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Enantioselective Total Syntheses of Methanoquinolizidine-Containing Akuammiline Alkaloids and Related Studies

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ABSTRACT: The akuammiline alkaloids are a structurally diverse class of bioactive natural products isolated from plants found in various parts of the world. A particularly challenging subset of akuammiline alkaloids are those that contain a methanoquinolizidine core. We describe a synthetic approach to these compounds that has enabled the first total syntheses of (+)-strictamine, (–)-2(*S*)-cathafoline, (+)-akuammiline, and (–)-Ψ-akuammigine. Our strategy relies on the development of the reductive interrupted Fischer indolization reaction to construct a common pentacyclic intermediate bearing five contiguous stereocenters, in addition to late-stage formation of the methanoquinolizidine framework using a deprotection–cyclization cascade. The total syntheses of (–)-Ψ-akuammigine and (+)-akuammiline mark the first preparations of akuammiline alkaloids containing both a methanoquinolizidine core and vicinal quaternary centers. Lastly, we describe the bioinspired reductive rearrangements of (+)-strictamine and (+)-akuammiline to ultimately provide (–)-10-demethoxyvincorine and a new analogue thereof.

Introduction

The akuammiline alkaloids are an important class of natural products isolated from plants found in India, Africa, and Southeast Asia. These alkaloids, thought to be the active ingredients in traditional medicines used to treat a multitude of ailments in humans and livestock,[1] have been the subject of intense investigations spanning structural elucidation, biosynthesis, biological evaluation, and chemical synthesis.[2] More than 75 akuammilines have now been unambiguously characterized,[3] many of which display exciting biological profiles, and all of which possess provocative chemical structures. Despite their enticing characteristics and biosynthetic relation to the popular *Strychnos* alkaloids,[4] the akuammiline family has been comparatively less studied by synthetic chemists relative to the *Strychnos* alkaloids. It was not until recently that the synthetic community launched efforts toward the akuammiline alkaloids, which have now culminated in total syntheses of several subclasses.[5] This is particularly noteworthy, as even the simplest akuammilines contain at least five interconnected rings, a multitude of stereocenters, and one or more basic nitrogen atoms.

We became interested in a subset of the akuammiline alkaloids that possess a methanoquinolizidine core. This cage-like scaffold, along with several methanoquinolizidine-containing akuammilines, are shown in Figure 1 (i.e., **1**–**4**).[6] (+)-Strictamine (**1**)[7] features an indolenine and four stereocenters, whereas (–)-2(*S*)-cathafoline (**2**)[8] has an indoline core resulting in five contiguous stereocenters. (+)-Akuammiline (**3**) and (–)-Ψ-akuammigine (**4**)[9] display an additional layer of complexity with vicinal quaternary centers at C7 and C16. Moreover, (–)-Ψ-akuammigine (**4**) also bears a furoindoline motif, leading to six interconnected rings and five contiguous stereocenters, thereby rendering it the most complex member of this akuammiline subclass.

The complexity of **1**–**4**, coupled with attractive biological activities (vide infra), have prompted numerous synthetic efforts. Following seminal studies by Dolby,[10] Bosch and Bennasar,[11] and Sakai[12] beginning more than four decades ago, the laboratories of Cook,[13] Tokuyama,[14] and Matsuo[15] have more recently described promising synthetic approaches. However, a total synthesis of any methanoquinolizidine-containing akuammiline alkaloid had proven elusive.[16] Moreover, to date, no total syntheses of methanoquinolizidine-containing akuammilines that also bear vicinal quaternary centers (e.g., **3** and **4**) have been reported.

Herein, we describe a full account of our enantioselective approach to several methanoquinolizidine-containing akuammilines and subsequent biomimetic manipulations. Key to the success of these studies is the development of the reductive interrupted Fischer indolization reaction[17,18,19] to construct a complex pentacyclic intermediate, as well as the late-stage formation of the methanoquinolizidine framework using a deprotection–cyclization cascade. These studies result in the

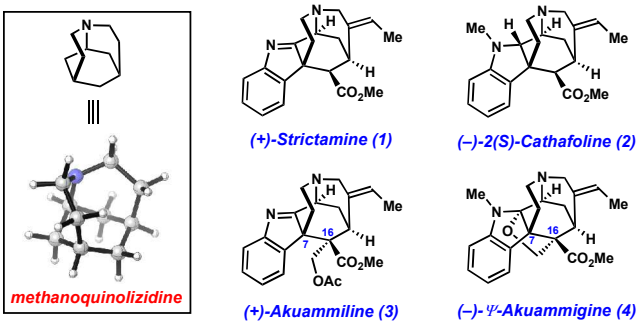


Figure 1. Representative methanoquinolizidine-containing akuammiline alkaloids.

first total syntheses of (+)-strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**), which we communicated in 2016.[51] We then exploit a previously undesired epimerization event to access (+)-akuammiline (**3**) and (–)-Ψ-akuammigine (**4**), each of which bear vicinal quaternary stereocenters embedded in their methanoquinolizidine cores. Lastly, we describe late-stage reductive rearrangements of (+)-strictamine (**1**) and (+)-akuammiline (**3**), inspired by the proposed biosynthesis of akuammiline alkaloids[20] to give pyrrolidinoindoline scaffolds.

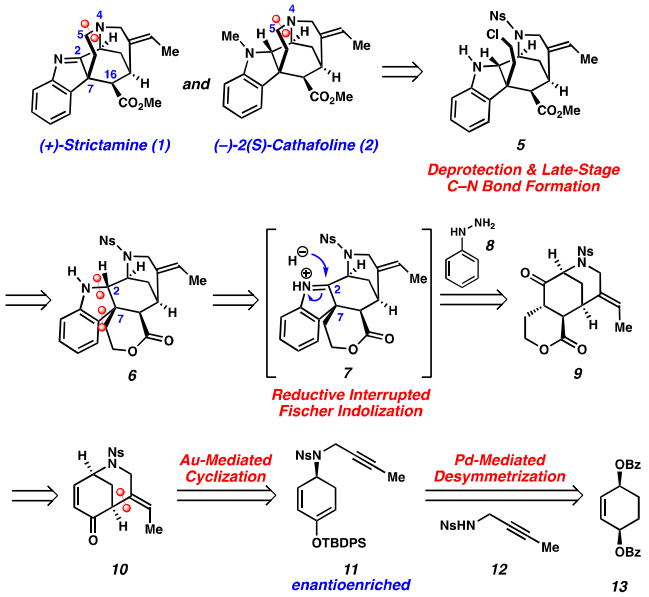
Results and Discussion

(+)-Strictamine and (–)-2(*S*)-Cathafoline: Isolation, Biological Activity, and Retrosynthetic Analysis

