# Iminium Ion Cascade Reactions: Stereoselective Synthesis of Quinolizidines and Indolizidines 

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#### Abstract

A novel iminium ion cascade reaction has been developed that allows for the stereoselective synthesis of a variety of substituted aza-fused bicycles. The combination of amino allylsilanes and aldehydes (or ketones) was used to synthesize a number of quinolizidines and indolizidines in an one-pot reaction sequence. This technology has been used to effect the facile syntheses of several indolizidine and quinolizidine natural products including, $( \pm)$-epilupinine, $( \pm$ )-tashiromine, and ( - )-epimyrtine. Substrate scope has been examined varying the type of amino allylsilanes (primary, secondary and conjugated) and carbonyl compounds (aldehydes and ketones) to give a variety of fused ring structures. Varying the components chosen allows for the inclusion of synthetically useful functional groups at different positions on the core structure. The methodology has been used to construct the tricyclic core structures present in the cylindricine family and halichlorine.


## Keywords

Iminium ion; cascade reaction; alkaloid synthesis; stereoselective

## 1. Introduction

The quinolizidine and indolizidine ring systems comprise core structural subunits found in a large number of natural products ranging from simple bicyclic alkaloids such as epilupinine (1), ${ }^{\text {i }}$ tashiromine (2), ${ }^{\text {ii }}$ and epimyrtine (3) ${ }^{\text {iii }}$ to more complex multicyclic molecules like halichlorine (4) ${ }^{\text {iv }}$ and cylindricine $\mathrm{B}(\mathbf{5}) .{ }^{\mathrm{v}}$ The diverse structures of these compounds coupled with the biological activity exhibited by many members of these families of alkaloids have made natural products containing these ring systems popular targets for synthesis.
Consequently it does not occasion surprise that numerous methods and strategies have been developed for the stereoselective construction of substituted quinolizidine and indolizidines. ${ }^{\text {vi }}$

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We have had a longstanding interest in developing useful and general entries to substituted quinolizidine and indolizidines during the normal course of our general programs in alkaloid synthesis. ${ }^{\text {ive, vii }}$ In that context, we recognized that imines and their activated derivatives play pivotal roles in the synthesis of nitrogen heterocycles via a diverse array of bond forming reactions. ${ }^{\text {viii }}$ We therefore became intrigued by the challenge of combining some of these different constructions and inventing new cascade reactions involving imines and allylsilanes as the key reaction partners to rapidly access the quinolizidine and indolizidine frameworks. Cascade reactions are becoming increasingly attractive as synthetic tools because they involve multiple reactants and sequential bond-forming events in which the product of one reaction is preprogrammed to be the starting material for the next one in a domino-like process. ${ }^{\text {ix }}$ Such methods have gained popularity because they may enable the rapid assembly of complex molecular architectures in one-pot operations that can be highly efficient. ${ }^{\mathrm{X}}$

Our design strategy was guided by evaluating various possibilities in which the different reactivity modes of imines as electrophiles and nucleophiles might be combined in tandem with the nucleophilic reactivity profile of allylsilanes to prepare nitrogen heterocycles having bridgehead nitrogen atoms. The plan that eventuated is outlined in general terms in Scheme 1 and enables the synthesis of a diverse array of nitrogen heterocycles $7-9$ from the cascade reactions of monoprotected dicarbonyl compounds of the general form $\mathbf{6}$ with the amino allylsilanes $\mathbf{1 0}-\mathbf{1 3}$, followed by a terminating step in which the penultimate intermediate iminium ion is trapped with a nucleophile. The ring sizes in 7-9 could be controlled by simply varying the number of carbon atoms in the tethers linking the reacting functional groups in 6 and 10-13. ${ }^{\text {xi }}$ An attractive feature of this entry to quinolizidines and indolizidines is the high level of convergency wherein three components may be integrated into a product in a single chemical operation.

The putative mechanistic underpinnings for forming bicyclic nitrogen heterocycles related to $\mathbf{7}$ are exemplified in Scheme 2 for the formation of $\mathbf{1 5}$ from the acid-catalyzed reaction of the amino allylsilane 11 with the monoprotected dialdehyde 14 , which corresponds to $6(\mathrm{R}=\mathrm{H}$, $\mathrm{n}=1$ ), followed by quenching the penultimate iminium ion intermediate with a generic nucleophile, $\mathrm{Nu}^{-}$. Thus, the sequence commences with the condensation of $\mathbf{1 1}$ with $\mathbf{1 4}$ to give the acyclic imine 16. Although several reaction manifolds are available to 16, acid-catalyzed expulsion of methanol would form an intermediate oxocarbenium ion, cyclization of which onto the imine nitrogen atom would furnish $\mathbf{1 7}$ that could in turn undergo cyclization via addition of the allylsilane moiety to the iminium ion to provide $\mathbf{1 8}$.viiia, xii Ionization of the $\mathrm{N}, \mathrm{O}$-acetal moiety of $\mathbf{1 8}$ in situ would generate another iminium ion that would be trapped with the nucleophile, $\mathrm{Nu}^{-}$, to deliver the fused bicyclic amine 15 . Based upon principles of
stereoelectronic control, ${ }^{\text {xii }}$ we anticipated that the nucleophile would add from an axial direction. Notably, four new bonds and two rings are formed from three different components in a single chemical operation. Similar mechanistic pathways may be set forth for the reactions of $\mathbf{1 4}$ with the branched allylsilane $\mathbf{1 2}$ and the pentadienyl silane $\mathbf{1 3}$ to give $\mathbf{1 9}$ and $\mathbf{2 0}$, respectively.

## 2. Results and Discussion

Having conceived of the iminium cascade processes outlined in Schemes 1 and 2, the first task was to establish the feasibility of such constructions. Toward that end, we first condensed the known aminosilane $\mathbf{1 1}^{\text {xiv }}$ with the monoacetal aldehyde $\mathbf{1 4}$, which was prepared by the procedure of Schreiber, ${ }^{\mathrm{xv}}$ and the resulting imine was treated directly with a number of different Brønsted and Lewis acids to induce the desired cascade. After rather extensive experimentation using different temperatures, solvents, and acids, we eventually discovered that cyclization of the intermediate imine proceeded best at $-40^{\circ} \mathrm{C}$ in acetonitrile in the presence of trifluoroacetic acid. After adding triethylsilane to reduce the putative iminium ion generated in situ, the quinolizidine $\mathbf{2 2}$ was isolated in $75 \%$ yield as a single diastereomer (Scheme 3).

Using the standardized conditions developed for the optimized preparation of 22, the known allyl aminosilane $\mathbf{1 0}^{\mathrm{xvi}}$ was allowed to condense with the aldehyde $\mathbf{1 4}$, and the resultant imine was treated sequentially with TFA and then $\mathrm{Et}_{3} \mathrm{SiH}$ to provide the indolizidine $\mathbf{2 3}$ as a single stereoisomer in $45 \%$ yield. ${ }^{\text {ic }}$ Similarly, reaction of the allylic aminosilane $\mathbf{1 1}$ with the monoprotected dialdehyde 21, xv followed by addition of TFA and then $\mathrm{Et}_{3} \mathrm{SiH}$ furnished the indolizidine $\mathbf{2 4}$ in $36 \%$ yield as a single stereoisomer. The relative stereochemistry between the two newly created stereocenters at $C(1)$ and $C(9 a)$ of 22 was tentatively assigned based upon the observed coupling constant of 12.0 Hz of the trifluoroacetate salt of $\mathbf{2 2}$. This assignment as well as the structural assignments for $\mathbf{2 3}$ and $\mathbf{2 4}$ were confirmed by the conversion of these intermediates into known compounds (vide infra). Although the syntheses of indolizidines via this cascade reaction were less efficient than for quinolizidines, the levels of stereoselectivity were high. Unfortunately, preliminary efforts to extend such processes to the preparation of pyrrolizidines have proven unsuccessful.

