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Fischer Indolizations as a Strategic Platform for the Total Synthesis of Picrinine

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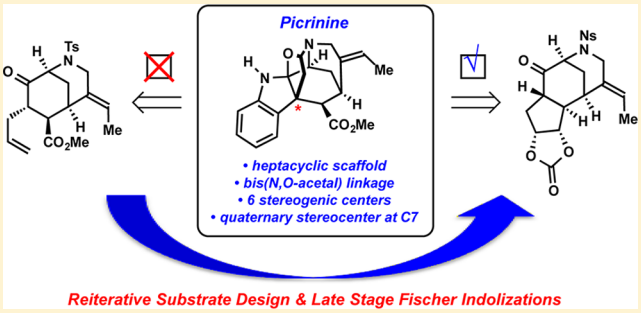
Supporting Information

ABSTRACT: Picrinine, which is a member of the akuammiline family of alkaloids, was first isolated in 1965 from the leaves of *Alstonia scholaris*. The natural product possesses a daunting polycyclic skeleton that contains a furanoindoline, a bridged [3.3.1]azabicycle, two *N*,*O*-acetal linkages, and six stereogenic centers. These structural features render picrinine a challenging and attractive target for total synthesis. This paper provides a full account of our synthetic forays toward picrinine, which culminates in the first total synthesis of this long-standing target. Central to the success of our approach is the use of the Fischer indolization reaction to introduce the C7 quaternary stereocenter and the indoline nucleus of the natural product's scaffold. We probe some of the subtleties of this classic transformation by examining some of the most complex Fischer indolization substrates to date. Additionally, we describe various roadblocks encountered in our experimental efforts, which were successfully overcome to complete the total synthesis of picrinine.



INTRODUCTION

The plant *Alstonia scholaris*, also known as the Dita Bark tree, has been a rich source of alkaloid natural products for close to a century. In fact, extracts from its bark, leaves, seeds, fruitpods, flowers, and roots have been used in traditional folk medicines to treat various ailments in humans and livestock.[1] Among the alkaloids found in *Alstonia scholaris*, picrinine (**1**) is one of the major constituents that was first isolated and structurally elucidated in 1965 by Chatterjee and co-workers (Figure 1).[2] Following its isolation, an X-ray crystal structure of **1** was obtained, which highlights the densely functionalized, cagelike structure of the natural product.[3] Structural features of **1** include a fused furanoindoline framework, a [3.3.1]azabicycle, and a highly functionalized cyclohexyl unit that bears five of the natural product's six stereocenters. The C7 stereocenter is quaternary and presents a notable synthetic challenge. The remaining stereocenter is at C5, which is a part of the bis(*N*,*O*-acetal) moiety that links the furanoindoline to N4 of the piperidine ring. Picrinine (**1**) has shown in vitro anti-inflammatory activity via inhibition of the 5-lipoxygenase enzyme.[4] Moreover, **1** is a major constituent of the leaf extracts of *Alstonia scholaris* that have been approved for clinical trials in China due to their antitussive and antiasthmatic properties.[5]

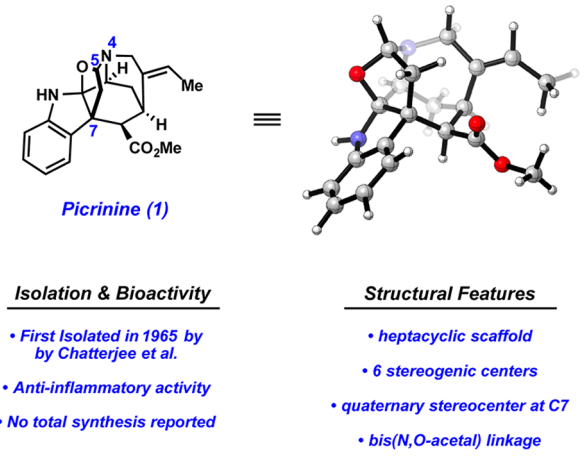


Figure 1. Picrinine (**1**) and 3D representation from X-ray structure.

Picrinine (**1**) belongs to a larger family of alkaloids called the akuammilines.[6] More than 30 akuammilines have been isolated over the past 90 years, and their sources, much like *Alstonia scholaris*, have served as traditional ailment remedies across the Eastern Hemisphere. Biological testing of the akuammilines has revealed promising activities for combating illnesses that are viral, plasmodial, and cancerous.[4a] Central to the biological efficacy of the akuammiline alkaloids are their structures, which share a common biosynthetic origin.

Figure 2 highlights the hypothesized biosynthetic origins of picrinine and other related indole alkaloids.[7c] First, the union of tryptamine (**2**) and secologanin (**3**) affords the natural product geissoschizine (**4**), which serves as the biosynthetic precursor to several families of monoterpenoid alkaloids via various intramolecular oxidative coupling pathways.[7] The coupling of

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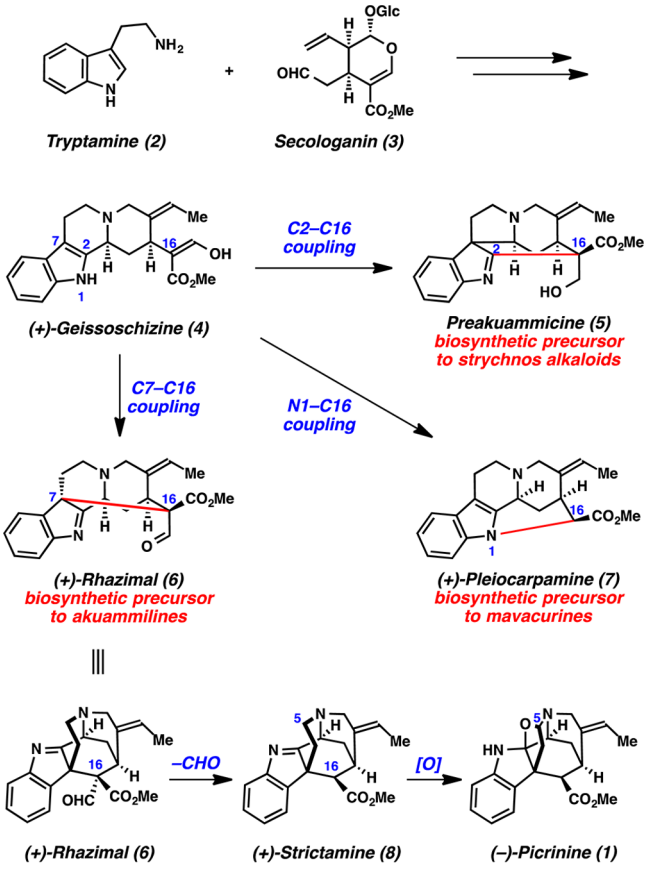

Figure 2. Biosynthesis of picrinine (**1**) and other indole monoterpene alkaloids.

