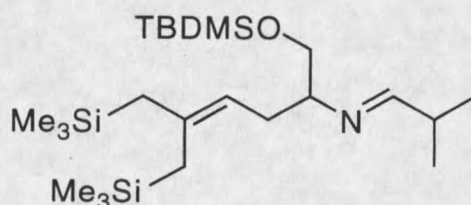


(2 α ,3 α ,5 β)-N-Tosyl-5-methyl-3-[(trimethylsilyl)isopropenyl]-2-methylpyrrolidine (28c). A 5.0 mL, single-necked, round-bottomed flask containing a solution of amine **1c** (100 mg, 0.39 mmol) in THF (0.5 mL) and 4 Å molecular sieves (260 mg) was cooled to -10 °C. Acetaldehyde in THF (800 μL , 0.80 mmol, 1.0 M) was added dropwise over 2 min. The mixture was stirred for 2h at -10 °C and was then diluted with Et₂O (2 mL). The cold reaction mixture was filtered through Celite, concentrated and the resulting crude imine was used *immediately* in the next step. The colorless imine was obtained as a single isomer (NMR) in pure form: ^1H NMR (300 MHz, CDCl_3) δ 7.62 (q, J = 4.7

Hz, 1H, N=CH), 4.67 (t, $J = 7.2$ Hz, 1H, C=CH), 2.99 (sx, $J = 6.5$ Hz, 1H, NCH), 2.06 (t, $J = 7.4$ Hz, 2H, CH₂), 1.89 (d, $J = 4.9$ Hz, 3H, CH₃C=N), 1.43 (s, 2H, SiCH₂), 1.35 (s, 2H, SiCH₂), 1.10 (d, 6.3 Hz, 1H, CH₃), -0.02 (s, 9H, (CH₃)₃Si), -0.04 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 157.84, 135.87, 116.47, 67.04, 37.28, 29.53, 24.03, 22.18, 22.03, -0.62, -1.12; IR (film) 2954, 2836, 1671, 1247, 1152, 1064, 852, 699, cm⁻¹.

Following the general cyclization procedure used for **14a** and using reaction times of 1h at -78 °C followed by 36h at -20 °C, the freshly prepared imine was converted into a mixture of pyrrolidine **27c** and a minor stereoisomer (75 mg, 91% from **1c**, 6.8:1.0 by NMR). It should be noted that additional trials showed deviance in the isomer ratio in favor of the other diastereomer. In order for complete characterization, the mixture of diastereomers was converted into the corresponding *N*-tosyl derivatives using the procedure previously described for **15a**. The title compound and the minor isomer (129 mg, 91%, 6.1:1.0 by NMR) were obtained as a colorless viscous material and were found to be inseparable on silica gel. Fractional crystallization (petroleum ether) of the mixture afforded a pure sample of the major, title diastereomer which was isolated as a white solid: mp 84.8-87.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, $J = 8.1$ Hz, 2H, ArH), 7.20 (d, $J = 7.9$ Hz, 2H, ArH), 4.62 (s, 1H, C=CHH), 4.49 (s, 1H, C=CHH), 4.11 (p, $J = 6.4$ Hz, 1H, NCH), 3.93 (m, 1H, NCH), 2.77 (ddd, $J = 13.2, 6.7, 6.0$ Hz, 1H, C=CCH), 2.38 (s, 3H, ArCH₃), 2.23 (ddd, $J = 16.5, 12.3, 3.9$ Hz, 1H, CHH), 1.58 (d, $J = 13.6$ Hz, 1H, SiCHH), 1.43 (dd, $J = 12.0, 5.5$ Hz, 1H, CHH), 1.24 (d, $J = 13.9$ Hz, 1H, SiCHH), 1.19 (d, $J = 6.2$ Hz, 3H, CH₃), 0.88 (dd, $J = 6.2, 0.9$ Hz, 3H, CH₃), -0.03 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 143.89, 142.59, 129.37, 127.54, 126.99, 108.91,

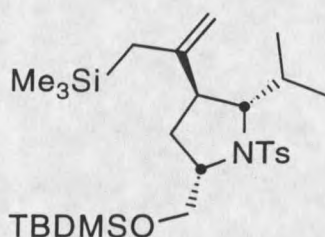
58.07, 54.44, 46.55, 34.12, 27.03, 22.51, 21.38, 15.44, -1.39; IR (film) 3079, 2953, 1634, 1599, 1464, 1379, 1328, 1247, 1163, 1095, 1059, 848, 663 cm^{-1} ; HRMS, calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_2\text{SSi}$ (M^+) 365.1845, found 365.1848.



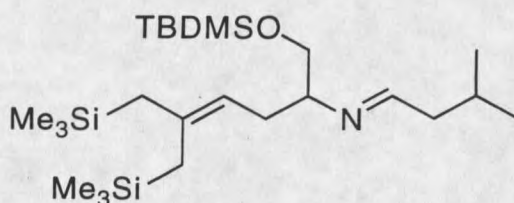
***N*-(2-Methylpropylidene)-1-*tert*-butyldimethylsilyloxy-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (30a).**

Following the general procedure used for the preparation of imine **11a**, amine **1d** (169 mg, 0.44 mmol) and isobutyraldehyde (48 μL , 0.52 mmol) were converted into the title imine (188 mg, 98%) which was isolated as a clear oil:

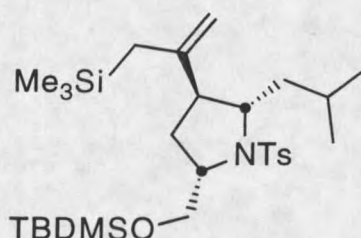
^1H NMR (300 MHz, CDCl_3) δ 7.43 (d, $J = 5.4$ Hz, 1H, $\text{N}=\text{CH}$), 4.69 (t, $J = 7.2$ Hz, 1H, $\text{C}=\text{CH}$) 3.63 (dd, $J = 10.0, 4.6$ Hz, 1H, SiOCHH), 3.48 (dd, $J = 9.9, 8.4$ Hz, 1H, SiOCHH), 2.90 (p, $J = 4.8$ Hz, 1H, NCH), 2.39 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 2.20 (ddd, $J = 14.1, 8.0, 6.0$ Hz, 1H, CHH), 1.98 (dq, $J = 7.1, 6.9$ Hz, 1H, CHH), 1.43 (ABq, $\Delta\nu = 29.2$ Hz, $J = 13.3$ Hz, 2H, SiCH_2), 1.35 (s, 2H, SiCH_2), 1.04 (d, $J = 6.8$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$), 0.84 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.04 (s, 3H, $(\text{CH}_3)_3\text{CSiCH}_3$), 0.00 (s, 9H, $\text{Si}(\text{CH}_3)_3$), -0.01 (s, 3H, $(\text{CH}_3)_3\text{CSiCH}_3$), -0.04 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 169.62, 135.87, 115.96, 73.51, 66.36, 34.05, 31.80, 29.53, 25.94, 24.06, 19.70, 18.30, -0.61, -1.05, -5.22, -5.32; IR (film) 2956, 2858, 1670, 1472, 1464, 1248, 1115, 838, 775 cm^{-1} .



(2 α ,3 β ,5 α)-N-Tosyl-5-(*tert*-butyldimethylsilyloxy)methyl-3-[(trimethylsilyl)isopropenyl]-2-isopropylpyrrolidine (32a). Imine **30a** (188 mg, 0.42 mmol) was subjected to the general cyclization protocol used for **14a** to produce a mixture of the corresponding pyrrolidine and the monodesilylated imine isomer (1.3:1.0 by NMR). This crude mixture was directly exposed to TsCl in the manner previously described to provide the crude *N*-tosylate. Purification by flash chromatography on silica gel (1%-5% EtOAc/hexane) furnished the title compound (93 mg, 42% from **1d**) as a colorless viscous material: ^1H NMR (300 MHz, CDCl_3) δ 7.67 (d, J = 8.1 Hz, 2H, ArH), 7.25 (d, J = 8.0 Hz, 2H, ArH), 4.13 (s, 1H, C=CHH), 4.05 (s, 1H, C=CHH), 3.93 (dd, J = 9.5, 3.8 Hz, 1H, SiOCHH), 3.64 (m, 1H, NCH), 3.54 (dd, J = 9.1, 9.1 Hz, 1H, SiOCHH), 3.44 (t, J = 5.2 Hz, 1H, NCHCH(CH₃)₂), 2.40 (s, 3H, ArCH₃), 2.39 (unresolved, 1H, C=CCH), 2.09 (m, 1H, CH(CH₃)₂), 1.90 (dq, J = 6.9, 6.3 Hz, 1H, CHH), 1.53 (dq, J = 6.7, 6.5 Hz, 1H, CHH), 1.17 (ABq, Δv = 32.4 Hz, J = 14.0 Hz, 2H, SiCH₂), 0.96 (dd, J = 9.5, 7.0 Hz, 6H, (CH₃)₂CH), 0.88 (s, 9H, (CH₃)₃CSi), 0.07 (s, 3H, (CH₃)₃CSiCH₃), 0.06 (s, 3H, (CH₃)₃CSiCH₃), -0.09 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 146.52, 143.14, 135.31, 129.27, 128.04, 108.26, 71.10, 66.07, 61.59, 46.23, 33.21, 32.98, 25.93, 24.78, 21.45, 20.27, 18.30, 18.02, -1.23, -5.30; IR (film) 3084, 2956, 2857, 1634, 1599, 1471, 1347, 1250, 1163, 1094, 1005, 838, 778, 734 cm^{-1} HRMS calcd for C₂₇H₅₀NO₃SSi₂ (MH⁺) 524.3050, found 524.3038.

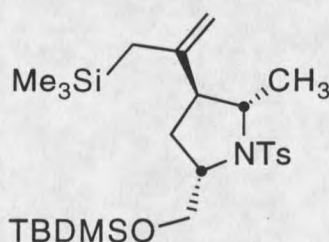


***N*-(3-Methylbutylidene)-1-*tert*-butyldimethylsilyloxy-5-trimethylsilylmethyl-6-trimethylsilyl-4-hexen-2-amine (30b).** Upon using amine **1d** (112 mg, 0.29 mmol) and isovaleraldehyde (37 μ l 0.35 mmol) in the general procedure used for the preparation of **11a**, the title imine (129 mg, 98%) was obtained as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.57 (t, $J = 5.3$ Hz, 1H, $\text{N}=\text{CH}$), 4.70 (t, $J = 7.1$ Hz, 1H, $\text{C}=\text{CH}$), 3.64 (dd, $J = 10.0, 4.6$ Hz, 1H, SiOCHH), 3.50 (dd, $J = 9.8, 8.0$ Hz, 1H, SiOCHH), 2.94 (p, $J = 5.3$ Hz, 1H, NCH), 2.22 (ddd, $J = 14.0, 5.9, 5.9$ Hz, 1H, CHH), 2.10 (dd, $J = 6.4, 5.7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.00 (ddd, $J = 14.2, 7.0, 7.0$ Hz, 1H, CHH), 1.86 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.43 (ABq, $\Delta\nu = 20.9$ Hz, $J = 13.3$ Hz, 2H, SiCH_2), 1.36 (s, 2H, SiCH_2), 0.93 (s, $J = 6.6$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$), 0.84 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.00 (s, 3H, $(\text{CH}_3)_3\text{CSiCH}_3$), -0.02 (s, 12H, $(\text{CH}_3)_3\text{Si}$ and $(\text{CH}_3)_3\text{CSiCH}_3$), -0.04 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 164.31, 136.01, 115.89, 73.84, 66.38, 44.81, 31.79, 29.54, 26.40, 25.93, 24.00, 22.55, 18.30, -0.63, -1.08, -5.24, -5.32; IR (film) 2955, 2858, 1669, 1463, 1248, 1114, 838, 775 cm^{-1} .



(2 α ,3 β ,5 α)-*N*-Tosyl-5-(*tert*-butyldimethylsilyloxy)methyl-3-[(trimethylsilyl)isopropenyl]-2-isobutylpyrrolidine (32b). The general TiCl_4 mediated aldimine cyclization procedure used for **14a** was followed utilizing imine **30b** (129 mg, 0.28 mmol) to produce a mixture of diastereomeric pyrrolidines (87 mg, 80%, 3.9:1.0 by NMR) as a light gold oil after elution of the crude material through a Florisil plug (CH_2Cl_2 for elution). For complete characterization, the mixture was treated with TsCl as previously described to furnish an inseparable mixture of the title compound and a minor *N*-tosyl pyrrolidine diastereomer (106 mg, 87%, 3.6:1.0 by NMR) as a clear, viscous gel upon silica gel chromatography of the crude products (5% EtOAc/hexane for elution): ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, $J = 8.1$ Hz, 2H, ArH), 7.26 (d, $J = 8.0$ Hz, 2H, ArH), 4.29 (s, 1H, C=CHH), 4.21 (s, 1H, C=CHH), 3.81 (dd, $J = 10.0$, 3.9 Hz, 1H, SiOCHH), 3.76 (m, 1H, NCHCH₂OSi), 3.56 (dd, $J = 9.3$, 7.6 Hz, 1H, SiOCHH), 3.53 (dd, $J = 8.3$, 3.8 Hz, 1H, NCH), 2.40 (s, 3H, ArCH₃), 2.38 (ddd, $J = 13.4$, 7.5, 7.5 Hz, 1H, C=CCH), 1.90 (ddd, $J = 12.9$, 7.2, 4.3 Hz, 1H, CHH), 1.72 (m, 2H, (CH₃)₂CH and CHH), 1.48 (m, 2H, (CH₃)₂CHCH₂), 1.21 (d, $J = 13.8$ Hz, 1H, SiCHH), 1.00 (d, $J = 14.0$ Hz, 1H SiCHH), 0.91 (dd, $J = 5.9$, 5.9 Hz, 6H, (CH₃)₂CH), 0.88 (s, 9H, (CH₃)₃CSi), 0.06 (d, $J = 1.9$ Hz, 6H, (CH₃)₃CSi(CH₃)₂), -0.10 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 HMz, CDCl_3 , ^1H decoupled) δ 146.15, 143.07, 135.81, 129.41, 127.73, 127.28, 108.57, 66.02, 63.42, 61.76, 51.74, 47.95, 32.71, 25.94, 25.02, 23.75, 22.07, 21.43, 18.29, -

1.25, -5.33; IR (film) 3083, 3029, 2956, 2858, 1635, 1599, 1472, 1356, 1250, 1163, 1098, 1005, 839, 814, 777, cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{51}\text{NO}_3\text{SSi}_2$ (M^+) 537.3128, found 537.3111.