(+)-Strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**) were selected as our initial synthetic targets. (+)-Strictamine (**1**) was isolated in 1966[7] from the plant *Rhazya stricta*, whereas (–)-2(*S*)-cathafoline (**2**) was extracted from *Alstonia macrophylla* in 2014.[8] (+)-Strictamine (**1**) inhibits the transcription factor NF-κB,[21] and may therefore serve as a lead compound for the discovery of new drugs for the treatment of cancer or inflammatory diseases. (–)-2(*S*)-Cathafoline (**2**) shows moderate activity in overturning drug resistance in vincristine-resistant KB cells.[8] Despite the aforementioned synthetic pursuits, neither **1** or **2** had succumbed to total synthesis. In the case of (+)-strictamine (**1**), this is especially noteworthy given that the compound had been known for more than 50 years.

Our retrosynthetic analysis of (+)-strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**) is shown in Scheme 1. We envisioned forming the methanoquinolizidine scaffold by late-stage construction of the C5–N4 bond. Thus, **1** and **2** would be accessed from primary alkyl chloride **5** through a tandem deprotection–cyclization reaction, followed by manipulation of the indoline ring system. Chloride **5** would derive from indoline lactone **6** through methanolysis and halide formation. In a key retrosynthetic disconnection, we envisaged indoline lactone **6** arising from ketolactone **9** and phenylhydrazine (**8**) via a reductive interrupted Fischer indolization reaction.[17] If successful, this transformation would introduce two new rings. Moreover, two stereogenic centers would be generated, including the C2 stereocenter seen in 2(*S*)-cathafoline (**2**) (via **7**) and the challenging C7 quaternary center common to all akuammilines. Ketolactone **9** would ultimately be obtained from enone **10**, which, in turn, would arise from a gold-catalyzed cyclization of silyl enol ether **11**.[22] Finally, **11** would be accessed in enantioenriched fashion from sulfonamide **12** and dibenzoate **13** via a Pd-catalyzed desymmetrization and subsequent manipulations.[23]

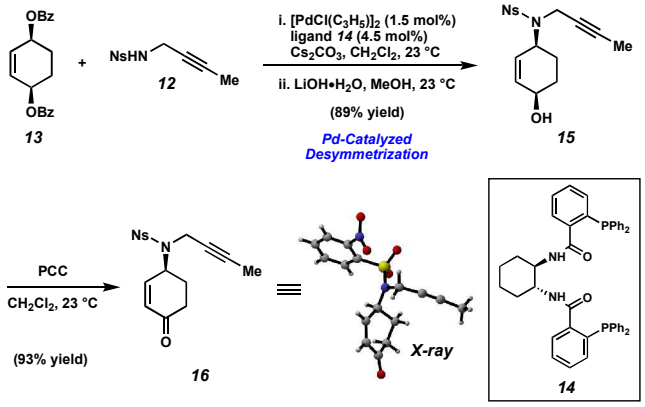
Scheme 1. Retrosynthetic analysis of (+)-strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**).



Enantioselective Synthesis of the Fischer Indolization Substrate

To initiate our forward synthetic studies, we sought to prepare enone **16** in enantioenriched form, as this could serve as a precursor for later construction of the necessary [3.3.1]-azabicycle (Scheme 2). Although we initially examined several possible routes, including enzymatic desymmetrization[24] and the use of Koga bases,[25] we found a Pd-catalyzed Trost desymmetrization[23] was ultimately most successful. Upon treatment of dibenzoate **13** and sulfonamide **12** with a suitable Pd precatalyst and (*R*,*R*)-DACH-phenyl Trost ligand **14**, the desired desymmetrization took place. Direct saponification of the product furnished alcohol **15** in 89% yield. Subsequent PCC-mediated oxidation of the resultant secondary alcohol delivered enone **16** in excellent yield. Enone **16** could be crystallized at the interface of EtOAc and heptane; X-ray diffraction studies confirmed the desired absolute stereochemistry had been obtained in the desymmetrization reaction.[26]

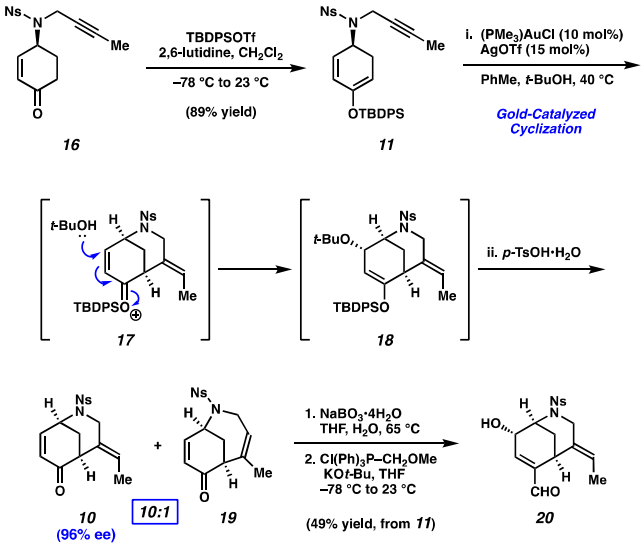
Scheme 2. Trost desymmetrization and synthesis of enone **16**.