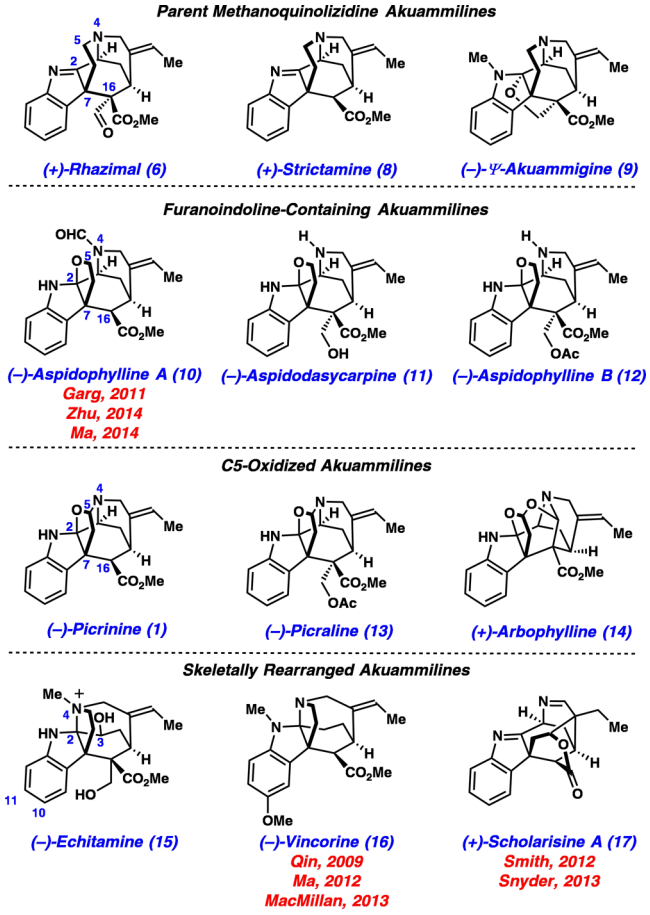

Figure 3. Representative akuammiline alkaloids and synthetic achievements.

C2 and C16 results in the *Strychnos* skeleton as exemplified by the natural product preakuammicine (**5**), which is the biosynthetic progenitor to the other *Strychnos*-type alkaloids. Second, oxidative coupling of N1 and C16 forges the mavacurine alkaloid skeleton (e.g., pleiocarpamine (**7**)). Finally, the C7−C16 coupling of geissoschizine (**4**) results in the formation of rhazimal (**6**),[8] which bears vicinal quaternary centers and the akuammiline scaffold. Deformylation of rhazimal (**6**) is thought to give strictamine (**8**),[9] which undergoes selective oxidation at C5, to afford picrinine (**1**). It is worth noting that despite the common origins and impressive structures of the *Strychnos*, mavacurine, and akuammiline alkaloids, the *Strychnos* alkaloids have garnered the greatest attention from the synthetic community.[10]

The biosynthetic manipulation of rhazimal through oxidation and rearrangement events, in addition to furnishing picrinine (**1**), provides the remarkable structural diversity seen in the akuammiline alkaloids (e.g., **1**, **6**, and **8**−**17**, Figure 3). These biosynthetic transformations have been summarized in recent review articles.[6b,c] On the basis of structure, most akuammilines can be classified into one of four categories. The first three categories are comprised of akuammiline scaffolds that have not undergone skeletal rearrangements from rhazimal (**6**) but differ with regard to C5 oxidation state and functionalization. Strictamine (**8**)[9] and ψ-akuammigine (**9**)[11] are examples of the parent methanoquinolizidine type that, like **6**, are minimally functionalized at C5. Notably, ψ-akuammigine (**9**) contains an additional ring that forms a complex [3.2.1]-bridged oxabicyclic motif. The second group is composed of the furanoindoline-containing akuammilines and is represented by aspidophylline A (**10**),[12] aspidodasycarpine (**11**),[13] and aspidophylline B (**12**).[14] Members of this group contain an oxygen linkage between C5 and C2 as a salient feature of their furanoindoline cores but lack the N4−C5 bond found in the parent methanoquinolizidine akuammilines. It is notable that this bond is absent, indicating a possible reduction at C5 in the course of their biosynthesis. The third representative class of nonrearranged akuammilines is composed of members with additional oxidation at C5. The resulting oxygenation at C5 provides the C5−O−C2 linkage seen in picrinine (**1**), picraline (**13**),[15] and the remarkable compound arbophylline (**14**).[16] Finally, the rearranged akuammiline structural class includes the alkaloids echitamine (**15**),[17] vincorine (**16**),[18] and scholarisine A (**17**).[19] The former two examples contain a N4−C2 linkage that presumably arises from a reorganization of the N4−C3 bond found in the parent methanoquinolizidine akuammilines. Scholarisine A (**17**) is proposed to arise from picrinine (**1**) through formation of its unique [2.2.2]-bicyclic lactone embedded within its polycyclic cagelike structure.[19]

Recent efforts have led to the successful total synthesis of three akuammiline alkaloids. The first akuammiline alkaloid accessed by total synthesis was vincorine (**16**) by Qin's laboratory in 2009.[20] This was a significant achievement because of the longstanding synthetic challenge that the akuammiline natural products had posed for decades.[6] Qin's racemic synthesis of vincorine (**16**) was soon followed by enantioselective syntheses by Ma in 2012[21] and MacMillan in 2013.[22] The second akuammiline alkaloid to be synthesized was

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(±)-aspidophylline A (**10**), completed by our research group in 2011.[23] More recent syntheses of this target have been completed by the research groups of Zhu[24] and Ma.[25] Scholarisine A (**17**) has been elegantly synthesized by Smith in 2012[26] and Snyder in 2013.[27]

This paper describes a full account of our efforts to achieve the first total synthesis of picrinine (**1**).[28] The approaches described herein were inspired by our laboratory's prior total synthesis of aspidophylline A (**10**).[23] Central to our synthetic approach to **10** was the key interrupted Fischer indolization reaction shown in Figure 4.[29] Phenylhydrazine (**18**) was