The ultimate test of any new synthetic method or strategy lies in its applicability to the preparation of targets that may be of interest, and it did not escape attention that compounds 22 and $\mathbf{2 4}$ might be readily transformed into natural quinolizidines and indolizidines. Indeed, although compound 22 was a known intermediate in a previous synthesis of ( $\pm$ )-epilupinine (1), ${ }^{\text {ic }}$ we developed an improved protocol for effecting this conversion. Namely, ozonolysis of the trifluoroacetate salt of 22, followed by reduction of the intermediate ozonide with $\mathrm{LiAlH}_{4}$ furnished synthetic ( $\pm$ )-epilupinine (1), which gave ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectral data consistent with those reported, in $88 \%$ yield (Scheme 3 ). ${ }^{\text {if }}$ Compound 24 was converted into the natural product ( $\pm$ )-tashiromine (2) in $56 \%$ yield via ozonolysis of its trifluoroacetate salt followed by hydride reduction of the ozonide thus obtained. The synthetic 2 gave ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectral data consistent with those reported.iia,d Similarly, compound $\mathbf{2 3}$ was converted into the known indolizidine 25. ic, xvii

Having succeeded in preparing simple vinyl-substituted quinolizidines and indolizidines, we turned our attention to trapping the penultimate iminium ion with nucleophiles other than a hydride ion. Perhaps not unexpectedly, several initial attempts to trap the iminium ion generated from the reaction of with organometallic reagents such as alkyllithium and alkyl Grignard reagents formed an unstable enamine as the major product. However, we discovered that the intermediate iminium ion 26 could be readily trapped by the nucleophilic addition of cyanide ion under phase-transfer conditions to give the aminonitrile 27 as a single diastereomer in $79 \%$ overall yield (Scheme 4). As will be demonstrated in discussions that follow, it is
noteworthy that $\alpha$-aminonitriles such as 27 are versatile synthetic intermediates that may serve as precursors of nucleophiles (via deprotonation)xviii or electrophiles via Bruylants reactions.xix

We had thus established the viability of using cascade reactions of dialdehyde monoacetals and the linear amino allylsilanes $\mathbf{1 0}$ and $\mathbf{1 1}$ for the rapid formation of indolizidine and quinolizidine alkaloids and their precursors. At this juncture, we wished to explore related processes involving branched amino allylsilanes and keto aldehyde monoacetals. Toward this end, we first applied this chemistry to the branched allylsilane $\mathbf{1 2}$ and the monoprotected dialdehyde 14. In the event, condensation 12 with 14 followed by sequential treatment of the imine thus generated in situ with TFA and then aqueous NaCN furnished an excellent yield of an epimeric mixture (88:12) of the aminonitrile 31, favoring the $\alpha-\mathrm{CN}$ isomer (Scheme 5). ${ }^{\mathrm{xx}}$ The presence of Bohlmann bands (2800-2700) in the IR spectrum of $\mathbf{3 1}$ was consistent with a trans-ring fused quinolizidine ring. The axial orientation of the cyano group, which is consistent with the preferred conformation of cyano groups in quinolizidine systems, ${ }^{\mathrm{xxi}}$ in the major isomer was assigned based upon examination of the ${ }^{1} \mathrm{H}$ NMR spectrum of $\mathbf{3 1}$. The ${ }^{1} \mathrm{H}$ NMR spectrum of the minor stereoisomer, which was assigned as having a $\beta-\mathrm{CN}$ group, the hydrogen at $\mathrm{C}(6)$ exhibited a large coupling constant ( $J=10.4 \mathrm{~Hz}$ ) indicative of an axial-axial interaction and suggesting that the cyano group was equatorial.

The nature of the monoprotected dicarbonyl component was then extended to include the ketal aldehydes 28-30, which were generally prepared according to the plan outlined in Scheme 6. These aldehydes were each condensed with the branched allylsilane 12, and the intermediate imines were treated with trifluoroacetic acid to initiate cyclization; addition of cyanide ion in the last step then afforded the aminonitriles 32-34 (Scheme 5). Because there was no observed nOe interaction between the bridgehead hydrogen atom and those on the R group at $\mathrm{C}(6)$, these groups were tentatively assigned as being trans to each other. ${ }^{\text {xii }}$

It is noteworthy that the quinolizidines $\mathbf{3 1 - 3 4}$ each bear functionality that might be further elaborated to give a variety of derivatives. In order to illustrate the utility of this process, it was applied to a concise, enantioselective synthesis of the quinolizidine alkaloid (-)-epimyrtine (3) (Scheme 7). Thus, the known amino silane 39xxiii was condensed with the dialdehyde monoacetal 14 to give an imine that was then treated sequentially with trifluoroacetic acid and aqueous NaCN to give a mixture of diastereomeric amino nitriles $\mathbf{4 0}$ in $90 \%$ yield. Subsequent reduction of $\mathbf{4 0}$ with $\mathrm{NaCNBH}_{3}$ then provided a mixture (95:5) of epimeric quinolizidines 41a,b. We were also able to reduce the intermediate bicyclic iminium ion generated from the cascade reaction of $\mathbf{3 9}$ with $\mathbf{1 4}$ directly, but the yield of 41a,b was only about $60 \%$. Formation of the trifluoroacetate salt of $\mathbf{4 1 a , b}$ followed by ozonolysis of the exocyclic olefin gave an inseparable mixture (95:5) of (-)-epimyrtine (3) and (+)-myrtine (42) was obtained. The ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectral data for synthetic $\mathbf{3}$ and the specific rotation for $\mathbf{3}$ were consistent with those reported. ${ }^{\text {xxiv }}$

The potential utility of the $\alpha$-aminonitriles formed in these sequences did not escape our attention. For example, $\alpha$-aminonitriles may be deprotonated with strong bases to generate stabilized carbanions that may undergo reactions with a number of different electrophiles, and they may also serve as iminium ion equivalents in Bruylants and related processes. ${ }^{\mathrm{xxv}}$ In order to exemplify the utility of $\alpha$-aminonitriles derived from our cascade reaction as precursors of interesting heterocyclic targets, a mixture of epimeric $\alpha$-aminonitriles $\mathbf{3 1}$ was readily transformed into the tricycle 45, which possesses a skeletal framework related to the core of halichlorine (4). Thus, deprotonation of $\mathbf{3 1}$ with LDA followed by alkylation of the carbanion with the known tosylate $\mathbf{4 3}^{\mathrm{xxvi}}$ gave $\mathbf{4 4}$ in good yield. Subsequent exposure of $\mathbf{4 4}$ to AgOTf generated an iminium ion in situ that underwent efficient cyclization via addition of the allylsilane to give $\mathbf{4 5}$ as a single diastereomer.

That the cyclization to give $\mathbf{4 5}$ proceeded in accord with the principles of stereoelectronic control was verified by NMR spectroscopy.xiii'xxvii In particular, the relative stereochemistry of the spiro and bridgehead centers at $C(9 a)$ and $C(6)$ in $\mathbf{4 5}$ was assigned on the basis of nOe correlations observed in a GOESY experiment performed on the TFA salt in which a strong interaction was observed between the bridgehead proton at $C(9 a)$ and one of the hydrogen atoms on the $\mathrm{C}(10)$ methylene group. This observation is consistent with the cis-relationship between these protons in 45 .

In order to extend this chemistry to the preparation of more highly substituted spirocyclic quinolizidines that might better serve as intermediates in syntheses of halichlorine and derivatives thereof, we identified 47 as a potential target. Toward this end, quinolizidine 34 was allowed to react with 3-butenylmagnesium bromide to deliver quinolizidine 46 as a single diastereomer in virtually quantitative yield (Scheme 9). The stereochemistry of 46 was assigned on the basis of a GOESY experiment in which NOE interactions were observed between the protons at $C(9 a)$ and $C(13)$. The hydrochloride salt of 46 underwent facile enyne ring-closing metathesis in the presence of Grubbs II catalyst (48) to provide 47 in $97 \%$ yield. The synthesis of 47, which comprises the tricyclic core of halichlorine (4) is remarkable for its brevity, only three steps from acyclic starting materials, and efficiency of $72 \%$ overall yield.

The versatility of this cascade approach to substituted quinolizidines may be further illustrated by the synthesis of the $\mathrm{C}(6)$ epimer of $\mathbf{4 6}$ in an unoptimized, two-step sequence of reactions from 31 (Scheme 10). Thus, deprotonation of $\mathbf{3 1}$ followed by alkylation with 4-bromobutane led to aminonitrile 49, which underwent a Bruylants reaction with propynylmagnesium bromide to deliver quinolizidine $\mathbf{5 0}$ as a single diastereomer.xxiiia, ${ }^{\mathrm{xxv}}$ The stereochemistry of 50 was assigned on the basis of a GOESY experiment that revealed a nOe interaction between the equatorial proton on $\mathrm{C}(2)$ with the $\mathrm{C}(10)$ proton. There was no nOe between the protons at $\mathrm{C}(9 \mathrm{a})$ and $\mathrm{C}(10)$.

We had thus verified that the cascade processes generally outlined in Scheme 1 could be applied to the syntheses of quinolizidines and indolizidines lacking substituents at the bridgehead position. However, there are a number of quinolizidine alkaloids such as cylindricine (5) that bear alkyl substituents on the bridgehead carbon atom. In order to probe whether cascade iminium ion reactions could be implemented to fabricate the tricyclic core of cylindricine, the known keto acetal 51xxviii was first condensed with the amino allylsilane 12. Trifluoroacetic acid was then added to the reaction, and the resulting tricyclic iminium was trapped with cyanide ion to provide a mixture (2.8:1.0:1.7:1.7) of diastereomers 52a,b and 53a,b in $66 \%$ combined yield (Scheme 11). Compound 52a was isolated and crystallized, and x-ray crystallographic analysis enabled its unambiguous stereochemical assignment. When the mixture of $\mathbf{5 2 a}, \mathbf{b}$ and $\mathbf{5 3 a}, \mathbf{b}$ was treated with sodium borohydride, an inseparable mixture (1.1:1.0) of the two diastereomeric tricyclic amines $\mathbf{5 4}$ and $\mathbf{5 5}$ was obtained.