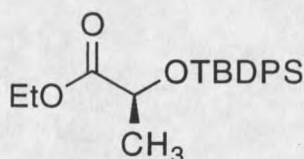
(2 α ,3 β ,5 α)-N-Tosyl-5-(*tert*-butyldimethylsilyloxy)methyl-3-[(trimethylsilyl)isopropenyl]-2-methylpyrrolidine (32c). The procedure used for the preparation of *N*-tosylpyrrolidine **28c** was employed using amine **1d** (150 mg, 0.39 mmol) and acetaldehyde (775 μL , 0.77 mmol, 1.0 M in THF). The corresponding imine (160 mg, 100%) was obtained as a colorless oil and was used *immediately* in the next step: ^1H NMR (300 MHz, CDCl_3) δ 7.60 (q, J = 4.8 Hz, 1H, $\text{N}=\text{CH}$), 4.67 (t, J = 7.1 Hz, 1H, $\text{C}=\text{CH}$), 3.63 (dd, J = 10.0, 4.7 Hz, SiOCHH), 3.48 (dd, J = 9.9, 7.8 Hz, 1H, SiOCHH), 2.95 (m, 1H, NCH), 2.18 (dq, J = 7.3, 6.9 Hz, 1H, CHH), 2.00 (dq, J = 7.3, 7.3 Hz, 1H, CHH), 1.91 (d, J = 4.8 Hz, 3H, CH_3), 1.42 (s, 2H, SiCH_2), 1.35 (s, 2H, SiCH_2), 0.84 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.00 (s, 6H, $(\text{CH}_3)_3\text{CSi}(\text{CH}_3)_2$), -0.02 (s, 9H, $\text{Si}(\text{CH}_3)_3$), -0.05 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 160.38, 136.09, 115.87, 73.60, 66.25, 31.64, 29.53, 25.90, 24.05, 22.06, 18.28, -0.62, -1.12, -5.24; IR (film) 2854, 2857, 1673, 1472, 1361, 1248, 1113, 838, 775 cm^{-1} .

The freshly prepared imine was cyclized into an inseparable mixture of diastereomeric pyrrolidines (115 mg, 87%, 5.0:1.0 by NMR) which was obtained as a gold oil after elution of the crude products through a plug of Florisil

(CH₂Cl₂ for elution). The mixture of pyrrolidines was converted into an inseparable mixture of the title compound and the minor *N*-tosylpyrrolidine (150 mg, 90%, 5.0:1.0 by NMR) which was obtained as a viscous, colorless gel after purification on silica gel (1%-5% EtOAc/hexane for elution): ¹H NMR (300 MHz, C₆D₆) δ 7.75 (d, J = 8.1 Hz, 2H, ArH), 6.76 (d, J = 7.9 Hz, 2H, ArH), 4.50 (d, J = 13.4 Hz, 2H, C=CH₂), 4.03 (m, 1H, NCH), 4.00 (dd, J = 10.4, 4.1 Hz, 1H, SiOCHH), 3.69 (t, J = 9.8 Hz, 1H, SiOCHH), 3.48 (dq, J = 6.1, 2.5 Hz, 1H, NCHCH₃), 2.48 (ddd, J = 15.1, 6.8, 6.8 Hz, 1H, C=CCH), 2.00 (dd, J = 12.6, 6.4 Hz, 1H, CHH), 1.88 (s, 3H, ArCH₃), 1.61 (d, J = 6.1 Hz, 3H, CH₃), 1.22 (m, 1H, CHH), 1.16 (d, 13.6 Hz, 1H, SiCHH), 1.09 (d, J = 13.6 Hz, 1H, SiCHH), 0.96 (s, 9H, (CH₃)₃CSi), 0.12 (s, 3H, (CH₃)₃CSiCH₃), 0.11 (s, 3H, (CH₃)₃CSiCH₃), -0.10 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 145.26, 143.28, 135.15, 129.54, 127.62, 108.86, 65.80, 61.85, 60.62, 53.34, 32.41, 25.94, 23.99, 22.06, 21.44, 18.31, -1.23, -5.34; IR (film) 3082, 2955, 2857, 1632, 1600, 1472, 1349, 1250, 1166, 1094, 1029, 838, 778, cm⁻¹; HRMS calcd for C₂₅H₄₅NO₃SSi₂ (M⁺) 495.2659, found 495.2654.

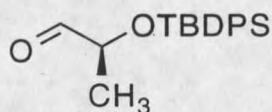
Cyclization of (S)-Ethyl Lactate-Derived Imines

General Information: The following experimental procedures constitute the methods used to prepare silyl ethers **41a-c**, aldehydes **42a-c**, the corresponding imines **43a-c** and pyrrolidines **44a-c**. The oxazolidinone derivative **45** derived from all major pyrrolidines was identical with respect to spectrometric (^1H and ^{13}C NMR) and chromatographic (TLC) properties. (S)-(-)-Ethyl lactate ($[\alpha]^{14}_{\text{D}} -10^\circ$) was purchased from Aldrich Chemical Company, Inc. and was used without additional purification.

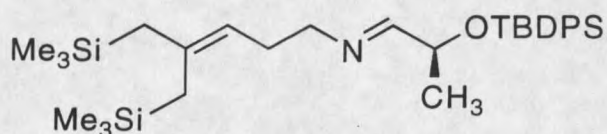


(S)-Ethyl-(O-*tert*-butyldiphenylsilyl)lactate (41c). To a 25 mL, single-necked, round-bottomed flask containing a solution of *tert*-butyl-chlorodiphenylsilane (2.60 mL, 10.0 mmol) and imidazole (1.63 g, 24.0 mmol) in DMF (5.0 mL) was added (S)-ethyl lactate (1.36 mL, 12.0 mmol) dropwise over 30 min via a 5.0 mL, addition funnel. During the course of the addition, mild exotherms and precipitation of a clear oil were observed. The reaction mixture was stirred for 5h at rt, poured into a separatory funnel and the layers were allowed to separate. The upper layer was removed and the remaining portion was extracted with hexane (3 x 3 mL). The combined product layer and hexane extracts were washed with H_2O (2 x 5 mL), dried over MgSO_4 , filtered and concentrated. The residue was eluted through a plug of silica gel (Et_2O for elution) to furnish the title ester (3.35 g, 94%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.70 (dt, $J = 7.7, 1.8$ Hz, 4H, ArH), 7.38 (m, 6H, ArH), 4.28 (q, $J =$

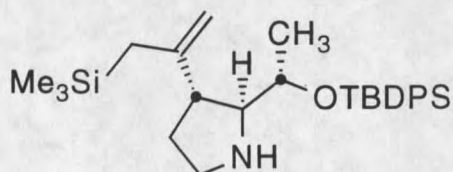
6.7 Hz, 1H, CH), 4.02 (q, $J = 7.1$ Hz, 2H, CH_2), 1.38 (d, $J = 6.8$ Hz, 3H, CH_3), 1.15 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 1.11 (s, 9H, $(\text{CH}_3)_3\text{CSi}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 173.61, 135.88, 135.72, 133.67, 133.30, 129.70, 127.58, 127.51, 68.99, 60.47, 26.82, 21.21, 19.23, 14.01, IR (film) 3072, 3050, 2933, 2859, 1753, 1428, 1273, 1196, 1138, 1061, 974, 823, 739, 703, cm^{-1} .



(S)-2-(*tert*-Butyldiphenylsilyloxy)propanal (42c). A 25 mL, single-necked, round-bottomed flask containing a solution of **41c** (2.00 g, 5.61 mmol) in toluene (11 mL) was cooled to -78 $^{\circ}\text{C}$ and diisobutylaluminum hydride (6.17 mL, 6.17 mmol, 1.0 M in toluene) was added dropwise over 20 minutes via a 10 mL, addition funnel. The reaction mixture was stirred for 2h at -78 $^{\circ}\text{C}$ and was carefully poured into half-saturated brine (30 mL). The biphasic mixture was stirred for 30 minutes at rt, transferred to a separatory funnel and the layers were allowed to separate overnight. The organic phase was removed and the remaining aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (25 mL), dried over MgSO_4 , filtered and concentrated. The residue was eluted through a thin pad of silica gel (hexane for elution) to provide the title aldehyde (1.61g, 92%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 9.63 (d, $J = 1.1$ Hz, 1H, $\text{O}=\text{CH}$), 7.64 (m, 4H, ArH), 7.39 (m, 6H, ArH), 4.08 (dq, $J = 6.9, 0.9$ Hz, 1H, CH), 1.21 (d, $J = 6.9$ Hz, 3H, CH_3), 1.10 (s, 9H, $(\text{CH}_3)_3\text{CSi}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 203.45, 135.69, 133.34, 132.99, 130.00, 129.95, 127.81, 127.75, 74.43, 26.87, 19.20, 18.33; IR (film) 3072, 3051, 2932, 2859, 2720, 1739, 1472, 1428, 1375, 1112, 1008, 823, 703 cm^{-1} .

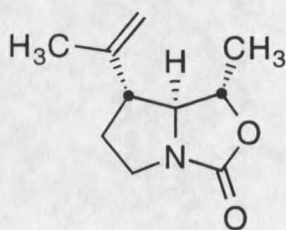


(S)-N-[(2-(*tert*-Butyldiphenylsilyloxy)propylidene]-4-trimethylsilylmethyl-5-trimethylsilyl-3-penten-1-amine (43c). To a 10 mL, single-necked, round-bottomed flask containing a solution of aldehyde **42c** (384 mg, 1.23 mmol) in THF (4.0 mL) was added freshly activated 4 Å molecular sieves (750 mg) followed by amine **1a** (300 mg, 1.23 mmol). The reaction mixture was stirred for 24h at rt after which time anhydrous hexane (6.0 mL) was added. The resulting cloudy mixture was filtered through a pad of Celite and the solvents were removed *in vacuo* to yield the title imine (658 mg, 99%) as a colorless, viscous oil: ^1H NMR (300 MHz, CDCl_3) δ 7.67 (ddd, $J = 6.1, 3.8, 1.1$ Hz, 4H, ArH), 7.59 (dd, $J = 5.0, 1.0$ Hz, 1H, $\text{N}=\text{CH}$), 7.38 (m, 6H, ArH), 4.75 (t, $J = 7.0$ Hz, 1H, $\text{C}=\text{CH}$), 4.36 (p, $J = 5.9$ Hz, 1H, CH), 3.23 (t, $J = 7.6$ Hz, 2H, CH_2N), 2.11 (m, 2H, CH_2), 1.47 (s, 2H, CH_2Si), 1.39 (s, 2H, CH_2Si), 1.23 (d, $J = 6.9$ Hz, 3H, CH_3), 1.08 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 166.94, 135.83, 135.77, 134.15, 133.92, 130.01, 129.62, 127.76, 127.55, 116.39, 71.35, 61.29, 30.25, 29.49, 27.00, 23.84, 21.60, 19.23, -0.65, -1.12; IR (film) 3072, 2955, 2858, 1676, 1473, 1428, 1370, 1248, 1112, 1007, 854, 701, cm^{-1} .



[2S-[2 α (S^*),3 β]]]-2-[(1-(*tert*-Butyldiphenylsilyloxy)ethyl]-3-[(3-trimethylsilyl)isopropenyl]pyrrolidine (44c). A 10 mL, single-necked,

round-bottomed flask containing a solution of imine **43c** (500 mg, 0.93 mmol) in CH_2Cl_2 (6.0 mL) was cooled to $-78\text{ }^\circ\text{C}$ and TiCl_4 (930 μL , 0.93 mmol, 1.0 M in toluene) was added dropwise over 2 min via syringe. The resulting deep red-orange solution was stirred for 1h at $-78\text{ }^\circ\text{C}$, followed by 24h at $-20\text{ }^\circ\text{C}$. The cold reaction mixture was neutralized and the crude product was isolated in the manner previously described for the preparation of **14a**. The crude material was dissolved in hexane and eluted through a plug of Florisil (Et_2O for elution) to provide the title pyrrolidine (394 mg, 91%) as a viscous oil: ^1H NMR (300 MHz, CDCl_3) δ 7.67 (dt, $J = 8.0, 1.7\text{ Hz}$, 4H, ArH), 7.37 (m, 6H, ArH), 4.51 (d, $J = 6.9\text{ Hz}$, 2H, $\text{C}=\text{CH}_2$), 3.85 (dq, $J = 6.4, 3.0\text{ Hz}$, 1H, CHOSi), 2.94 (m, 2H, NCH_2), 2.80 (dd, $J = 7.5, 3.1\text{ Hz}$, 1H, NCH), 2.40 (q, $J = 8.0\text{ Hz}$, 1H, $\text{C}=\text{CCH}$), 2.25 (br s, 1H, NH), 1.90 (dddd, $J = 15.1, 12.4, 6.5, 2.4\text{ Hz}$, 1H, CHH), 1.69 (dq, $J = 12.6, 7.4\text{ Hz}$, 1H, CHH), 1.39 (ABq, $\Delta\nu = 25.1\text{ Hz}$, $J = 14.1\text{ Hz}$, 2H, CH_2Si), 1.10 (d, $J = 6.3\text{ Hz}$, 3H, CH_3), 1.05 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), -0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 148.44, 135.99, 135.92, 134.42, 133.51, 129.72, 129.52, 127.65, 127.38, 108.23, 69.93, 69.75, 49.50, 46.30, 32.91, 27.12, 24.38, 22.08, 19.36, -1.09 , IR (film) 3072, 3049, 2957, 2858, 1629, 1472, 1428, 1248, 1112, 1073, 851, 702 cm^{-1} ; HRMS calcd for $\text{C}_{28}\text{H}_{44}\text{NOSi}_2$ (MH^+) 466.2961, found 466.2960.

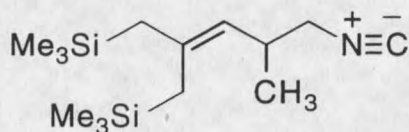


4S-(4 α ,5 α ,6 α)-4-Methyl-6-(1-methylethenyl)-3-oxo-1-azabicyclo[3.3.0]octa-2-one (45). To a 10 mL, single-necked, round-

bottomed flask containing a solution of pyrrolidine **44c** (100 mg, 0.12 mmol) in THF (2.0 mL) was added tetrabutylammonium fluoride hydrate (169 mg, 0.53 mmol) in one portion and the reaction mixture was stirred for 3h at rt. The mixture was concentrated and the residue was triturated with Et₂O (2 x 2 mL). The Et₂O extracts were dried thoroughly over Na₂SO₄ and filtered through a pad of Celite (Et₂O for elution) into a 5.0 mL, single-necked, round-bottomed flask. The solvent was evaporated and the resulting colorless residue was dissolved in THF (1.5 mL). The solution was treated with carbonyl-diimidazole (52 mg, 0.32 mmol) in one portion and the reaction mixture was stirred for 12h at rt. The reaction mixture was concentrated *in vacuo* and the residue was directly subjected to column chromatography on silica gel (40% EtOAc/hexane for elution) to provide the title oxazolidinone (21 mg, 53% from **44c**) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.81 (s, 1H, C=CHH), 4.71 (s, 1H, C=CHH), 4.38 (dq, J = 6.5, 3.2 Hz, 1H, OCH), 3.56 (dt, J = 11.2, 8.6 Hz, 1H, NCHH), 3.34 (dd, J = 9.6, 3.1 Hz, 1H, NCH), 3.26 (ddd, J = 13.7, 11.5, 2.5 Hz, 1H, NCHH), 2.30 (dt, J = 10.6, 2.8 Hz, 1H, C=CCH), 2.21 (ddd, J = 10.4, 7.8, 2.7 Hz, 1H, CHH), 1.84 (dq, J = 11.0, 9.1 Hz, 1H, CHH), 1.69 (s, 3H, CH₃C=C), 1.41 (d, J = 6.4 Hz, 3H, CH₃CH); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 160.99, 141.92, 112.26, 75.46, 68.64, 50.86, 45.09, 31.41, 21.32, 20.57; IR (film) 3081, 2975, 1751, 1645, 1383, 1247, 1051, 900, 772, cm⁻¹; HRMS calcd for C₁₀H₁₅NO₂ (M⁺) 181.1103, found 181.1102.