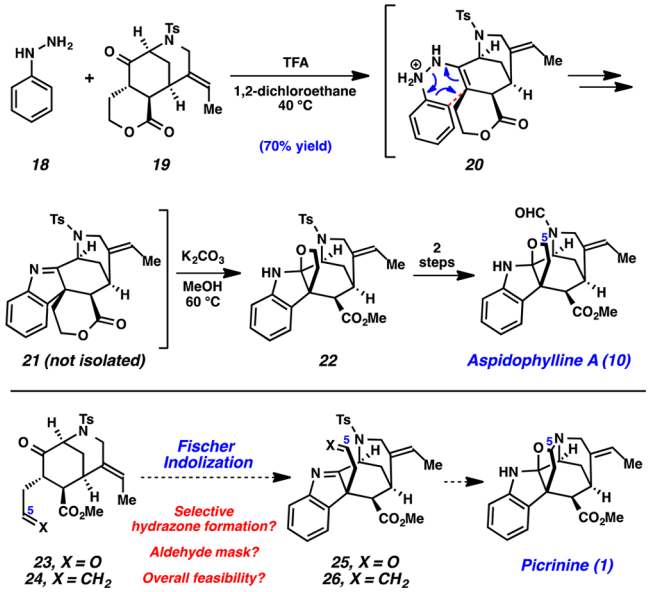

Figure 4. Summary of total synthesis of aspidophylline A (**10**) and initial synthetic plan for picrinine (**1**) utilizing the key Fischer indolization reaction.

reacted with ketolactone (**19**) in the presence of trifluoroacetic acid (TFA) in 1,2-dichloroethane (DCE) at 40 °C to first give a hydrazone intermediate. Following tautomerization, charge-accelerated [3,3]-sigmatropic rearrangement (see transition structure **20**), and subsequent loss of ammonia, intermediate indolenine **21** was obtained. Removal of the volatiles, followed by the addition of K_2CO_3 and methanol, promoted lactone cleavage and spontaneous cyclization to build the pentacyclic furanoindoline product **22** in 70% yield. This process occurred with complete diastereoselectivity. Further elaboration through two additional steps provided the natural product (**10**), thus completing its first total synthesis.

We envisioned a similarly attractive stategy in our approach to picrinine (**1**) as suggested in Figure 4. Ideally, we sought to utilize interrupted Fischer indolization substrate **23** to access the core of the natural product but foresaw challenges in achieving selective hydrazone formation of the ketone in the presence of the C5 aldehyde en route to **25**. The use of an alkene as an aldehyde mask presented a viable workaround and led to the design of substrate **24**.[30] After the Fischer indolization of **24** to furnish **26**, the alkene would be oxidatively cleaved at a late stage to access the correct C5 aldehyde oxidation state found in the natural product.[23,31] Finally, the viability of the Fischer indolization reaction was a notable concern considering the substrate's complexity, its differences compared to ketolactone **19** used in the synthesis of aspidophylline A,[23] and our prior experiences with challenging Fischer indolizations of related substrates.[32]

RESULTS AND DISCUSSION

Initial Forays and First-Generation Retrosynthetic Analysis. Based on the synthetic plan mentioned above, we tested the Fischer indolization of ketone **24**, a known intermediate from our prior synthesis of aspidophylline A (Figure 5).[23] Upon treatment of **24** with phenylhydrazine (**18**)

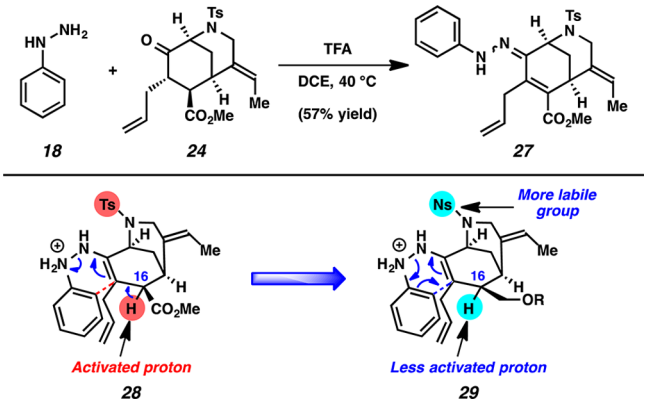

Figure 5. Unsuccessful Fischer indolization of **24** and design of modified substrate.

under the same Fischer indolization conditions used for the aspidophylline A synthesis, none of the desired product (**26**) was observed, with only oxidized hydrazone derivative **27** forming as the major product in 57% yield. When the reaction was studied with different acid sources and/or temperatures, the same outcome was obtained. Similarly, attempts to rigorously exclude molecular oxygen from the reaction mixture also led to the formation of **27**. We hypothesized that the putatively formed ene hydrazine **28** was prone to deprotonation at C16 and that the deprotonation would ultimately result in N−N bond cleavage. Such N−N bond cleavage processes have been observed in Fischer indolizations and studied by Houk and co-workers.[33] Following this formal oxidation event (i.e., deprotonation and N−N bond cleavage), excess hydrazine in the reaction mixture could condense on the ketone to give the observed product **27**. As the desired [3,3]-sigmatropic rearrangement was presumably being outcompeted by this unproductive reaction pathway, we sought to design an alternate Fischer indolization substrate. It was hypothesized that by converting the exocyclic ester to a protected alcohol derivative, the undesired N−N bond cleavage might be suppressed due to the reduced acidity of the C16 proton (see structure **29**). Consequently, the desired [3,3]-sigmatropic rearrangement could be rendered the predominant reaction pathway. Additionally, we opted to switch the nitrogen protecting group from tosyl to the more labile nosyl group in order to facilitate removal at a late stage in the synthesis.[34]

With the key elements and modifications of our design plans established, we devised the retrosynthetic analysis of **1** shown in Scheme 1. It was envisioned that the natural product could arise from the spontaneous cyclization of an intermediate such as **30**, which would result from oxidation and deprotection of indolenine **31**. In turn, indolenine **31** would arise from a late-stage Fischer indolization of phenylhydrazine (**18**) and ketone **32**.[35] Ketone **32** would be derived from enone **33**, an