As foreshadowed in the introductory discussion of our general approach to polycyclic nitrogen heterocycles via the iminium ion cascade reactions outlined in Scheme 1, we were also intrigued by the possibility of using amino dienylsilanes as $\mathbf{1 3}$ as reacting partners to allow access to more highly functionalized products. Because $\mathbf{1 3}$ was unknown, it was necessary to devise a means for its synthesis. Toward this end propargyl alcohol (56) was treated with allyl chlorodimethylsilane (57) in the presence of base to give silyloxy ether 58 (Scheme 12). Ringclosing enyne metathesis of $\mathbf{5 8}$ using $3 \mathrm{~mol} \%$ of the Grubbs II Hoveyda catalyst $\mathbf{5 9}$ under an ethylene atmosphere gave the volatile cyclic silyloxy ether $\mathbf{6 0}$, which was not isolated by rather treated directly with methylmagnesium bromide to yield the hydroxy allylsilane $\mathbf{6 1}$ in 58\% yield over two steps. ${ }^{\text {xxix }}$ The hydroxyl group of the allylsilane $\mathbf{6 1}$ was converted into an azide function via a Mitsunobu reaction that surprisingly proceeded to give a mixture (3:1) of $E$-and Z-isomers. Preliminary efforts to avoid forming a mixture of geometric isomers were
unsuccessful. Because the obtention of a mixture of geometric isomers was presumably inconsequential for the purpose at hand, we did not attempt to separate the isomers. Subsequent reduction of the azide gave the desired amino $E$-/Z-dienylsilanes $\mathbf{1 3}$.

Gratifyingly, we found that condensation of $\mathbf{1 3}$ with the monoprotected dialdehyde 14 , followed by the addition of trifluoroacetic acid and subsequent nucleophilic trapping with cyanide furnished a separable mixture (18:82) of aminonitriles 62a,b in $32 \%$ combined yield (Scheme 13). The relative chemistry between $\mathrm{C}(5 \mathrm{a})$ and $\mathrm{C}(9)$ was assigned based upon the observation of nOe interactions between the protons at these positions in a GOESY experiment with the minor diastereoisomer 62a. Despite the modest yield in this reaction, the result is noteworthy as it represents the first example of the use of a conjugated dienylsilane in an intramolecular Mannich-like reaction. ${ }^{\mathrm{xxx}}$

## 3. Conclusion

In summary we have developed a number of related cascade reactions in which iminium ions are generated and trapped by allylsilanes and other nucleophiles such as cyanide ion and hydride donors to give functionalized quinolizidines and indolizidines according to the general plan set forth in Scheme 1. This novel cascade sequence features a one-pot process involving the formation of two rings and four new bonds from simple acyclic starting materials. A variety of amino allylsilanes and monoprotected dicarbonyl compounds may serve as inputs in these reactions. The practical utility of this new entry to polycyclic nitrogen heterocycles was convincingly demonstrated by its application to the facile syntheses of a number of quinolizidine and indolizidine alkaloids, including ( $\pm$ )-epilupinine, ( - )-epimyrtine, and ( $\pm$ )tashiromine as well as the tricyclic core structures of the more complex alkaloids halichlorine and cylindricine. Significantly, the amino nitrile function that may be obtained in some of these cascade reactions serves as a convenient functional handle for the introduction of a variety of other substituents onto the heterocyclic framework. Further applications of these processes to the preparation of targets of biological interest are under active investigation, and the results will be reported in due course.

## 4. Experimental

### 4.1 General

Tetrahydrofuran, dimethylformamide, acetonitrile, and toluene were dried according to the procedure described by Grubbs. ${ }^{\text {xxi }}$ All solvents were determined to contain less than 50 ppm $\mathrm{H}_{2} \mathrm{O}$ by Karl Fischer coulometric moisture analysis. Triethylamine was distilled from calcium hydride prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Thin layer chromatography was run on pre-coated silica gel plates with a 0.25 mm thickness containing 60F-254 indicator (Merck), and the plates were visualized by staining with AMCAN (ammonium molybdate/cerium ammonium nitrate), potassium permanganate, or $p$-anisaldehyde. Flash chromatography was performed using the indicated solvent system on 230-400 mesh silica gel (E. Merck reagent silica gel 60) according to Still's protocol.xxxii Melting points are uncorrected. Infrared (IR) spectra were obtained as solutions in the solvent indicated. Proton nuclear magnetic resonance spectra ( ${ }^{1} \mathrm{H} N \mathrm{NR}$ ) were obtained in $\mathrm{CDCl}_{3}$ solutions, and chemical shifts are reported in parts per million (ppm) referenced to the solvent. Coupling constants $(J)$ are reported in Hz and the splitting abbreviations used are: s , singlet; d, doublet; t, triplet; app t, apparent triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Carbon nuclear magnetic resonance spectra ( ${ }^{13} \mathrm{C} \mathrm{NMR}$ ) were obtained using $\mathrm{CDCl}_{3}$ as the internal reference.

### 4.2.1 Representative Procedure for the Reductive Cascade Reaction: Synthesis of ( $1 \mathrm{~S}^{*}$, 9aS*)-1-vinyloctahydro-1H-quinolizine (22)

Freshly prepared amine $\mathbf{1 1}(363 \mathrm{mg}, 2.12 \mathrm{mmol})$ was added dropwise to a suspension of freshly prepared aldehyde $14(310 \mathrm{mg}, 2.12 \mathrm{mmol})$ and molecular sieves ( $4 \AA, 0.50 \mathrm{mg}$ ) in $\mathrm{CH}_{3} \mathrm{CN}$ $(2.0 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The ice bath was removed, and the reaction was stirred for 2 h at which time the solution was transferred via syringe to a flame dried round-bottom flask. Additional $\mathrm{CH}_{3} \mathrm{CN}(30 \mathrm{~mL})$ was added, and the mixture was cooled to $0^{\circ} \mathrm{C}$ with stirring. Freshly distilled $\mathrm{CF}_{3} \mathrm{CO}_{2} \mathrm{H}(2.4 \mathrm{~g}, 1.6 \mathrm{~mL}, 21.2 \mathrm{mmol})$ was added dropwise, and the reaction mixture was stirred for 2 h . The ice bath was removed, and the solution was stirred at room temperature for 12 h . Neat $\mathrm{Et}_{3} \mathrm{SiH}(2.5 \mathrm{~g}, 3.2 \mathrm{~mL}, 21.2 \mathrm{mmol})$ was then added dropwise, and the mixture was heated under reflux for 24 h . The reaction mixture was cooled to room temperature, and the solvents were removed under reduced pressure. The crude residue was dissolved in $\mathrm{Et}_{2} \mathrm{O}$ ( 15 mL ), and a solution of $2 \mathrm{~N} \mathrm{HCl}(15 \mathrm{~mL})$ was added dropwise. The layers were separated, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 15 \mathrm{~mL})$. The aqueous layer was made basic with a solution of $5 \% \mathrm{NaOH}$ saturated with $\mathrm{NaCl}(15 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 15 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure ( 300 mm Hg ). The crude residue was purified by flash chromatography eluting with pentane/EtOH (60:1). An aliquot of the fractions containing pure $\mathbf{2 2}$ was concentrated under reduced pressure ( 300 mm Hg ) to give an analytical sample for characterization. The remaining fractions containing pure 22 were combined, $\mathrm{CF}_{3} \mathrm{CO}_{2} \mathrm{H}(1.5 \mathrm{~mL})$ was added, and the mixture was concentrated under reduced pressure to give $444 \mathrm{mg}(75 \%)$ of the trifluoroacetate salt of $\mathbf{2 2}$ as a single diastereomer as a pale yellow oil; ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 5.60$ (ddd, $J=17.5,10.0$, $9.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.99$ (ddd, $J=17.5,2.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.94(\mathrm{dd}, J=10.0,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.76-2.69$ (comp, 2 H ), 2.00-1.93 (comp, 2 H ), 1.85 (app tdd, $J=11.0,9.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.74 (app dp, $J=13.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.74-1.64(\mathrm{comp}, 2 \mathrm{H}), 1.63-1.54$ (comp, 4 H ), 1.54-1.46 (m, 1 H ), 1.23-1.13 (comp, 2 H ), 1.04 ( $\mathrm{app} \mathrm{dq}, ~ J=10.5,3.5 \mathrm{~Hz}, 1 \mathrm{H}$ ) ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 142.2$, $114.8,66.5,57.2,56.9,48.3,32.5,31.3,26.4,25.6,25.2$; IR (neat) $3400,3079,2953,2869$, $2723,2627,2584,1738,1671,1448,1201 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z}, 166.1591$ $\left[\mathrm{C}_{11} \mathrm{H}_{20} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 166.1596], 164, 194, 248, 327, 329, 341, 399, 401.