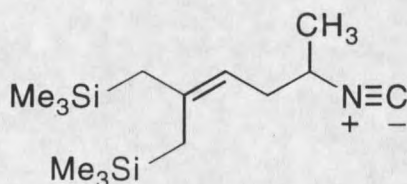
2-Propylidene-1,3-bis(silane) Acylnitrilium Ion Cyclizations

General Information: Silver (I) trifluoromethanesulfonate was purchased from Aldrich Chemical Company, Inc. and was used without additional purification. Acetic formic anhydride was prepared following known literature procedure.⁶⁹ Commercially purchased acid chlorides and ethyl formate were distilled from CaH₂ under argon prior to use. (*E*)-3-carbomethoxy-2-methylpropenoyl chloride and 3-carbomethoxypropionyl chloride were prepared using reported procedures.⁶⁶ Employing published procedures¹⁰⁰, methyl-2-(1,3-dioxanyl)acetate was prepared from methacrolien and 1,3-propanediol.



1-Isocyano-2-methyl-5-trimethylsilyl-4-(trimethylsilylmethyl)pent-3-ene (46b). A 25 mL, single-necked, round-bottomed flask was charged with amine **1b** (2.00 g, 7.76 mmol) and freshly distilled ethyl formate (6.0 mL). The flask was fitted with a condenser and the solution was heated at reflux for 14h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was filtered through a silica gel plug (Et₂O for elution) to furnish the corresponding formamide as a viscous, colorless oil. A 50 mL, three-necked, round-bottomed flask equipped with a thermometer and a 5.0 mL, addition funnel was charged with the formamide, THF (20 mL) and triethylamine (5.15 mL, 38.8 mmol). The solution was cooled to 0 °C and phosphorus oxychloride (800 μL, 8.54 mmol) in THF (2.0 mL) was added dropwise over 15 min via the addition funnel. During the

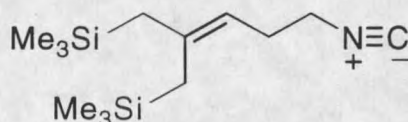
time of addition, the internal reaction temperature was not permitted to exceed 5 °C. The reaction mixture was stirred for 2h at 0 °C and was poured into chilled water (40 mL). The organic layer was separated and the remaining aqueous phase was extracted with Et₂O (3 x 15 mL). The combined organic fractions were washed with brine (40 mL) and dried over anhydrous MgSO₄. The solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography (5% EtOAc/hexane for elution) to yield isonitrile **46b** (1.80 g, 87% from **1b**) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.56 (d, J = 9.7 Hz, 1H, C=CH), 3.16 (m, 2H, C=NCH₂), 2.57 (m, 1H, CH), 1.57 (d, J = 13.5 Hz, 1H, SiCHH), 1.38 (q, J = 13.0 Hz, 3H, SiCHH and SiCH₂), 1.03 (d, J = 6.6 Hz, 3H, CH₃), 0.02 (s, 9H, (CH₃)₃Si), -0.01 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 156.17, 137.58, 120.13, 47.93 (t), 32.89, 29.58, 24.67, 18.49, -0.74, -1.18; IR (film) 2956, 2897, 2145, 1645, 1417, 1249, 1156, 1068, 961, 853, 700, 625 cm⁻¹; HRMS calcd for C₁₄H₂₉NSi₂ (M⁺) 267.1839, found 267.1845.



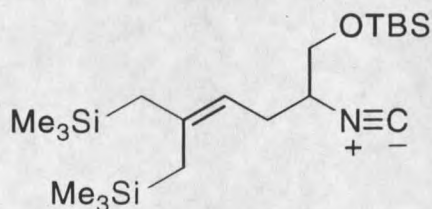
2-Isocyano-6-trimethylsilyl-5-(trimethylsilylmethyl)hex-4-ene

(46c). Sequential formylation/ dehydration of amine **1c** (2.00 g, 7.76 mmol) using the procedure described for the preparation of **46b** provided isonitrile **46c** (1.65 g, 80%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.80 (t, J = 7.3 Hz, 1H, C=CH), 3.53 (app tsx, J = 6.4, 1.4 Hz, 1H, CHN=C), 2.21 (m, 2H, CH₂), 1.47 (d, J = 3.7 Hz, 2H, SiCH₂), 1.42 (s, 2H, SiCH₂), 1.32 (ddd, J = 8.9,

4.4, 2.3 Hz, 3H, CH_3), 0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$), 0.00 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 139.31, 112.79, 50.62, 36.05, 29.85, 24.21, 21.14, -0.69, -1.13; IR (film) 2983, 2955, 2897, 2137, 1646, 1415, 1248, 1153, 1065, 851, 699, 625 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{29}\text{NSi}_2$ (M^+) 267.1839, found 267.1831.

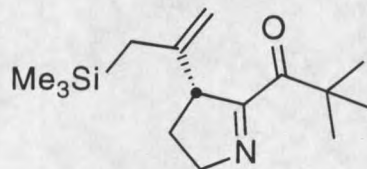


1-Isocyano-5-trimethylsilyl-4-(trimethylsilylmethyl)pent-3-ene (46a). Sequential formylation/ dehydration of amine **1a** (2.00 g, 8.21 mmol) using the procedure described for the preparation of **46b** provided isonitrile **46a** (1.77 g, 85%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.75 (t, J = 7.0 Hz, 1H, $\text{C}=\text{CH}$), 3.28 (app tt, J = 6.9, 1.8 Hz, 2H, $\text{CH}_2\text{C}=\text{N}$), 2.28 (app tq, J = 6.9, 1.8 Hz, 2H, CH_2), 1.47 (s, 2H, SiCH_2), 1.41 (s, 2H, SiCH_2), 0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (CDCl_3 , 75 MHz, ^1H decoupled) δ 155.96, 139.22, 113.13, 41.81, 29.69, 28.81, 24.04, -0.81, -1.28; IR (film) 2985, 2954, 2896, 2146, 1647, 1415, 1247, 1153, 1063, 852, 699, 625 cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{27}\text{NSi}_2$ (M^+) 253.1682, found 253.1675.



1-tert-Butyldimethylsilyloxy-2-isocyano-6-trimethylsilyl-5-(trimethylsilylmethyl)hex-4-ene (46d). A 50 mL, single-necked, round-bottomed flask containing a solution of amine **1d** (1.50 g, 3.87 mmol) in Et_2O

(25 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and freshly prepared formic acetic anhydride (360 mg, 4.06 mmol) was added dropwise over 5 min via a syringe. The reaction mixture was stirred for 45 min at $-78\text{ }^{\circ}\text{C}$ and was then transferred slowly by cannula into vigorously stirred, saturated aqueous KHCO_3 (40 mL). The resulting biphasic mixture was stirred for 30 min and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic fractions were washed once with brine (35 mL), dried over MgSO_4 and filtered through a silica gel pad (Et_2O for elution) to afford the corresponding formamide as a colorless viscous oil. Dehydration of the formamide with POCl_3 in the manner previously described for the preparation of **46b** gave the title isonitrile (1.26 g, 85% from **1d**) as a colorless oil after purification of the crude product by filtration through a silica gel plug (5% EtOAc /hexane for elution): ^1H NMR (300 MHz, CDCl_3) δ 4.81 (t, $J = 7.3$ Hz, 1H, $\text{C}=\text{CH}$), 3.65 (d, $J = 4.6$ Hz, 2H, OCH_2), 3.47 (p, $J = 6.1$ Hz, 1H, CH), 2.27 (m, 2H, CH_2), 1.49 (s, 2H, SiCH_2), 1.42 (s, 2H, SiCH_2), 0.89 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.07 (s, 6H, $\text{OSi}(\text{CH}_3)_2$), 0.01 (s, 18H, $\text{Si}(\text{CH}_3)_3 \times 2$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 156.00, 139.55, 112.41, 64.31, 57.11, 30.58, 29.86, 25.79, 24.18, 18.21, -0.71, -1.12, -5.40; IR (film) 2955, 2897, 2858, 2139, 1646, 1472, 1464, 1412, 1362, 1249, 1129, 836, 778, 700, 626 cm^{-1} ; HRMS calcd for $\text{C}_{20}\text{H}_{43}\text{NOSi}_3$ (M^+) 397.2652, found 397.2641.

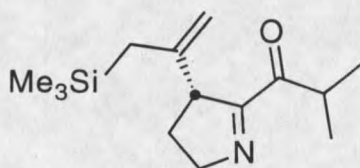


5-Trimethylacetyl-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (48a). The following procedure, employed for the

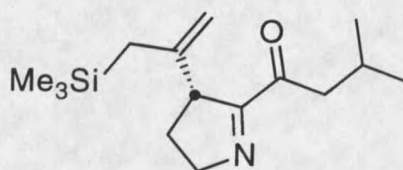
preparation of pyrroline **48a**, constitutes the general procedure used for the silver ion mediated cyclization of ketoimidoyl chlorides. To a 5.0 mL, tear-dropped flask containing a solution of isonitrile **46a** (200 mg, 0.79 mmol) in CH_2Cl_2 (500 μL) was added trimethylacetyl chloride (117 μL , 0.95 mmol) and the mixture was stirred for 12h at room temperature. The volatile components were removed under reduced pressure during which time exposure of the reaction mixture to air was kept at a minimum. The residue was dissolved in a 1:1 mixture of CH_2Cl_2 and $\text{ClCH}_2\text{CH}_2\text{Cl}$ (800 μL) and the resulting solution of the crude keto imidoyl chloride was used *immediately* in the next step.

A 10 mL, single-necked, round-bottomed flask was charged with AgOTf (304 mg, 1.18 mmol) and 1:1 $\text{CH}_2\text{Cl}_2/\text{ClCH}_2\text{CH}_2\text{Cl}$ (4.0 mL). The suspension was cooled to $-78\text{ }^\circ\text{C}$ and the freshly prepared solution of the crude ketoimidoyl chloride was added dropwise via a gas-tight syringe. The mixture was stirred at a temperature range of $-78\text{ }^\circ\text{C}$ to $-65\text{ }^\circ\text{C}$ for 2h during which time a white solid precipitated. Stirring was continued at $-20\text{ }^\circ\text{C}$ for an additional 6h after which time the cold reaction mixture was transferred dropwise via cannula into vigorously stirred, aqueous saturated KHCO_3 (8 mL) at 0°C . The biphasic mixture was stirred for 15 min at room temperature, decanted into a separatory funnel, and the organic layer was separated. The remaining aqueous phase was extracted with Et_2O (2 x 4 mL) and the combined organic fractions were dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was subjected to chromatography on silica gel (5% EtOAc /hexane for elution) to furnish pyrroline **48a** (171 mg, 82% from **46a**) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.51 (s, 1H, $\text{C}=\text{CHH}$), 4.31 (s, 1H, $\text{C}=\text{CHH}$), 4.06 (m, 2H, $\text{CH}_2\text{N}=\text{C}$), 3.60 (ddd, $J = 10.0, 4.3, 2.2\text{ Hz}$, 1H, $\text{C}=\text{CCH}$), 2.12 (m, 1H, CHH), 1.71 (dddd, J

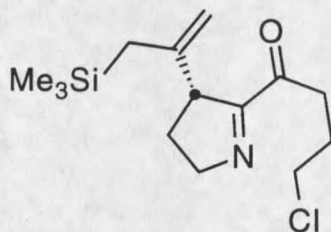
= 17.0, 12.2, 6.9, 4.7 Hz, 1H, CHH), 1.65 (d, $J = 14.0$ Hz, 1H, SiCHH), 1.50 (d, $J = 13.8$ Hz, 1H, SiCHH), 1.29 (s, 9H, $(CH_3)_3C$), 0.05 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR (75 MHz, $CDCl_3$, 1H decoupled) δ 205.02, 173.89, 147.82, 107.27, 61.40, 55.29, 44.03, 30.54, 28.19, 27.02, -1.31; IR (film) 3077, 2955, 2870, 1684, 1630, 1482, 1459, 1249, 1162, 1055, 982, 848, 694 cm^{-1} ; HRMS calcd for $C_{15}H_{27}NOSi$ (M^+) 265.1862, found 265.1856.



5-(2-Methylpropanoyl)-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (48b). Using isonitrile **46a** (100 mg, 0.39 mmol) and isobutyryl chloride (62 μL , 0.59 mmol) in the general procedure described for the preparation of **48a** provided the title pyrroline (67 mg, 68%) as a light yellow oil after silica gel chromatography (5% EtOAc/hexane for elution): 1H NMR (300 MHz, $CDCl_3$) δ 4.50 (s, 1H, $C=CHH$), 4.24 (s, 1H, $C=CHH$), 4.06 (m, 2H, $CH_2N=C$), 3.60 (m, 1H, $CH(CH_3)_2$), 3.57 (dd, $J = 8.9, 1.9$ Hz, 1H, $C=CCH$), 2.18 (dq, $J = 8.8, 3.6$ Hz, 1H, CHH), 1.81 (ddd, $J = 16.4, 7.6, 3.7$ Hz, 1H, CHH), 1.69 (d, $J = 13.4$ Hz, 1H, SiCHH), 1.52 (d, $J = 13.7$ Hz, 1H, SiCHH), 1.10 (dd, $J = 7.0, 3.4$ Hz, 6H, $(CH_3)_2C$), 0.06 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR (75 MHz, $CDCl_3$, 1H decoupled) δ 202.96, 174.67, 147.52, 106.92, 60.90, 53.37, 35.77, 31.31, 28.15, 18.65, 17.87, -1.36; IR (film) 3076, 2955, 2875, 1698, 1630, 1468, 1383, 1299, 1159, 1052, 983, 694 cm^{-1} ; HRMS calcd for $C_{14}H_{25}NOSi$ (M^+) 251.1705, found 251.1705.

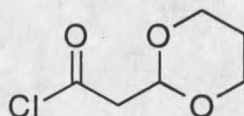


5-(3-Methylbutanoyl)-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (48c). The general procedure employed for the preparation of **48a** was followed using isonitrile **46a** (100 mg, 0.39 mmol) and isovaleryl chloride (72 μ L, 0.59 mmol) to provide the title pyrroline (81 mg, 77%) as a light yellow oil after purification of the product by chromatography on silica gel (5% EtOAc/hexane for elution): ^1H NMR (300 MHz, CDCl_3) δ 4.49 (s, 1H, $\text{C}=\text{CHH}$), 4.20 (s, 1H, $\text{C}=\text{CHH}$), 4.03 (m, 2H, $\text{CH}_2\text{N}=\text{C}$), 3.57 (dt, $J = 10.0$, 2.6 Hz, 1H, $\text{C}=\text{CCH}$), 2.76 (app t, $J = 7.6$ Hz, 2H, $\text{O}=\text{CCH}_2$), 2.17 (m, 2H, $\text{CH}(\text{CH}_3)_2$ and CHH), 1.81 (ddd, $J = 12.6$, 7.5, 3.7 Hz, 1H, CHH), 1.69 (d, $J = 13.4$ Hz, 1H, SiCHH), 1.51 (d, $J = 13.5$ Hz, 1H, SiCHH), 0.90 (app t, $J = 6.2$ Hz, 6H, $(\text{CH}_3)_2\text{CH}$), 0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 199.15, 175.70, 147.48, 106.96, 60.83, 53.32, 47.65, 31.31, 28.09, 24.43, 22.69, 22.43, -1.34; IR (film) 3075, 2956, 1696, 1630, 1466, 1369, 1249, 1023, 989, 845, 693 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{27}\text{NOSi}$ (M^+) 265.1862, found 265.1852.