Having synthesized enone **16**, we sought to introduce the [3.3.1]-azabicycle of the natural product and perform further elaborations (Scheme 3). Upon treatment with TBDPSOTf and 2,6-lutidine, enone **16** was converted to silyl enol ether **11** in high yield. This set the stage for a pivotal gold-mediated cyclization, inspired by precedent from Li and coworkers.[22] Using our optimized protocol, silyl enol ether **11** was treated with $(PMe_3)AuCl$ and AgOTf, followed by quenching with tosic acid hydrate in the same pot, to ultimately afford bicycle **10** as the major product. This sequence is thought to proceed by initial formation of oxocarbenium ion intermediate **17**, which undergoes nucleophilic attack by *t*-BuOH to give silyl enol ether **18**. In the presence of acid and water, **18** is hydrolyzed to give the desired enone **10**. Chiral SFC analysis

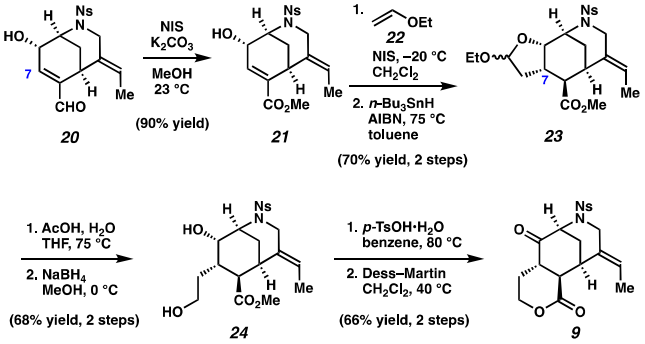
at this stage revealed that **10** had been prepared in 96% ee. It should also be noted that the key gold-mediated cyclization gave an undesired by product, **19**, in minor quantities. Although **10** and **19** were inseparable, the mixture could be taken forward through an epoxidation and Wittig homologation.[5h,k] Aqueous workup of the Wittig product led to enol ether hydrolysis with epoxide fragmentation to cleanly deliver enal **20** as a single constitutional isomer in 49% yield from silyl enol ether **11**.

Scheme 3. Gold-catalyzed cyclization to construct the [3.3.1]-azabicycle and elaboration to enal **20**.



Using the sequence shown in Scheme 4, enal **20** was elaborated to ketolactone **9**, the substrate for our key reductive interrupted Fischer indolization reaction. One of the synthetic challenges we encountered was the introduction of a hydroxyethyl group on C7. Initial approaches using metal-mediated conjugate addition strategies were met without success, so instead we targeted Ueno–Stork cyclization methodology.[27] En route to testing this approach, aldehyde **20** was converted to the corresponding methyl ester, **21**, using an NIS-based oxidative esterification protocol.[28] Next, **21** was treated with ethyl vinyl ether (**22**) and NIS to give a mixed iodoacetal

Scheme 4. Synthesis of ketolactone **9**, the substrate for the reductive Fischer indolization reaction.

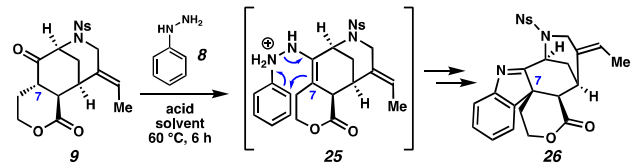


intermediate. Subsequent reaction with tributyltin hydride and AIBN led to cyclization at C7 to deliver acetal **23** as an inconsequential mixture of diastereomers.[27] Acid-mediated hydrolysis of the acetal and reduction of the resultant lactol provided diol **24**. Finally, lactonization, followed by alcohol oxidation, afforded the desired ketolactone **9**.

Reductive Interrupted Fischer Indolization Reaction

With ketolactone **9** in hand, we developed the key reductive interrupted Fischer indolization reaction. Our laboratory had extensive experience in developing Fischer indolizations in the context of methodology[18] and complex molecule synthesis.[5b,h,k] Thus we began by surveying a range of acid sources that were utilized in the Fischer indolization reaction literature and those we had previously deemed most promising. As shown in Table 1, the reactions of phenylhydrazine (**8**, 3 equiv) and ketolactone **9** using 5.0 equiv of acid were performed at 60 °C for 6 h to provide meaningful comparison data. Most attempts, including those with Lewis acids and very strong protic acids, were met with disappointment (entries 1–5). Whereas the use of AcOH gave modest yield using water as the solvent (entry 6), an improvement was seen in switching the solvent to acetic acid (entry 7). Lastly, the use of TFA gave the most promising result, delivering Fischer indolization product **26** in 38% yield (entry 8). It should be noted that this transformation proceeds with complete diastereoselectivity and sets the C7 quaternary stereocenter. The diastereoselectivity is thought to be governed by approach of the phenyl ring on the less hindered faced of the [3.3.1]-azabicycle during the charge-accelerated [3,3]-sigmatropic rearrangement (see transition structure **25**).

Table 1. Survey of acids to promote the Fischer indolization reaction of ketolactone **9** and **8**.

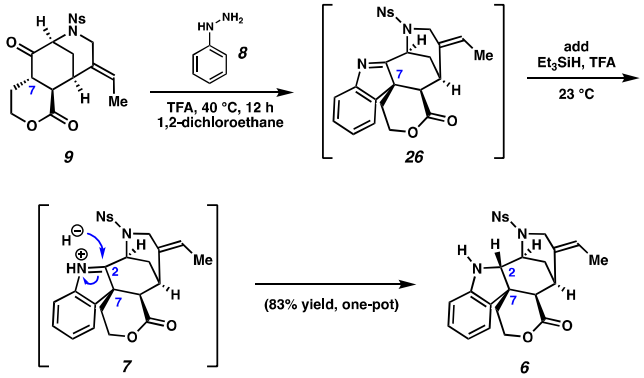


entry	acid source	solvent	yield[a] (%)
1	PCl_3	benzene	<5
2	$ZnCl_2$	EtOH	<5
3	*p*-TsOH·H_2O	EtOH, H_2O	<5
4	5% HCl	CH_3CN	<5
5	4% H_2SO_4	CH_3CN	<5
6	AcOH	H_2O	9
7	AcOH	AcOH	14
8	TFA	1,2-dichloroethane	38

[a] Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

Our next objective was to further optimize the Fischer indolization reaction and develop the desired reductive variant.[17] We were delighted to find that slight changes in our reaction conditions (i.e., 40 °C and 12 h), greatly improved conversion to indolenine lactone **26** (Scheme 5). Moreover, it was found that by simply adding triethylsilane and additional TFA to the Fischer indolization reaction with stirring at 23 °C, we obtained the reductive Fischer indolization product **6** in 83% yield. Overall, the conversion of ketolactone **9** to indoline **6** proceeds with installation of two new rings, three new bonds, and two new stereocenters, all with complete diastereoselectivity. This transformation represents one of the most complex Fischer indolization reactions reported in the literature.[29] Interestingly, hydride approach from the more congested face of the [3.3.1]-azabicycle appears to be favorable (see transition structure **7**). Although counterintuitive in some respects, the stereochemical outcome may be rationalized by the kinetic preference for the formation of a cis ring juncture between the pyrrolidine and cyclohexyl units. The stereochemical outcome is consistent with reports from the *Styrchnos* alkaloid literature[30] as well as a similar C2 reduction in akuammiline synthesis.[5v]