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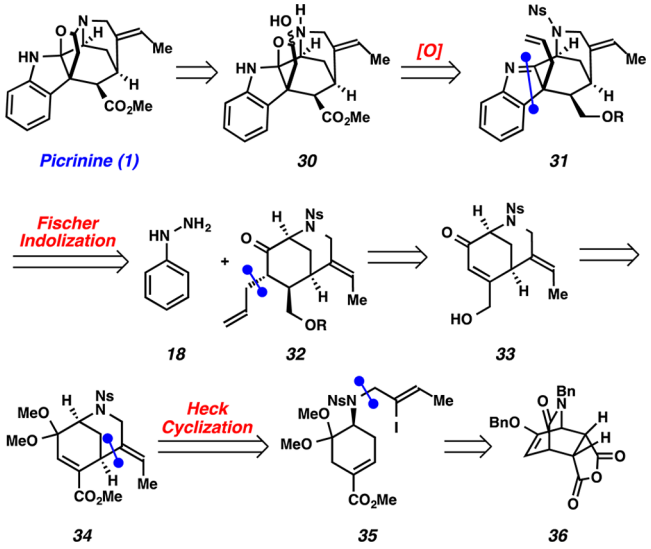
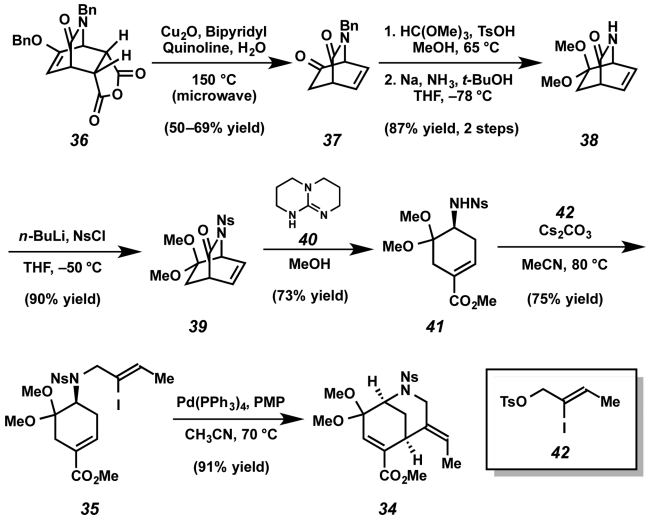
Scheme 1. Initial Retrosynthetic Plan for the Total Synthesis of Picrinine (1)



intermediate that could be accessed from enoate **34**. This bicyclic enoate would arise by Heck cyclization of vinyl iodide **35**.[36,37] Finally, the Heck cyclization substrate (**35**) would be derived from the known bicyclic lactam **36**,[38] which can be readily prepared from commercially available starting materials.

Synthesis of [3.3.1]Azabicycle and Elaboration to Fischer Indolization Substrate. Our first goal was to assemble the [3.3.1]azabicyclic core of the natural product using the Heck cyclization strategy mentioned previously. Our synthesis of the desired bicyclic enoate **34** is depicted in Scheme 2. We were first able to access >20 g quantities of the

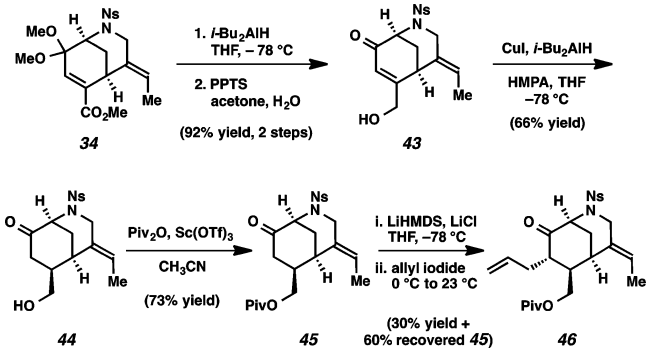
Scheme 2. Synthesis of [3.3.1]Azabicycle 34



starting tricyclic lactam **36** from a known Diels–Alder protocol.[38] This intermediate was then subjected to a mixture of copper(I) oxide in water and quinoline under microwave irradiation to promote an oxidative bis(decarboxylation) reaction.[39] This transformation gave ketone **37** in 50–69% yield, although yields were lower and less consistent if the reaction was run above a 40 mg scale. To facilitate material throughput, we employed an automated microwave reactor to prepare gram quantities of **37**.[40] Next, a two-step sequence involving ketalization and debenzylation afforded bicyclic lactam **38** in excellent yield. Bicycle **38** was then protected as the 2-nitrobenzenesulfonamide upon treatment with *n*-BuLi at low temperature, followed by quenching with NsCl to give **39**. We next sought to achieve methanolysis of the lactam with olefin transposition, but this transformation proved challenging. Typical cleavage conditions utilizing K_2CO_3 and methanol resulted in low yields of enoate **41**, in addition to substantial nonspecific decomposition. After surveying a number of bases to effect methanolysis, it was found that utilizing 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**40**) in methanol[41] was most effective and delivered enoate **41** in 73% yield. Following methanolysis, alkylation with tosylate **42**[42] in the presence of Cs_2CO_3 at elevated temperature provided vinyl iodide **35**, the substrate for the key Heck cyclization. Following precedent from the groups of Rawal and Vanderwal,[37] iodide **35** was exposed to $Pd(PPh_3)_4$ (5 mol %) in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) at 70 °C in acetonitrile to furnish **34** in 91% yield. Notably, this Heck cyclization efficiently constructed the important [3.3.1]azabicycle found in the natural product.

With enoate **34** in hand, we were poised to complete the synthesis of the desired Fischer indolization substrate **46** (Scheme 3). Reduction of the enoate, followed by acid-

Scheme 3. Synthesis of Fischer Indolization Substrate 46



promoted cleavage of the dimethyl ketal with pyridinium *p*-toluenesulfonate (PPTS), gave enone **43** in 92% yield over two steps. Enone **43** was then subjected to a conjugate reduction protocol, which proceeded with complete diastereoselectivity to give ketone **44** in 66% yield.[43] The primary alcohol was then protected as the corresponding pivaloate ester to give **45**. To access Fischer indolization substrate **46**, it would be necessary to introduce an allyl substituent. Thus, ketone **45** was treated with lithium hexamethyldisilazide (LiHMDS) and quenched with allyl iodide to afford the desired product, albeit in modest yield. The addition of various additives (HMPA, DMPU, etc.) did not improve the reaction yield. Furthermore, this challenging alkylation was hampered by the low reactivity of the enolate at low temperatures and the propensity for double alkylation to occur at warmer temperatures. As a result, our optimal procedure involves stopping the reaction in a manner that allows for the recovery of ketone **45** (60% recovered yield) and material recycling. Nonetheless, the aforementioned sequence provided adequate quantities of **46** to test the pivotal Fischer indolization reaction.