### 4.2.2 (1S*, 8aS*)-1-Vinyloctahydroindolizine (23)

Prepared in $45 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 5.70$ (ddd, $\left.J=17.0,10.5,8.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.18$ (ddd, $\left.J=17.0,1.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.18$ (ddd, $J=10.5,1.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.62-3.56 (comp, 2 H ), 3.05-2.97 (m, 1 H ), 2.86-2.74 (comp, $2 \mathrm{H}), 2.64(\mathrm{app} \mathrm{p}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.20(\mathrm{app} \mathrm{ddt}, J=11.5,9.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.04-1.94(\mathrm{~m}, 1$ H), 1.90-1.80 (comp, 3 H ), 1.73-1.64 (m, 1 H), 1.55-1.40 (comp, 2 H ); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 137.9,118.7,70.7,53.4,52.7,47.2,27.6,27.1,23.8,22.8$. The spectral data are in accordance with reported spectra for $\mathbf{2 3}$. ${ }^{\text {ic }}$

### 4.2.3 (8S*, 8aS*)-8-Vinyloctahydroindolizine (24)

Prepared in $36 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 5.71$ (ddd, $\left.J=17.0,10.0,8.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.23(\mathrm{~d}, J=17.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.13(\mathrm{~d}, J=10.0$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 3.70-3.60 (comp, 2 H ), 3.07-2.88 (comp, 2 H ), 2.39-2.33 (m, 1 H), 2.28-2.22 (m, 1 H), 2.06-2.00 (comp, 3 H ), 1.92-1.82 (comp, 2 H ), 1.75-1.67 (m, 1 H ), 1.52-1.44 (m, 1 H); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 138.3,117.7,70.4,54.1,52.3,45.7,30.1,28.4,24.0,20.0$; IR (neat) 2923, 1454, 1376, 725; mass spectrum (CI) m/z $152.143559\left[\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 152.143925], 371, 222, 152 (base), 97.

### 4.2.4 ( $\pm$ )-Epilupinine (1)

The trifluoroactetate salt of $22(75 \mathrm{mg}, 0.27 \mathrm{mmol})$ was dissolved in $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{~mL})$ and ozone was passed through the stirred solution at $-78^{\circ} \mathrm{C}$ until the solution turned blue. Air was then
passed through the reaction mixture for 5 min . A solution of $\mathrm{LiAlH}_{4}(51 \mathrm{mg}, 1.5 \mathrm{mmol})$ in THF ( 2 mL ) was added, the dry ice bath was removed, and the suspension was stirred at room temperature for $12 \mathrm{~h} . \mathrm{H}_{2} \mathrm{O}(0.05 \mathrm{~mL}), 5 \% \mathrm{NaOH}(0.05 \mathrm{~mL})$, and $\mathrm{H}_{2} \mathrm{O}(0.15 \mathrm{~mL})$ were added dropwise sequentially with stirring, and the mixture was stirred until the suspension turned white. The solids were removed by vacuum filtration and washed with $\mathrm{Et}_{2} \mathrm{O}$. The combined filtrate and washings were concentrated under reduced pressure to give $40 \mathrm{mg}(88 \%)$ of $\mathbf{1}$ as a colorless oil. Recrystallization of the crude product from pentane provided a white solid; (mp $79-80^{\circ} \mathrm{C}$; lit. ${ }^{\text {if }} 78-79^{\circ} \mathrm{C}$ ); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{MeOD}$ ) $\delta 3.55(\mathrm{dd}, J=11.0,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.50$ (dd, $J=11.0,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.83-2.74$ (comp, 2 H ), 2.10-2.01 (comp, 2 H ), 1.98-1.94 (m, 1 H ), 1.84-1.54 (comp, 7 H ), 1.37-1.23 (comp, 3 H ), 1.16 (app tdd, $J=13.5,11.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR (125 MHz) $865.8,64.4,57.9,57.7,44.9,30.4,29.3,26.3,25.8,25.4$; IR (neat) 3382, 2940, 2850, 2800, 2750, 2681, 2540, 2252, 2070, 1819, 1795, 1467, 1379, 1298, 1121, 1094 $\mathrm{cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 170.1537\left[\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{NO}(\mathrm{M}+1)\right.$ requires 170.1545], 170 (base), 168,152 . These spectral data are in accordance with reported spectra for ( $\pm$ )-epilupinine. ${ }^{\text {if }}$

### 4.2.5 ( $\pm$ )-Tashiromine (2)

The trifluoroactetate salt of $\mathbf{2 4}(142 \mathrm{mg}, 0.57 \mathrm{mmol})$ was dissolved in $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ and ozone was passed through the stirred solution at $-78^{\circ} \mathrm{C}$ until the solution turned blue. Air was then passed through the reaction mixture for 5 min . A solution of $\mathrm{LiAlH}_{4}(215 \mathrm{mg}, 4.46 \mathrm{mmol})$ in THF ( 3 mL ) was added, the dry ice bath was removed, and the suspension was stirred at room temperature for $12 \mathrm{~h} . \mathrm{H}_{2} \mathrm{O}(0.2 \mathrm{~mL}), 5 \% \mathrm{NaOH}(0.2 \mathrm{~mL})$, and $\mathrm{H}_{2} \mathrm{O}(0.6 \mathrm{~mL})$ were added dropwise sequentially with stirring, and the mixture was stirred until the suspension turned white. The solids were removed by vacuum filtration and washed with $\mathrm{Et}_{2} \mathrm{O}$. The combined filtrate and washings were concentrated under reduced pressure to give $44 \mathrm{mg}(56 \%)$ of $\mathbf{2}$ as a colorless oil; ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 3.46(\mathrm{dd}, J=11.0,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.30(\mathrm{dd}, J=$ $11.0,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.98(\operatorname{app~dp}, J=11.0,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.93(\operatorname{app~dt}, J=9.0,2.5 \mathrm{~Hz}, 1 \mathrm{H})$, $1.98(\mathrm{appq}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.91-1.78(\mathrm{comp}, 3 \mathrm{H}), 1.70-1.48(\mathrm{comp}, 5 \mathrm{H}), 1.40-1.28$ (comp, $2 \mathrm{H}), 1.04-0.90(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 667.3 , 65.4, 54.8, 53.4, 45.6, 29.9, 28.6, 26.1, 21.5; IR (neat) 3622, 3100 (broad peak), 2928, 2876, 2789, 2760, 2755, 2241, 2171, 1459, $1442,1386,1329 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 156.1391\left[\mathrm{C}_{9} \mathrm{H}_{18} \mathrm{NO}(\mathrm{M}+1)\right.$ requires 156.1388], 156 (base). The spectral data are in accordance with reported spectra for ( $\pm$ )tashiromine.iia,d

### 4.3.1 Representative Procedure for the Cascade Reaction with Cyanide-Trapping: Synthesis of ( $4 \mathrm{R}^{\star}, 9 \mathrm{aR} \mathrm{R}^{\star}$ )-8-methyleneoctahydro-1H-quinolizine-4-carbonitrile (31)

Freshly prepared amine $\mathbf{1 2}$ ( $696 \mathrm{mg}, 4.4 \mathrm{mmol}$ ) was added dropwise to a mixture of freshly prepared $14(642 \mathrm{mg}, 4.4 \mathrm{mmol})$ and molecular sieves ( $4 \AA, 0.70 \mathrm{mg}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(2.0 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The ice bath was removed, and the mixture was stirred at room temperature for 2 h . The supernatant was transferred via syringe to another round-bottom flask, and additional $\mathrm{CH}_{3} \mathrm{CN}$ $(50 \mathrm{~mL})$ was added. The mixture was cooled to $-40^{\circ} \mathrm{C}$, and freshly distilled $\mathrm{CF}_{3} \mathrm{CO}_{2} \mathrm{H}(2.5 \mathrm{~g}$, $1.7 \mathrm{~mL}, 22.0 \mathrm{mmol}$ ) was added dropwise. The reaction mixture was stirred at $-40^{\circ} \mathrm{C}$ for 4 h , whereupon the cooling bath was removed and the mixture stirred at room temperature for 2 h . The solvents were removed under reduced pressure and the residue was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(2.2 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. A solution of $\mathrm{NaCN}(1.0 \mathrm{~g}, 20.4 \mathrm{mmol})$ in $\mathrm{H}_{2} \mathrm{O}(3 \mathrm{~mL})$ was added to the reaction, the ice bath was removed and the reaction mixture stirred at room temperature for 12 h. $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ and 0.5 M NaOH saturated with NaCl were added, and the layers were separated. The aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 25 \mathrm{~mL})$, and the combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure ( 300 mmHg ). The crude residue was purified by flash chromatography eluting with pentane/ $\mathrm{Et}_{2} \mathrm{O}$ (10:1). The fractions were combined and concentrated under reduced pressure ( 300 mm Hg ) to give 690 $\mathrm{mg}(89 \%)$ of an epimeric mixture (88:12) of $\mathbf{3 1}$ as a pale yellow oil: For $\alpha \mathrm{H}:{ }^{1} \mathrm{H}$ NMR ( 500 $\left.\mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 4.71-4.67(\mathrm{comp}, 2 \mathrm{H}), 3.90(\mathrm{appt}, J=3.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.82-2.78(\mathrm{~m}, 1 \mathrm{H})$,
2.30-2.20 (comp, 5 H ), 2.07 ( $\mathrm{app} \mathrm{tt}, J=11.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.92-1.85 (m, 1 H ), 1.78 (app ddt, $J=11.0,4.5,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.72-1.62(\mathrm{comp}, 2 \mathrm{H}), 1.54(\mathrm{app} \mathrm{qt}, J=13.5,3.5,1 \mathrm{H}), 1.50-1.28$ $(\mathrm{m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (125 MHz) $\delta 146.0,117.0,107.8,58.2,55.1,54.9,41.7,34.3,32.8,28.8$, 20.4 4. IR (neat) $3061,2925,2812,2223,1653,1438,1279,1172,1115,889 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 177.1400\left[\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 177.1391], 150 (base), 177.