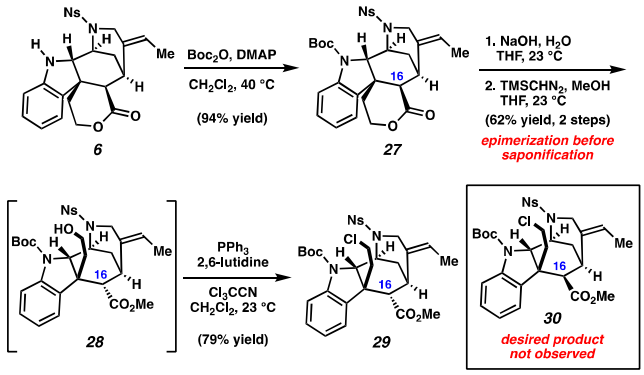
Scheme 5. Reductive interrupted Fischer indolization reaction delivers **6**.



Undesired C16 Epimerization and Synthesis of Unnatural C16 Epimers of Strictamine and 2(*S*)-Cathafoline

Having executed the key reductive interrupted Fischer indolization reaction, we sought to prepare chloroester **30** en route to the desired natural products through a seemingly straightforward sequence (Scheme 6). Boc protection of indoline **6** proceeded smoothly to furnish **27**. Subsequently, a two step hydrolysis/methylation protocol was used to arrive at hydroxyester **28**. Although we found **28** to be somewhat unstable, we found it could be used directly in the subsequent step. Treatment under Appel-like conditions cleanly provided **29**, which unfortunately possessed the undesired stereochemistry at C16. Despite a survey of alternative methanoloysis conditions prior to performing the chlorination, the undesired C16 epimer, **29**, was routinely formed as the major product. We surmise that C16 epimerization of **27** occurs more favorably than methanolysis or hydrolysis of the lactone. Several workarounds were pursued, such as attempted lactone opening via amidation,[31] Pd-catalyzed ring-opening,[32] or S_N2 displacements,[33] none of which were successful. Additionally, efforts to epimerize C16 of **29** and related compounds to provide the desired C16 epimer also proved fruitless.

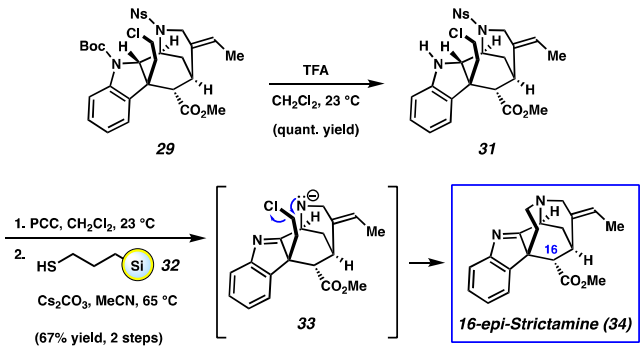
Scheme 6. Undesired C16 epimerization.



Faced with the undesired epimerization leading to chloroester **29**, we saw an opportunity to develop late-stage transformations and synthesize unnatural epimeric analogs of strictamine and 2(*S*)-cathafoline. As shown in Scheme 7, the C16 epimer of strictamine **34** could be accessed in three steps from chloroester **29**. Deprotection of **29** furnished indoline **31** in quantitative yield. Treatment of **31** with PCC led to indoline oxidation, thus providing the corresponding indolenine motif. Lastly, we pursued the key deprotection–cyclization step, analogous to that outlined in our retrosynthetic analysis (see Figure 1). Exposure of the indolenine intermediate to a solid-supported thiol resin **32**[34] and Cs_2CO_3 in acetonitrile at 65 °C delivered 16-*epi*-strictamine (**34**), presumably by way of transition structure **33**. Analogous to our earlier study toward the total synthesis of picrinine,[5h,k] the use of **32** proved instrumental in facilitating purification of the basic tertiary amine product. More importantly, this sequence demonstrated

that our overall approach involving a late-stage deprotection–cyclization could be used to access the challenging methanoquinzolidine framework.

Scheme 7. Synthesis of 16-*epi*-strictamine (**34**).



We also explored two complementary routes to the C16 epimer of 2(*S*)-cathafoline **35**, which are depicted in Figure 2. Beginning from intermediate alkyl chloride **31**, reductive amination using formaldehyde led to *N*-methylation.[5c] Subsequent deprotection–cyclization provided **35**, albeit in only 10% yield. Given the modest synthetic efficiency of this sequence, we pursued an alternative path that involved methanoquinolizidine formation prior to *N*-methylation. Deprotection–cyclization of sulfonamide **29**, followed by acidic deprotection of the indoline, furnished the methanoquinolizidine-containing product **36** in 76% yield over two steps. Finally, a reductive amination involving the indoline nitrogen afforded 16-*epi*-2(*S*)-cathafoline (**35**). The synthetic routes to **34** and **35** not only permitted access to unnatural analogs of strictamine and 2(*S*)-cathafoline, but also gave us critical experience in performing late-stage operations, particularly for introduction of the methanoquinolizidine unit and purification of polar natural product-like compounds.

