Total Synthesis of the Akuammiline Alkaloid Picrinine

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S *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,
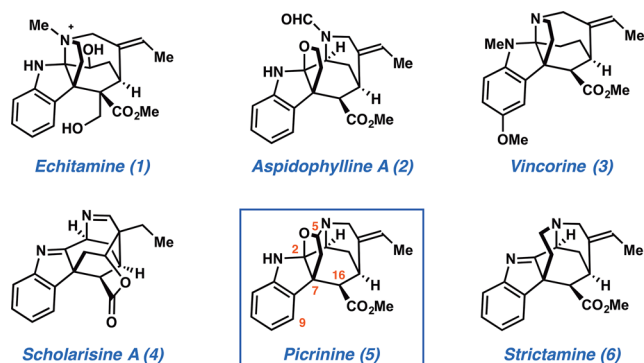

Figure 1. Representative akuammiline alkaloids 1−6.

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
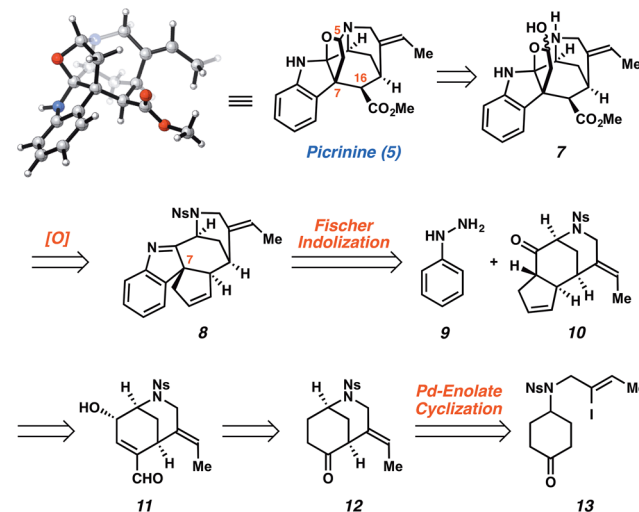
by late-stage introduction of the bis(*N,O*-acetal) linkage via a proximity-driven cyclization of aminolactol 7.[19] This intermediate would arise from pentacycle 8 through oxidative cleavage of the cyclopentene and subsequent functional group interconversions. Next, in a key step, it was thought that 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

Scheme 2
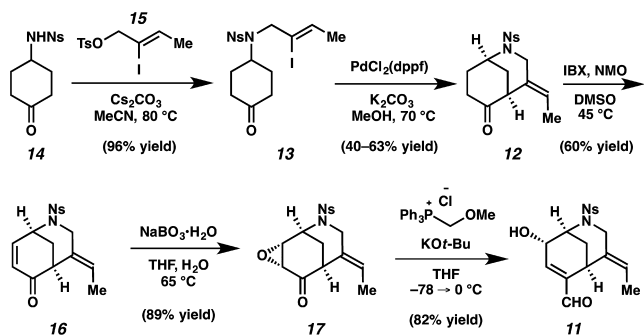
of **13** with PdCl$_2$(dppf) and K$_2$CO$_3$ in MeOH at 70 °C furnished bicycle **12** via a Pd-catalyzed enolate cyclization.[23] Bicyclic ketone **12** was processed to enone **16** by IBX oxidation.[24] Subsequent epoxidation, using sodium perborate as a mild oxidant,[25] transformed **16** into 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
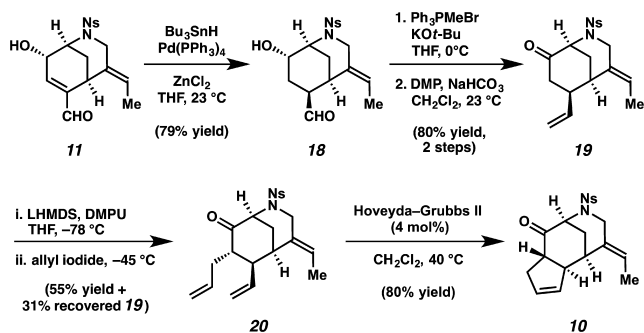
Reduction of **11** proceeded smoothly upon exposure to tributyltin hydride, catalytic Pd(PPh$_3$)$_4$, and zinc chloride[27] to furnish **18**.[28] Wittig olefination, followed by Dess–Martin oxidation delivered vinyl ketone **19** in 80% yield over two steps. Next, ketone **19** was treated with LHMDS 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
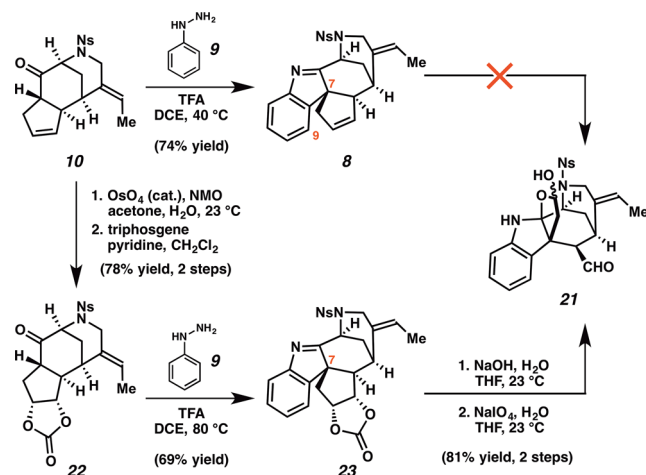
Thus, cyclopentene **10** was exposed to an oxidation[31] and protection[32] sequence, providing carbonate **22** in 78% yield over two steps. In the critical Fischer indolization, TFA-promoted reaction of **22** with phenylhydrazine **9** afforded the hexacyclic indolenine product **23** with complete 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
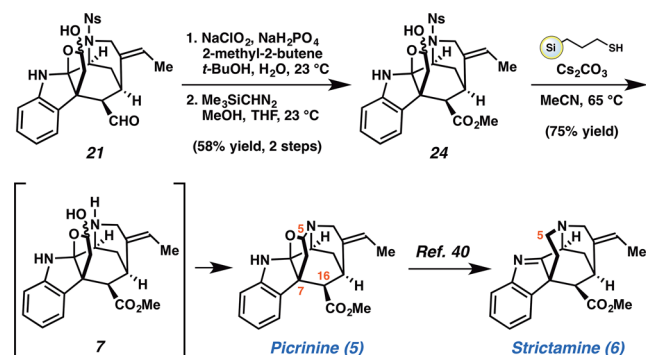
addressed by implementing a two-step sequence involving oxidation to the carboxylic acid,[37] followed by esterification. This generated ester **24** in 58% yield over the two steps without disturbing the lactol. Next, our attempts to remove the nosyl protecting group from **24** proved challenging. 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.

■ ACKNOWLEDGMENTS

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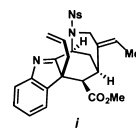
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(34) Exposure of **23** to mildly acidic media, such as chloroform or silica gel, led to variable amounts of hydrate formation (see compound **ii** below; the stereochemistry at C2 was not established). Separation of **23** from **ii** was achieved using careful chromatography, and NMR studies were performed in benzene-d_6 to suppress the hydration. Interestingly, hydrate **ii**, indolenine **23**, or variable mixtures of the two could be used in the subsequent transformation to give indolenine products.

ii
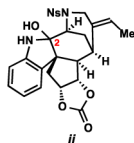
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