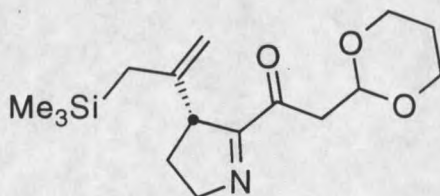
5-(4-Chlorobutanoyl)-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (48d). Utilization of isonitrile **46a** (100 mg, 0.39 mmol) and 4-chlorobutyl chloride (66 μ L, 0.59 mmol) in the general procedure

outlined for the preparation of **48a** furnished the title pyrroline (69 mg, 61%) as a light yellow oil after purification by silica gel chromatography (5% EtOAc/hexane for elution): ^1H NMR (300 MHz, CDCl_3) δ 4.49 (s, 1H, $\text{C}=\text{CHH}$), 4.18 (s, 1H, $\text{C}=\text{CHH}$), 4.03 (m, 2H, $\text{CH}_2\text{N}=\text{C}$), 3.54 (t, $J = 6.4$ Hz, 3H, CH_2Cl and $\text{C}=\text{CCH}$ (overlap)), 3.20 (dt, $J = 18.4, 7.2$ Hz, 1H, $\text{O}=\text{CCHH}$), 2.95 (dt, $J = 18.2, 7.2$ Hz, 1H, $\text{O}=\text{CCHH}$), 2.17 (dq, $J = 12.5, 9.9$ Hz, 1H, CHH), 2.07 (dp, $J = 7.0, 2.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{Cl}$), 1.81 (ddd, $J = 16.6, 7.6, 3.8$ Hz, 1H, CHH), 1.68 (d, $J = 13.7$ Hz, 1H, SiCHH), 1.51 (d, $J = 13.6$ Hz, 1H, SiCHH), 0.05 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 198.10, 175.13, 147.35, 106.99, 60.85, 53.38, 44.19, 35.92, 31.25, 27.99, 26.42, -1.35; IR (film) 3075, 2954, 1739, 1699, 1629, 1405, 1248, 1158, 1051, 983, 845, 695 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{24}\text{ClNOSi}$ (M^+) 285.1316, found 285.1306.



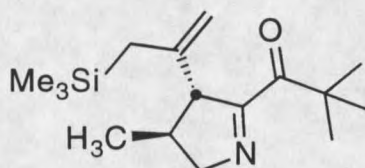
2-(1,3-Dioxanyl)acetyl chloride. A 250 mL, single-necked, round-bottomed flask was charged with potassium trimethylsilanolate (2.01 g, 15.7 mmol) and THF (65 mL). To the white suspension was added methyl-2-(1,3-dioxanyl) acetate (2.51 g, 15.7 mmol) in THF (7.5 mL) dropwise over 20 min via a 25 mL, addition funnel. The resulting cloudy suspension was stirred for 5.5h and then diluted with anhydrous Et_2O (60 mL) producing a white precipitate. The solid was collected on a fritted funnel, washed thoroughly with anhydrous Et_2O and dried *in vacuo* to provide the corresponding potassium salt as a white powder. A 100 mL, single-necked, round-bottomed flask was charged with the freshly prepared salt, benzene (30 mL) and two drops of DMF. To the white

suspension was added oxalylchloride (1.64 mL, 18.8 mmol) in benzene (5 mL) dropwise over 15 min via a 5.0 mL, addition funnel during which the evolution of gas was observed. The reaction mixture was stirred for 2h and was filtered through a Celite pad (anhydrous Et₂O for elution). The resulting solution was concentrated and the residue was bulb to bulb distilled to furnish the title acid chloride (1.97 g, 76%) as a colorless liquid: bp 50-55 °C, 250 μ torr; ¹H NMR (300 MHz, CDCl₃) δ 4.98 (t, J = 5.2 Hz, 1H, CH), 4.08 (dd, J = 10.9, 5.0 Hz, 2H, OCHH x 2) 3.77 (dt, J = 12.4, 2.3 Hz, 2H, OCHH x 2), 3.12 (d, J = 5.1 Hz, 2H, O=CCH₂), 2.05 (m, 1H, CHH), 1.34 (dd, J = 13.3, 1.1 Hz, 1H, CHH); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 169.22, 97.37, 66.93, 52.18, 25.23.



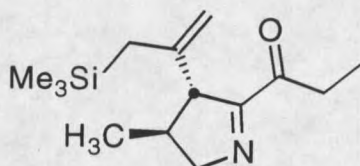
5-[2-(1,3-dioxanyl)acetyl]-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (48e). To a 5 mL tear-dropped flask containing a solution of 2-(1,3-dioxolanyl)acetyl chloride (61 mg, 0.37 mmol) in CH₂Cl₂ (200 μ L) was added isonitrile **46a** (94 mg, 0.37 mmol) via syringe. The flask was sealed and the reaction mixture was stirred at 40 °C for 14h. Upon cooling the mixture to room temperature, 1:1 CH₂Cl₂/ClCH₂CH₂Cl (0.5 mL) was added and the resulting solution of the crude ketoimidoyl chloride was treated with AgOTf (143 mg, 0.56 mmol) as described in the general procedure used for the preparation of **48a**. Isolation and purification of the crude product was achieved by the methods described for **48a** to furnish **48e** (105 mg, 91%) as a colorless viscous oil: ¹H NMR (300 MHz, CDCl₃) δ 5.05 (dd, J = 5.6, 5.2 Hz, 1H,

OCHO), 4.47 (s, 1H, C=CHH), 4.20 (s, 1H, C=CHH), 4.03 (m, 4H, C=NCH₂ and OCHH x 2), 3.74 (ddd, J = 12.8, 2.3, 1.1 Hz, 2H, OCHH x 2), 3.53 (dt, J = 10.1, 2.9 Hz, 1H, C=CCH), 3.27 (dd, J = 15.7, 5.8 Hz, 1H, O=CCHH), 3.10 (dd, J = 15.8, 4.7 Hz, 1H, O=CCHH), 2.11 (m, 2H, C=NCH₂CHH and OCH₂CHH), 1.80 (dddd, J = 12.7, 11.2, 7.4, 3.6 Hz, 1H, NCH₂CHH), 1.66 (d, J = 13.5 Hz, 1H, SiCHH), 1.47 (d, J = 13.6 Hz, 1H, SiCHH), 1.27 (app dt, J = 13.5, 1.1 Hz, 1H, OCH₂CHH), 0.04 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 195.02, 175.22, 146.87, 107.17, 98.99, 66.86, 60.81, 53.19, 44.63, 31.31, 27.79, 25.50, -1.34; IR (film) 3075, 2954, 2855, 1739, 1702, 1631, 1248, 1136, 1017, 847 cm⁻¹; HRMS calcd for C₁₆H₂₇NO₃Si (M⁺) 309.1760, found 309.1754.

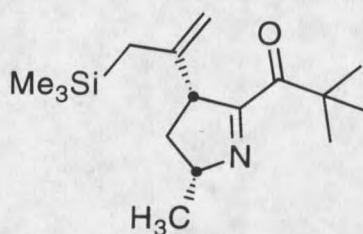


***Trans*-3-methyl-5-trimethylacetyl-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (49a).** The procedure previously described for the preparation of **48a** was followed employing isonitrile **46b** (144 mg, 0.54 mmol) and trimethylacetyl chloride (83 μL, 0.67 mmol). This provided **49a** (61 mg, 41%) as a colorless oil after purification by silica gel chromatography (1% EtOAc/hexane for elution): ¹H NMR (300 MHz, CDCl₃) δ 4.47 (s, 1H, C=CHH), 4.29 (s, 1H, C=CHH), 4.15 (ddd, J = 17.1, 7.1, 2.2 Hz, 1H, CHHN=C), 3.67 (dd, J = 17.1, 3.0 Hz, 1H, CHHN=C), 3.20 (t, J = 2.7 Hz, 1H, C=CCH), 2.11 (m, 1H, CHCH₃), 1.59 (d, J = 13.7 Hz, 1H, SiCHH), 1.43 (d, J = 13.7 Hz, 1H, SiCHH), 1.29 (s, 9H, (CH₃)₃C), 0.99 (d, J = 7.0 Hz, 3H, CH₃), 0.05 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 205.06, 173.41,

146.26, 107.24, 68.76, 63.92, 44.10, 38.32, 27.34, 27.08, 20.92, -1.19; IR (film) 3075, 2956, 2871, 1683, 1631, 1482, 1419, 1249, 1161, 1093, 955, 846, 696 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{29}\text{NOSi}$ (M^+) 279.2018, found 279.2011.



***Trans*-3-methyl-4-[1-(trimethylsilylmethyl)ethenyl]-5-propanoyl-3,4-dihydro-2H-pyrrole (49b).** The previously described procedure was followed employing isonitrile **46b** (241 mg, 0.87 mmol) and propionyl chloride (84 μL , 0.96 mmol) to provide **49b** (86 mg, 40%) as a colorless oil after purification by silica gel chromatography (1% - 5% EtOAc/hexane for elution): ^1H NMR (300 MHz, CDCl_3) δ 4.44 (s, 1H, $\text{C}=\text{CHH}$), 4.16 (s, 1H, $\text{C}=\text{CHH}$), 4.12 (ddd, $J = 17.4, 6.9, 2.4$ Hz, 1H, $\text{CHHN}=\text{C}$), 3.67 (dd, $J = 17.5, 2.4$ Hz, 1H, $\text{CHHN}=\text{C}$), 3.17 (t, $J = 2.1$ Hz, 1H, $\text{C}=\text{CCH}$), 3.05 (dq, $J = 18.1, 7.5$ Hz, 1H, CHHCH_3), 2.78 (dq, $J = 18.8, 7.4$ Hz, 1H, CHHCH_3), 2.19 (m, 1H, CH_3CH), 1.64 (d, $J = 13.5$ Hz, 1H, SiCHH), 1.45 (d, $J = 13.7$ Hz, 1H, SiCHH), 1.08 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.00 (d, $J = 7.5$ Hz, 3H, CH_3), 0.07 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 200.07, 174.60, 146.03, 106.77, 68.22, 62.07, 39.12, 32.00, 27.27, 21.30, 7.58, -1.24; IR (film) 3076, 2956, 1700, 1631, 1460, 1377, 1249, 1159, 1096, 950, 848, 698 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{25}\text{NOSi}$ (M^+) 251.1705, found 251.1705.



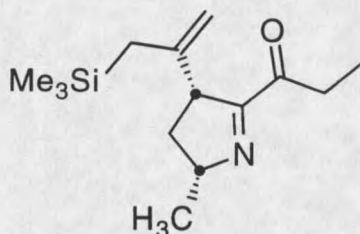
***Cis*- and *trans*-2-methyl-5-trimethylacetyl-4-[1-(trimethylsilylmethyl)-ethenyl]-3,4-dihydro-2*H*-pyrrole (**50a_{trans}** and **50a_{cis}**).**

Utilizing isonitrile **46c** (200 mg, 0.75 mmol) and trimethylacetyl chloride (110 μ L, 0.90 mmol) in the procedure outlined for the preparation of **48a**, a mixture of pyrrolines **50_{cis}** and **50_{trans}** (189 mg, 90%, 4.4 : 1.0 by NMR) was obtained as a light yellow oil after filtration of the crude product mixture through a plug of silica gel (5% EtOAc/hexane for elution). The mixture of diastereomeric pyrrolines was subjected to column chromatography on silica gel (1% - 5% EtOAc/hexane for elution) to afford the major pyrroline **50a_{cis}** (131 mg, 63% from **46c**) as a colorless oil.

50_{cis}: ^1H NMR (300 MHz, CDCl_3) δ 4.56 (s, 1H, $\text{C}=\text{CHH}$), 4.39 (s, 1H, $\text{C}=\text{CHH}$), 4.19 (sx, $J = 6.7$ Hz, 1H, $\text{CH}_3\text{CHN}=\text{C}$), 3.58 (dt, $J = 9.6, 1.5$ Hz, 1H, $\text{C}=\text{CCH}$), 2.41 (ddd, $J = 18.0, 9.9, 8.1$ Hz, 1H, CHH), 1.65 (d, $J = 13.5$ Hz, 1H, SiCHH), 1.52 (d, $J = 13.4$ Hz, 1H, SiCHH), 1.35 (d, $J = 6.9$ Hz, 3H, CH_3), 1.29 (m, 1H, CHH), 1.27 (s, 9H, $(\text{CH}_3)_3\text{C}$), 0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 206.31, 172.10, 149.32, 108.23, 68.77, 56.67, 43.99, 38.34, 28.47, 27.06, 22.16, -1.28; IR (film) 3077, 2957, 2871, 1685, 1630, 1482, 1457, 1364, 1249, 1161, 1050, 841, 695, cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{29}\text{NOSi}$ (M^+) 279.2018, found 279.2012.

50_{trans}: ^1H NMR (300 MHz, CDCl_3) δ 4.47 (s, 1H, $\text{C}=\text{CHH}$), 4.32 (m, 1H, $\text{CH}_3\text{CHN}=\text{C}$), 4.31 (s, 1H, $\text{C}=\text{CHH}$), 3.66 (dt, $J = 9.9, 2.9$ Hz, 1H, $\text{C}=\text{CCH}$), 1.91 (ddd, $J = 12.9, 7.2, 3.5$ Hz, 1H, CHH), 1.64 (d, $J = 13.0$ Hz, 1H, SiCHH),

1.63 (ddd, $J = 17.7, 9.9, 7.3$ Hz, 1H, CHH), 1.48 (d, $J = 13.0$ Hz, 1H, SiCHH), 1.29 (s, 9H, $(\text{CH}_3)_3\text{C}$), 0.04 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 205.25, 171.74, 147.43, 106.95, 68.78, 55.90, 44.19, 38.67, 29.87, 27.66, 21.63, -1.27; IR (film) 3077, 2954, 2858, 1687, 1630, 1472, 1463, 1361, 1250, 1161, 1125, 1004, 840, 777, 696 cm^{-1} .

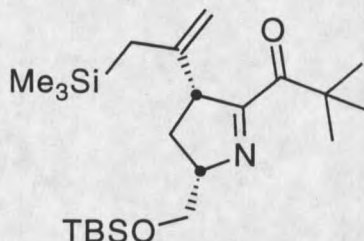


***Cis*- and *trans*-3-methyl-4-[1-(trimethylsilylmethyl)ethenyl]-5-propanoyl-3,4-dihydro-2H-pyrrole (50b_{cis} and 50b_{trans})**. The general procedure employed for the preparation of **48a** was followed using isonitrile **46c** (215 mg, 0.78 mmol) and propionyl chloride (80 μL , 0.92 mmol) to furnish a mixture of pyrrolines **50b_{cis}** and **50b_{trans}** (152 mg, 78%, 3.9 : 1.0 by NMR) which was isolated as a light yellow-green oil after elution of the crude material through a silica gel plug (5% EtOAc/hexane for elution). The mixture of isomeric pyrrolines was subjected to chromatography on silica gel (1% - 5% EtOAc/hexane for elution) to provide the major diastereomer **50b_{cis}** (95 mg, 49% from **46c**) as a colorless oil.