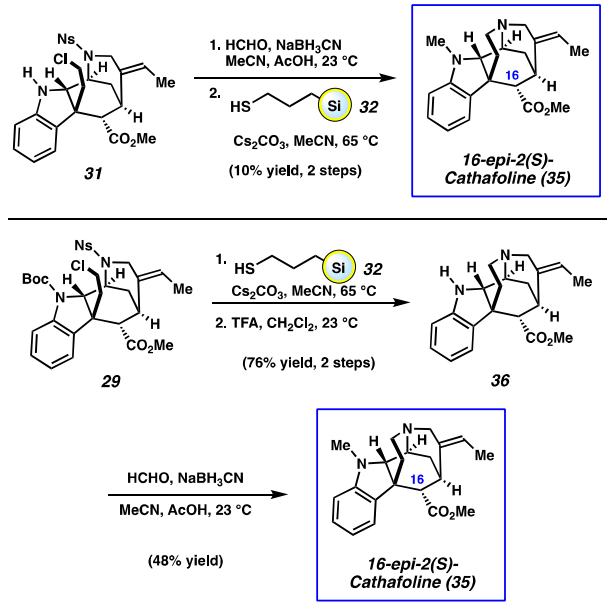
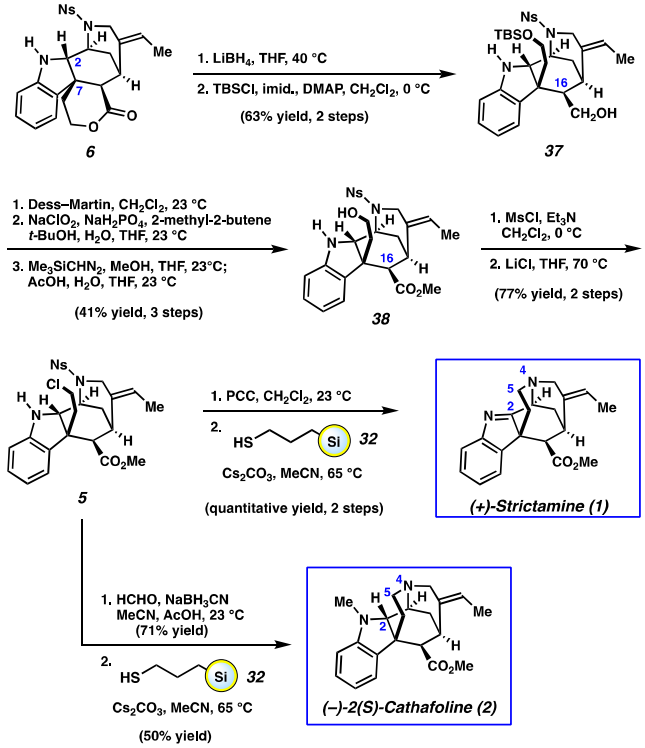


Figure 2. Synthetic routes to 16-*epi*-2(*S*)-cathafoline (**35**).

Enantioselective Total Syntheses of (+)-Strictamine and (–)-2(*S*)-Cathafoline

Despite the C16 epimerization setback, we returned to the primary task of completing the total syntheses of (+)-strictamine and (–)-2(*S*)-cathafoline (Scheme 8). We first sought a means to open the lactone ring of **6** under non-basic reaction conditions, to hopefully avoid the undesired epimerization. To this end, indoline lactone **6** was treated with lithium borohydride to give the corresponding diol with the C16 stereochemistry unperturbed. Subsequent protection of the more accessible primary alcohol furnished silyl ether **37**. Next, a straightforward three-step sequence was performed to elaborate the C16 hydroxymethyl group of **37** to the corresponding methyl ester, **38**. From hydroxyester **38**, a two-step chlorination protocol gave alkyl chloride **5**,[35] which proceeded in the presence of the free N–H of the indoline unit and set the stage for the final steps of the total syntheses. (+)-Strictamine (**1**) was accessed in quantitative yield from **5** by indoline oxidation, followed by deprotection–cyclization. Similarly, the total synthesis of (–)-2(*S*)-cathafoline (**2**) was achieved by *N*-methylation of **5**, followed by deprotection–cyclization. In both cases, the pentacyclic methanoquinolizidine framework was established in the final step of the total synthesis. NMR spectra of synthetic (+)-**1** and (–)-**2** correlated with spectra of the natural samples. This synthetic effort marked the first total syntheses of **1** and **2**, which was initially communicated concurrently with Zhu's synthesis of **1**.[16] Other synthetic routes to **1** have subsequently been reported by the labs of Fujii and Ohno,[5o] Gaich,[5p,t] Snyder,[5r] Qin,[5u] and Zu.[5v]

Scheme 8. Total syntheses of (+)-strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**).

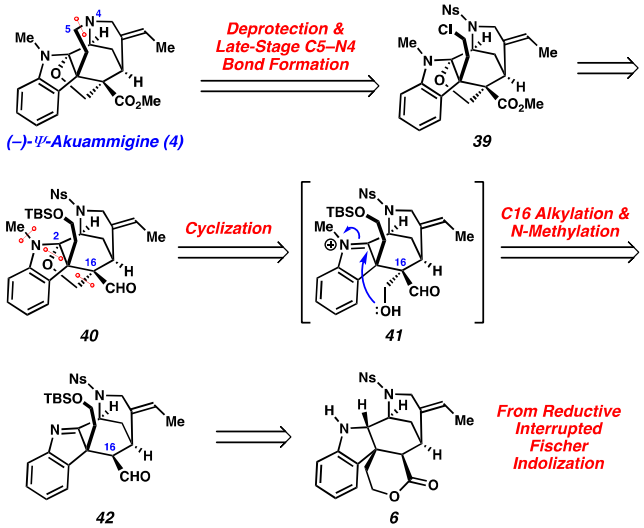


(–)-Ψ-Akuammigine: Isolation, Biological Activity, and Retrosynthetic Analysis

Having validated our strategy toward the total syntheses of natural products containing the methanoquinolizidine core, we directed our attention toward (–)-Ψ-akuammigine (**4**), the most structurally complex of the methanoquinolizidine-containing akuammiline alkaloids. (–)-Ψ-Akuammigine (**4**) was isolated from *Picralima klaineana* in 1932.[9] Biological studies later revealed promising activity as an anti-inflammatory agent.[36] Moreover, (–)-Ψ-akuammigine (**4**) belongs to a subset of akuammilines bearing vicinal quaternary centers, a structural motif which continues to be a notable synthetic challenge. In fact, only recently have there been reported total syntheses of akuammiline alkaloids bearing this motif.[5w–y] Despite these triumphant efforts, akuammilines containing both the methanoquinolizidine and vicinal quaternary centers have yet to succumb to total synthesis.[37]

Our initial retrosynthetic analysis of (–)-Ψ-akuammigine (**4**) is shown in Scheme 9. The natural product (**4**) was proposed to arise from late-stage intermediate **39**, possessing a furoindoline motif and an alkyl chloride. In the forward sense, removal of the nosyl group was expected to enable C5–N4 bond formation and forge the methanoquinolizidine core, analogous to the strategy used to synthesize (+)-strictamine (**1**) and (–)-2(*S*)-cathafoline (**2**). Chloride **39** would be synthesized from furoindoline **40** through oxidative esterification and elaboration of the silyl ether. In a key maneuver, furoindoline **40** would ultimately be derived from aldehyde **42** through a sequence involving C16 hydroxymethylation, followed by *N*-methylation and cyclization (see transition structure **41**). Although not depicted, it was envisioned that the namesake of the natural product family, (+)-akuammiline (**4**), could also be accessed from **42** or derivatives thereof. Finally, aldehyde **42** was anticipated to be available from indoline lactone **6**, which should be readily accessible by the reductive interrupted Fischer indolization reaction[17] described above (see Scheme 5).

