



Iminium ion cascade reactions: stereoselective synthesis of quinolizidines and indolizidines

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ABSTRACT

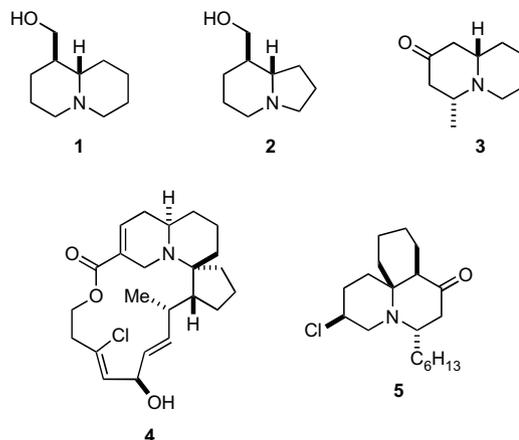
A novel iminium ion cascade reaction has been developed that allows for the stereoselective synthesis of a variety of substituted aza-fused bicycles. The combination of amino allylsilanes and aldehydes (or ketones) was used to synthesize a number of quinolizidines and indolizidines in a one-pot reaction sequence. This technology has been used to effect the facile syntheses of several indolizidine and quinolizidine natural products including (\pm)-epilupinine, (\pm)-tashiromine, and (–)-epimyrtime. 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.

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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**),¹ tashiromine (**2**),² and epimyrtime (**3**)³ to more complex multicyclic molecules like halichlorine (**4**)⁴ and cylindricine B (**5**).⁵ 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.⁶

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.^{4e,7} 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.⁸ 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

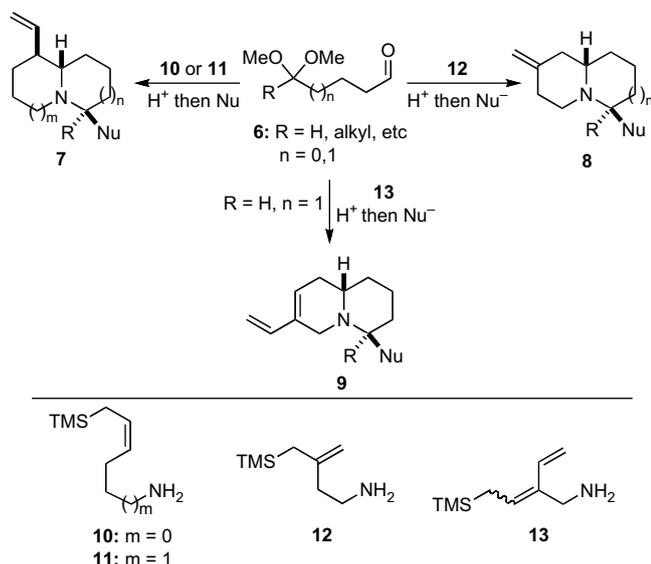


tools because they involve multiple reactants and sequential bond-forming events in which the product of one reaction is pre-programmed to be the starting material for the next one in a domino-like process.⁹ Such methods have gained popularity because they may enable the rapid assembly of complex molecular architectures in one-pot operations that can be highly efficient.¹⁰

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

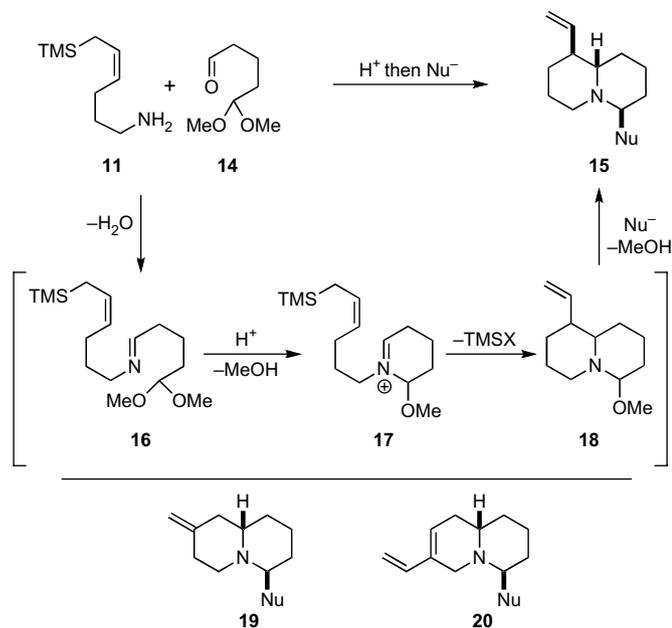
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the synthesis of a diverse array of nitrogen heterocycles **7–9** from the cascade reactions of monoprotected dicarbonyl compounds of the general form **6** with the amino allylsilanes **10–13**, followed by a terminating step in which the penultimate 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**.¹¹ An attractive feature of this entry to quinolizidines and indolizidines is the high level of convergence wherein three components may be integrated into a product in a single chemical operation.



Scheme 1.

The putative mechanistic underpinnings for forming bicyclic nitrogen heterocycles related to **7** are exemplified in Scheme 2 for the formation of **15** from the acid-catalyzed reaction of the amino allylsilane **11** with the monoprotected dialdehyde **14**, which corresponds to **6** ($R=H, n=1$), followed by quenching the penultimate iminium ion intermediate with a generic nucleophile, Nu^- . Thus, the sequence commences with the condensation of **11** with **14** to

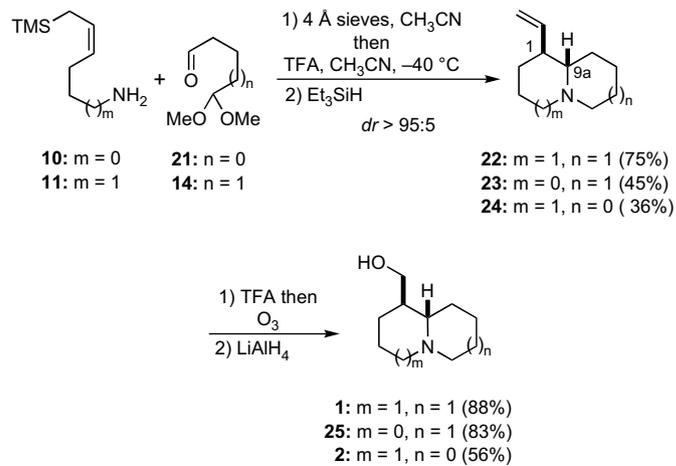


Scheme 2.

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 **17** that could in turn undergo cyclization via addition of the allylsilane moiety to the iminium ion to provide **18**.^{8a,12} Ionization of the N,O -acetal moiety of **18** in situ would generate another iminium ion that would be trapped with the nucleophile, Nu^- , to deliver the fused bicyclic amine **15**. Based upon principles of stereoelectronic control,¹³ 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 **14** with the branched allylsilane **12** and the pentadienyl silane **13** to give **19** and **20**, 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 **11**¹⁴ with the monoacetal aldehyde **14**, which was prepared by the procedure of Schreiber,¹⁵ 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 $-40^\circ C$ in acetonitrile in the presence of trifluoroacetic acid. After adding triethylsilane to reduce the putative iminium ion generated in situ, the quinolizidine **22** was isolated in 75% yield as a single diastereomer (Scheme 3).



