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Total Synthesis of the Akuammiline Alkaloid Picrinine

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Supporting Information

ABSTRACT: We report the first total synthesis of the complex akuammiline alkaloid picrinine, which was first isolated nearly five decades ago. Our synthetic approach features a concise assembly of the [3.3.1]-azabicyclic core, a key Fischer indolization reaction to forge the natural product's carbon framework, and a series of delicate late-stage transformations to complete the synthesis. Our synthesis of picrinine also constitutes a formal synthesis of the related polycyclic alkaloid strictamine.

Natural products belonging to the akuammiline family of alkaloids have a rich history in the chemical literature.[1] Representative akuammilines **1**–**6** are depicted in Figure 1,

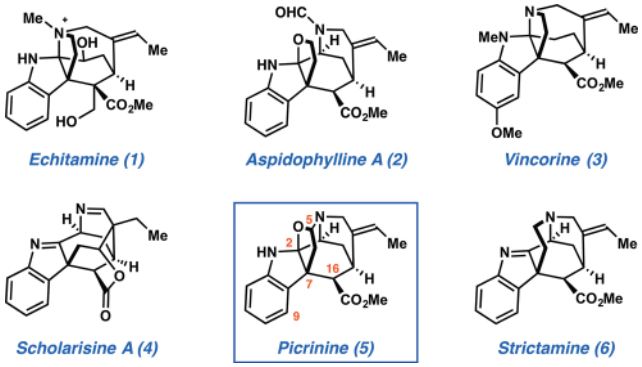


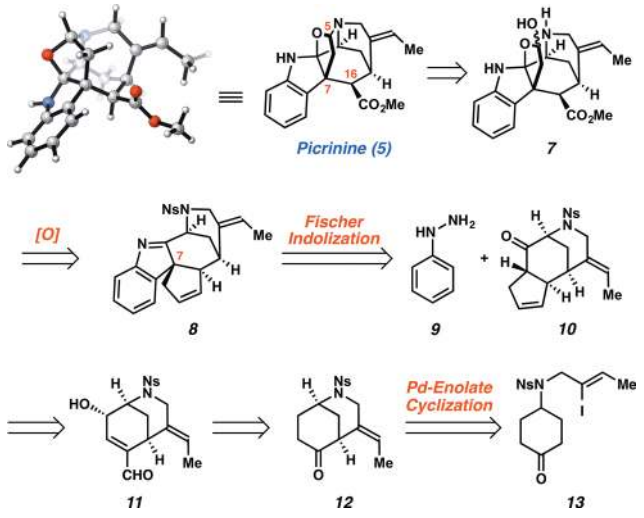
Figure 1. Representative akuammiline alkaloids **1**–**6**.

each of which possesses an indoline or indolenine core fused to a daunting polycyclic framework.[2−7] Since the initial isolation report of echitamine (**1**) in 1875,[2] more than 30 compounds in this family have been isolated from plants predominantly in Southeast Asia. The complex structures of these molecules, along with their interesting biological properties,[1] have recently prompted a number of synthetic investigations. Notable achievements in this arena include total syntheses of aspidophylline A (**2**) by Zhu,[8] Ma,[9] and our group,[10] vincorine (**3**) by Qin,[11] Ma,[12] and MacMillan,[13] and scholarisine A (**4**) by Smith[14] and Snyder.[15,16]

The present study focuses on picrinine (**5**), which has not previously been prepared by total synthesis. First discovered in 1965 from the leaves of *Alstonia scholaris*,[6] picrinine (**5**) is a highly complex, cage-like molecule that contains a furoindoline core fused to a densely functionalized cyclohexyl ring. In turn, the central cyclohexyl ring is part of a bridged [3.3.1]-azabicyclic framework. Picrinine (**5**) possesses six stereogenic centers, five of which are contiguous, and contains two *N,O*-acetal linkages within its polycyclic skeleton. In vitro studies show that picrinine (**5**) exhibits anti-inflammatory activity through inhibition of the 5-lipoxygenase enzyme.[17] In this Communication, we report the first total synthesis of picrinine (**5**).