For $\beta-\mathrm{H}:{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 4.71-4.67$ (comp, 2 H ), 3.40 (app dt, $J=10.4,3.2 \mathrm{~Hz}$, 1 H ), 3.06 (app dd, $J=11.6,3.2,1 \mathrm{H}$ ), 2.34-1.20 (comp, 13 H ); ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) $\delta 146.8$, $121.1,108.3,63.6,56.2,55.8,42.4,34.8,33.2,31.7,23.5 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z}$ $177.1400\left[\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 177.1391], 150 (base), 177.

### 4.3.2 (1R*, $\mathbf{6} \mathbf{R}^{*}, 9 \mathrm{aS}{ }^{*}$ )-1-Vinyl-6-cyanoquinolizidine (27)

Prepared in $79 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz})$ $\delta 5.64$ (ddd, $J=17.0,10.0,9.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.02$ (ddd, $J=17.0,2.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.97$ (dd, $J=$ $10.0,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\operatorname{app} \mathrm{t}, J=3.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.67(\operatorname{app~dp}, J=11.0,2.0 \mathrm{~Hz}, 2 \mathrm{H}), 2.33(\mathrm{app}$ $\mathrm{dt}, J=11.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.86-1.44(\mathrm{comp}, 10 \mathrm{H}), 1.28-1.20(\mathrm{~m}, 1 \mathrm{H}), 1.07-0.99(\mathrm{~m}, 1$ H); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 142.1,115.9,99.2,61.2,56.2,54.7,49.0,32.3,31.2,25.7,21.5$; IR (neat) 3075, 2935, 2858, 2814, 2747 (Bohlmann Bands), 2221, 1641, $1442 \mathrm{~cm}^{-1}$; mass spectrum $(\mathrm{CI}) m / z 191.1539\left[\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 191.1548], 164 (base), 191, 220, 236, 263.

### 4.3.3 (4R*, 9aR*)-4-Methyl-8-methyleneoctahydro-1H-quinolizine-4-carbonitrile (32)

Prepared in $65 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\mathrm{C}_{6} \mathrm{H}_{6}$ ) $\delta 4.57-4.55(\mathrm{~m}, 2 \mathrm{H}), 3.10-3.07(\mathrm{~m}, 1 \mathrm{H}), 2.18-2.05(\mathrm{comp}, 5 \mathrm{H}), 1.91-1.86(\mathrm{~m}, 1 \mathrm{H})$, 1.82-1.79 (m, 1 H ), 1.61-1.51 (comp, 4 H ), $1.40(\mathrm{~s}, 1 \mathrm{H}), 1.20-1.15(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 $\mathrm{MHz}) 144.9,119.1,107.7,59.2,49.4,42.1,38.5,34.4,33.2$, 21.2; IR (neat) 2976, 2938, 2860, $2814,1659,1444,1371,1281,1228,1198,1122,1096,1036,890 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 191.1544\left[\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 191.1548], 191, 164 (base).

### 4.3.4 (4R*, 9aR*)-4-Ethyl-8-methyleneoctahydro-1H-quinolizine-4-carbonitrile (33)

Prepared in $60 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz})$ $\delta 4.64-4.63(\mathrm{~m}, 2 \mathrm{H}), 3.10(\mathrm{app} \mathrm{dt}, J=10.7,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.26-2.17(\mathrm{~m}, 4 \mathrm{H}), 2.12-2.06(\mathrm{~m}, 1$ H), 1.98 (app t, $J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.88-1.81(\mathrm{~m}, 3 \mathrm{H}), 1.72-1.60(\mathrm{~m}, 4 \mathrm{H}), 1.28-1.18(\mathrm{~m}, 2 \mathrm{H})$, $0.97(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 145.1, 119.1, 107.5, 62.2, 59.2, 48.9, 42.3, $34.5,33.8,33.2,30.8,21.0,7.4$; IR (neat) 2880, 2838, 2817, 1660, 1444, 1382, 1281, 1186, 1098, $891 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 205.1707\left[\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 205.1705], 205, 178 (base).

### 4.3.5 8-Methylene-4-(prop-1-ynyl)octahydro-1H-quinolizine-4-carbonitrile (34)

Prepared in $75 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\left.\mathrm{CD}_{3} \mathrm{CN}\right) \delta 4.66(\mathrm{ddt}, J=11.3,1.8,1.7 \mathrm{~Hz}, 2 \mathrm{H}), 3.61(\mathrm{ddd}, J=10.6,4.7,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.36-2.28$ (m, 2 H$), 2.27-2.17$ (m, 4H), 2.10-1.95 (m, 2 H ), 1.85 (s, 3 H$)$ 1.73-1.62 (m, 3 H ) 1.34-1.24 (m, 1 H ); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 144.7, 115.4, 108.2, 82.2. 75.6, 58.4, 56.8, 51.8, 41.9, 38.4, 34.3, 32.5, 20.5, 3.6; IR (neat) 2939, 2868, 2819, 2360, 1658, 1442, 1284, 1207, 1106, 1018, $\mathrm{cm}^{-1}$; mass spectrum (CI) $m / z 215.1552\left[\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 215.1548], 219 (base), 215, 205.

### 4.3.6 (4R)-2-Methylenyl-4-methyl-6-cyanoquinolizidine (40)

Prepared in $90 \%$ yield in accordance with the representative procedure. ${ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 4.70(\mathrm{appt}, J=2.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.35(\operatorname{app} \mathrm{t}, J=3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.35-2.18$ (comp, 4 H ), 2.07-1.95 (comp, 3 H ), 1.82-1.70 (comp, 3 H ), 1.59 (app qt, $J=12.0,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.31-1.23
$(\mathrm{m}, 1 \mathrm{H}), 1.14(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 146.3,117.4,107.8,59.3,58.3$, 50.7, 43.7, 42.8, 33.9, 29.6, 21.3, 20.3; IR (neat) 3074, 2939 2868, 2825, 2736, 2221, 1778, 1726, 1659, 1444, 1379, 1328, $1182 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 191.1541\left[\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}(\mathrm{M}\right.$ +1 ) requires 191.1548], 220, 191, 164 (base).

### 4.3.7 7-Vinyl-1,3,4,6,9,9a-hexahydro-2H-quinolizine-4-carbonitrile (62a, 62b)

Prepared in $79 \%$ yield in accordance with the representative procedure. $(\beta-\mathrm{CN}){ }^{1} \mathrm{H}$ NMR ( 500 $\mathrm{MHz}) \delta 6.27(\mathrm{dd}, J=17.8,10.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.27(\mathrm{~s}, 1 \mathrm{H}), 5.06(\mathrm{~d}, J=17.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.96(\mathrm{~d}, J$ $=10.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{~d}, J=15.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.08(\mathrm{dd}, J=12.1,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.81(\mathrm{dd}, J=15.1$, $2.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.20-2.08(\mathrm{comp}, 4 \mathrm{H}), 1.98-1.90(\mathrm{~m}, 1 \mathrm{H}), 1.84-1.81(\mathrm{~m}, 1 \mathrm{H}), 1.76-1.73(\mathrm{~m}, 1$ H), 1.37-1.29 (comp, 2 H ); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 136.6, 132.2, 125.7, 119.3, 111.0, 57.0, 55.8, 52.7, 33.9, 32.2, 30.7, 22.9; IR (neat) 2867, 2817, 2787, 2356, 1661, 1611, 1440, 1370, 1310, $1249,1165,1119,1044,994,894,853 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 189.1397\left[\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{2}\right.$ $(\mathrm{M}+1)$ requires 189.1392$], 252,217,189,163($ base $) .(\alpha-\mathrm{CN}){ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}) \delta 6.28(\mathrm{dd}$, $J=11.01,17.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.71(\mathrm{~s}, 1 \mathrm{H}), 5.01(\mathrm{~d}, J=17.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.95(\mathrm{~d}, J=11.0 \mathrm{~Hz}, 1 \mathrm{H})$, 3.97 (app t, $J=3.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.31 (comp, 2 H ), $2.55-2.52(\mathrm{~m}, 1 \mathrm{H}), 2.26(\mathrm{~d}, J=16.7 \mathrm{~Hz}, 1 \mathrm{H})$, 2.07-1.80 (m, 4 H ), 1.84-1.81 (m, 1 H ), 1.77-1.71 (m, 2 H ), 1.27-1.21 (comp, 1 H ); ${ }^{13} \mathrm{C}$ NMR $(125 \mathrm{MHz}) 136.7,132.9,125.4,117.1,110.8,54.9,52.0,51.2,33.9,32.9,28.8,20.3$; IR (neat) $2870,2849,2822,2361,1657,1144,1440,1267,1127,852,837,738 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m z 189.1391\left[\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 189.1392], 189, 162 (base).