Fischer Indolization and Unsuccessful Late-State Studies. With ketone **46** in hand, we attempted the key

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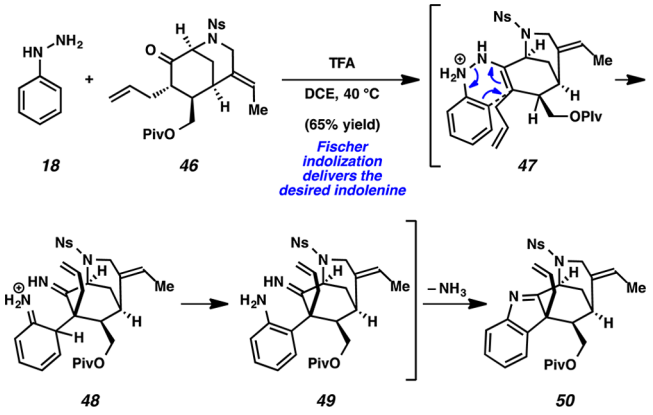
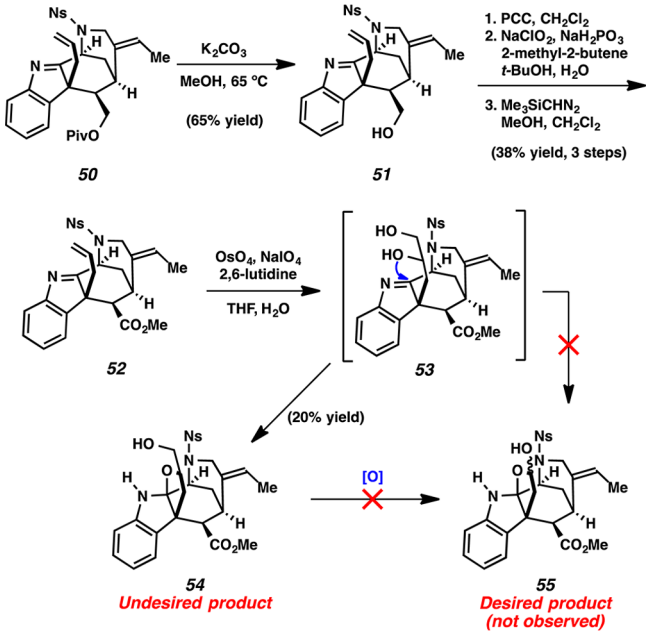
Fischer indolization (Scheme 4). Gratifyingly, upon exposure of the substrate to phenylhydrazine (**18**) and TFA in DCE at 40 °C, we observed clean conversion to indolenine **50** in 65% yield. Of note, the undesired oxidation observed in our earlier studies (see Figure 5) was not seen. Based on this result, we concluded that the putative ene hydrazine underwent the desired [3,3]-sigmatropic rearrangement (see transition structure **47**) to form intermediate **48** instead of undergoing N−N bond cleavage. Following tautomerization of **48**, intermediate **49** presumably cyclizes with loss of ammonia to deliver the desired indolenine **50**. It is worth noting that the Fischer indolization of ketone **46** is more sluggish compared to the corresponding reaction of lactone **19** (see Figure 4) used in the aspidophylline A (**10**) synthesis (24 h vs 16 h).[23] We attribute this difference to the presence of the freely rotating allyl group in **46**, which provides additional steric encumberance in the [3,3]-sigmatropic rearrangement step. Nonetheless, the successful Fischer indolization of substrate **46** to give tetracyclic indolenine **50** validated our hypothesis that, by the judicious modification of substrate, we could suppress the undesired formal oxidation pathway and promote the critical [3,3]-sigmatropic rearrangement process.

Scheme 4. Successful Fischer Indolization of Ketone 46



With most of the carbon framework of the natural product intact, we set our sights on completing the synthesis of picrinine (**1**) (Scheme 5). Our first goal was to introduce the methyl ester, which was achieved in four operations. First, deprotection of the alcohol occurred smoothly to give **51**. Subsequent PCC oxidation and Lindgren oxidation with $NaClO_2$ in the presence of 2-methyl-2-butene gave an intermediate carboxylic acid. Methylation using (trimethylsilyl)-diazomethane afforded ester **52** in 38% yield over the three steps.[44] At this point, all that remained was to implement a chemoselective oxidative cleavage of the terminal olefin[45] and to remove the sulfonamide protecting group. Upon treatment of ester **52** with aqueous osmium tetraoxide in the presence of $NaIO_4$ and 2,6-lutidine, selective oxidation occurred to putatively give diol **53**. However, instead of undergoing the desired oxidative C−C bond cleavage to deliver lactol **55**, cyclization took place to give furanoindoline **54**. Considerable efforts were undertaken to effect the desired oxidative cleavage of **54**; however, the formation of **55** was never observed.[46] Thus, despite the excitement of having circumvented the problems associated with the key Fischer indolization in this particular synthetic approach to picrinine (**1**), further

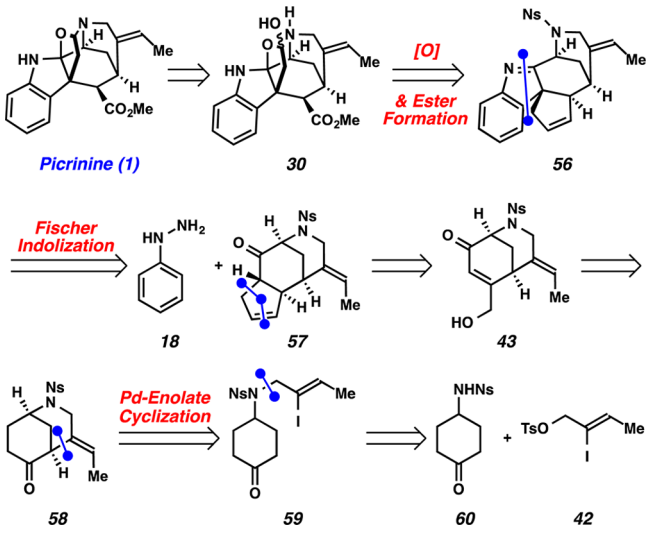
Scheme 5. Unsuccessful Attempts To Elaborate Fischer Indolization Product 50



modification of our synthetic plan would be required in order to access the natural product.