50b_{cis}: ^1H NMR (300 MHz, CDCl_3) δ 4.52 (s, 1H, C=CHH), 4.26 (s, 1H, C=CHH), 4.21 (sx, $J = 7.0$ Hz, 1H, $\text{CH}_3\text{CHN}=\text{C}$), 3.53 (dd, $J = 9.5, 6.9$ Hz, 1H, C=CCH), 3.05 (dq, 18.1, 7.3 Hz, 1H, CHHCH₃), 2.72 (dq, $J = 18.1, 7.4$ Hz, 1H, CHHCH₃), 2.48 (ddd, $J = 18.6, 10.4, 8.6$ Hz, 1H, CHH), 1.68 (d, $J = 13.5$ Hz, 1H, SiCHH), 1.51 (d, $J = 13.5$ Hz, 1H, SiCHH), 1.35 (q, $J = 6.3$ Hz, 1H, CHH), 1.33 (d, $J = 6.9$ Hz, 3H, CH₃), 1.06 (t, $J = 7.4$ Hz, 3H, CH₂CH₃), 0.04 (s, 9H,

(CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 200.73, 173.34, 149.69, 107.78, 68.41, 54.76, 38.80, 32.48, 28.27, 22.10, 7.50, -1.30; IR (film) 3074, 2967, 2896, 1701, 1631, 1451, 1410, 1374, 1321, 1249, 1159, 1111, 919, 854, 696 cm⁻¹; HRMS calcd for C₁₄H₂₅NOSi (M⁺) 251.1705 found 251.1701.

50b_{trans}: ¹H NMR (300 MHz, CDCl₃) δ 4.46 (s, 1H, C=CHH), 4.26 (dsx, J = 6.7, 1.8 Hz, 1H, CH₃CHN=C), 4.21 (s, 1H, C=CHH), 3.64 (dt, J = 9.9, 2.3 Hz, 1H, C=CCH), 3.06 (dq, J = 18.2, 7.2 Hz, 1H, CHHCH₃), 2.77 (dq, J = 18.1, 7.4 Hz, 1H, CHHCH₃), 2.00 (ddd, J = 12.6, 6.9, 2.6 Hz, 1H, CHH), 1.67 (dd, J = 18.3, 12.8 Hz, 1H, CHH), 1.67 (d, J = 13.1 Hz, 1H, SiCHH), 1.49 (d, J = 13.8 Hz, 1H, SiCHH), 1.35 (d, J = 6.9 Hz, 3H, CH₃), 1.08 (t, J = 7.3 Hz, 3H, CH₂CH₃), 0.06 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 200.30, 173.47, 146.96, 106.65, 68.14, 54.18, 39.37, 32.13, 27.90, 21.46, 7.53, -1.33; IR (film) 3075, 2960, 2890, 1701, 1654, 1631, 1449, 1376, 1308, 1249, 1158, 1099, 854, 695 cm⁻¹.

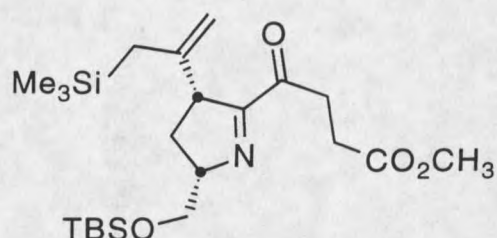


Cis-and-trans-2-(*t*-butyldimethylsilyloxy)methyl-5-trimethylacetyl-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2H-pyrrole (50c_{cis} and 50c_{trans}). Isonitrile **46d** (205 mg, 0.51 mmol) and trimethylacetyl chloride (76 μL, 0.62 mmol) were used in the general procedure outlined for the preparation **48a** to yield a mixture of diastereomeric pyrrolines **50c_{cis}** and **50c_{trans}** (184 mg, 87%, 2.8 : 1.0 by NMR) as a light gold oil after

purification of the crude material via filtration through a silica gel plug (5% EtOAc/hexane for elution). Separation of the mixture by column chromatography on silica gel (1% - 5% EtOAc/hexane for elution) furnished the major diastereomer **50c_{cis}** (118 mg, 56% from **46d**) as a light yellow oil.

50c_{cis}: ^1H NMR (300 MHz, CDCl_3) δ 4.57 (s, 1H, C=CHH), 4.49 (s, 1H, C=CHH), 4.17 (m, 1H, CHN=C), 3.86 (d, J = 4.8 Hz, 2H, CH_2O), 3.59 (dt, J = 10.7, 2.1 Hz, 1H, C=CCH), 2.26 (ddd, J = 18.1, 9.2, 8.2, 1H, CHH), 1.65 (dd, J = 16.2, 12.8 Hz, 1H, CHH), 1.59 (ABq, $\Delta\nu$ = 33.4 Hz, J = 13.6 Hz, 2H, SiCH_2), 1.27 (s, 9H, $(\text{CH}_3)_3\text{C}$), 0.87 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.05 (s, 3H, $\text{CH}_3\text{SiC}(\text{CH}_3)_3$), 0.04 (s, 3H, $\text{CH}_3\text{SiC}(\text{CH}_3)_3$), 0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 206.53, 173.95, 148.88, 108.83, 74.86, 65.52, 56.35, 43.88, 32.75, 28.43, 27.04, 25.94, 18.38, -1.26, -5.34; IR (film) 3077, 2954, 2859, 1687, 1630, 1482, 1472, 1463, 1391, 1361, 1250, 1160, 1123, 1037, 1001, 940, 837, 776 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{43}\text{NO}_2\text{Si}_2$ (M^+) 409.2832, found 409.2826.

50c_{trans}: ^1H NMR (300 MHz, CDCl_3) δ 4.49 (s, 1H, C=CHH), 4.38 (m, 1H, CHN=C), 4.34 (s, 1H, C=CHH), 3.80 (dd, J = 4.2, 2.4 Hz, 2H, OCH_2), 3.66 (ddd, J = 9.8, 4.2, 2.3 Hz, 1H, C=CCH), 2.04 (ddd, J = 16.4, 10.0, 6.4 Hz, 1H, CHH), 1.75 (ddd, J = 12.5, 7.8, 4.6 Hz, 1H, CHH), 1.65 (d, J = 13.5 Hz, 1H, SiCHH), 1.50 (d, J = 13.3 Hz, 1H, SiCHH), 1.29 (s, 9H, $(\text{CH}_3)_3\text{C}$), 0.84 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.06 (s, 3H, $\text{CH}_3\text{SiC}(\text{CH}_3)_3$), 0.04 (s, 9H, $(\text{CH}_3)_3\text{Si}$), 0.02 (s, 3H, $\text{CH}_3\text{SiC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 205.27, 173.63, 148.25, 107.17, 75.15, 65.51, 56.11, 44.07, 33.24, 28.18, 27.08, 25.85, 18.26, -1.25, -5.39; IR (film) 3076, 2954, 2858, 1686, 1630, 1482, 1472, 1463, 1391, 1361, 1250, 1161, 1125, 1004, 840, 777, 696, 627 cm^{-1} .

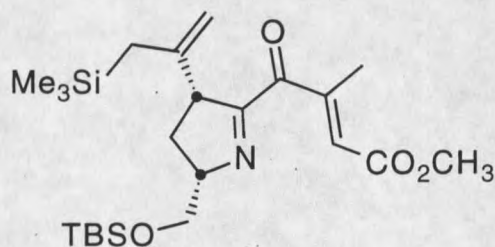


***Cis*-and-*trans*-2-(*t*-butyldimethylsilyloxy)methyl-5-(3-carbomethoxypropanoyl)-4-[1-(trimethylsilylmethyl)ethenyl]-3,4-dihydro-2*H*-pyrrole (50d_{*cis*} and 50d_{*trans*}).** Using the procedure outlined for the preparation of **48a**, isonitrile **46d** (188 mg, 0.47 mmol) and 3-carbomethoxypropionyl chloride (85 mg, 0.57 mmol) were converted into a mixture of diastereomeric pyrrolines **50d_{*cis*}** and **50d_{*trans*}** (160 mg, 77%, 4.3 : 1.0 by NMR). In this instance, exposure of the crude ketoimidoyl chloride to AgOTf was performed at -78 °C for 2 h followed by an abbreviated reaction time of 2 h at -25 °C. Isolation of the major pyrroline **50d_{*cis*}** (99 mg, 48% from **46d**) was achieved by separation of the mixture by silica gel chromatography (5% EtOAc/hexane for elution).

50d_{*cis*}: ¹H NMR (300 MHz, CDCl₃) δ 4.55 (s, 1H, C=CHH), 4.33 (s, 1H, C=CHH), 4.24 (m, 1H, C=NCH), 3.88 (dd, *J* = 10.1, 4.6 Hz, 1H, SiOCHH), 3.77 (dd, *J* = 10.2, 6.1 Hz, 1H, SiOCHH), 3.64 (s, 3H, CH₃O), 3.54 (ddd, *J* = 9.5, 7.3, 1.5 Hz, 1H, C=CCH), 3.44 (dt, *J* = 18.8, 6.8 Hz, 1H, O=CCHH), 2.97 (dt, *J* = 18.9, 6.6 Hz, 1H, O=CCHH), 2.61 (t, *J* = 6.7 Hz, 2H, O=CCH₂CH₂), 2.35 (ddd, *J* = 18.7, 10.0, 8.7 Hz, 1H, CHH), 1.70 (dd, *J* = 19.9, 6.8 Hz, 1H, CHH), 1.68 (d, *J* = 13.9 Hz, 1H, SiCHH), 1.52 (d, *J* = 13.6 Hz, 1H, SiCHH), 0.88 (s, 9H, (CH₃)₃CSi), 0.06 (s, 3H, (CH₃)₃CSiCH₃), 0.05 (s, 3H, (CH₃)₃CSiCH₃), 0.04 (s, 9, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 197.81, 174.56, 172.88, 149.14, 108.40, 74.70, 65.66, 54.45, 51.63, 34.26, 33.63, 28.16, 27.60,

25.95, 18.43, -1.28, -5.24; IR (film) 2954, 2929, 2857, 1744, 1705, 1632, 1472, 1437, 1361, 1250, 1212, 1162, 1123, 1006, 841, 777 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{41}\text{NO}_4\text{Si}_2$ (M^+) 439.2574, found 439.2563.

50d_{trans}: ^1H NMR (300 MHz, CDCl_3) δ 5.20 (d, J = 1.0 Hz, 1H, $\text{C}=\text{CHH}$), 4.08 (m, 1H, $\text{C}=\text{NCH}$), 3.93 (m, 4H, SiOCH_2 , $\text{C}=\text{CCH}$ and $\text{C}=\text{CHH}$), 3.63 (s, 3H, OCH_3), 3.34 (dt, J = 19.0, 6.8 Hz, 1H, $\text{O}=\text{CCHH}$), 3.01 (dt, J = 18.9, 6.8 Hz, 1H, $\text{O}=\text{CCHH}$), 2.60 (dt, J = 7.0, 1.8 Hz, 2H, $\text{O}=\text{CH}_2\text{CH}_2$), 2.08 (ddd, J = 16.5, 9.5, 8.6 Hz, 1H, CHH), 1.70 (ddd, J = 19.4, 9.8, 9.8 Hz, 1H, CHH), 1.39 (dd, J = 15.1, 1.3 Hz, 1H, SiCHH), 1.10 (d, J = 15.2 Hz, 1H, SiCHH), 0.89 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.11 (s, 6H, $(\text{CH}_3)_3\text{CSi}(\text{CH}_3)_2$), -0.01 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 197.31, 174.37, 172.87, 152.84, 126.25, 73.76, 65.45, 57.21, 51.61, 33.97, 31.50, 27.53, 25.96, 23.99, 18.46, -0.53, -5.20; IR (film) 2954, 2898, 2858, 1744, 1705, 1599, 1472, 1438, 1373, 1360, 1249, 1168, 1125, 1047, 1015, 837, 779, 734, 690 cm^{-1} .



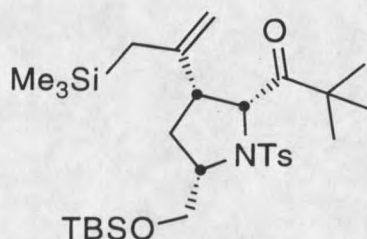
Cis-and-trans-2-(*t*-butyldimethylsilyloxy)methyl-5-(*E*-3-carbomethoxy-2-methylpropenoyl)-4-[1-(trimethylsilylmethyl)-ethenyl]-3,4-dihydro-2*H*-pyrrole (50e_{cis} and 50e_{trans}). Employing isonitrile **46d** (259 mg, 0.65 mmol) and (*E*)-3-carbomethoxy-2-methylpropenoyl chloride (127 mg, 0.78 mmol) in the general procedure used for **48a** provided a mixture of diastereomeric pyrrolines **50e_{cis}** and **50e_{trans}** (225 mg, 76%, 3.0 :

1.0 by NMR) after elution of the crude material through a silica gel plug (5% EtOAc/hexane for elution). Separation of the diastereomers was achieved by subjecting the mixture to column chromatography on silica gel (1% - 5% EtOAc/hexane for elution) to afford **50e_{cis}** (138 mg, 47% from **46d**) as a light yellow oil.

50e_{cis}: ^1H NMR (300 MHz, CDCl_3) δ 6.92 (d, $J = 1.3$ Hz, 1H, $\text{C}=\text{CH}$), 4.57 (s, 1H, $\text{C}=\text{CHH}$), 4.52 (s, 1H, $\text{C}=\text{CHH}$), 4.18 (m, 1H, $\text{C}=\text{NCH}$), 4.06 (dd, $J = 10.2, 4.1$ Hz, 1H, SiOCHH), 3.81 (dd, $J = 10.2, 3.5$ Hz, 1H, SiOCHH), 3.73 (dt, $J = 9.3, 2.5$ Hz, 1H, $\text{C}=\text{CCH}$), 3.72 (s, 3H, OCH_3), 2.34 (ddd, $J = 17.9, 9.7, 8.3$ Hz, 1H, CHH), 2.25 (d, $J = 1.5$ Hz, 3H, $\text{C}=\text{CCH}_3$), 1.81 (ddd, $J = 17.0, 8.6, 8.6$ Hz, 1H, CHH), 1.56 (ABq, $\Delta\nu = 28.6$ Hz, $J = 13.6$ Hz, 2H, SiCH_2), 0.88 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.06 (s, 6H, $(\text{CH}_3)_3\text{CSi}(\text{CH}_3)_2$), 0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 193.60, 174.02, 166.41, 148.81, 148.10, 130.23, 109.26, 74.81, 64.88, 56.39, 51.43, 32.62, 28.16, 25.93, 18.37, 13.23, -1.32, -5.48; IR (film) 3076, 2953, 2897, 2858, 1729, 1667, 1635, 1472, 1436, 1361, 1251, 1206, 1119, 1041, 840, 777 cm^{-1} ; HRMS calcd for $\text{C}_{23}\text{H}_{41}\text{NO}_4\text{Si}_2$ (M^+) 451.2574, found 451.2571.