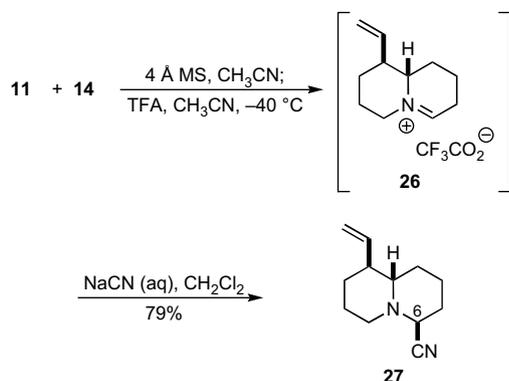
Scheme 3.

Using the standardized conditions developed for the optimized preparation of **22**, the known allyl aminosilane **10**¹⁶ was allowed to condense with the aldehyde **14**, and the resultant imine was treated sequentially with TFA and then Et_3SiH to provide the indolizidine **23** as a single stereoisomer in 45% yield.^{1c} Similarly, reaction of the allylic aminosilane **11** with the monoprotected dialdehyde **21**,¹⁵ followed by addition of TFA and then Et_3SiH furnished the indolizidine **24** in 36% yield as a single stereoisomer. The relative stereochemistry between the two newly created stereocenters at C(1) and C(9a) of **22** was tentatively assigned based upon the observed coupling constant of 12.0 Hz of the trifluoroacetate salt of **22**. This assignment as well as the structural assignments for **23** and **24** 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 **24** might be readily transformed into natural quinolizidines and indolizidines. Indeed, although compound **22** was a known intermediate in a previous synthesis of (±)-epilupinine (**1**),^{1c} 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 LiAlH₄ furnished synthetic (±)-epilupinine (**1**), which gave ¹H and ¹³C NMR spectral data consistent with those reported, in 88% yield (Scheme 3).^{1f} Compound **24** was converted into the natural product (±)-tashiromine (**2**) in 56% yield via ozonolysis of its trifluoroacetate salt followed by hydride reduction of the ozonide thus obtained. The synthetic **2** gave ¹H and ¹³C NMR spectral data consistent with those reported.^{2a,d} Similarly, compound **23** was converted into the known indolizidine **25**.^{1c,17}

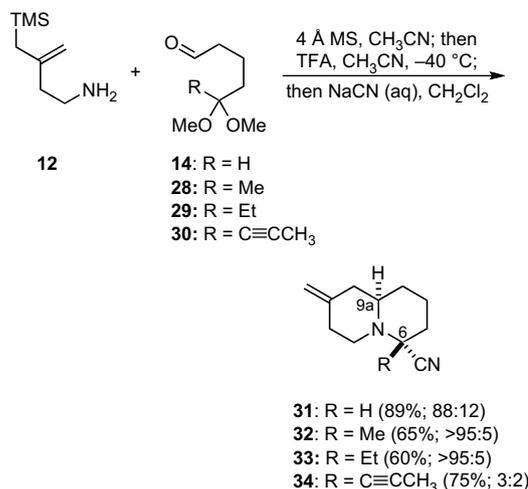
Having succeeded in preparing simple vinyl-substituted quinolizidines and indolizidines, we turned our attention to trap the penultimate iminium ion with nucleophiles other than a hydride ion. Perhaps not unexpectedly, several initial attempts to trap the iminium ion generated from the reaction of with 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 α-aminonitriles such as **27** are versatile synthetic intermediates that may serve as precursors of nucleophiles (via deprotonation)¹⁸ or electrophiles via Bruylants reactions.¹⁹



Scheme 4.

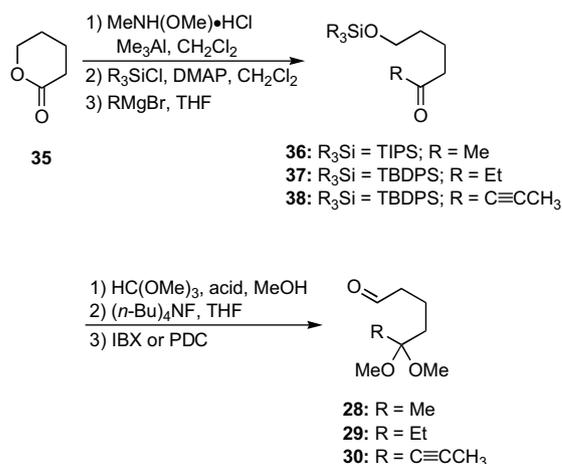
We had thus established the viability of using cascade reactions of dialdehyde monoacetals and the linear amino allylsilanes **10** and **11** for the rapid formation of indolizidine and quinolizidine alkaloids and their precursors. At this juncture, we wished to explore related processes involving branched amino allylsilanes and keto aldehyde monoacetals. Toward this end, we first applied this chemistry to the branched allylsilane **12** and the monoprotected dialdehyde **14**. In the event, condensation of **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 α-CN isomer (Scheme 5).²⁰ The presence of Bohlmann bands (2800–2700) in the IR spectrum of **31** 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,²¹ in the major isomer was assigned based upon examination of the ¹H NMR spectrum of **31**. The ¹H NMR spectrum of the minor stereoisomer, which was assigned as having a β-CN group, the hydrogen at C(6) exhibited a large coupling constant (*J*=10.4 Hz) indicative of an axial–axial interaction and suggesting that the cyano group was equatorial.



Scheme 5.

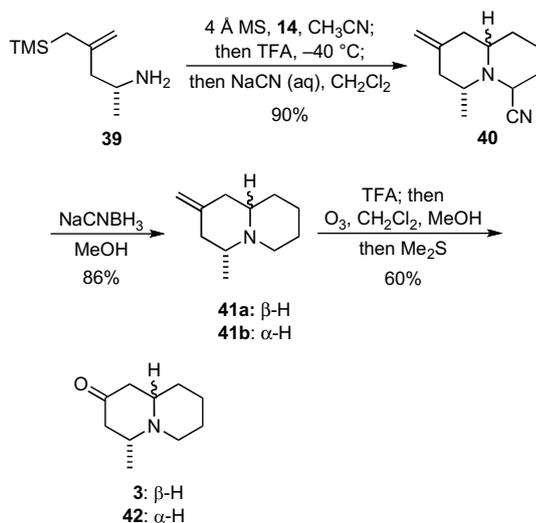
The nature of the monoprotected dicarbonyl component was then extended to include the ketal aldehydes **28–30**, which were generally prepared according to the plan outlined in Scheme 6. These aldehydes were each condensed with the branched allylsilane **12**, and the intermediate imines were treated 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 C(6), these groups were tentatively assigned as being trans to each other.²²



Scheme 6.