Our retrosynthetic analysis of picrinine (**5**) is highlighted in Scheme 1.[18] We envisioned that picrinine (**5**) could be accessed

Scheme 1



by late-stage introduction of the bis(*N,O*-acetal) linkage via a proximity-driven cyclization of aminolactol **7**.[19] This intermediate would arise from pentacycle **8** through oxidative cleavage of the cyclopentene and subsequent functional group interconversions. Next, in a key step, it was thought that pentacycle **8** could be constructed from a Fischer indolization reaction[20] between phenylhydrazine **9** and tricyclic cyclopentene **10**. If successful, this would allow for the introduction of the C7 quaternary stereocenter and provide the complex carbon framework of the natural product. Tricycle **10** would be assembled from enal **11**, which could be generated from bridged [3.3.1]-azabicycle **12**. Finally, it was hypothesized that bicycle **12** would be accessible from readily available vinyl iodide **13** using a Pd-catalyzed enolate cyclization.

Our synthesis commenced with the preparation of enal **11** (Scheme 2). Sulfonamide **14**, which is available from commercial sources or can be readily prepared,[21] was identified as a suitable starting material. Alkylation of **14** with tosylate **15**[22] afforded vinyl iodide **13** in excellent yield. Next, treatment

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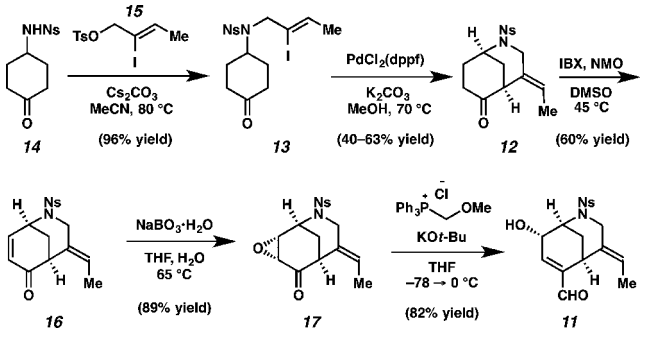
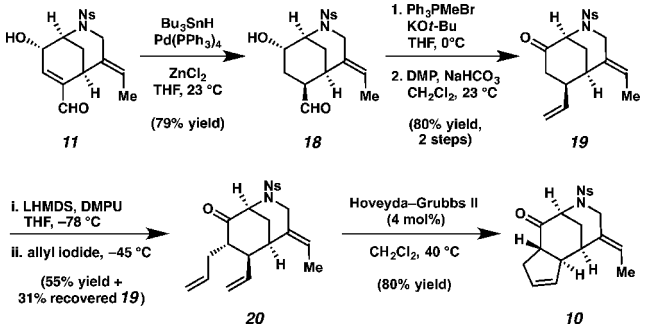
Scheme 2



of **13** with $PdCl_2$(dppf) and K_2CO_3 in MeOH at 70 °C furnished bicycle **12** via a Pd-catalyzed enolate cyclization.[23] Bicyclic ketone **12** was processed to enone **16** by IBX oxidation.[24] Subsequent epoxidation, using sodium perborate as a mild oxidant,[25] transformed **16** into epoxide **17** in 89% yield with complete diastereoselectivity. To arrive at the desired enal intermediate **11**, epoxide **17** was subjected to Wittig olefination using (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide.[26] Fragmentation of the presumed epoxy enol ether intermediate occurred spontaneously in situ to deliver **11** in 82% yield.

As shown in Scheme 3, enal **11** could be elaborated to tricyclic cyclopentene **10** through a five-step sequence.

Scheme 3

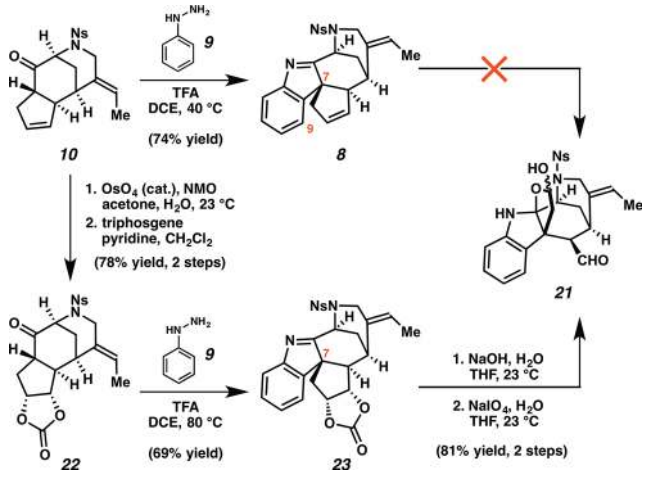


Reduction of **11** proceeded smoothly upon exposure to tributyltin hydride, catalytic $Pd(PPh_3)_4$, and zinc chloride[27] to furnish **18**.[28] Wittig olefination, followed by Dess–Martin oxidation delivered vinyl ketone **19** in 80% yield over two steps. Next, ketone **19** was treated with LHMDS and DMPU, followed by allyl iodide. This step afforded allyl vinyl ketone **20**, which was subjected to the Hoveyda–Grubbs second-generation catalyst in refluxing dichloromethane to give tricyclic cyclopentene **10**.[29]