Second-Generation Retrosynthetic Analysis. Our second-generation retrosynthetic analysis of **1** is shown in Scheme 6. Identical to our first strategy, we envisioned picrinine (**1**)

Scheme 6. Revised Retrosynthetic Analysis of Picrinine (1)



arising from cyclization of the penultimate lactol **30**. However, we now sought to access this lactol from indolenine **56**, which bears a cyclopentene moiety. The cyclopentene would serve as a "tethered" variant of the previously problematic allyl side chain. Specifically, we envisaged that the oxidative cleavage of cyclopentene **56**[47] would not be hampered by cyclization of the presumed diol intermediate due to geometric constraints; accordingly, C−C bond cleavage could occur. Indolenine **56** would be derived from late-stage Fischer indolization of phenylhydrazine (**18**) and ketone **57**, the latter of which would be derived from enone **43**. Although we previously had

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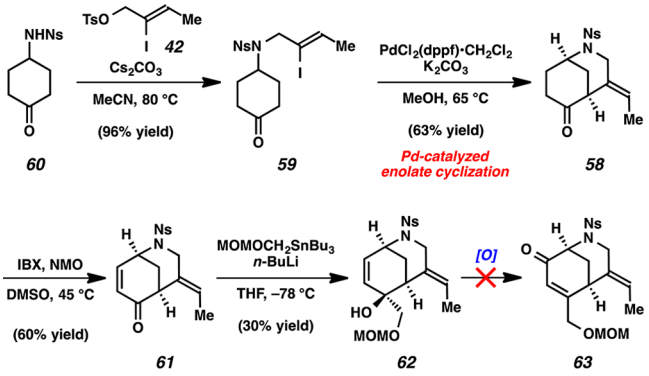
been able to access **43** (see Scheme 3), our route was significantly hampered by poor material throughput. Thus, we took the opportunity to design a new and scalable synthetic route to this key intermediate. We envisioned that enone **43** could be accessed from bicyclic ketone **58**,[43] the product of an intramolecular Pd-catalyzed enolate coupling of vinyl iodide **59**. Finally, the iodide would be prepared from readily available fragments cyclohexanone **60** and tosylate **42**.

Development of a Synthetic Route To Access Substrate 57 and Fischer Indolization. Scheme 7 shows

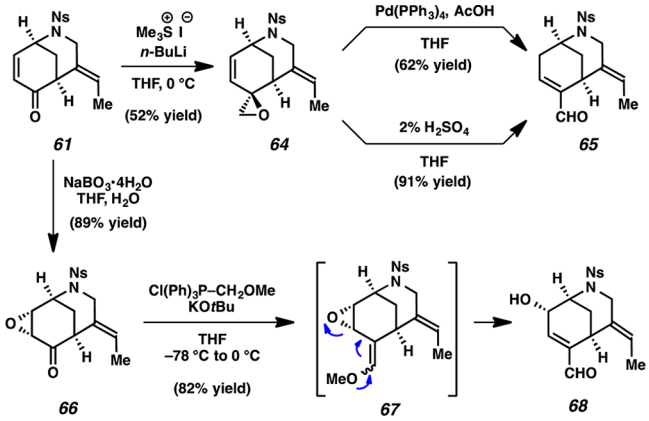
Scheme 7. Assembly of the [3.3.1]Azabicycle and Attempted Elaboration to Enone 63



the successful synthesis of bicyclic ketone **58** and our initial attempt to elaborate it to enone **63**. Starting with cyclohexanone **60**,[48] alkylation with tosylate **42**[42] in the presence of Cs_2CO_3 provided vinyl iodide **59** in excellent yield. When treated with $PdCl_2(dppf)\cdot CH_2Cl_2$ (20 mol %) and K_2CO_3 in methanol at 65 °C, iodide **59** underwent efficient conversion to bicyclic ketone **58** in 63% yield.[49] This transformation was performed on multigram scale and allowed access to the important [3.3.1]azabicycle in just two steps from **60**, which was a notable improvement compared to our earlier approach to assembling the azabicycle. With ketone **58** in hand, IBX oxidation provided enone **61** in 60% yield.[50] Enone **61** was treated with a preformed MOM-protected alkyllithium species at low temperature to give tertiary allylic alcohol **62**, albeit in low yield.[51] Unfortunately, all attempts to oxidatively rearrange allylic alcohol **62** to enone **63** were unsuccessful. The use of various Cr (VI)[52] reagents, hypervalent iodine reagents,[53] or *N*-oxoammonium salts[54] was ineffective and largely resulted in the recovery of starting material or decomposition. Attempts to isomerize the allylic alcohol without oxidation were also unsuccessful. We surmise that the difficulties encountered in our attempts to manipulate **62** are due to the tertiary alcohol being sterically hindered.

To side step our inability to utilize allylic alcohol **62**, we pursued the epoxidation/fragmentation sequence shown in Scheme 8. First, enone **61** was exposed to a Corey–Chaykovsky homologation with a preformed sulfur ylide to produce spiroepoxide **64**.[55] With the goal of introducing oxygenation through an S_N2'-type substitution process, epoxide **64** was treated with $Pd(PPh_3)_4$ in the presence of AcOH.[56] However, the only product obtained was enal **65**, which presumably arises by initial formation of a π-allylpalladium complex and subsequent β-hydride elimination and tautomerization. A second effort to open epoxide **64** was attempted using dilute sulfuric acid,[57] but this also delivered the undesired

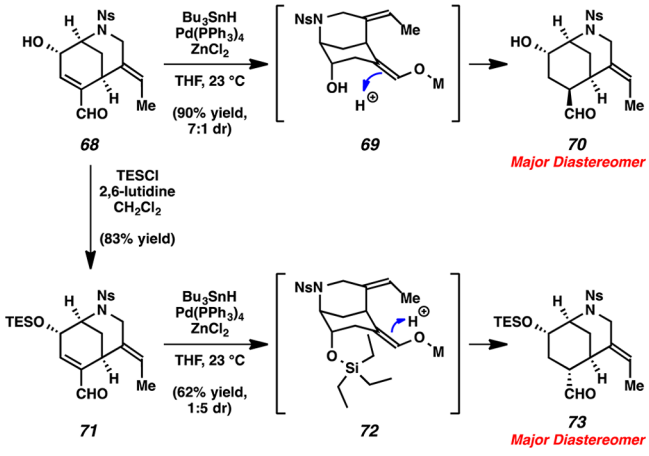
Scheme 8. Approaches To Homologate and Oxidize Enone 61



enal **65**. In an alternate strategy, we returned to enone **61** and performed an oxidation using sodium perborate tetrahydrate in THF and water,[58] which furnished epoxide **66** in 89% yield. This epoxide was subsequently treated with (methylmethoxy)-triphenylphosphonium chloride in the presence of base to furnish enal **68** in 82% yield.[59] Presumably, this transformation proceeds via Wittig olefination, followed by epoxide fragmentation and hydrolysis (see transition structure **67**). Using this sequence, gram quantities of enal **68** were accessible.