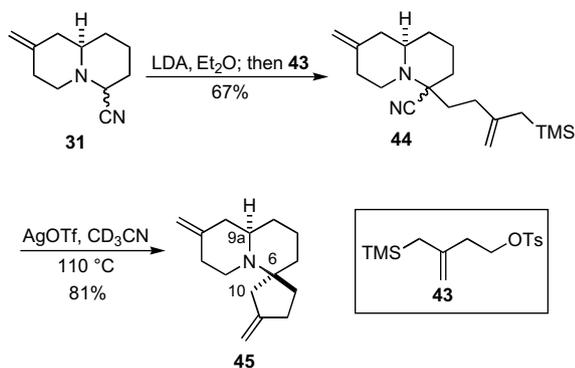
It is noteworthy that the quinolizidines **31–34** each bear functionality that might be further elaborated to give a variety of derivatives. In order to illustrate the utility of this process, it was applied to a concise, enantioselective synthesis of the quinolizidine alkaloid (–)-epimyrine (**3**) (Scheme 7). Thus, the known amino-silane **39**²³ 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

aminonitriles **40** in 90% yield. Subsequent reduction of **40** with NaCNBH₃ 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 **39** with **14** directly, but the yield of **41a,b** was only about 60%. Formation of the trifluoroacetate salt of **41a,b** followed by ozonolysis of the exocyclic olefin gave an inseparable mixture (95:5) of (–)-epimyrtine (**3**) and (+)-myrtine (**42**). The ¹H and ¹³C NMR spectral data for synthetic **3** and the specific rotation for **3** were consistent with those reported.³



Scheme 7.

The potential utility of the α-aminonitriles formed in these sequences did not escape our attention. For example, α-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.^{18a} In order to exemplify the utility of α-aminonitriles derived from our cascade reaction as precursors of interesting heterocyclic targets, a mixture of epimeric α-aminonitriles **31** was readily transformed into the tricycle **45**, which possesses a skeletal framework related to the core of halichlorine (**4**) (Scheme 8). Thus, deprotonation of **31** with LDA followed by alkylation of the carbanion with the known tosylate **43**²⁴ gave **44** in good yield. Subsequent exposure of **44** to AgOTf generated an iminium ion in situ that underwent efficient cyclization via addition of the allylsilane to give **45** as a single diastereomer.

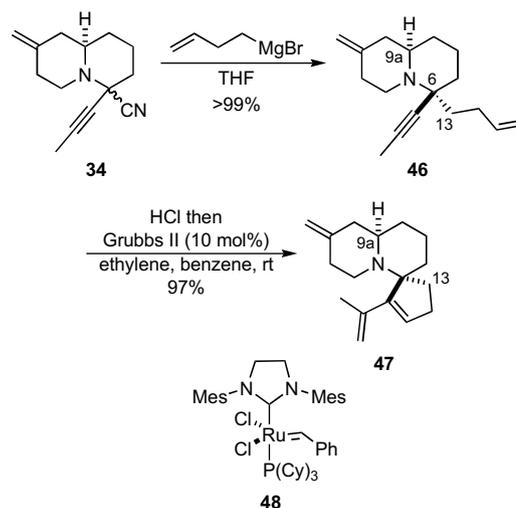


Scheme 8.

That the cyclization to give **45** proceeded in accord with the principles of stereoelectronic control was verified by NMR

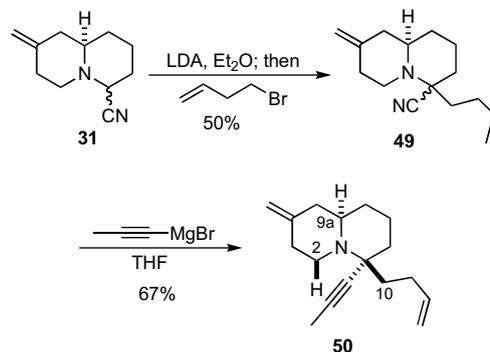
spectroscopy.^{13,25} In particular, the relative stereochemistry of the spiro and bridgehead centers at C(9a) and C(6) in **45** was assigned on the basis of NOE correlations observed in a GOESY experiment performed on the TFA salt in which a strong interaction was observed between the bridgehead proton at C(9a) and one of the hydrogen atoms on the 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(9a) 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.



Scheme 9.

The versatility of this cascade approach to substituted quinolizidines may be further illustrated by the synthesis of the C(6) epimer of **46** in an unoptimized, two-step sequence of reactions

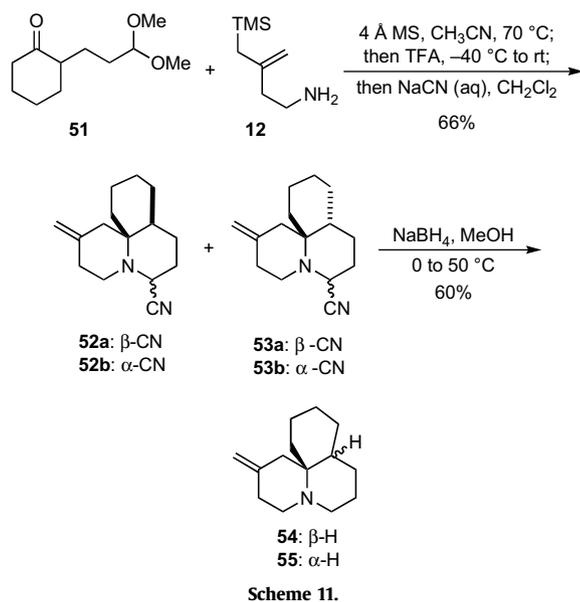


Scheme 10.

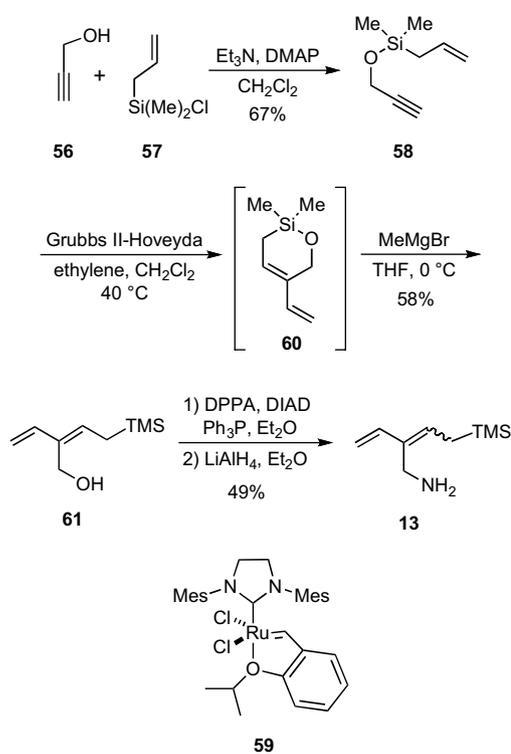
from **31** (Scheme 10). Thus, deprotonation of **31** followed by alkylation with 4-bromobutane led to aminonitrile **49**, which underwent a Bruylants reaction with propynylmagnesium bromide to deliver quinolizidine **50** as a single diastereomer.^{18a,23} The

stereochemistry of **50** was assigned on the basis of a GOESY experiment that revealed a NOE interaction between the equatorial proton on C(2) with the C(10) proton. There was no NOE between the protons at C(9a) and C(10).