## 4.4 (4R)-2-Methylenyl-4-methylquinolizidine (41)

Acetic acid ( $276 \mathrm{mg}, 4.6 \mathrm{mmol}$ ) was added dropwise to a solution of $\mathrm{NaBH}_{3} \mathrm{CN}(145 \mathrm{mg}, 2.3$ $\mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(2 \mathrm{~mL})$ with stirring, whereupon $\mathbf{1 8}(88 \mathrm{mg}, 0.46 \mathrm{mmol})$ was added dropwise over 2 min . The solution was stirred for 24 h at rt , and then $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ and a solution of $2 \mathrm{~N} \mathrm{HCl}(5 \mathrm{~mL})$ were added. The layers were separated, and the aqueous layer was made basic with a solution of $5 \% \mathrm{NaOH}$ saturated with NaCl and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 15 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right), \mathrm{CF}_{3} \mathrm{CO}_{2} \mathrm{H}(60 \mathrm{mg})$ was added dropwise, and the crude mixture was concentrated under reduced pressure to give $111 \mathrm{mg}(86 \%)$ of $\mathbf{4 0}$ as an inseparable mixture (95:5) of diastereomers (based on GC/MS and ${ }^{1} \mathrm{H}$ NMR) as a pale yellow oil. Major isomer - ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 4.85$ (app t, $J=2.0, \mathrm{~Hz}, 2 \mathrm{H}$ ), 3.77-3.70 $(\mathrm{m}, 1 \mathrm{H}), 3.06(\mathrm{app} \mathrm{ttd}, J=10.0,6.5,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.95(\mathrm{app} \mathrm{tdt}, J=12.0,9.0,3.0 \mathrm{~Hz}, 1 \mathrm{H})$, 2.65 (app tdd, $J=13.0,10.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.54-2.33$ (comp, 4 H ), 1.92-1.89 (comp, 2 H ), 1.81-1.70 (comp, 2 H ) 1.49 (app tdd, $J=17.0,7.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.36 (d, $J=6.5 \mathrm{~Hz}, 1$ $\mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 140.9,111.8,66.6,63.7,52.3,40.6,39.3,31.7,24.3,22.6,17.8$; IR $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}\right) 2943,2869,2263,1785,1673,1453,1415,1198,1131 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 166.1591\left[\mathrm{C}_{11} \mathrm{H}_{20} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 166.1596], 107, 150, 166 (base), 224. The spectral data were in accordance with reported values. iiib

## 4.5 (-)-Epimyrtine (3a)

The trifluoroacetate salt of $\mathbf{1 9}(115 \mathrm{mg}, 0.41 \mathrm{mmol})$ was dissolved in a mixture of $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3$ $\mathrm{mL})$ and $\mathrm{MeOH}(0.5 \mathrm{~mL})$ and ozone was bubbled through the solution at $-78^{\circ} \mathrm{C}$ until a blue color persisted ( 5 min ). Air was passed through the reaction mixture for 5 min . Methyl sulfide $(128 \mathrm{mg}, 0.15 \mathrm{~mL}, 2.06 \mathrm{mmol})$ was added dropwise, the dry ice bath was removed and the reaction mixture stirred at room temperature for 12 h . A solution of $5 \% \mathrm{NaOH}$ saturated with $\mathrm{NaCl}(1 \mathrm{~mL})$ was added dropwise with stirring. The layers were separated, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 15 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure $(300 \mathrm{~mm} \mathrm{Hg})$. The residue was purified by flash chromatography eluting with hexanes/EtOH (10:1) to give 40 mg ( $60 \%$ ) of a mixture (95:5) of 3a and 3b as a pale yellow oil. $[\alpha]^{23}{ }_{\mathrm{D}}{ }^{-18.0}\left(c 0.4, \mathrm{CDCl}_{3}\right)$; [lit. $\mathrm{iiib}\left([\alpha]^{20}{ }_{\mathrm{D}}{ }^{-17.4}\right.$ (c 0.7, $\mathrm{CHCl}_{3}$ ); $\left.\left.[\alpha]^{23} \mathrm{D}^{-19.0(c ~ 0.4, ~} \mathrm{CHCl}_{3}\right)\right] ;{ }^{1} \mathrm{H} \operatorname{NMR}(500 \mathrm{MHz}) \delta 3.30-3.26(\mathrm{~m}, 1 \mathrm{H})$,
2.40-2.12 (comp, 6 H), 1.83-1.52 (comp, 5 H), 1.41-1.33 (m, 1 H), 1.30-1.20 (m, 1 H ), 1.17 $(\mathrm{d}, J=5.5 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 208.4,62.1,59.3,51.0,49.8,48.7,34.2,25.9$, 23.9, 20.7; IR (neat) 2929, 2846, 2788, 2741, 1718, 1442, 1336, 1283, $1166 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 168.1388\left[\mathrm{C}_{10} \mathrm{H}_{18} \mathrm{NO}(\mathrm{M}+1)\right.$ requires 168.1388], 240, 196, 168 (base), 152. The spectral data were in accordance with reported values for $(-)$-epimyrtine. iii

### 4.6 6-Cyano-6-(3'-methyltrimethylsilyl-3'-butenyl)-2-methylenylquinolizidine (44)

A solution of $n$-butyllithium in hexanes ( 0.21 mL of $2.5 \mathrm{M}, 0.44 \mathrm{mmol}$ ) was added dropwise to a solution of diisopropylamine ( $101 \mathrm{mg}, 0.07 \mathrm{~mL}, 0.44 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$. The solution was stirred for 0.5 h at which time $31(60 \mathrm{mg}, 0.35 \mathrm{mmol})$ was added dropwise. The reaction mixture was stirred for 0.5 h , and $43(215 \mathrm{mg}, 0.69 \mathrm{mmol})$ was added dropwise. The ice bath was removed, and the reaction was stirred for 1 h . A solution of 0.5 M NaOH saturated with $\mathrm{NaCl}(5 \mathrm{~mL})$ was added, and the layers were separated. The aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 10 \mathrm{~mL})$, and the combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/ $\mathrm{Et}_{2} \mathrm{O}$ (95:5) to give $67 \mathrm{mg}(62 \%)$ of 44 as a pale yellow oil. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}$, $\mathrm{CD}_{3} \mathrm{CN}$ ) $\delta 4.67-4.54(\mathrm{comp}, 4 \mathrm{H}$ ), 3.14 (app dq, $J=11.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.29-1.15 (comp, 16 H), 1.57 (s, 3 H ), 0.02 (s, 9 H ); ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 148.0,146.9,119.8,107.8,107.8,62.6$, $60.5,50.2,27.4,-1.3,42.9,37.0,35.2,35.0,33.8,31.5,21.9$; IR (neat) 3067, 2939, 2820, 2726, $2358,2213,1658,1632,1440,1239 \mathrm{~cm}^{-1}$; mass spectrum (CI) m/z $317.2408\left[\mathrm{C}_{19} \mathrm{H}_{32} \mathrm{NSi}(\mathrm{M}\right.$ +1 ) requires 317.2413], 290 (base), 154, 218, 274, 317.

### 4.7 6-(2'-Methenylcyclopentyl)-2-methylenylquinolizidine (45)

Silver triflate ( $55 \mathrm{mg}, 0.22 \mathrm{mmol}$ ) was added to a suspension of $4 \AA$ molecular sieves $(0.10$ $\mathrm{mg})$ in $\mathrm{CH}_{3} \mathrm{CN}(0.5 \mathrm{~mL})$ at room temperature. The suspension was wrapped in tin foil and a solution of cyano amine $44(62 \mathrm{mg}, 0.20 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(0.5 \mathrm{~mL})$ was added dropwise. The resulting mixture was stirred at room temperature for 1 h , at which time the suspension was filtered through a cotton plug and washed with $\mathrm{CH}_{3} \mathrm{CN}(2 \mathrm{~mL})$. The combined supernatant was heated at $120^{\circ} \mathrm{C}$ (oil bath) with stirring for 24 h . The reaction was cooled to room temperature, and $\mathrm{Et}_{2} \mathrm{O}(10 \mathrm{~mL})$ was added. A solution of $2 \mathrm{~N} \mathrm{HCl}(5 \mathrm{~mL})$ was added, and the layers were separated. The aqueous layer was washed with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$ and then made basic with a solution of $5 \% \mathrm{NaOH}$ saturated with NaCl . The mixture was then extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5$ $\mathrm{mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure to give $34 \mathrm{mg}(81 \%)$ of $\mathbf{4 5}$ as a single diastereomer (based on ${ }^{1} \mathrm{H} N \mathrm{NR}$ ) as a colorless oil. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 4.77(\operatorname{app} \mathrm{p}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.74(\operatorname{app} \mathrm{p}, J=2.0 \mathrm{~Hz}, 1$ H), 4.59-4.56 (m, 1 H), 4.56 (br s, 1H), 3.00 (app dt, $J=9.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.48(\mathrm{~d}, J=16.5$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 2.31-2.11 (comp, 6 H ), 2.10-1.98 (comp, 2 H ), 1.86 (dddd, $J=11.5,9.5,2.0,1.5 \mathrm{~Hz}$, $1 \mathrm{H}), 1.55-1.40(\mathrm{comp}, 5 \mathrm{H}), 1.32-1.25(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (125 MHz) $\delta 153.7$, 148.1, 107.0, 106.0, 66.9, 58.9, 47.9, 43.5, 39.2, 37.9, 36.0, 35.6, 33.0, 31.6, 21.8; IR ( $\left.\mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$ 2943, 2872, $2249,1672,1443,1414,1196 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 218.1904\left[\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 218.1908], 250, 218 (base), 152, 109.