50e_{trans}: ^1H NMR (300 MHz, CDCl_3) δ 6.88 (d, $J = 1.3$ Hz, 1H, $\text{C}=\text{CH}$), 4.53 (s, 1H, $\text{C}=\text{CHH}$), 4.44 (m, 1H, $\text{C}=\text{NCH}$), 4.38 (s, 1H, $\text{C}=\text{CHH}$), 3.80 (m, 3H, SiOCH_2 and $\text{C}=\text{CCH}$), 3.74 (s, 3H, OCH_3), 2.26 (d, $J = 1.2$ Hz, 3H, $\text{C}=\text{CCH}_3$), 2.23 (ddd, 15.3, 9.9, 5.4 Hz, 1H, CHH), 1.84 (ddd, $J = 13.4, 8.1, 5.8$ Hz, 1H, CHH), 1.55 (ABq, $\Delta\nu = 37.1$ Hz, $J = 13.5$ Hz, 2H, SiCH_2), 0.83 (s, 9H, $(\text{CH}_3)_3\text{CSi}$), 0.03 (s, 9H, $(\text{CH}_3)_3\text{Si}$), 0.00 (s, 3H, $(\text{CH}_3)_3\text{CSiCH}_3$), -0.02 (s, 3H, $(\text{CH}_3)_3\text{CSiCH}_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 193.07, 174.15, 166.42, 149.27, 147.81, 129.21, 107.69, 75.01, 65.21, 56.22, 51.55, 33.54,

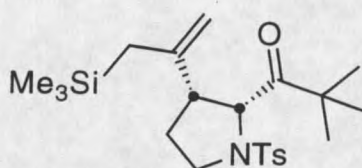
27.97, 25.83, 18.22, 13.64, -1.33, -5.49; IR (film) 3075, 2954, 2858, 1727, 1667, 1631, 1472, 1436, 1361, 1251, 1203, 1119, 1035, 1005, 837, 777 cm^{-1} .



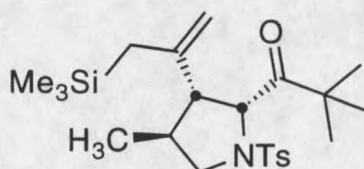
(2 α ,3 α ,5 α)-N-Tosyl-5-(*t*-butyldimethylsilyloxy)methyl-2-trimethylacetate-3-[1-(trimethylsilylmethyl)ethenyl]pyrrolidine (53). A 5.0 mL, single-necked, round-bottomed flask was charged with pyrroline **50c_{cis}** (66 mg, 0.16 mmol) and MeOH (1.1 mL). To the solution was added NaBH_3CN (41 mg, 0.65 mmol) in one portion and the mixture was immediately cooled to -78°C . Trifluoroacetic acid (13 μL , 0.17 mmol) was added dropwise via a syringe and the mixture was stirred for 1 h at -78°C . The cold reaction mixture was poured into pH 7 buffer (3 mL) and the aqueous solution was stirred for 30 min at rt. The solution was saturated with NaCl and extracted with three portions of CH_2Cl_2 (1.5 mL). The combined CH_2Cl_2 extracts were thoroughly dried over Na_2SO_4 , filtered through a pad of celite (CH_2Cl_2 for elution) and concentrated to afford the crude pyrrolidine as a viscous, colorless oil which was used immediately in the next step.

A 5.0 mL, single-necked, round-bottomed flask containing a solution of DMAP (24 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0°C and TsCl (34 mg, 0.18 mmol) was added in one portion. The mixture was stirred at 0°C for 30 min, cooled to -78°C and treated dropwise with a solution of the crude pyrrolidine in CH_2Cl_2 (0.20 mL) via syringe. The reaction mixture was stirred

for 2h at -78 °C then for an additional 12h at -20 °C. Water (2.0 mL) was added to the cold mixture and the resulting biphasic mixture was stirred for 1h at rt. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 1.0 mL). The organic phases were combined and dried over Na₂SO₄. Removal of solvent *in vacuo* afforded the crude product which was purified by chromatography on silica gel (5% EtOAc/hexane for elution) to provide the title compound (60 mg, 67% from **50c_{cis}**) as a colorless, viscous oil: ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 8.2 Hz, 2H, ArH), 7.35 (d, J = 8.1 Hz, 2H, ArH), 4.86 (d, J = 7.4 Hz, O=CCHN), 4.55 (d, J = 5.3 Hz, 2H, C=CH₂), 4.08 (dd, J = 9.0, 4.7 Hz, 1H, SiOCHH), 3.91 (dd, J = 9.7, 9.3 Hz, 1H, SiOCHH), 3.60 (m, 1H, SiOCH₂CHN), 2.42 (s, 3H, ArCH₃), 2.27 (dt, J = 13.1, 8.8 Hz, 1H, CHH), 1.85 (ddd, J = 12.8, 6.5, 6.5 Hz, 1H, CHH), 1.54 (ddd, J = 13.6, 7.7, 7.7 Hz, 1H, C=CCH), 1.53 (d, J = 13.2 Hz, SiCHH), 1.10 (s, 9H, (CH₃)₃CC=O), 1.03 (d, J = 12.5 Hz, SiCHH), 0.89 (s, 9H, (CH₃)₃CSi), 0.09 (s, 6H, (CH₃)₃CSi(CH₃)₂), -0.23 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 213.45, 143.88, 140.97, 134.79, 129.90, 127.56, 110.49, 67.12, 62.32, 61.81, 49.28, 44.64, 33.58, 29.71, 26.30, 25.98, 21.44, 18.33, -1.93, -5.23; IR (film) 2956, 2929, 2887, 2857, 1711, 1633, 1597, 1473, 1354, 1250, 1165, 1090, 991, 838, 776 cm⁻¹; HRMS calcd for C₂₈H₄₈NO₄SSi₂ (M⁺-CH₃) 550.2843 found 550.2842.



***Cis*-N-Tosyl-2-trimethylacetyl-3-[1-(trimethylsilylmethyl)ethenyl]-pyrrolidine (51).** Utilizing pyrroline **48a** (100 mg, 0.38 mmol) in the procedure described for the preparation of **53** furnished the title compound (87 mg, 55% from **48a**) which was obtained as a white, crystalline solid: mp 112.3-114.7 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, J = 8.2 Hz, 2H, ArH), 7.30 (d, J = 8.1 Hz, 2H, ArH), 5.02 (d, J = 7.4 Hz, 1H, $\text{O}=\text{CCHN}$), 4.60 (d, J = 7.0 Hz, 2H, $\text{C}=\text{CH}_2$), 3.59 (dt, J = 9.9, 1.4 Hz, 1H, NCHH), 3.36 (ddd, J = 16.9, 9.6, 7.4 Hz, 1H, NCHH), 2.45 (ddd, J = 15.8, 12.6, 3.3 Hz, 1H, $\text{C}=\text{CCH}$), 2.40 (s, 3H, ArCH_3), 2.06 (ddd, J = 13.5, 6.8, 6.8 Hz, 1H, CHH), 1.72 (ddd, J = 12.1, 6.0, 6.0 Hz, 1H, CHH), 1.61 (d, J = 13.1 Hz, 1H, SiCHH), 1.24 (d, J = 13.0 Hz, 1H, SiCHH), 1.10 (s, 9H, $(\text{CH}_3)_3\text{C}$), -0.13 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 214.24, 143.49, 141.34, 135.89, 129.69, 127.26, 110.84, 61.67, 50.31, 47.51, 44.39, 29.81, 28.44, 26.39, 21.44, -1.76; IR (film) 2956, 2922, 1709, 1631, 1595, 1478, 1351, 1248, 1163, 1093, 992, 849, 663 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{36}\text{NO}_3\text{SSi}$ (MH^+) 422.2185, found 422.2167.



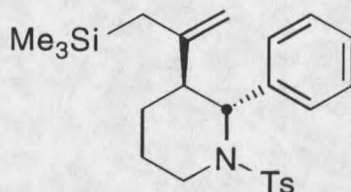
(2 α ,3 α ,4 β)-N-Tosyl-4-methyl-3-[1-(trimethylsilylmethyl)ethenyl]-2-trimethyl acetylpyrrolidine (52). The procedure used for the preparation of **53** was employed using pyrroline **49a** (109 mg, 0.39 mmol) and a reaction time of 2 hr at -78 °C for the reduction with NaBH_3CN / TFA to provide

a mixture of diastereomeric *N*-tosyl pyrrolidines (106 mg, 63% from **49a**, 4.0 : 1.0 by NMR) which was obtained as a white solid after filtration of the crude material through a silica gel plug (5% EtOAc/hexane for elution).

Recrystallization of the mixture (petroleum ether) provided a pure sample of the major, *N*-tosylpyrrolidine isomer **52** as a crystalline white solid: m.p. 136.0 - 137.2 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, J = 8.1 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 5.09 (d, J = 7.4 Hz, 1H, O=CCHN), 4.66 (s, 1H, C=CHH), 4.52 (s, 1H, C=CHH), 3.69 (t, J = 7.5 Hz, 1H, NCHH), 2.91 (dd, J = 15.8, 7.4 Hz, 1H, NCHH), 2.90 (m, 1H, NCH₂CHCH₃), 2.40 (s, 3H, ArCH₃), 1.70 (dd, J = 11.4, 7.6 Hz, 1H, C=CCH), 1.63 (d, J = 13.2 Hz, 1H, SiCHH), 1.23 (d, J = 13.1 Hz, 1H, SiCHH), 1.10 (s, 9H, (CH₃)₃CC=O), 0.80 (d, J = 6.2 Hz, 3H, CH₃), -0.11 (s, 9H, (CH₃)₃Si); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 214.21, 143.51, 139.92, 135.70, 129.65, 127.30, 111.11, 62.78, 57.00, 54.79, 44.30, 34.43, 30.38, 26.52, 21.44, 15.66, -1.37; IR (film) 3068, 2958, 2884, 1706, 1631, 1596, 1481, 1343, 1243, 1154, 1058, 1041, 852, 661 cm^{-1} ; HRMS calcd for C₂₃H₃₈NO₃SSi (MH⁺) 436.2342, found 436.2340.

Stereocontrolled Synthesis of Piperidines

General Information: Titanium tetrachloride was distilled under an atmosphere of nitrogen and was stored as a stock solution in toluene (1.0 M) under an argon atmosphere. All aldehydes were provided by commercial suppliers and were distilled under argon prior to use. Molecular sieves (4 Å) were activated by flame drying under high vacuum.

***Trans-N-tosyl-2-phenyl-3-[(3-trimethylsilyl)isopropenyl]***

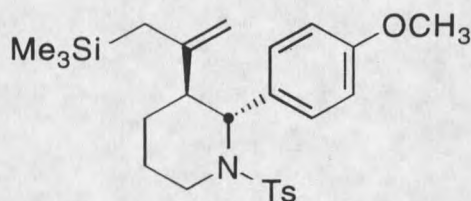
piperidine (65c). The following serves as the general experimental procedure used for the preparation of *N*-tosylpiperidines from amine **54**. A 5.0 mL, single-necked, round-bottomed flask was charged with THF (2.5 mL) and activated 4Å molecular sieves (200 mg). Amine **54** (129 mg, 0.50 mmol) and freshly distilled benzaldehyde (61 μ L, 0.60 mmol) were sequentially added via syringe and the mixture was stirred for 12h at rt. The reaction mixture was diluted with hexane (2.5 mL) and filtered through a Celite pad into a 10 mL, single-necked, round-bottomed flask. Evaporation of solvents and excess aldehyde *in vacuo* afforded the crude imine as a colorless oil which was used immediately in the next step.

To the flask containing the freshly prepared imine was added CH_2Cl_2 (5 mL) and the resulting solution was cooled to -78°C . Titanium tetrachloride (500 μ L, 0.50 mmol of a 1.0 M toluene solution) was added dropwise over 2 min via a syringe and the resulting, deep orange solution was allowed to gradually

warm to room temperature (2-3h). Stirring was maintained for an additional 3h after which the reaction mixture was transferred dropwise via cannula into vigorously stirred, saturated aqueous KHCO_3 (10 mL) at 0 °C. The resulting biphasic mixture was stirred for 30 min at rt. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were then dried with Na_2SO_4 , filtered and concentrated. The residual oil was dissolved in pentane (10 mL), filtered through a Celite pad and concentrated to furnish a diastereomeric mixture of crude piperidines which was directly converted into the corresponding *N*-tosyl derivatives.

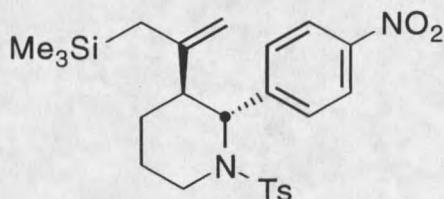
To a 10 mL, single-necked, round-bottomed flask containing a solution of the crude piperidines in CH_2Cl_2 (3.0 mL) was added pyridine (145 μL , 1.80 mmol) and the solution was cooled to 0 °C. Tosyl chloride (114 mg, 0.60 mmol) was added in one portion and the reaction mixture was stirred at 0 °C for 2h followed by an additional 2h at rt. Distilled H_2O (3.0 mL) was added and the resulting biphasic mixture was stirred for 1h. The organic layer was removed and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified of flash chromatography on silica gel (0%-1%-5% EtOAc/hexanes for elution) to furnish an inseparable mixture of the title compound and the minor diastereomer (9.5 : 1.0 by NMR, 178 mg, 83% from **54**) as a colorless, viscous oil: ^1H NMR (300 MHz, C_6D_6) δ 7.73 (d, J = 8.0 Hz, 2H, CH_3ArH), 7.30 (dd, J = 7.5, 1.4 Hz, 2H, ArH), 7.09 (m, 3H, ArH), 6.74 (d, J = 8.1 Hz, 2H, CH_3ArH), 5.44 (d, J = 5.3 Hz, 1H, NCH), 5.19 (s, 1H, C=CHH), 4.85 (s, 1H, C=CHH), 3.83 (ddd, J = 13.1, 6.2, 3.1 Hz, 1H, NCHH), 3.25 (ddd, J = 15.7, 11.0, 4.7 Hz, 1H, NCHH), 2.39 (ddd, J = 11.5, 5.1, 5.1 Hz, 1H, C=CCH), 1.95 (s, 3H,

CH_3Ar), 1.87 (m, 1H, CHH), 1.50 (m, 2H, CH_2), 1.37 (s, 2H, SiCH_2), 1.24 (m, 1H, CHH), 0.00 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 147.70, 142.49, 141.29, 137.30, 128.98, 127.99, 127.44, 127.20, 126.81, 109.92, 61.78, 46.77, 42.42, 26.46, 23.63, 21.33, -1.28; IR (film) 3089, 3063, 3033, 2952, 1631, 1599, 1495, 1454, 1341, 1248, 1161, 1092, 941, 853, 699, 659 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{33}\text{NO}_2\text{SSi}$ (M^+) 427.2001, found 427.1989.



***Trans*-N-tosyl-2-(4-methoxyphenyl)-3-[(3-trimethylsilyl)-isopropenyl]piperidine (65b).** Using the above procedure outlined for the preparation of *N*-tosyl piperidine **65c**, amine **54** (150 mg, 0.58 mmol) and 4-anisaldehyde (78 μL , 0.64 mmol) were converted into an inseparable mixture of the title compound and the minor diastereomer (6.3 : 1.0 by NMR, 194 mg, 73% from **54**) which was isolated as a viscous, colorless oil upon purification by chromatography on silica gel (0%-1%-5% EtOAc/hexanes for elution): ^1H NMR (300 MHz, C_6D_6) δ 7.64 (d, $J = 8.2\text{ Hz}$, 2H, ArH), 7.23 (d, $J = 8.4\text{ Hz}$, 2H, ArH), 6.76 (d, $J = 8.1\text{ Hz}$, 2H, ArH), 6.69 (d, $J = 8.7\text{ Hz}$, 2H, ArH), 5.37 (d, $J = 5.5\text{ Hz}$, 1H, NCH), 5.18 (s, 1H, $\text{C}=\text{CHH}$), 4.85 (s, 1H, $\text{C}=\text{CHH}$), 3.79 (ddd, $J = 13.0, 6.0, 3.4\text{ Hz}$, 1H, NCHH), 3.35 (s, 3H, CH_3OAr), 3.29 (ddd, $J = 15.4, 10.7, 4.6\text{ Hz}$, 1H, NCHH), 2.40 (ddd, $J = 11.9, 4.9, 4.9\text{ Hz}$, 1H, $\text{C}=\text{CCH}$), 1.94 (s, 3H, CH_3Ar), 1.88 (m, 1H, CHH), 1.53 (m, 2H, CH_2), 1.41 (s, 2H, SiCH_2), 1.30 (m, 1H, CHH), 0.02 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 158.43, 147.85, 142.39, 137.39, 133.24, 128.94, 128.69, 127.19, 113.28, 109.80, 61.58, 55.16,

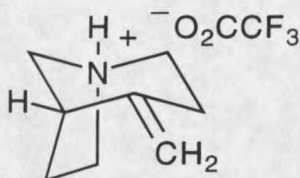
46.92, 42.45, 26.52, 23.93, 21.55, 21.38, -1.25; IR (film) 3070, 3035, 2952, 2836, 1631, 1611, 1513, 1463, 1340, 1248, 1160, 1091, 1036, 975, 942, 852, 680, 659 cm^{-1} ; HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_3\text{SSi}$ (M^+) 457.2107, found 457.2099.