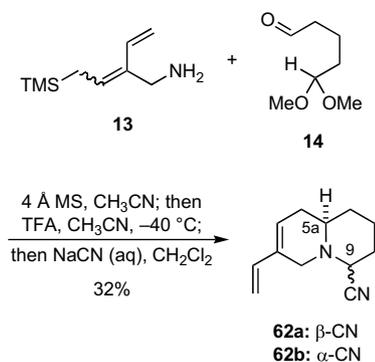
We had thus verified that the cascade processes generally outlined in Scheme 1 could be applied to the syntheses of quinolizidines and indolizidines lacking substituents at the bridgehead position. However, there are a number of quinolizidine alkaloids such as cylindricine (**5**) that bear alkyl substituents 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 **51**²⁶ 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 **52a,b** and **53a,b** was treated with sodium borohydride, an inseparable mixture (1.1:1.0) of the two diastereomeric tricyclic amines **54** and **55** 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 dienyilsilanes **13** as reacting partners to allow access to more highly functionalized products. Because **13** 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). Ring-closing enyne metathesis of **58** using 3 mol % of the Grubbs II–Hoveyda catalyst **59** under an ethylene atmosphere gave the volatile cyclic silyloxy ether **60**, which was not isolated by rather treated directly with methylmagnesium bromide to yield the hydroxy allylsilane **61** in 58% yield over two steps.²⁷ The hydroxyl group of the allylsilane **61** was converted into an azide function via a Mitsunobu reaction that surprisingly proceeded to give a mixture (3:1) of *E*- and *Z*-isomer. 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*-dienyilsilanes **13**.



Gratifyingly, we found that condensation of **13** 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 C(5a) and 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 dienyilsilane in an intramolecular Mannich-like reaction.²⁸



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.²⁹ All solvents were determined to contain less than 50 ppm H₂O 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.³⁰ Melting points are uncorrected. Infrared (IR) spectra were obtained as solutions in the solvent indicated. Proton nuclear magnetic resonance spectra (¹H NMR) were obtained in CDCl₃ solutions, and chemical shifts are reported in parts per million (ppm) referenced to the solvent. Coupling constants (*J*) are reported in hertz (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 (¹³C NMR) were obtained using CDCl₃ as the internal reference.

4.2. Representative procedure for the reductive cascade reaction: synthesis of (1*S**,9*aS**)-1-vinyloctahydro-1*H*-quinolizine (22)

Freshly prepared amine **11** (363 mg, 2.12 mmol) was added dropwise to a suspension of freshly prepared aldehyde **14** (310 mg, 2.12 mmol) and molecular sieves (4 Å, 0.50 mg) in CH₃CN (2.0 mL) at 0 °C. The ice bath was removed, and the mixture was stirred for 2 h at which time the solution was transferred via syringe to a flame dried round-bottom flask. Additional CH₃CN (30 mL) was added, and the mixture was cooled to 0 °C with stirring. Freshly distilled CF₃CO₂H (2.4 g, 1.6 mL, 21.2 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 Et₃SiH (2.5 g, 3.2 mL, 21.2 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 Et₂O (15 mL), and a solution of 2 N HCl (15 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The aqueous layer was made basic with a solution of 5%

NaOH saturated with NaCl (15 mL) and extracted with Et₂O (3 × 15 mL). The combined organic layers were dried (K₂CO₃) and concentrated under reduced pressure (300 mmHg). The crude residue was purified by flash chromatography eluting with pentane/EtOH (60:1). An aliquot of the fractions containing pure **22** was concentrated under reduced pressure (300 mmHg) to give an analytical sample for characterization. The remaining fractions containing pure **22** were combined, CF₃CO₂H (1.5 mL) was added, and the mixture was concentrated under reduced pressure to give 444 mg (75%) of the trifluoroacetate salt of **22** as a single diastereomer as a pale yellow oil. ¹H NMR (500 MHz, CD₃CN) δ 5.60 (ddd, *J*=17.5, 10.0, 9.0 Hz, 1H), 4.99 (ddd, *J*=17.5, 2.0, 1.0 Hz, 1H), 4.94 (dd, *J*=10.0, 2.0 Hz, 1H), 2.76–2.69 (comp, 2H), 2.00–1.93 (comp, 2H), 1.85 (app tdd, *J*=11.0, 9.0, 3.0 Hz, 1H), 1.74 (app dp, *J*=13.0, 2.5 Hz, 1H), 1.74–1.64 (comp, 2H), 1.63–1.54 (comp, 4H), 1.54–1.46 (m, 1H), 1.23–1.13 (comp, 2H), 1.04 (app dq, *J*=10.5, 3.5 Hz, 1H); ¹³C NMR (125 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 166.1591 [C₁₁H₂₀N (M+1) requires 166.1596], 164, 194, 248, 327, 329, 341, 399, 401.

4.3. (1*S**,8*aS**)-1-Vinyloctahydroindolizine (23)

Prepared in 45% yield in accordance with the representative procedure. ¹H NMR (500 MHz, CD₃CN) δ 5.70 (ddd, *J*=17.0, 10.5, 8.0 Hz, 1H), 5.18 (ddd, *J*=17.0, 1.5, 1.0 Hz, 1H), 5.18 (ddd, *J*=10.5, 1.5, 1.0 Hz, 1H), 3.62–3.56 (comp, 2H), 3.05–2.97 (m, 1H), 2.86–2.74 (comp, 2H), 2.64 (app p, *J*=8.5 Hz, 1H), 2.20 (app ddt, *J*=11.5, 9.5, 7.5 Hz, 1H), 2.04–1.94 (m, 1H), 1.90–1.80 (comp, 3H), 1.73–1.64 (m, 1H), 1.55–1.40 (comp, 2H); ¹³C NMR (125 MHz) δ 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 **23**.^{1c}

4.4. (8*S**,8*aS**)-8-Vinyloctahydroindolizine (24)

Prepared in 36% yield in accordance with the representative procedure. ¹H NMR (500 MHz, CD₃CN) δ 5.71 (ddd, *J*=17.0, 10.0, 8.0 Hz, 1H), 5.23 (d, *J*=17.0 Hz, 1H), 5.13 (d, *J*=10.0 Hz, 1H), 3.70–3.60 (comp, 2H), 3.07–2.88 (comp, 2H), 2.39–2.33 (m, 1H), 2.28–2.22 (m, 1H), 2.06–2.00 (comp, 3H), 1.92–1.82 (comp, 2H), 1.75–1.67 (m, 1H), 1.52–1.44 (m, 1H); ¹³C NMR (125 MHz) δ 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 [C₁₀H₁₇N (M+1) requires 152.143925], 371, 222, 152 (base), 97.