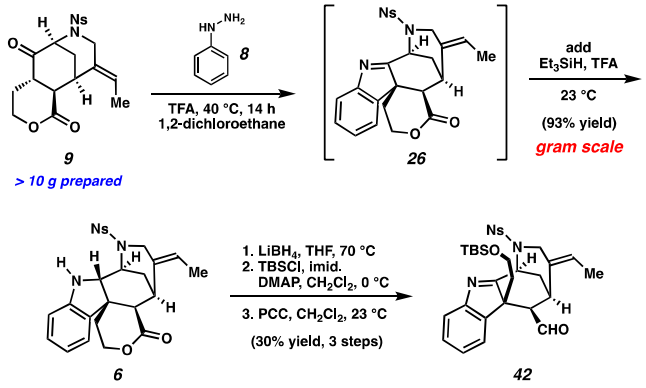
Scheme 9. Retrosynthetic analysis of (–)-Ψ-akuammigine (**4**).



Attempted Introduction of the Furoindoline Motif

To initiate our studies toward (–)-Ψ-akuammigine (**4**), we focused on the scalable preparation of aldehyde **42** following the route shown in Scheme 10. Knowing the commonly encountered difficulties associated with late-stage endeavors in akuammiline total synthesis, we expected our expedition would require us to perform the key, reductive interrupted Fischer indolization[17] step on a large scale. Thus, we first prepared more than 10 grams of ketolactone **9**. In the key reductive Fischer indolization step, we were heartened to find that gram-scale reaction of ketolactone **9** and phenylhydrazine (**8**) under acidic conditions proceeded smoothly to deliver intermediate indolenine **26**. Reduction in the same pot using triethylsilane then furnished the pentacyclic indoline lactone **6**

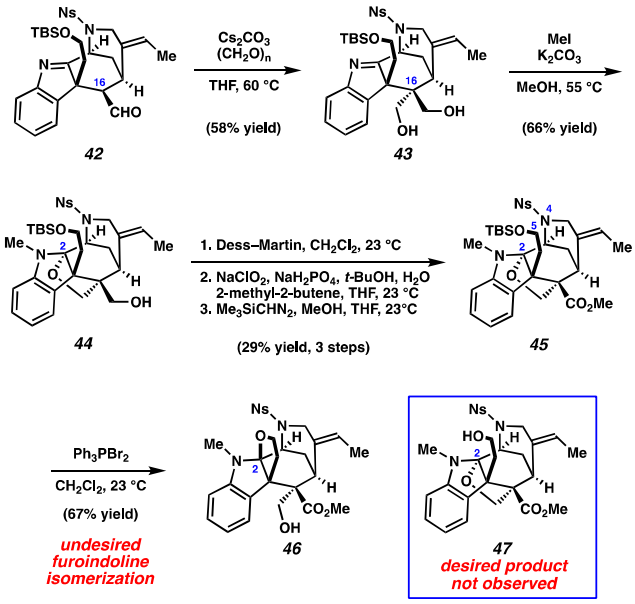
Scheme 10. Scalable preparation of aldehyde **42**.



in 93% yield. Elaboration of indoline lactone **6** through a 3-step sequence involving lactone reduction, selective alcohol protection, and simultaneous oxidation of the indoline and remaining alcohol afforded indolenine aldehyde **42**.

With aldehyde **42** in hand, we sought to tackle three structural challenges presented by Ψ-akuammigine (**4**): the vicinal quaternary centers, the furoindoline moiety, and the methanoquinolizidine core. As shown in Scheme 11, treatment of aldehyde **42** with paraformaldehyde under basic conditions[5x,y] provided diol **43** in 58% yield. Of note, this transformation establishes the second of the vicinal quaternary centers and proceeds with Tischenko-type reduction of the aldehyde.[38] Next, we pursued introduction of the furoindoline moiety by exposing diol **43** to excess methyl iodide and K_2CO_3.[39] This allowed for differentiation of the C16 hydroxymethyl groups and furnished furoindoline alcohol **44** in 66% yield. Lastly, we sought to forge the methanoquinolizidine core of the natural product. A three-step oxidation/esterification sequence delivered ester **45**, which was poised to undergo C5–N4 bond formation upon C5 activation and removal of the nosyl group. Unfortunately, removal of the silyl ether group present in **45** failed to deliver the desired alcohol **47**. Instead, we exclusively obtained an undesired isomer, furoindoline **46**, in 67% yield using Ph_3PBr_2,[40] and in high efficiencies under other conditions (e.g., acetic acid, TBAF). It is hypothesized that the presumed in situ structural rearrangement of furoindoline **47** to isomer **46** is thermodynamically driven, with **46** being significantly more stable.[41]

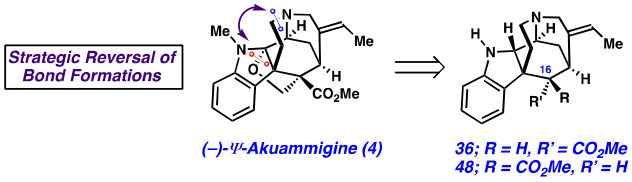
Scheme 11. Attempted introduction of the furoindoline motif and undesired isomerization to afford **46**.



Enantioselective Total Synthesis of (–)-Ψ-Akuammigine

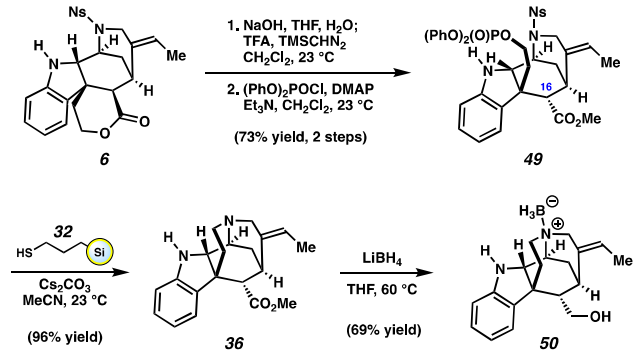
The discovery of the undesired furoindoline isomerization prompted us to reassess our synthetic approach toward (–)-Ψ-akuammigine (**4**) (Scheme 12). Rather than installing the furoindoline prior to the methanoquinolizidine, we sought to reverse the order in which these key structural features were formed. Thus, we targeted epimeric esters **36** or **48** and derivatives thereof that contain the methanoquinolizidine core, but lack the vicinal quaternary centers and furoindoline, as potential precursors to (–)-Ψ-akuammigine (**4**).[42] It should be noted that the C16 stereochemistry was considered inconsequential, as this stereocenter would be controlled during a subsequent alkylation step. However, the strategy would likely require the handling and purification of polar compounds due to the earlier installation of the tertiary amine. Given limited options, we pursued this revised strategy.