### 4.8 2-Methylenyl-6-cyano-6-butenylquinolizidine (49)

A solution of $n$-butyllithium in hexanes $(0.74 \mathrm{~mL}$ of $2.5 \mathrm{M}, 1.40 \mathrm{mmol})$ was added dropwise to a solution of $i-\mathrm{Pr}_{2} \mathrm{NEt}(0.17 \mathrm{~mL}, 1.40 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The solution was stirred for 0.5 h and then was cooled to $-78^{\circ} \mathrm{C}$. Cyanoamine $\mathbf{3 1}(211 \mathrm{mg}, 1.20 \mathrm{mmol})$ was added dropwise with stirring and the dry-ice/acetone bath was replaced with an ice-water bath. The mixture was stirred for 0.5 h at $0^{\circ} \mathrm{C}$ then cooled to $-78^{\circ} \mathrm{C}$. 4 -Bromobutene ( $186 \mathrm{mg}, 0.14 \mathrm{~mL}$, 1.4 mmol ) was added dropwise, and the dry-ice/acetone bath was again replaced with an icewater bath. The reaction was stirred for 1 h at $0^{\circ} \mathrm{C}$, whereupon a solution of $0.5 \mathrm{M} \mathrm{NaOH}(10$ mL ) was added dropwise. The ice bath was removed, and the mixture was stirred for 15 min .

The layers were separated, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 10 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure ( 300 $\mathrm{mm} \mathrm{Hg})$. The crude residue was purified by flash chromatography eluting with pentane $/ \mathrm{Et}_{2} \mathrm{O}$ (9:1) to give $137 \mathrm{mg}(50 \%)$ of 49 as a single diastereomer of a pale yellow oil; ${ }^{1} \mathrm{H}$ NMR ( 500 $\left.\mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 5.84(\mathrm{ddt}, J=17.0,10.0,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.07(\mathrm{dq}, J=17.0,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.97$ (ddt, $J=10.0,2.0,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.65(\mathrm{dp}, J=8.0,2.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.15(\mathrm{ddd}, J=10.0,4.5,2.5$ $\mathrm{Hz}, 1 \mathrm{H}), 2.27-2.06(\mathrm{comp}, 6 \mathrm{H}), 2.10(\mathrm{app} \mathrm{tt}, J=11.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.00-1.91(\mathrm{comp}, 3 \mathrm{H})$, $1.86-1.80(\mathrm{comp}, 2 \mathrm{H}), 1.75$ (app dt, $J=13.5,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.68-1.61$ (comp, 2 H ), 1.56 (app tdd, $J=17.5,8.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.20(\mathrm{app} \operatorname{tdd}, J=15.0,11.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (125 MHz ) $\delta 146.9,138.8,119.7,115.6,107.8,62.6,60.5,50.2,42.9,37.7,35.1,35.0,33.8,27.6$, $21.9 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z} 204$ (base), 231.

### 4.9 6-(1'-Propynyl)-6-(3'-butenyl)-2-methylenylquinolizidine (50)

A solution of propynylmagnesium chloride in $\mathrm{Et}_{2} \mathrm{O}(3.4 \mathrm{~mL}$ of $0.5 \mathrm{M}, 1.7 \mathrm{mmol})$ was added dropwise to a solution of cyanoamine $49(137 \mathrm{mg}, 0.60 \mathrm{mmol})$ in THF $(3.0 \mathrm{~mL})$ at room temperature. The solution was stirred for 5 h , at which time a solution of $2 \mathrm{~N} \mathrm{HCl}(5 \mathrm{~mL})$ was added dropwise. The layers were separated, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}$ (3 $\times 5 \mathrm{~mL}$ ). The aqueous layer was made basic with a solution of $5 \% \mathrm{NaOH}$ saturated with NaCl and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ and concentrated under reduced pressure to give $116 \mathrm{mg}(80 \%)$ of $\mathbf{5 0}$ as a single diastereomer (based on ${ }^{1} \mathrm{H}$ NMR) as a colorless oil; ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{CN}\right) \delta 5.84$ (ddt, $J=17.0$, $10.5,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.02(\mathrm{dq}, J=17.0,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.92(\mathrm{dq}, J=9.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.58$ (dd, $J=4.0,2.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.00(\mathrm{ddd}, J=11.0,4.5,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.21-2.06(\mathrm{comp}, 6 \mathrm{H}), 2.00(\mathrm{app}$ $\mathrm{td}, J=11.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.87(\mathrm{app} \mathrm{t}, J=12.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.79(\mathrm{~s}, 3 \mathrm{H}), 1.76$ (ddd, $J=16.5$, $14.0,5.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.70-1.60 (comp, 2 H ), 1.59-1.49 (comp, 4 H ), 1.14 (app dtd, $J=15.5,13.5$, $4.0 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) $\delta 148.4,140.2,114.6,106.8,82.0,80.1,59.4,59.2,49.3$, $43.5,40.6,37.1,35.6,34.8,30.9,28.3,21.8 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / z 244.2074$ $\left[\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 244.2065], 244 (base), 204, 188.

### 4.10 (6R,9aR)-6-(But-3-enyl)-2-methylene-6-(prop-1-ynyl)octahydro-1H-quinolizine (46)

4-Bromo-butene ( $0.23 \mathrm{~mL}, 2.27 \mathrm{mmol}$ ) was added to a suspension of Mg ( $48 \mathrm{mg}, 1.98 \mathrm{mmol}$ ) in THF ( 3 mL ), and the solution was heated to $70^{\circ} \mathrm{C}$ for 1.5 h . A portion of the solution ( 1 mL ) was added to $34(14 \mathrm{mg}, 0.07 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(0.40 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$. The reaction was allowed to warm to room temperature with stirring over 8 h . The reaction was cooled to $0^{\circ} \mathrm{C}$, and $2.9 \mathrm{~N} \mathrm{HCl}(3 \mathrm{~mL})$ was added. The mixture was washed with $\mathrm{Et}_{2} \mathrm{O}(3 \times 4 \mathrm{~mL})$. The aqueous layer was cooled to $0^{\circ} \mathrm{C}, 6 \mathrm{~N} \mathrm{NaOH}(5 \mathrm{~mL}$.) was added, and the mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 3 \mathrm{~mL})$. The combined organic extracts were concentrated under reduced pressure to yield $17 \mathrm{mg}(100 \%)$ of $\mathbf{4 6}$ as a single diastereomer of a clear oil. ${ }^{1} \mathrm{H}$ NMR $(500 \mathrm{MHz}) \delta$ 5.89-5.81 (comp, 1 H ), 5.04-5.00 (ddt, $J=17.2,1.8,1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.94-4.91 (ddt, $J=10.2,1.4$, $1.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.59-4.56(\mathrm{~m}, 2 \mathrm{H}), 3.50-3.48(\mathrm{~m}, 1 \mathrm{H}), 2.34-2.29(\mathrm{app} \mathrm{tt}, J=10.9,3.1 \mathrm{~Hz}, 1 \mathrm{H})$ $2.25-2.12(\mathrm{~m}, 5 \mathrm{H}) 2.03-1.86(\mathrm{~m}, 3 \mathrm{H}) 1.81(\mathrm{~s}, 3 \mathrm{H}) 1.76-1.70(\mathrm{app} \mathrm{td}, J=12.8,5.4 \mathrm{~Hz}, 1 \mathrm{H})$ $1.64-1.55(\mathrm{~m}, 5 \mathrm{H}), 1.50-1.45(\mathrm{~m}, 1 \mathrm{H}) 1.40-1.32(\mathrm{appqt}, J=13.3,3.3 \mathrm{~Hz}, 1 \mathrm{H}) 1.28-1.20(\mathrm{~m}$, $1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 147.9, 139.5, 114.2, 106.5, 84.0, 78.6, 58.5, 55.9, 49.6, 43.7, 35.8, $35.7,34.5,30.0,26.7,19.3,3.6$; IR (neat) 2934, 2863, 2812, 1656, 1450, 1091, $885 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 244.2066\left[\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 244.2065], 269, 244 (base), 243.