4.5. (\pm)-Epilupinine (1)

The trifluoroacetate salt of **22** (75 mg, 0.27 mmol) was dissolved in Et₂O (3 mL) and ozone was passed through the stirred solution at –78 °C until the solution turned blue. Air was then passed through the reaction mixture for 5 min. A solution of LiAlH₄ (51 mg, 1.5 mmol) in THF (2 mL) was added, the dry ice bath was removed, and the suspension was stirred at room temperature for 12 h. H₂O (0.05 mL), 5% NaOH (0.05 mL), and H₂O (0.15 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 Et₂O. The combined filtrate and washings were concentrated under reduced pressure to give 40 mg (88%) of **1** as a colorless oil. Recrystallization of the crude product from pentane provided a white solid; (mp 79–80 °C; lit.^{1f} 78–79 °C). ¹H NMR (500 MHz, MeOD) δ 3.55 (dd, *J*=11.0, 3.5 Hz, 1H), 3.50 (dd, *J*=11.0, 5.5 Hz, 1H), 2.83–2.74 (comp, 2H), 2.10–2.01 (comp, 2H), 1.98–1.94 (m, 1H), 1.84–1.54 (comp, 7H), 1.37–1.23 (comp, 3H), 1.16 (app tdd, *J*=13.5, 11.0, 4.0 Hz, 1H); ¹³C NMR (125 MHz) δ 65.8, 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 cm^{-1} ; mass spectrum (CI) m/z 170.1537 [$\text{C}_{10}\text{H}_{19}\text{NO}$ (M+1) requires 170.1545], 170 (base), 168, 152. These spectral data are in accordance with reported spectra for (\pm)-epilupinine.^{1f}

4.6. (\pm)-Tashiromine (2)

The trifluoroacetate salt of **24** (142 mg, 0.57 mmol) was dissolved in Et_2O (5 mL) and ozone was passed through the stirred solution at -78°C until the solution turned blue. Air was then passed through the reaction mixture for 5 min. A solution of LiAlH_4 (215 mg, 4.46 mmol) in THF (3 mL) was added, the dry ice bath was removed, and the suspension was stirred at room temperature for 12 h. H_2O (0.2 mL), 5% NaOH (0.2 mL), and H_2O (0.6 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 Et_2O . The combined filtrate and washings were concentrated under reduced pressure to give 44 mg (56%) of **2** as a colorless oil. ^1H NMR (500 MHz, CD_3CN) δ 3.46 (dd, $J=11.0, 5.0$ Hz, 1H), 3.30 (dd, $J=11.0, 7.0$ Hz, 1H), 2.98 (app dp, $J=11.0, 2.0$ Hz, 1H), 2.93 (app dt, $J=9.0, 2.5$ Hz, 1H), 1.98 (app q, $J=9.0$ Hz, 1H), 1.91–1.78 (comp, 3H), 1.70–1.48 (comp, 5H), 1.40–1.28 (comp, 2H), 1.04–0.90 (m, 1H); ^{13}C NMR (125 MHz) δ 67.3, 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 cm^{-1} ; mass spectrum (CI) m/z 156.1391 [$\text{C}_9\text{H}_{18}\text{NO}$ (M+1) requires 156.1388], 156 (base). The spectral data are in accordance with reported spectra for (\pm)-tashiromine.^{2a,d}

4.7. Representative procedure for the cascade reaction with cyanide-trapping: synthesis of (4R*,9aR*)-8-methylene-octahydro-1H-quinolizine-4-carbonitrile (31)

Freshly prepared amine **12** (696 mg, 4.4 mmol) was added dropwise to a mixture of freshly prepared **14** (642 mg, 4.4 mmol) and molecular sieves (4 Å, 0.70 mg) in CH_3CN (2.0 mL) at 0°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 CH_3CN (50 mL) was added. The mixture was cooled to -40°C , and freshly distilled $\text{CF}_3\text{CO}_2\text{H}$ (2.5 g, 1.7 mL, 22.0 mmol) was added dropwise. The reaction mixture was stirred at -40°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 CH_2Cl_2 (2.2 mL) at 0°C . A solution of NaCN (1.0 g, 20.4 mmol) in H_2O (3 mL) was added to the reaction, the ice bath was removed, and the reaction mixture stirred at room temperature for 12 h. CH_2Cl_2 (10 mL) and 0.5 M NaOH saturated with NaCl were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL), and the combined organic layers were dried (K_2CO_3), and concentrated under reduced pressure (300 mmHg). The crude residue was purified by flash chromatography eluting with pentane/ Et_2O (10:1). The fractions were combined and concentrated under reduced pressure (300 mmHg) to give 690 mg (89%) of an epimeric mixture (88:12) of **31** as a pale yellow oil: For α -H: ^1H NMR (500 MHz, CD_3CN) δ 4.71–4.67 (comp, 2H), 3.90 (app t, $J=3.4$ Hz, 1H), 2.82–2.78 (m, 1H), 2.30–2.20 (comp, 5H), 2.07 (app tt, $J=11.0, 3.0$ Hz, 1H), 1.92–1.85 (m, 1H), 1.78 (app ddt, $J=11.0, 4.5, 4.0$ Hz, 1H), 1.72–1.62 (comp, 2H), 1.54 (app qt, $J=13.5, 3.5, 1\text{H}$), 1.50–1.28 (m, 1H); ^{13}C NMR (125 MHz) δ 146.0, 117.0, 107.8, 58.2, 55.1, 54.9, 41.7, 34.3, 32.8, 28.8, 20.4; IR (neat) 3061, 2925, 2812, 2223, 1653, 1438, 1279, 1172, 1115, 889 cm^{-1} ; mass spectrum (CI) m/z 177.1400 [$\text{C}_{11}\text{H}_{16}\text{N}_2$ (M+1) requires 177.1391], 150 (base), 177.

For β -H: ^1H NMR (500 MHz, CD_3CN) δ 4.71–4.67 (comp, 2H), 3.40 (app dt, $J=10.4, 3.2$ Hz, 1H), 3.06 (app dd, $J=11.6, 3.2, 1\text{H}$), 2.34–

1.20 (comp, 13H); ^{13}C NMR (100 MHz) δ 146.8, 121.1, 108.3, 63.6, 56.2, 55.8, 42.4, 34.8, 33.2, 31.7, 23.5 cm^{-1} ; mass spectrum (CI) m/z 177.1400 [$\text{C}_{11}\text{H}_{16}\text{N}_2$ (M+1) requires 177.1391], 150 (base), 177.

4.8. (1R*,6R*,9aS*)-1-Vinyl-6-cyanoquinolizidine (27)

Prepared in 79% yield in accordance with the representative procedure. ^1H NMR (500 MHz) δ 5.64 (ddd, $J=17.0, 10.0, 9.0$ Hz, 1H), 5.02 (ddd, $J=17.0, 2.0, 1.0$ Hz, 1H), 4.97 (dd, $J=10.0, 2.0$ Hz, 1H), 3.88 (app t, $J=3.0$ Hz, 2H), 2.67 (app dp, $J=11.0, 2.0$ Hz, 2H), 2.33 (app dt, $J=11.0, 1.0$ Hz, 1H), 1.86–1.44 (comp, 10H), 1.28–1.20 (m, 1H), 1.07–0.99 (m, 1H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 191.1539 [$\text{C}_{12}\text{H}_{19}\text{N}_2$ (M+1) requires 191.1548], 164 (base), 191, 220, 236, 263.

4.9. (4R*,9aR*)-4-Methyl-8-methyleneoctahydro-1H-quinolizine-4-carbonitrile (32)

Prepared in 65% yield in accordance with the representative procedure. ^1H NMR (500 MHz, C_6H_6) δ 4.57–4.55 (m, 2H), 3.10–3.07 (m, 1H), 2.18–2.05 (comp, 5H), 1.91–1.86 (m, 1H), 1.82–1.79 (m, 1H), 1.61–1.51 (comp, 4H), 1.40 (s, 1H), 1.20–1.15 (m, 1H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 191.1544 [$\text{C}_{12}\text{H}_{19}\text{N}_2$ (M+1) requires 191.1548], 191, 164 (base).