***Trans*-N-tosyl-2-(4-nitrophenyl)-3-[(3-trimethylsilyl)-**

isopropenyl]piperidine (65d). Using the above procedure outlined for the preparation of *N*-tosyl piperidine **65c**, amine **54** (150 mg, 0.58 mmol) and 4-nitrobenzaldehyde (92 mg, 0.61 mmol) were converted into an inseparable mixture of the title compound and the minor diastereomer (21 : 1.0 by NMR, 110 mg, 40% from **54**) which was isolated as white solid upon purification by chromatography on silica gel (20% EtOAc/hexanes for elution): m.p. 104.5 - 107.6 °C; ^1H NMR (300 MHz, C_6D_6) δ 7.77 (d, J = 8.5 Hz, 2H, ArH), 7.49 (d, J = 8.2 Hz, 2H, ArH), 7.02 (d, J = 8.7 Hz, 2H, ArH), 6.69 (d, J = 8.1 Hz, 2H, ArH), 5.03 (d, J = 6.4 Hz, 1H, NCH), 4.94 (s, 1H, C=CHH), 4.74 (s, 1H, C=CHH), 3.64 (ddd, J = 13.1, 4.3, 4.3 Hz, 1H, NCHH), 3.20 (ddd, J = 13.4, 10.2, 4.7 Hz, 1H, NCHH), 2.11 (ddd, J = 7.4, 4.1, 4.1 Hz, 1H, C=CCH), 1.94 (s, 3H, CH_3Ar), 1.73 (m, 1H, CHH), 1.30 (m, 3H, CH_2 and CHH), 1.19 (ABq, $\Delta\nu$ = 26.7 Hz, J = 14.1 Hz, 2H, SiCH_2), -0.03 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 149.02, 147.10, 146.74, 143.42, 136.40, 129.64, 129.30, 128.41, 127.24, 110.50, 62.74, 48.27, 43.30, 26.61, 25.17, 21.85, 21.43, -1.28; IR (film) 3072, 3035, 2952, 1631, 1598, 1522, 1344, 1248, 1160, 1092, 1037, 1013, 974, 937,

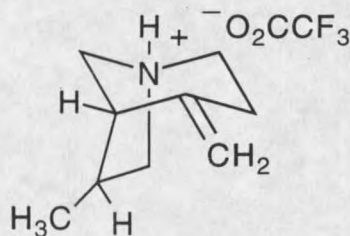
852, 738, 763, 680 cm^{-1} ; HRMS calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4\text{SSi}$ (M^+) 472.1852, found 472.1859.

Synthesis of Isotropane Alkaloids and Azabicyclononanes**4-Methyldene-1-azabicyclo[3.2.1]octane, trifluoroacetate salt**

(67a). A 25 mL, single-necked, round-bottomed flask containing a solution of amine **1a** (300 mg, 1.23 mmol) in CH_3CN (6 mL) was treated with aqueous CH_2O (400 μL , 4.92 mmol, 37% in H_2O) dropwise over 1 min via syringe. The resulting cloudy mixture was stirred for 2h after which TFA (95 μL , 1.23 mmol, freshly distilled from KMnO_4) was added dropwise via syringe. The resulting homogeneous solution was stirred for 8h, basified with NaOH (3 mL, 2 M) and partitioned with brine (6 mL). The organic phase was removed, washed with brine (3 mL), dried (MgSO_4) and filtered into a 25 mL, single-necked, round-bottomed flask. The resulting solution of the crude, volatile isotropane (97% by GC) was cooled to 0 °C and TFA (95 μL , 1.23 mmol) was added dropwise. After stirring for 1h at 0 °C, the reaction mixture was concentrated *in vacuo* and the resulting viscous oil was washed with hexane (3 x 5 mL). The residue was dissolved in Et_2O and filtered through a Celite plug to furnish the title compound (257 mg, 88%) as a colorless, viscous oil which solidified upon cold storage:

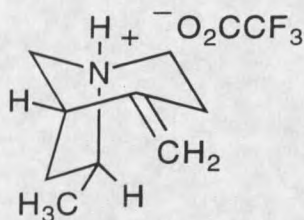
^1H NMR (300 MHz, CDCl_3) δ 9.98 (br s, 1H, ^+NH), 4.89 (d, $J = 2.1$ Hz, 1H, $\text{C}=\text{CHH}$), 4.82 (d, $J = 2.0$ Hz, 1H, $\text{C}=\text{CHH}$), 3.72 (ddd, $J = 13.4, 7.4, 5.2$ Hz, 1H, $^+\text{NHCHH}$), 3.40 (br t, $J = 10.6$ Hz, 3H, $^+\text{NHCH}_2$ and $^+\text{NHCHH}$), 3.29 (dq, $J = 13.4, 5.5$ Hz, 1H, $^+\text{NHCHH}$), 3.17 (unresolved, 1H, $^+\text{NHCHH}$), 3.15 (dd, $J = 10.7, 4.4$ Hz, 1H, CH), 2.67 (m, 1H, $\text{C}=\text{CCHH}$), 2.47 (dd, $J = 16.0, 5.4$ Hz, 1H, CHCHH), 2.32 (m, 1H, $\text{C}=\text{CCHH}$), 1.97 (dddd, $J = 14.4, 6.9, 5.2, 1.7$ Hz, 1H,

CHCHH); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 162.02, 142.57, 119.05, 110.55, 58.96, 52.68, 49.78, 42.22, 28.23, 25.15; IR (film) 3414, 3072, 2993, 1680, 1654, 1470, 1173, 1012, 911, 798, cm^{-1} ; HRMS ($-\text{HO}_2\text{CCF}_3$) calcd for $\text{C}_8\text{H}_{13}\text{N}$ (M^+) 123.1048, found 123.1047.

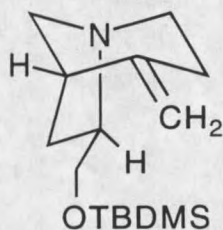


exo-6-Methyl-4-methylened-1-azabicyclo[3.2.1]octane,

trifluoroacetate salt (67b). Following the procedure used for the preparation of isotropane salt **67a**, amine **1b** (129 mg, 0.50 mmol) was converted into the title compound (103 mg, 82%) which was isolated as a colorless gelatinous material: ^1H NMR (300 MHz, CDCl_3) δ 12.17 (br s, 1H, HN^+), 4.85 (d, $J = 1.9$, 1H, $\text{C}=\text{CHH}$), 4.80 (d, $J = 1.7$ Hz, $\text{C}=\text{CHH}$), 3.51 (m, 2H, HN^+CH_2), 3.34 (dd, $J = 12.6, 7.2$ Hz, 1H, HN^+CHH), 3.23 (ddd, $J = 18.3, 12.0, 6.0$ Hz, 2H, HN^+CH_2), 3.05 (d, $J = 11.1$ Hz, 1H, CH), 2.71 (d, $J = 3.9$ Hz, 1H, HN^+CHH), 2.62 (m, 1H, $\text{C}=\text{CHH}$), 2.45 (dd, $J = 16.2, 5.5$ Hz, 1H, $\text{C}=\text{CHH}$), 2.38 (sx, $J = 7.2$ Hz, 1H, CH_3CH), 1.17 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 161.35(q), 142.12, 115.77(q), 110.70, 57.69, 56.96, 52.45, 49.77, 35.86, 25.43, 19.88; IR (film) 3415, 2971, 1674, 1467, 1173, 1025, 910, 798, 706 cm^{-1} ; HRMS ($-\text{HO}_2\text{CCF}_3$) calcd for $\text{C}_9\text{H}_{15}\text{N}$ (M^+) 137.1204, found 137.1207.

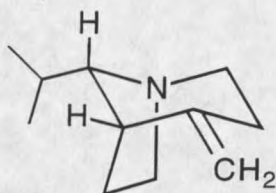


exo-7-Methyl-4-methylenedecahydro-1H-indole, trifluoroacetate salt (67c). Employing amine **1c** (129 mg, 0.50 mmol) in the procedure outlined for the preparation of **67a** yielded an inseparable mixture of the title isotropane and a minor diastereoisomer (94 mg, 75%, 6.0:1.0) which was isolated as a clear viscous material: ^1H NMR (300 MHz, CDCl_3) δ 11.45 (br s, 1H, ^+NH), 4.86 (d, $J = 1.8$ Hz, 1H, $\text{C}=\text{CHH}$), 4.80 (d, $J = 1.7$ Hz, 1H, $\text{C}=\text{CHH}$), 3.85 (sx, $J = 6.8$ Hz, 1H, H^+NCHCH_3), 3.49 (m, 2H, H^+NCH_2), 3.21 (dddd, $J = 14.2, 13.0, 5.7, 1.5$ Hz, 1H, H^+NCHH), 3.10 (unresolved, 2H, H^+NCHH and CH), 2.62 (m, 1H, $\text{C}=\text{CCHH}$), 2.44 (dd, $J = 16.0, 5.5$ Hz, 1H, $\text{C}=\text{CCHH}$), 2.21 (ddd, $J = 13.5, 8.1, 1.4$ Hz, 1H, CHH), 1.85 (dt, $J = 13.1, 6.0$ Hz, 1H, CHH), 1.47 (d, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 160.69(q), 141.72, 115.75(q), 111.05, 60.62, 56.60, 53.20, 42.69, 37.57, 25.32, 20.00; IR (film) 3402, 2989, 1676, 1455, 1175, 911, 799, 706 cm^{-1} ; HRMS ($-\text{HO}_2\text{CCF}_3$) calcd for $\text{C}_9\text{H}_{15}\text{N}$ (M^+) 137.1204, found 137.1201.



exo-7-(tert-Butyldimethylsilyloxy)methyl-4-methylenedecahydro-1H-indole (67d). To a 10 mL, single-necked, round-bottomed flask containing a solution of amine **1d** (194 mg, 0.50 mmol) in

CH₃CN (2.5 mL) was added aqueous CH₂O (163 μ L, 2.0 mmol, 37% in H₂O) dropwise over 1 min via syringe. The resulting cloudy mixture was stirred vigorously for 2h and was cooled to 5 °C. Trifluoroacetic acid (39 μ L, 0.50 mmol, freshly distilled from KMnO₄) was added via syringe and the resulting homogeneous solution was stirred for 5 minutes at 5 °C followed by 10h at room temperature. Aqueous NaOH (0.5 mL, 2 M) was added and stirring was continued for 5 minutes. The mixture was diluted with H₂O (2.5 mL) and the aqueous mixture was extracted with Et₂O (3 x 2 mL). The Et₂O extracts were combined, dried (MgSO₄), filtered and concentrated. The residue was passed through a plug of Florisil (Et₂O for elution) to furnish isotropane **67d** (127 mg, 95%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.51 (d, J = 2.1 Hz, 1H, C=CHH), 4.44 (d, J = 2.0 Hz, 1H, C=CHH), 3.62 (ddd, J = 11.9, 6.2, 1.9 Hz, 1H, SiOCHH), 3.32 (ddd, J = 11.7, 7.5, 1.8 Hz, 1H, SiOCHH), 3.11 (p, J = 6.6 Hz, 1H, NCH), 2.90-2.71 (m, 4H, NCH₂ x 2), 2.59 (d, J = 11.1 Hz, 1H, CH), 2.33 (m, 1H, C=CCHH), 1.97 (dd, J = 14.9, 4.4 Hz, 1H, C=CCHH), 1.76 (dd, J = 13.1, 8.0 Hz, 1H, CHH), 1.62 (ddd, J = 13.1, 5.6, 1.9 Hz, 1H, CHH), 0.85 (s, 9H, (CH₃)₃CSi), 0.02 (s, 6H, (CH₃)₂Si); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 150.90, 103.89, 66.55, 63.94, 59.95, 56.22, 45.41, 35.16, 29.04, 25.95, 18.33, -5.24, -5.32; IR (film) 3071, 2935, 2857, 1646, 1472, 1253, 1114, 1082, 837, 776 cm⁻¹; HRMS calcd for C₁₅H₂₉NOSi (M⁺) 267.2018, found 267.2026.

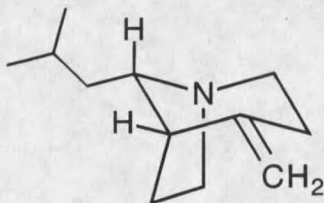


***anti*-8-Isopropyl-4-methylidene-1-azabicyclo[3.2.1]octane**

(71a). To a 10 mL, single-necked, round-bottomed flask containing a heterogeneous mixture of pyrrolidine **14a** (203 mg, 0.90 mmol) in 3:1 H₂O / THF (4.5 mL) was added aqueous CH₂O (146 μ L, 1.80 mmol, 37% in H₂O) over 1 min via syringe. The resulting cloudy mixture was stirred vigorously for 1.5h. Upon cooling the reaction mixture to 0 °C, TFA (73 μ L, 0.94 mmol, freshly distilled from KMnO₄) was added dropwise via syringe and the resulting homogeneous solution was stirred for 10 min at 0 °C followed by 2h at room temperature. Aqueous NaOH (2 mL, 2 M) was added dropwise and stirring was continued for an additional 30 min. The mixture was diluted with H₂O (2 mL) and was extracted with Et₂O (3 x 4 mL). The extracts were washed with brine (2 x 4 mL), dried over MgSO₄, filtered and concentrated. Purification of the residue by silica gel chromatography (10% IPA/EtOAc) afforded isotropane **71a** (115 mg, 77%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.51 (t, *J* = 2.2 Hz, 1H, C=CHH), 4.24 (t, *J* = 2.2 Hz, 1H, C=CHH), 2.92 (dt, *J* = 13.1, 7.1 Hz, 2H, NCH₂), 2.78 (d, *J* = 6.2, 1H, CH), 2.75 (dt, *J* = 13.0, 7.0 Hz, 2H, NCH₂), 2.28 (m, 1H, CHHC=C), 2.19 (d, *J* = 10.3 Hz, 1H, NCH), 1.92 (dd, *J* = 14.8, 5.1 Hz, 1H, CHCHH), 1.80 (m, 1H, CHHC=C), 1.56 (ddd, *J* = 13.5, 8.9, 5.1 Hz, 1H, CHCHH), 1.33 (m, 1H, CH(CH₃)₂), 0.92 (d, *J* = 6.5 Hz, 3H, CH₃CHCH₃), 0.86 (d, *J* = 6.6 Hz, 3H, CH₃CHCH₃); ¹³C NMR (75 MHz, CDCl₃, ¹H decoupled) δ 152.64, 103.02, 80.00, 57.17, 48.99, 45.76, 30.23, 28.45, 27.68, 20.17, 19.95; IR (film)

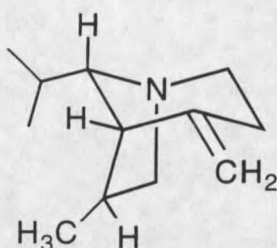
3070, 2956, 2873, 1644, 1469, 1457, 1090, 1078, 1030, 1013, 920, 879 cm^{-1} ;

HRMS calcd for $\text{C}_{11}\text{H}_{19}\text{N}$ 165.1517, found 165.1516.