Scheme 12. Reassessment of synthetic approach.



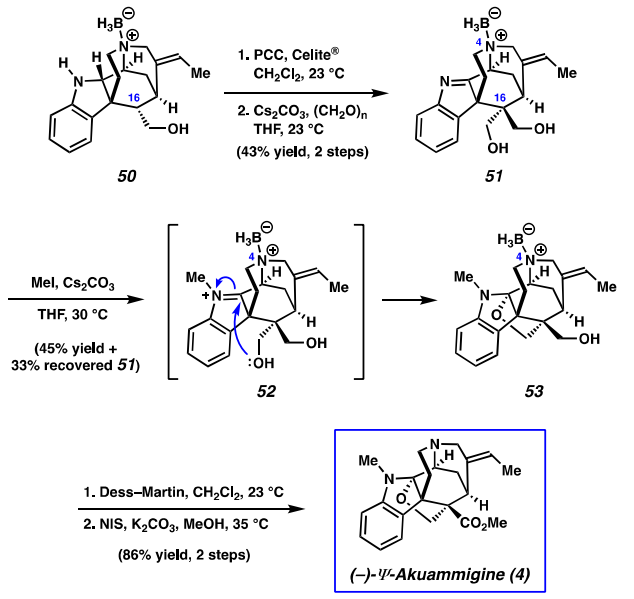
With the aim of installing the methanoquinolizidine and setting the stage for furoindoline formation, we developed the sequence described in Scheme 13. Beginning with the product of our reductive interrupted Fischer indolization reaction, indoline lactone **6**, we performed a one-pot saponification/methylation reaction. This net methanolysis of the lactone proceeded smoothly, with the expected epimerization of the C16 stereocenter. Several attempts were made to activate the resultant primary alcohol (e.g., tosylate, mesylate, halides, etc.), but the desired products of such efforts were highly unstable and could not be isolated. We ultimately found that the alcohol intermediate could be activated by conversion to diphenyl phosphate ester **49**.[43] This set the stage for methanoquinolizidine formation. Treatment of **49** with solid-supported thiol resin **32** under basic conditions provided ester **36**.[5h,k,l] Reduction of ester **36** with $LiBH_4$ afforded the corresponding alcohol with concomitant borylation of the tertiary amine to give indoline alcohol **50** in 69% yield.[44] Although unintentional, the introduction of the amine-borane functional group proved beneficial, as it masked the basic tertiary amine and dramatically facilitated purification of late-stage intermediates.

Scheme 13. Introduction of the methanoquinolizidine framework and fortuitous amine-borane complexation.



The final steps to complete the total synthesis of (–)-Ψ-akuammigine (**4**) focused on installation of the C16 quaternary stereocenter and the furoindoline motif (Scheme 14). Double oxidation of indoline alcohol **50** with PCC yielded the corresponding indolenine aldehyde, which was a suitable substrate for C16 alkylation. Exposure of the indolenine aldehyde to paraformaldehyde (9 equivalents) and Cs_2CO_3 provided diol **51** in 43% yield over two steps. In a key ploy, we pursued furoindoline formation by exposing **51** to methyl iodide under basic conditions.[39] This gave rise to the desired product, furoindoline alcohol **53**, in 45% yield, with 33% recovered **51**. We presume the reaction proceeds through activated indolenium **52** to deliver an intricate scaffold bearing both the methanoquinolizidine and the furoindoline motifs. Notably, if the reaction was allowed to proceed with higher conversion, borane removal and N4-methylation occured to give an undesired ammonium salt byproduct. Nonetheless, oxidation to the aldehyde, followed by oxidative esterification[28] with borane removal,[45] furnished (–)-Ψ-akuammigine (**4**) in 86% yield over two steps. All spectral data for (–)-Ψ-akuammigine (**4**) were consistent with reported data and authentic samples.[46]

Scheme 14. Total synthesis of (–)-Ψ-akuammigine (**4**).

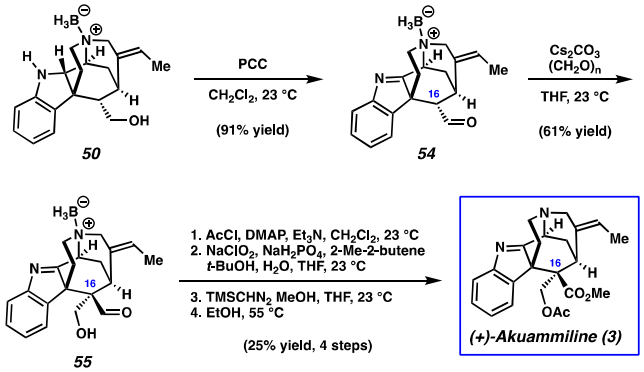


Enantioselective Total Synthesis of (+)-Akuammiline

Lastly with regard to the synthesis of methanoquinolizidine-containing akuammilines, we sought to prepare (+)-akuammiline (**3**, Scheme 15), the namesake of the natural product family. Akuammiline (**3**) was isolated alongside (–)-Ψ-akuammigine (**4**) in 1932 and has not been synthesized previously.[9] (+)-Akuammiline (**3**) is structurally similar to (–)-Ψ-akuammigine (**4**), but possesses a C16 acetoxymethyl group, rather than a furoindoline unit.