4.10. (4R*,9aR*)-4-Ethyl-8-methyleneoctahydro-1H-quinolizine-4-carbonitrile (33)

Prepared in 60% yield in accordance with the representative procedure. ^1H NMR (500 MHz) δ 4.64–4.63 (m, 2H), 3.10 (app dt, $J=10.7, 3.8$ Hz, 1H), 2.26–2.17 (m, 4H), 2.12–2.06 (m, 1H), 1.98 (app t, $J=1.4$ Hz, 1H), 1.88–1.81 (m, 3H), 1.72–1.60 (m, 4H), 1.28–1.18 (m, 2H), 0.97 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 205.1707 [$\text{C}_{13}\text{H}_{21}\text{N}_2$ (M+1) requires 205.1705], 205, 178 (base).

4.11. 8-Methylene-4-(prop-1-ynyl)octahydro-1H-quinolizine-4-carbonitrile (34)

Prepared in 75% yield in accordance with the representative procedure. ^1H NMR (500 MHz, CD_3CN) δ 4.66 (ddt, $J=11.3, 1.8, 1.7$ Hz, 2H), 3.61 (ddd, $J=10.6, 4.7, 4.5$ Hz, 1H), 2.36–2.28 (m, 2H), 2.27–2.17 (m, 4H), 2.10–1.95 (m, 2H), 1.85 (s, 3H), 1.73–1.62 (m, 3H), 1.34–1.24 (m, 1H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 215.1552 [$\text{C}_{14}\text{H}_{19}\text{N}_2$ (M+1) requires 215.1548], 219 (base), 215, 205.

4.12. (4R)-2-Methylenyl-4-methyl-6-cyanoquinolizidine (40)

Prepared in 90% yield in accordance with the representative procedure. ^1H NMR (500 MHz, CD_3CN) δ 4.70 (app t, $J=2.0$ Hz, 2H), 4.35 (app t, $J=3.5$ Hz, 1H), 2.35–2.18 (comp, 4H), 2.07–1.95 (comp, 3H), 1.82–1.70 (comp, 3H), 1.59 (app qt, $J=12.0, 1.5$ Hz, 1H), 1.31–1.23 (m, 1H), 1.14 (d, $J=6.0$ Hz, 1H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 191.1541 [$\text{C}_{15}\text{H}_{23}\text{N}$ (M+1) requires 191.1548], 220, 191, 164 (base).

4.13. 7-Vinyl-1,3,4,6,9,9a-hexahydro-2H-quinolizine-4-carbonitriles (62a, 62b)

Prepared in 79% yield in accordance with the representative procedure. (β -CN) ^1H NMR (500 MHz) δ 6.27 (dd, $J=17.8$, 10.9 Hz, 1H), 5.27 (s, 1H), 5.06 (d, $J=17.8$ Hz, 1H), 4.96 (d, $J=10.9$ Hz, 1H), 4.00 (d, $J=15.5$ Hz, 1H), 3.08 (dd, $J=12.1$, 3.1 Hz, 1H), 2.81 (dd, $J=15.1$, 2.6 Hz, 1H), 2.20–2.08 (comp, 4H), 1.98–1.90 (m, 1H), 1.84–1.81 (m, 1H), 1.76–1.73 (m, 1H), 1.37–1.29 (comp, 2H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 189.1397 [$\text{C}_{12}\text{H}_{17}\text{N}_2$ ($M+1$) requires 189.1392], 252, 217, 189, 163 (base); (α -CN) ^1H NMR (500 MHz) δ 6.28 (dd, $J=11.01$, 17.9 Hz, 1H), 5.71 (s, 1H), 5.01 (d, $J=17.3$ Hz, 1H), 4.95 (d, $J=11.0$ Hz, 1H), 3.97 (app t, $J=3.4$ Hz, 1H), 3.31 (comp, 2H), 2.55–2.52 (m, 1H), 2.26 (d, $J=16.7$ Hz, 1H), 2.07–1.80 (m, 4H), 1.84–1.81 (m, 1H), 1.77–1.71 (m, 2H), 1.27–1.21 (comp, 1H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 189.1391 [$\text{C}_{12}\text{H}_{17}\text{N}_2$ ($M+1$) requires 189.1392], 189, 162 (base).

4.14. (4R)-2-Methylenyl-4-methylquinolizidine (41)

Acetic acid (276 mg, 4.6 mmol) was added dropwise to a solution of NaBH_3CN (145 mg, 2.3 mmol) in CH_3CN (2 mL) with stirring, whereupon **18** (88 mg, 0.46 mmol) was added dropwise for 2 min. The solution was stirred for 24 h at room temperature, and then CH_2Cl_2 (5 mL) and a solution of 2 N HCl (5 mL) were added. The layers were separated, and the aqueous layer was made basic with a solution of 5% NaOH saturated with NaCl and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (K_2CO_3), $\text{CF}_3\text{CO}_2\text{H}$ (60 mg) was added dropwise, and the crude mixture was concentrated under reduced pressure to give 111 mg (86%) of **40** as an inseparable mixture (95:5) of diastereomers (based on GC/MS and ^1H NMR) as a pale yellow oil. Major isomer: ^1H NMR (500 MHz, CD_3CN) δ 4.85 (app t, $J=2.0$, Hz, 2H), 3.77–3.70 (m, 1H), 3.06 (app ttd, $J=10.0$, 6.5, 3.5 Hz, 1H), 2.95 (app ttd, $J=12.0$, 9.0, 3.0 Hz, 1H), 2.65 (app ttd, $J=13.0$, 10.0, 3.0 Hz, 1H), 2.54–2.33 (comp, 4H), 1.92–1.89 (comp, 2H), 1.81–1.70 (comp, 2H), 1.49 (app ttd, $J=17.0$, 7.0, 4.0 Hz, 1H), 1.36 (d, $J=6.5$ Hz, 1H); ^{13}C NMR (125 MHz) δ 140.9, 111.8, 66.6, 63.7, 52.3, 40.6, 39.3, 31.7, 24.3, 22.6, 17.8; IR (CH_2Cl_2) 2943, 2869, 2263, 1785, 1673, 1453, 1415, 1198, 1131 cm^{-1} ; mass spectrum (CI) m/z 166.1591 [$\text{C}_{11}\text{H}_{20}\text{N}$ ($M+1$) requires 166.1596], 107, 150, 166 (base), 224. The spectral data were in accordance with reported values.^{3b}

4.15. (–)-Epimyrtine (3a)

The trifluoroacetate salt of **19** (115 mg, 0.41 mmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and MeOH (0.5 mL) and ozone was bubbled through the solution at -78°C until a blue color persisted (5 min). Air was passed through the reaction mixture for 5 min. Methyl sulfide (128 mg, 0.15 mL, 2.06 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% NaOH saturated with NaCl (1 mL) was added dropwise with stirring. The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure (300 mmHg). 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. $[\alpha]_{\text{D}}^{23} -18.0$ (c 0.4, CDCl_3); [lit.^{3b} $[\alpha]_{\text{D}}^{20} -17.4$ (c 0.7, CHCl_3); $[\alpha]_{\text{D}}^{23} -19.0$ (c 0.4, CHCl_3)]. ^1H NMR (500 MHz) δ 3.30–3.26 (m, 1H), 2.40–2.12 (comp, 6H), 1.83–1.52 (comp, 5H), 1.41–1.33 (m,