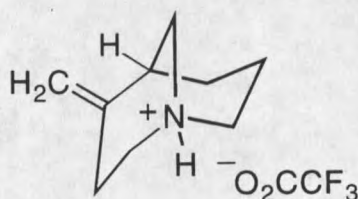
***anti*-8-isobutyl-4-methyldiene-1-azabicyclo[3.2.1]octane**

(71b). Using the procedure described for the preparation of **71a**, pyrrolidine **14b** (174 mg, 0.73 mmol) was converted into isotropane **71b** (97 mg, 74%) which was obtained as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.48 (t, J = 2.2 Hz, 1H, $\text{C}=\text{CHH}$), 4.41 (t, J = 2.2 Hz, 1H, $\text{C}=\text{CHH}$), 2.69 - 3.01 (m, 5H, NCH_2 x 2 and NCH), 2.52 (d, J = 6.4 Hz, 1H, CH), 2.26 (m, 1H, $\text{C}=\text{CCHH}$), 1.89 (dd, J = 14.9, 5.0 Hz, 1H, CHCHH), 1.85 (m, 1H, $\text{C}=\text{CCHH}$), 1.60 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.56 (ddd, J = 13.5, 8.9, 5.0 Hz, 1H, CHCHH), 1.45 (dt, J = 13.8, 7.1 Hz, 1H, $\text{CHHCH}(\text{CH}_3)_2$), 0.98 (dt, J = 13.7, 7.4 Hz, 1H, $\text{CHHCH}(\text{CH}_3)_2$); 0.87 (d, J = 2.3 Hz, 3H, CH_3CHCH_3), 0.85 (d, J = 2.4 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 152.44, 103.01, 70.92, 57.00, 49.05, 47.84, 40.50, 30.07, 28.30, 25.41, 22.94, 22.57; IR (film) 3071, 2954, 2871, 1652, 1456, 1095, 1080, 1028, 922, 879, 743, 734 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{N}$ (M^+) 179.1674, found 179.1681.



***exo-anti*--6-Methyl-4-methylidene-8-isopropyl-1-azabicyclo**

[3.2.1]octane (72a). The procedure outlined for the preparation of **71a** was carried out utilizing pyrrolidine **24a** (100 mg, 0.42 mmol) and a reaction time of 8h at room temperature following the addition of TFA to furnish the title compound (51 mg, 68%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.47 (t, $J = 2.2$ Hz, 1H, $\text{C}=\text{CHH}$), 4.37 (t, $J = 2.3$ Hz, 1H, $\text{C}=\text{CHH}$), 3.00 (dd, $J = 12.8$, 8.4 Hz, 1H, NCHH), 2.92 (dd, $J = 13.2$, 7.7 Hz, NCHH), 2.74 (dt, $J = 12.3$, 5.6 Hz, 1H, NCHH), 2.59 (dd, $J = 13.0$, 6.0 Hz, 1H, NCHH), 2.53 (s, 1H, CH), 2.28 (m, 1H, $\text{C}=\text{CCHH}$), 2.11 (d, $J = 10.7$ Hz, 1H, NCH), 1.98 (sx, $J = 7.4$ Hz, 1H, CH_3CH), 1.92 (dd, $J = 15.0$, 5.5 Hz, 1H, $\text{C}=\text{CCHH}$), 1.56 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.04 (d, $J = 7.4$ Hz, 3H, CH_3CH), 0.92 (d, $J = 6.4$ Hz, 3H, CH_3CHCH_3), 0.86 (d, $J = 6.7$ Hz, 3H, CH_3CHCH_3); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 153.27, 102.28, 81.16, 58.53, 56.86, 53.38, 39.15, 28.96, 28.24, 21.04, 21.00, 19.60; IR (film) 3070, 2957, 2872, 1646, 1469, 1385, 1201, 1056, 1005, 878, 772 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{N}$ (M^+) 179.1674, found 179.1668.



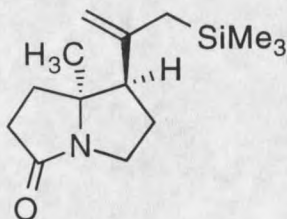
4-Methylidene-1-Azabicyclo[3.3.1]nonane, trifluoroacetate

salt (75). Utilizing the standard condensation-bicyclization protocol previously

used for the preparation of isotropane **67a**, amine **54** (387 mg, 1.50 mmol) was converted into the title compound (353 mg, 94%) which was secured as a gold tinted, viscous oil which solidified upon slight cooling: ^1H NMR (300 MHz, CDCl_3) δ 11.90 (br s, 1H, +NH), 4.99 (s, 2H, $\text{C}=\text{CH}_2$), 3.54 (m, 1H, NCHH), 3.37 (m, 3H, NCH_2 and NCHH), 3.27 (s, 2H, NCH_2), 2.84 (m, 1H, $\text{C}=\text{CCHH}$), 2.76 (s, 1H, CH), 2.60 (ddd, $J = 16.4, 6.9, 3.2$ Hz, 1H, $\text{C}=\text{CCHH}$), 2.14 (m, 1H, CHH), 1.89, (m, 3H, CHH and CH_2); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 162.22 (q, $J = 34.9$ Hz), 142.13, 116.81 (q, $J = 292$ Hz), 114.01, 52.56, 52.05, 50.65, 34.25, 28.91, 28.76, 18.84; IR (film) 3389, 3070, 2948, 1663, 1475, 1417, 1163, 1055, 1021, 978, 909, 832, 799, 721 cm^{-1} ; HRMS calcd for $\text{C}_9\text{H}_{15}\text{N}$ (M^+) 137.1204, found 137.1203.

Model Synthesis of the Tricyclic Core of Stemofoline

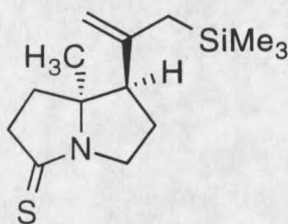
General Information: Ethyl levulinate was used as purchased from Aldrich Chemical Company, Inc. Lawesson's reagent was freshly prepared using reported procedures.⁸⁵ Triethyloxonium tetrafluoroborate was prepared following known procedures⁸⁹ and was stored as a CH_2Cl_2 solution (1.24 M) at low temperatures ($0\text{ }^\circ\text{C}$) under argon.



(5 α ,6 β)-5-Methyl-6-[1-(trimethylsilylmethyl)ethenyl]-1-azabicyclo[3.3.0]octa-2-one (85). Applying the method outlined previously for the preparation of imine **11a**, condensation of amine **1a** (4.02 g, 16.5 mmol) and ethyl levulinate (2.58 mL, 18.1 mmol) over a 24h period afforded imine **83** (6.15 g, 100%) as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 4.76 (t, $J = 7.1$ Hz, 1H, $\text{C}=\text{CH}$), 4.07 (q, $J = 7.3$ Hz, 2H, CH_3CH_2), 3.14 (t, $J = 7.6$ Hz, 2H, NCH_2), 2.51 (br s, 4H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.14 (q, $J = 7.3$ Hz, 2H, $\text{CH}_2\text{C}=\text{C}$), 1.77 (s, 3H, CH_3), 1.44 (s, 2H, SiCH_2), 1.35 (s, 2H, SiCH_2), 1.20 (t, $J = 7.2$ Hz, 3H, CH_3CH_2), -0.02 (s, 9H, $(\text{CH}_3)_3\text{Si}$), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 173.51, 166.33, 135.28, 117.29, 60.07, 51.89, 36.37, 30.52, 30.37, 29.43, 23.81, 17.69, 14.21, -0.71, -1.20.

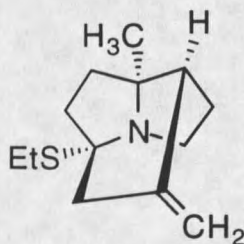
Imine **83** was immediately subjected to the general cyclization conditions used for the preparation of **14a** to yield pyrrolizidine **85** (3.31 g, 80%) as a colorless, crystalline solid upon purification by silica gel chromatography (90%

EtOAc/ hexane for elution): mp 74.2 - 75.9°C (light pet. ether); ^1H NMR (300 MHz, C_6D_6) δ 4.56 (s, 1H, $\text{C}=\text{CHH}$), 4.38 (s, 1H, $\text{C}=\text{CHH}$), 3.82 (ddd, $J = 13.5, 8.4, 5.3$ Hz, 1H, NCHH), 2.65 (ddd, $J = 11.9, 8.0, 7.0$ Hz, 1H, NCHH), 2.41 (dt, $J = 16.3, 9.9$ Hz, 1H, $\text{O}=\text{CCHH}$), 2.19 (ddd, $J = 16.3, 9.8, 2.4$ Hz, 1H, $\text{O}=\text{CCHH}$), 1.99 (app t, $J = 6.4$ Hz, 1H, $\text{CHC}=\text{C}$), 1.83 (dt, $J = 12.4, 10.1$ Hz, 1H, $\text{O}=\text{CCH}_2\text{CHH}$), 1.61 (m, 2H, $\text{CH}_2\text{CHC}=\text{C}$), 1.43 (d, $J = 13.4$ Hz, 1H, SiCHH), 1.26 (app tt, $J = 9.2, 2.2$ Hz, 1H, $\text{O}=\text{CCH}_2\text{CHH}$), 1.08 (d, $J = 13.4$ Hz, 1H, SiCHH), -0.06 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (75 MHz, CDCl_3 , ^1H decoupled) δ 174.38, 147.61, 107.70, 69.99, 53.20, 39.83, 33.47, 31.77, 29.36, 29.16, 28.10, -1.54; IR (film) 3082, 2956, 2926, 2855, 1696, 1630, 1457, 1402, 1248, 1170, 856 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{25}\text{NOSi}$ (M^+) 251.1705, found 251.1708.



(5 α ,6 β)-5-Methyl-6-[1-(trimethylsilylmethyl)ethenyl]-1-azabicyclo[3.3.0]octa-2-thione (88). To a 25 mL, single-necked, round-bottomed flask containing a vigorously stirred solution of lactam **85** (2.09 g, 8.31 mmol) and diisopropylethyl amine (362 μL , 2.08 mmol) in toluene (8 mL) was added Lawesson's reagent (1.85 g, 4.57 mmol) in one portion. Vigorous stirring was maintained for 1h after which the reaction mixture was concentrated *in vacuo*. The residue was triturated with 20% EtOAc/hexane (3 x 10 mL) and the resulting solution was filtered through a silica gel pad (20% EtOAc / hexane elution) to afford thiolactam **88** (2.07 g, 93%) as a white crystalline solid upon evaporation of solvents *in vacuo*: mp 86.0 - 88.3 °C; ^1H NMR (300 MHz,

CDCl_3 δ 4.63 (s, 1H, C=CHH), 4.33 (s, 1H, C=CHH), 3.85 (dt, $J = 14.0, 8.2$ Hz, 1H, NCHH), 3.22 (m, 2H, S=CCH₂), 2.95 (dd, $J = 17.3, 9.1$ Hz, 1H, C=CCH), 2.44 (m, 1H, NCHH), 2.29 (dd, $J = 7.9, 2.1$ Hz, CHH), 2.10 (m, 2H, CH₂), 1.70 (dd, $J = 12.3, 8.0$ CHH), 1.58 (d, $J = 13.3$ Hz, 1H, SiCHH), 1.34 (s, 3H, CH₃), 1.14 (d, $J = 13.3$ Hz, 1H, SiCHH), -0.05 (s, 9H, (CH₃)₃Si); ¹³C NMR (75 MHz, CDCl_3 , ¹H decoupled) δ 196.77, 147.35, 108.28, 77.98, 52.47, 47.00, 43.37, 31.67, 31.17, 29.35, 26.10, -1.51; IR (film) 3081, 2961, 2914, 2887, 1632, 1498, 1475, 1322, 1245, 1169, 1119, 1080, 845 cm^{-1} ; HRMS calcd for C₁₄H₂₅NSSi (M⁺) 267.1477, found 267.1466.



2-Ethylthio-5-methyl-2,6-[2-(methylidene)ethano]-1-

azabicyclo[3.3.0]octane (97a). A 10 mL, single-necked, round-bottomed flask containing a solution of thiolactam **88** (200 mg, 0.75 mmol) in CH_3CN (3.0 mL) was cooled to 0 °C and treated dropwise over 1 min with triethyloxonium tetrafluoroborate (700 μL , 0.87 mmol of a 1.24 M CH_2Cl_2 solution) via syringe. The reaction mixture was stirred for 2h at 0 °C, diluted with CH_3CN (3.0 mL) and allowed to reach ambient temperature. Stirring was continued for 8h after which the reaction mixture was poured into cold aqueous LiOH (10 mL, 2 M). After the biphasic mixture was stirred for 30 min at rt, the organic layer was removed and the aqueous phase was extracted with Et_2O (3 x 4 mL). The combined organic phases were washed with brine (2 x 10 mL) and dried over MgSO_4 . Filtration and evaporation of solvents followed by chromatographic

purification of the resulting oil on basic alumina (20% Et₂O/pentane) furnished tricyclic pyrrolizidine **97a** (152 mg, 90%) as a clear oil: ¹H NMR (300 MHz, C₆D₆) δ 4.48 (d, J = 1.9 Hz, 2H, C=CH₂), 3.28 (ddd, J = 13.8, 9.1, 5.4 Hz, 1H, NCHH), 2.73 (ddd, J = 14.3, 9.5, 4.3 Hz, 1H, NCHH), 2.71 (dq, J = 12.3, 7.6 Hz, 1H, SCHHCH₃), 2.48 (dq, J = 12.5, 7.5, 1H, SCHHCH₃), 2.16 (m, 2H, SCCH₂), 2.14 (d, J = 13.9 Hz, 1H, CHHC=C), 1.95 (d, J = 14.1 Hz, 1H, CHHC=C), 1.77 (m, 2H, CH₂), 1.66 (dq, J = 11.5, 2.6 Hz, 1H, CHCHH), 1.36 (m, 2H, CH and CHCHH), 1.18 (t, J = 7.5 Hz, 3H, CH₃CH₂S), 0.96 (s, 3H, CH₃); ¹³C NMR (75 MHz, C₆D₆, ¹H decoupled) δ 149.54, 106.24, 77.44, 71.44, 53.44, 42.59, 40.69, 36.46, 31.65, 31.19, 23.92, 21.01, 15.48; IR (film) 3070, 2964, 1648, 1459, 1372, 1257, 1227, 1121, 1103, 1024, 981, 932, 885, 743 cm⁻¹; HRMS calcd for C₁₃H₂₁NS (M⁺) 223.1395, found 223.1393.

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