With access to tricycle **10**, we explored the critical Fischer indolization and the ensuing furoindoline formation, as summarized in Scheme 4. We were delighted to find that treatment of **10** with phenylhydrazine (**9**) and trifluoroacetic acid in dichloroethane at 40 °C furnished the desired pentacycle **8** in 74% yield. However, exhaustive efforts to oxidatively cleave the cyclopentene of **8** en route to lactol aldehyde **21** were unsuccessful.[30]

Hypothesizing that access to the disubstituted olefin of cyclopentene **8** was obstructed by the [3.3.1]-bicycle and the C9 hydrogen, we pursued an alternate strategy, which involved olefin oxidation prior to the Fischer indolization (Scheme 4).

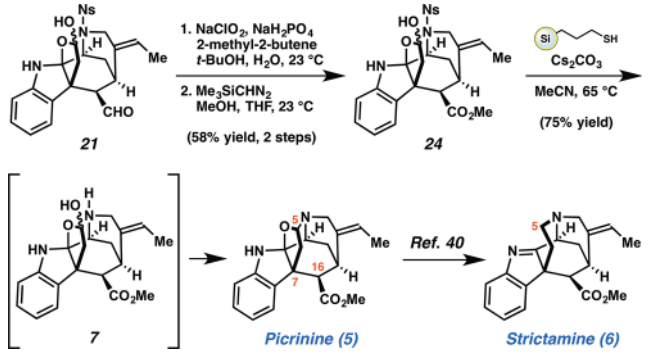
Scheme 4



Thus, cyclopentene **10** was exposed to an oxidation[31] and protection[32] sequence, providing carbonate **22** in 78% yield over two steps. In the critical Fischer indolization, TFA-promoted reaction of **22** with phenylhydrazine **9** afforded the hexacyclic indolenine product **23** with complete diastereoselectivity. This transformation marks one of the most complex examples of the Fischer indolization reaction[20] and is testament to the reliability of this venerable synthetic method.[33] It should be noted that indolenine **23** exists in equilibrium with its hydrate,[34] so careful purification and 2D NMR analysis were necessary to facilitate structure elucidation. Nonetheless, cleavage of the cyclic carbonate of **23**,[35] followed by oxidative cleavage[36] generated lactol **21** as an inconsequential mixture of diastereomers.

Having assembled the carbon scaffold of the natural product, three transformations remained in order to access picrinine (**5**). From late-stage intermediate **21**, this would involve conversion of the aldehyde to the corresponding methyl ester, cleavage of the nosyl group, and cyclization to forge the second *N*,*O*-acetal linkage. As shown in Scheme 5, the first of these challenges was

Scheme 5



addressed by implementing a two-step sequence involving oxidation to the carboxylic acid,[37] followed by esterification. This generated ester **24** in 58% yield over the two steps without disturbing the lactol. Next, our attempts to remove the nosyl protecting group from **24** proved challenging. We ultimately found, however, that denosylation could be achieved using a solid-supported thiol resin.[38,39] Much to our gratification, proximity-driven cyclization of the presumed aminolactol

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intermediate **7** occurred under the reaction conditions to provide the bis(*N,O*-acetal) linkage and furnish picrinine (**5**). Synthetic picrinine (**5**) was found to be identical to a sample of the natural material in all respects. It should be noted that our total synthesis of **5** also constitutes a formal synthesis of strictamine (**6**).[40]

In summary, we have completed the first total synthesis of the akuammiline alkaloid picrinine (**5**, 18 steps from known ketone **14**), which was first isolated nearly 50 years ago. Our synthetic approach features a concise assembly of the [3.3.1]-azabicyclic core, a key Fischer indolization reaction to forge the natural product's carbon framework, and a series of delicate late-stage transformations to complete the total synthesis. We expect our approach to **5** will enable the syntheses of other alkaloids in the akuammiline family of 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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Notes

The authors declare no competing financial interest.

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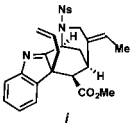

i

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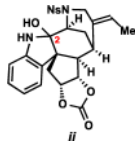

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