1H), 1.30–1.20 (m, 1H), 1.17 (d, $J=5.5$ Hz, 3H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 168.1388 [$\text{C}_{10}\text{H}_{18}\text{NO}$ ($M+1$) requires 168.1388], 240, 196, 168 (base), 152. The spectral data were in accordance with reported values for (–)-epimyrtine.³

4.16. 6-Cyano-6-(3'-methyltrimethylsilyl-3'-butenyl)-2-methylenylquinolizidine (44)

A solution of *n*-butyllithium in hexanes (0.21 mL of 2.5 M, 0.44 mmol) was added dropwise to a solution of diisopropylamine (101 mg, 0.07 mL, 0.44 mmol) in Et_2O (3 mL) at 0°C . The solution was stirred for 0.5 h at which time **31** (60 mg, 0.35 mmol) was added dropwise. The reaction mixture was stirred for 0.5 h, and **43** (215 mg, 0.69 mmol) was added dropwise. The ice bath was removed, and the mixture was stirred for 1 h. A solution of 0.5 M NaOH saturated with NaCl (5 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/ Et_2O (95:5) to give 67 mg (62%) of **44** as a pale yellow oil. ^1H NMR (500 MHz, CD_3CN) δ 4.67–4.54 (comp, 4H), 3.14 (app dq, $J=11.0$, 2.5 Hz, 1H), 2.29–1.15 (comp, 16H), 1.57 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz) δ 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 cm^{-1} ; mass spectrum (CI) m/z 317.2408 [$\text{C}_{19}\text{H}_{32}\text{NSi}$ ($M+1$) requires 317.2413], 290 (base), 154, 218, 274, 317.

4.17. 6-(2'-Methenylcyclopentyl)-2-methylenylquinolizidine (45)

Silver triflate (55 mg, 0.22 mmol) was added to a suspension of 4 Å molecular sieves (0.10 mg) in CH_3CN (0.5 mL) at room temperature. The suspension was wrapped in tin foil and a solution of cyanoamine **44** (62 mg, 0.20 mmol) in CH_3CN (0.5 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 CH_3CN (2 mL). The combined supernatant was heated at 120°C (oil bath) with stirring for 24 h. The mixture was cooled to room temperature, and Et_2O (10 mL) was added. A solution of 2 N HCl (5 mL) was added, and the layers were separated. The aqueous layer was washed with Et_2O (3×5 mL) and then made basic with a solution of 5% NaOH saturated with NaCl. The mixture was then extracted with Et_2O (3×5 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure to give 34 mg (81%) of **45** as a single diastereomer (based on ^1H NMR) as a colorless oil. ^1H NMR (500 MHz, CD_3CN) δ 4.77 (app p, $J=2.0$ Hz, 1H), 4.74 (app p, $J=2.0$ Hz, 1H), 4.59–4.56 (m, 1H), 4.56 (br s, 1H), 3.00 (app dt, $J=9.0$, 3.0 Hz, 1H), 2.48 (d, $J=16.5$ Hz, 1H), 2.31–2.11 (comp, 6H), 2.10–1.98 (comp, 2H), 1.86 (dddd, $J=11.5$, 9.5, 2.0, 1.5 Hz, 1H), 1.55–1.40 (comp, 5H), 1.32–1.25 (m, 1H); ^{13}C NMR (125 MHz) δ 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 (CH_2Cl_2) 2943, 2872, 2249, 1672, 1443, 1414, 1196 cm^{-1} ; mass spectrum (CI) m/z 218.1904 [$\text{C}_{15}\text{H}_{23}\text{N}$ ($M+1$) requires 218.1908], 250, 218 (base), 152, 109.

4.18. 2-Methylenyl-6-cyano-6-butenylquinolizidine (49)

A solution of *n*-butyllithium in hexanes (0.74 mL of 2.5 M, 1.40 mmol) was added dropwise to a solution of *i*-Pr₂NEt (0.17 mL, 1.40 mmol) in Et_2O (5 mL) at 0°C . The solution was stirred for 0.5 h and then was cooled to -78°C . Cyanoamine **31** (211 mg, 1.20 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 °C and then cooled to –78 °C. 4-Bromobutene (186 mg, 0.14 mL, 1.4 mmol) was added dropwise, and the dry-ice/acetone bath was again replaced with an ice-water bath. The mixture was stirred for 1 h at 0 °C, whereupon a solution of 0.5 M 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 Et₂O (3 × 10 mL). The combined organic layers were dried (K₂CO₃) and concentrated under reduced pressure (300 mmHg). The crude residue was purified by flash chromatography eluting with pentane/Et₂O (9:1) to give 137 mg (50%) of **49** as a single diastereomer of a pale yellow oil. ¹H NMR (500 MHz, CD₃CN) δ 5.84 (ddt, *J*=17.0, 10.0, 6.5 Hz, 1H), 5.07 (dq, *J*=17.0, 2.0 Hz, 1H), 4.97 (ddt, *J*=10.0, 2.0, 1.5 Hz, 1H), 4.65 (dp, *J*=8.0, 2.0 Hz, 2H), 3.15 (ddd, *J*=10.0, 4.5, 2.5 Hz, 1H), 2.27–2.06 (comp, 6H), 2.10 (app tt, *J*=11.0, 2.5 Hz, 1H), 2.00–1.91 (comp, 3H), 1.86–1.80 (comp, 2H), 1.75 (app dt, *J*=13.5, 4.0 Hz, 1H), 1.68–1.61 (comp, 2H), 1.56 (app tdd, *J*=17.5, 8.0, 4.0 Hz, 1H), 1.20 (app tdd, *J*=15.0, 11.0, 4.0 Hz, 1H); ¹³C NMR (125 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 204 (base), 231.

4.19. 6-(1'-Propynyl)-6-(3'-butenyl)-2-methylenyl-quinolizidine (**50**)

A solution of propynylmagnesium chloride in Et₂O (3.4 mL of 0.5 M, 1.7 mmol) was added dropwise to a solution of cyanoamine **49** (137 mg, 0.60 mmol) in THF (3.0 mL) at room temperature. The solution was stirred for 5 h, at which time a solution of 2 N HCl (5 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 5 mL). The aqueous layer was made basic with a solution of 5% NaOH saturated with NaCl and extracted with Et₂O (3 × 5 mL). The combined organic layers were dried (K₂CO₃) and concentrated under reduced pressure to give 116 mg (80%) of **50** as a single diastereomer (based on ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CD₃CN) δ 5.84 (ddt, *J*=17.0, 10.5, 6.5 Hz, 1H), 5.02 (dq, *J*=17.0, 1.5 Hz, 1H), 4.92 (dq, *J*=9.0, 1.0 Hz, 1H), 4.58 (dd, *J*=4.0, 2.5 Hz, 2H), 3.00 (ddd, *J*=11.0, 4.5, 3.0 Hz, 1H), 2.21–2.06 (comp, 6H), 2.00 (app td, *J*=11.0, 4.0 Hz, 1H), 1.87 (app t, *J*=12.5 Hz, 1H), 1.79 (s, 3H), 1.76 (ddd, *J*=16.5, 14.0, 5.5 Hz, 1H), 1.70–1.60 (comp, 2H), 1.59–1.49 (comp, 4H), 1.14 (app dtd, *J*=15.5, 13.5, 4.0 Hz, 1H); ¹³C NMR (125 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 244.2074 [C₁₇H₂₅N (M+1) requires 244.2065], 244 (base), 204, 188.