### 4.11 Spirocycle 47

A solution of $46(121 \mathrm{mg}, 0.50 \mathrm{mmol})$ in $3 \% \mathrm{HCl} / \mathrm{MeOH}(5 \mathrm{~mL})$ was stirred at room temperature for 15 min . and then concentrated. The resulting salt was dissolved in benzene ( 10 mL ) that had been sparged with ethylene, and a solution of Grubbs II catalyst ( $34 \mathrm{mg}, 0.04$ mmol ) in benzene ( 2 mL ) was added. The reaction was stirred at room temperature under
ethylene for 36 h , whereupon 3 M NaOH in saturated brine ( 10 mL ) was added. The mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 20 \mathrm{~mL})$, and the combined organic layers were washed with brine $(15 \mathrm{~mL})$, dried $\left(\mathrm{MgSO}_{4}\right)$, filtered and concentrated. The crude material was purified by silica gel column chromatography eluting with a $5-10 \%$ gradient of ether/pentane to yield 118 mg $(97 \%)$ of 47 as a colorless oil. ${ }^{1} \mathrm{H}$ NMR ( 500 MHz$) \delta 6.19(\mathrm{~d}, J=3.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.71(\mathrm{t}, J=2.7$ $\mathrm{Hz}, 1 \mathrm{H}), 4.92(\mathrm{~s}, 1 \mathrm{H}), 4.56-4.55(\mathrm{~m}, 2 \mathrm{H}), 2.74(\mathrm{ddd}, J=11.3,4.1,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.26-2.22$ (m, 2 H) 2.16-2.01 (m, 6 H) 1.96 (td, $J=10.7,4.5 \mathrm{~Hz}, 1 \mathrm{H}) 1.90-1.86(\mathrm{~m}, 1 \mathrm{H}) 1.89$ (s 3 H ) $1.69-1.50(\mathrm{~m}, 5 \mathrm{H}), 1.34-1.29(\mathrm{~m}, 1 \mathrm{H}), 1.29-1.24(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 125 MHz ) 148.6, 148.3, $138.1,128.8,113.4,105.9,74.2,57.8,48.9,43.9,35.6,35.2,35.0,29.9,24.6,23.3,21.3$; IR (neat) $2934,2859,1655,1444,1374,1100,1026,907,884 \mathrm{~cm}^{-1}$; mass spectrum (CI) $\mathrm{m} / \mathrm{z}$ $244.2066\left[\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 244.2065], 244, 243 (base), 242.

### 4.12 2-Methylenedodecahydropyrido[1,2-j]quinoline-6-carbonitrile (52a, 52b, 53a, 53b)

A solution of 2-(3,3-dimethoxypropyl)cyclohexanone ( $76 \mathrm{mg}, 0.38 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}$ ( 2 mL ) was added to a solution of 3-((trimethylsilyl)methyl)but-3-en-1-amine ( $60 \mathrm{mg}, 0.36 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(1 \mathrm{~mL})$ with $4 \AA$ molecular sieves ( 5 beads). The reaction was heated under reflux for 4 h under nitrogen. The reaction was cooled, and stirring was continued for 2 h at room temperature. The $4 \AA$ molecular sieves were removed, the reaction was cooled to $-40^{\circ} \mathrm{C}$, and $\mathrm{CF}_{3} \mathrm{CO}_{2} \mathrm{H}(3 \mathrm{~mL}, 40 \mathrm{mmol})$ was added. The reaction was allowed to warm to room temperature over 3 h and then stirred at room temperature for 21 h . The reaction was concentrated under reduced pressure, and the residue was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$. The reaction was cooled to $0^{\circ} \mathrm{C}, \mathrm{NaCN}$ aq. ( 1.9 mL of a 2 M soln.) was added, the ice bath was removed, and the reaction was stirred at room temperature for 4 h . The reaction was cooled to $0^{\circ} \mathrm{C}$, saturated $\mathrm{K}_{2} \mathrm{CO}_{3}(5 \mathrm{~mL})$ was added, and the mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$. The combined organic layers were washed with brine ( 10 mL ), dried $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with a $10-20 \%$ gradient of ether/pentane to yield $66 \mathrm{mg}(68 \%)$ of 52a, 52b, 53a, and 53b as a (2.8:1:1.7:1.7) mixture of isomers. The major isomer 52a was crystallized from ether/pentanes. For 52a: ${ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}) \delta 4.79(\operatorname{app~dd}, J=3.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.66(\operatorname{app} \mathrm{dd}, J=3.9,2.0$ $\mathrm{Hz}, 1 \mathrm{H}), 3.77-3.75(\mathrm{~m}, 1 \mathrm{H}), 3.10(\mathrm{td}, J=11.9,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.88(\mathrm{dd}, J=13.1,3.2 \mathrm{~Hz}, 1 \mathrm{H})$, 2.54 (ddd, $J=11.5,6.3,1.8 \mathrm{~Hz}, 1 \mathrm{H}) 2.38-2.20(\mathrm{~m}, 2 \mathrm{H}) 2.12-1.71(\mathrm{~m}, 6 \mathrm{H}) 1.60(\mathrm{~m}, 1 \mathrm{H})$ 2.37-2.22 (m, 2 H ), 1.69-1.50 (m, 5 H), 1.50-1.37 (m, 2 H); ${ }^{13} \mathrm{C}$ NMR ( 100 MHz ) 143.5, 120.7, 109.9, 58.1, 50.1, 48.6, 43.5, 41.9, 34.1, 29.2, 28.2, 22.7, 22.2, 20.5; IR (neat) 2932, 2863, $2360,1652,1456,888 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 231.1861\left[\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{2}(\mathrm{M}+1)\right.$ requires 231.1858], 243, 231 (base), 230.

### 4.13 2-Methylenedodecahydropyrido[1,2-j]quinoline $(54,55)$

Solid $\mathrm{NaBH}_{4}(27 \mathrm{mg}, 0.71 \mathrm{mmol})$ was added to a solution of $\mathbf{5 3 a - d}(32.4 \mathrm{mg}, 0.14 \mathrm{mmol})$ in $\mathrm{MeOH}(5 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The reaction was warmed to room temperature and then heated at $50^{\circ}$ C (oil bath) for 3 h . The reaction mixture was cooled to room temperature, $\mathrm{HCl}(1 \mathrm{M}, 2 \mathrm{~mL})$ was added, and the mixture was washed with $\mathrm{Et}_{2} \mathrm{O}(3 \times 4 \mathrm{~mL}) . \mathrm{NaOH}$ aq. $(2.5 \mathrm{M}, 3 \mathrm{~mL})$ was added, and the mixture was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 3 \mathrm{~mL})$. The combined ethereal extracts were concentrated under reduced pressure to yield $17 \mathrm{mg}(60 \%)$ of an inseparable mixture (1.1:1.0) of $\mathbf{5 4}$ and $\mathbf{5 5} .{ }^{1} \mathrm{H}$ NMR of the mixture $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.77-4.61$ (comp, 4 H ), 4.08 (dd, $J=12.1,5.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.38-3.21 (m, 1 H$), 2.87-2.83(\mathrm{~m}, 1 \mathrm{H})$, 2.70-2.38 (comp, 6 H), 2.28-1.16 (comp, 29 H ); ${ }^{13} \mathrm{C}$ NMR (100 MHz) 145.0, 143.4, 120.3, 109.6, 108.8, 58.7, $57.0,49.7,49.2,47.0,45.3,44.4,43.2,41.8,34.4,34.1,31.2,28.5,28.0,27.9,27.6,25.9,25.8$, 25.7, 25.6, 22.0, 21.9, 20.5; IR (neat) 2928, 2862, 2810, 1650, 1454, 1352, $1120 \mathrm{~cm}^{-1}$; mass spectrum (CI) $m / z 206.19146\left[\mathrm{C}_{14} \mathrm{H}_{24} \mathrm{~N}(\mathrm{M}+1)\right.$ requires 206.1909], 204, 206 (base).

## Supplementary Material

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9


10: $\mathrm{m}=0$
11: $m=1$


12


13

Scheme 1.


## Scheme 2.




Scheme 3.


Scheme 4.


Scheme 5.

35
36: $\mathrm{R}_{3} \mathrm{Si}=\mathrm{TIPS} ; \mathrm{R}=\mathrm{Me}$
37: $\mathrm{R}_{3} \mathrm{Si}=$ TBDPS; $\mathrm{R}=\mathrm{Et}$
38: $\mathrm{R}_{3} \mathrm{Si}=$ TBDPS; $\mathrm{R}=\mathrm{C} \equiv \mathrm{CCH}_{3}$

1) $\mathrm{HC}(\mathrm{OMe})_{3}$, acid, MeOH
2) $(n-\mathrm{Bu})_{4} \mathrm{NF}, \mathrm{THF}$
3) IBX or PDC


28: $R=M e$
29: $R=E t$
30: $\mathrm{R}=\mathrm{C} \equiv \mathrm{CCH}_{3}$

Scheme 6.


## Scheme 7.



Scheme 8.


## Scheme 9.



Scheme 10.


Scheme 11.


Scheme 12.


Scheme 13.


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    Supporting Information Available: Experimental procedures for the preparation of 13, 28-30, 58 and 61. Copies of ${ }^{1} \mathrm{H}$ NMR spectra for all new compounds, as well as ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of epilupinine (1), tashiromine (2), and epimyrtine (3) and a CIF file for 52a.