We were delighted to find that late-stage intermediate alcohol **50** served as a suitable precursor to (+)-akuammiline (**3**) (Scheme 15). Double oxidation of indoline alcohol **50** provided borane-protected indolenine aldehyde **54**. C16 alkylation of **54** proceeded smoothly to establish the vicinal quaternary centers and provide aldehyde **55**.[47] It was optimal to use only 1.2 equivalents of paraformaldehyde to preserve the aldehyde moiety and avoid reduction to the corresponding diol as we had observed earlier (see **51**, Scheme 14). To complete the total synthesis of (+)-akuammiline (**3**), aldehyde **55** was elaborated through a multistep protocol involving acetylation, conversion to the methyl ester, and borane removal.[48] Synthetic (+)-akuammiline (**3**) was spectroscopically comparable to an authentic sample of the natural product.[49]

Scheme 15. Total synthesis of (+)-akuammiline (**3**).



Structural Rearrangement of Methanoquinolizidines to Pyrrolidinoindolines

One interesting notion regarding the methanoquinolizidine-containing akuammiline alkaloids is that, biosynthetically, they serve as precursors to the pyrrolidinoindoline-containing akuammilines.[20] As such, we wondered if such structural rearrangements could efficiently be performed in the laboratory under mild reaction conditions. Exciting precedent for such conversions exists from the Zn/AcOH-mediated rearrangement of strictamine reported by Banerji and Chakrabarti in 1966, albeit without a reported yield.[50] We were particularly enticed to attempt the rearrangement of the methanoquinolizidine-containing natural products (+)-strictamine (**1**) and (+)-akuammiline (**3**) using the mild reducing agent samarium diodide[51] (Figure 3). Samarium diiodide has been utilized to reductively cleave C–N bonds of α-amino carbonyls, even in the context of akuammiline chemistry.[5v] However, there have been no previous examples of the corresponding reductive cleavage of C–N bonds with SmI_2 using α-amino imine substrates. Given that previous reductive rearrangements of the methanoquinolizidine core have been low yielding,[50] we viewed this as an opportunity to improve their efficiencies.

The results of our rearrangement studies are shown in Figure 3. Upon treatment of (+)-strictamine (**1**) with SmI_2 in THF and methanol at 23 °C, the desired reductive rearrangement took place to furnish pyrrolidinoindoline compound **56**. Subsequent methylation afforded (–)-10-demethoxyvincorine (**57**), a bioactive natural product isolated in 2014[8] from *Alstonia macrophylla*, that had yet to be synthesized. Next, we applied the same reductive rearrangement conditions to (+)-akuammiline (**3**). To our delight, the rearrangement proceeded in quantitative yield to provide the unnatural akuammiline derivative **58**. Of note, **58** bears a pyrrolidinoindoline core with vicinal quaternary stereocenters at C7 and C16, and is therefore reminiscent of complex akuammilines bearing those structural features.[52]

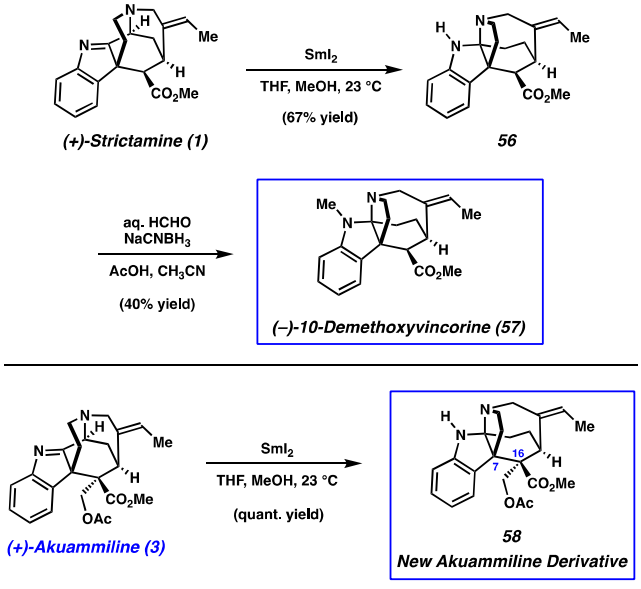


Figure 3. Structural rearrangement to access pyrrolidinoindolines (–)-10-demethoxyvincorine (**57**) and **58**.

Conclusion

We have completed the first enantioselective total syntheses of five akuammiline alkaloids, in addition to several unnatural compounds. Our synthetic approach to the methanoquinolizidine-containing natural products **1**–**4** features a number of key steps, including: a) a Trost desymmetrization to govern absolute stereochemistry, b) a gold-mediated cyclization to construct the [3.3.1]-azabicycle, c) a reductive interrupted Fischer indolization to arrive at pentacycle **6**, and d) late-stage formation of the methanoquinolizidine using a deprotection–cyclization cascade. In the case of (+)-akuammiline (**3**) and what is arguably the most complex methanoquinolizidine-containing alkaloid, (–)-Ψ-akuammigine (**4**), late-stage introduction of the vicinal quaternary stereocenters was achieved by employing challenging C16 alkylations. Additionally, in the case of (–)-Ψ-akuammigine (**4**), a means to install the furoindoline was crafted, while avoiding an undesired furoindoline isomerization that plagued our early approaches. Lastly, bioinspired reductive rearrangements of (+)-strictamine (**1**) and (+)-akuammiline (**3**) provided (–)-10-demethoxyvincorine (**57**) and a C16 analogue thereof **58**, by rearrangement of the methanoquinolizidine core to pyrrolidinoindoline scaffolds.

These efforts mark the first total syntheses of some of the most complex akuammilines known, including those that possess both a methanoquinolizidine core and vicinal quaternary stereocenters. It is expected that our studies will enable biological investigations of akuammilines and unnatural analogs. Moreover, the lessons learned from our synthetic endeavors, including the delicate late-stage manipulations and various undesired setbacks, will inform synthetic forays toward akuammilines and other challenging natural products.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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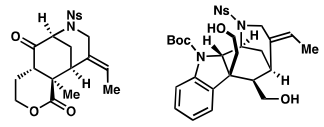
[42] Additional strategies were investigated. For example, we attempted to introduce the C16 quaternary stereocenter prior to Fischer indolization on a model system. However, Fischer indolization efforts using **i** were unsuccessful, presumably due to the difficulty of performing the [3,3]-sigmatropic rearrangement when trying to access vicinal quaternary stereocenters. With regard to late-stage efforts, intermediates such as diol **ii** could not be elaborated to substrates suitable for methanoquinolizidine formation.



i *ii*

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[52] An exemplary akuammiline natural product of this variety is echitamine, first isolated in 1875. For the seminal isolation report, see: Group-Besanez, v. *Justus Liebigs Ann. Chem.* **1875**, *176*, 88−89.

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