4.20. (6R,9aR)-6-(But-3-enyl)-2-methylene-6-(prop-1-ynyl)octahydro-1H-quinolizidine (**46**)

4-Bromobutene (0.23 mL, 2.27 mmol) was added to a suspension of Mg (48 mg, 1.98 mmol) in THF (3 mL), and the mixture was heated to 70 °C for 1.5 h. A portion of the solution (1 mL) was added to **34** (14 mg, 0.07 mmol) in CH₂Cl₂ (0.40 mL) at –78 °C. The mixture was allowed to warm to room temperature with stirring for 8 h. The solution was cooled to 0 °C, and 2.9 N HCl (3 mL) was added. The mixture was washed with Et₂O (3 × 4 mL). The aqueous layer was cooled to 0 °C, 6 N NaOH (5 mL) was added, and the mixture was extracted with Et₂O (3 × 3 mL). The combined organic extracts were concentrated under reduced pressure to yield 17 mg (100%) of **46** as a single diastereomer of a clear oil. ¹H NMR (500 MHz) δ 5.89–5.81 (comp, 1H), 5.04–5.00 (ddt, *J*=17.2, 1.8, 1.7 Hz, 1H), 4.94–4.91 (ddt, *J*=10.2, 1.4, 1.0 Hz, 1H), 4.59–4.56 (m, 2H), 3.50–3.48 (m, 1H), 2.34–2.29 (app tt, *J*=10.9, 3.1 Hz, 1H), 2.25–2.12 (m, 5H), 2.03–1.86 (m, 3H), 1.81 (s, 3H), 1.76–1.70 (app td, *J*=12.8, 5.4 Hz, 1H), 1.64–1.55 (m, 5H), 1.50–1.45 (m, 1H), 1.40–1.32 (app qt, *J*=13.3, 3.3 Hz, 1H), 1.28–1.20 (m, 1H); ¹³C NMR (125 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 244.2066 [C₁₇H₂₆N (M+1) requires 244.2065], 269, 244 (base), 243.

4.21. Spirocycle **47**

A solution of **46** (121 mg, 0.50 mmol) in 3% HCl/MeOH (5 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 mg, 0.04 mmol) in benzene (2 mL) was added. The mixture 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 Et₂O (3 × 20 mL), and the combined organic layers were washed with brine (15 mL), dried (MgSO₄), 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. ¹H NMR (500 MHz) δ 6.19 (d, *J*=3.3 Hz, 1H), 5.71 (t, *J*=2.7 Hz, 1H), 4.92 (s, 1H), 4.56–4.55 (m, 2H), 2.74 (ddd, *J*=11.3, 4.1, 3.0 Hz, 1H), 2.26–2.22 (m, 2H), 2.16–2.01 (m, 6H), 1.96 (td, *J*=10.7, 4.5 Hz, 1H), 1.90–1.86 (m, 1H), 1.89 (s, 3H), 1.69–1.50 (m, 5H), 1.34–1.29 (m, 1H), 1.29–1.24 (m, 1H); ¹³C NMR (125 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 244.2066 [C₁₇H₂₆N (M+1) requires 244.2065], 244, 243 (base), 242.

4.22. 2-Methylenedodecahydropyrido[1,2-*j*]quinoline-6-carbonitrile (**52a**, **52b**, **53a**, **53b**)

A solution of 2-(3,3-dimethoxypropyl)cyclohexanone (76 mg, 0.38 mmol) in CH₃CN (2 mL) was added to a solution of 3-((trimethylsilyl)methyl)but-3-en-1-amine (60 mg, 0.36 mmol) in CH₃CN (1 mL) with 4 Å molecular sieves (5 beads). The mixture was heated under reflux for 4 h under nitrogen. The mixture was cooled, and stirring was continued for 2 h at room temperature. The 4 Å molecular sieves were removed, the mixture was cooled to –40 °C, and CF₃CO₂H (3 mL, 40 mmol) was added. The mixture was allowed to warm to room temperature for 3 h and then stirred at room temperature for 21 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in CH₂Cl₂ (5 mL). The solution was cooled to 0 °C, aqueous NaCN (1.9 mL of a 2 M solution) was added, the ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The solution was cooled to 0 °C, saturated K₂CO₃ (5 mL) was added, and the mixture was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (K₂CO₃), 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 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**: ¹H NMR (400 MHz) δ 4.79 (app dd, *J*=3.5, 1.6 Hz, 1H), 4.66 (app dd, *J*=3.9, 2.0 Hz, 1H), 3.77–3.75 (m, 1H), 3.10 (td, *J*=11.9, 3.9 Hz, 1H), 2.88 (dd, *J*=13.1, 3.2 Hz, 1H), 2.54 (ddd, *J*=11.5, 6.3, 1.8 Hz, 1H), 2.38–2.20 (m, 2H), 2.12–1.71 (m, 6H), 1.60 (m, 1H), 2.37–2.22 (m, 2H), 1.69–1.50 (m, 5H), 1.50–1.37 (m, 2H); ¹³C NMR (100 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 231.1861 [C₁₅H₂₃N₂ (M+1) requires 231.1858], 243, 231 (base), 230.

4.23. 2-Methylenedodecahydropyrido[1,2-*j*]quinolines (**54**, **55**)

Solid NaBH₄ (27 mg, 0.71 mmol) was added to a solution of **53a-b** (32.4 mg, 0.14 mmol) in MeOH (5 mL) at 0 °C. The mixture was

warmed to room temperature and then heated at 50 °C (oil bath) for 3 h. The reaction mixture was cooled to room temperature, HCl (1 M, 2 mL) was added, and the mixture was washed with Et₂O (3 × 4 mL). Aqueous NaOH (2.5 M, 3 mL) was added, and the mixture was extracted with Et₂O (3 × 3 mL). The combined ethereal extracts were concentrated under reduced pressure to yield 17 mg (60%) of an inseparable mixture (1.1:1.0) of **54** and **55**. ¹H NMR of the mixture (400 MHz, CDCl₃) δ 4.77–4.61 (comp, 4H), 4.08 (dd, *J* = 12.1, 5.2 Hz, 1H), 3.38–3.21 (m, 1H), 2.87–2.83 (m, 1H), 2.70–2.38 (comp, 6H), 2.28–1.16 (comp, 29H); ¹³C NMR (100 MHz) δ 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 cm⁻¹; mass spectrum (CI) *m/z* 206.19146 [C₁₄H₂₄N (M+1) requires 206.1909], 204, 206 (base).

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Supplementary data

Experimental procedures for the preparation of **13**, **28–30**, **58**, and **61**. Copies of ¹H NMR spectra for all new compounds, as well as ¹H and ¹³C NMR spectra of epilupinine (**1**), tashiromine (**2**), and epimyrtiline (**3**) and a CIF file for **52a**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.074.

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