En route to the desired Fischer indolization substrate, we sought to perform a conjugate reduction of the enal (Scheme 9). Our initial attempts involved treatment of enal **68** with a

Scheme 9. Diastereoselective Reduction of Enal 68



number of copper-[60] or rhodium-based reducing agents;[61] however, these efforts were ineffective. Hypothesizing that the secondary alcohol was problematic, we silyl protected it to give **71** in 83% yield. Reduction of **71** in the presence of $Pd(PPh_3)_4$, Bu_3SnH, and $ZnCl_2$ in THF[62] proceeded in 62% yield, although with poor diastereoselectivity (dr = 1:5), favoring the undesired epimer **73**. The diastereoselectivity of this process is thought to be governed by the bulky triethylsilyl ether, which sterically hinders protonation (see **72**).[63] Although further attempts to reduce **71** were also unsuccessful, we found that treatment of unprotected enal **68** under the Pd-catalyzed reduction conditions gave the desired hydroxyaldehyde **70** in 90% yield (dr = 7:1). The favorable selectivity presumably arises from

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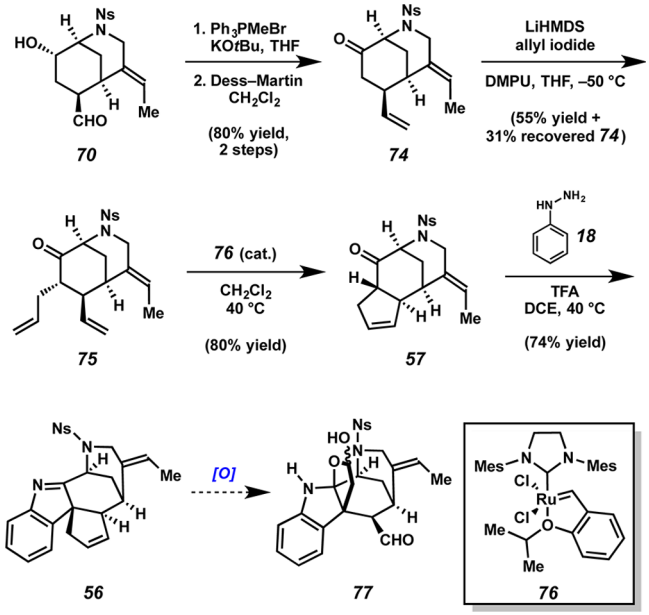
protonation of the intermediate enolate on the sterically more accessible face of the [3.3.1]azabicycle (see **69**).

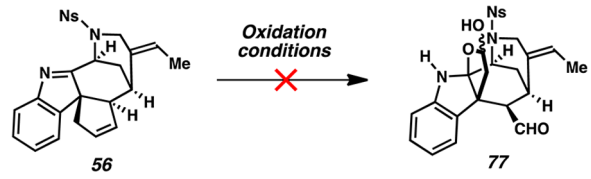
As shown in Scheme 10, aldehyde **70** could be readily elaborated to the desired Fischer indolization substrate. Wittig

Scheme 10. Synthesis of Cyclopentene 57 and Fischer Indolization



olefination of the aldehyde, followed by oxidation of the secondary alcohol with Dess–Martin periodinane, afforded ketone **74** in 80% over two steps. Next, allylic alkylation of **74** with allyl iodide in the presence of strong base and *N,N′*-dimethylpropyleneurea (DMPU) furnished **75** in 55% yield, along with 31% recovered ketone **74**. To arrive at the desired Fischer indolization substrate, **75** was treated with the Grubbs–Hoveyda second-generation catalyst (**76**) in CH_2Cl_2 at reflux to give cyclopentene **57** in good yield.[64] It is worth noting that epimerization was not observed in this reaction, and the *trans*-hydrindenone product (**57**) was the only product observed. To our delight, reaction of ketone **57** with phenylhydrazine (**18**) and TFA delivered indolenine **56** in 74% yield via late-stage Fischer indolization. Of note, only a single diastereomer was observed in this complexity-generating step. The transformation required only 2 h, which compares favorably to our earlier Fischer indolization studies. It is hypothesized that the rigid nature of the substrate is responsible for the facile nature of the [3,3]-sigmatropic rearrangement. Nonetheless, our ability to access **56** marked a critical juncture in our synthetic efforts, as we expected that oxidative cleavage of the cyclopentene could lead to assembly of the important furanoindoline motif present in the natural product.

Failed Oxidation and Modification of Synthetic Route. Our excitement in having accessed Fischer indolization product **56** was quickly thwarted by our inability to oxidatively cleave the cyclopentene ring. Figure 6 summarizes a variety of reaction conditions that were tested as a means to selectively oxidize the endocyclic olefin. Each of these efforts resulted in the recovery of starting material or substantial nonspecific decomposition of substrate **56**. Osmium-,[45,65] along with ruthenium-[66] and manganese-based oxidations,[67] were deemed ineffective. Similarly, attempted epoxidation with *m*-CPBA or direct



Oxidant	Additive(s)	Result
OsO_4 (cat.), $NaIO_4$	2,6-lutidine	recovery of **56** + decomposition
$KMnO_4$	TEBA-Cl	recovery of **56**
*m*CPBA	–	decomposition
OsO_4	pyridine	recovery of **56**
$RuCl_3 \cdot 3\,H_2O$ (cat.), $NaIO_4$	H_2O	recovery of **56**
K_2OsO_4 (cat.), $NaIO_4$	–	recovery of **56**
O_3	–	decomposition
OsO_4	DMAP	decomposition
K_2OsO_4 (cat.), $K_3Fe(CN)_6$	$MeSO_2NH_2$, $(DHQ)_2PHAL$	recovery of **56**

Figure 6. Attempted olefin oxidation of indolenine substrate **56**.

oxidative cleavage using ozonolysis conditions resulted in decomposition of the starting material.

Figure 7 suggests a reasonable hypothesis for the difficulties we experienced in attempting to oxidatively cleave cyclo-

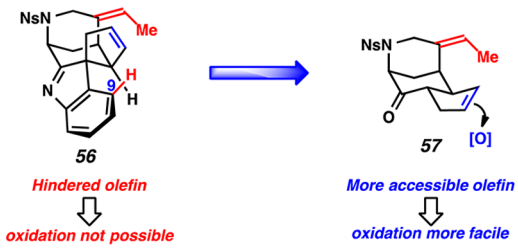


Figure 7. Hypothesis for oxidation difficulties and revision of strategy.

pentene **56**. A three-dimensional depiction of **56** shows that approach to the olefin is severely obstructed on both faces. On one hand, the proximal ethylidene moiety blocks approach of an oxidant, whereas approach to the other face is impeded by the hydrogen at C9. As a workaround, we considered performing the oxidative functionalization of cyclopentene **57** prior to performing the Fischer indolization step. Although the ethylidene similarly blocks approach of one face of the olefin in **57**, the other face appeared accessible.

Earlier Oxidation, Successful Fischer Indolization, and Late-Stage Challenges. Our efforts to carry out the revised endgame strategy are depicted in Scheme 11. First, chemo- and diastereoselective Upjohn dihydroxylation[68] of the *trans*-hydrindenone **57**, followed by protection of the resultant diol as the cyclic carbonate,[69] gave tetracyclic intermediate **78** in 78% yield over two steps. The success of this sequence validated our hypothesis shown in Figure 7 and allowed us to attempt the key Fischer indolization step. In the event, treatment of **78** with phenylhydrazine (**18**) and TFA at 80 °C in DCE gave a mixture of two products in a combined yield of 69%. After careful separation and 2D NMR analysis of each compound in C_6D_6, the two products were identified as indolenine **79** and hydrate **80**.[70] These compounds could be taken forward as an inconsequential mixture. It is worth noting that the Fischer indolization of substrate **78** is one of the most complex examples in the literature to date.[35]

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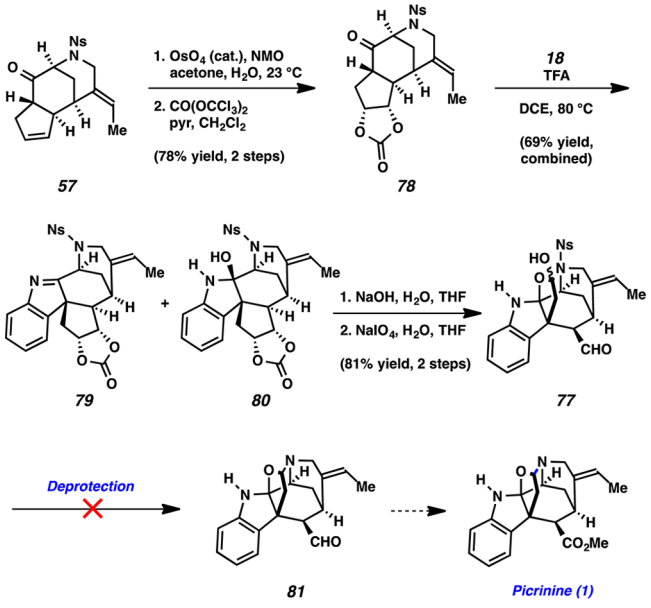
Scheme 11. Synthesis of Lactol 77 and Failed Late-Stage *N,O*-Acetal Formation



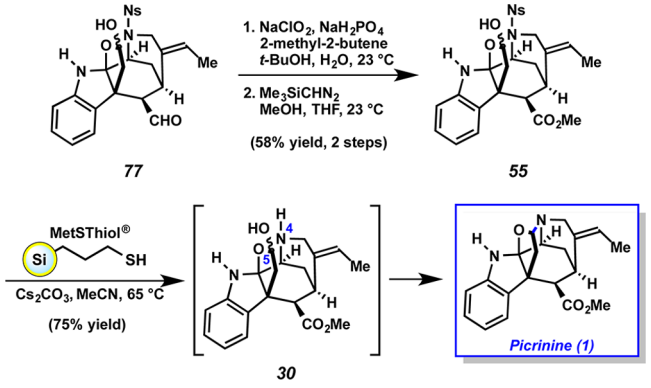
The next late-stage maneuver involved revealing the diol moiety and performing oxidative cleavage. This was achieved by treating the mixture of **79** and **80** with NaOH[71] followed by exposure of the intermediate diol to $NaIO_4$. The resulting lactol, **77**, was obtained in 81% yield over two steps.[72] Thus, by installing oxidation prior to the Fischer indolization, our problematic oxidation of cyclopentene **56** (see Figures 6 and 7) had been successfully circumvented. Having synthesized lactol **77**, all that remained was conversion of the exocyclic aldehyde to a methyl ester, cleavage of the sulfonamide, and construction of the *N,O*-acetal. In our first efforts, we attempted to cleave the sulfonamide group using thiol-based denosylation conditions.[34] Unfortunately, these attempts led to the formation of multiple products that proved difficult to isolate. To facilitate purification, the deprotection of **77** was tried using a resin-bound thiol (MetSThiol) in the presence of Cs_2CO_3.[73] Although it appeared that cleavage of the nosyl protecting group had occurred,[74] we regrettably did not detect formation of the desired product **81**. Thus, our efforts to access the natural product (**1**) had again been foiled.

Completion of the Total Synthesis of Picrinine (1). With limited options available, we decided to change the order of late-stage transformations by introducing the ester prior to denosylation (Scheme 12). Toward this end, Lindgren oxidation of **77** gave an intermediate carboxylic acid, which was methylated with (trimethylsilyl)diazomethane to afford ester **55** in 58% yield over 2 steps.[44] This delicate oxidation is noteworthy in that it occurred without any competitive oxidation of the lactol. With ester **55** in hand, we attempted the nosyl removal using the solid-supported conditions mentioned previously. Much to our pleasure, picrinine (**1**) was obtained as the sole product.[75] It is likely that the smooth formation of **1** occurs via cyclization of intermediate **30** due to the constrained proximity of N4 and C5. Our synthetic sample of picrinine (**1**) was found to be identical to a natural sample.

CONCLUSION

In conclusion, we have developed the first total synthesis of the daunting, polycyclic akuammiline alkaloid picrinine (**1**). Our

Scheme 12. Completion of the Total Synthesis of Picrinine (1)



initial synthetic efforts, which were largely inspired by our earlier total synthesis of aspidophylline A, were plagued by late-stage difficulties and material throughput problems. However, these challenges prompted us to develop a revised synthesis of the [3.3.1]azabicyclic core of the natural product, which proved far more robust and scalable compared to our initial route. In turn, efficient access to the azabicyclic core permitted the design and testing of substrates for late-stage Fischer indolization reactions. In fact, the substrates utilized in our synthetic forays toward picrinine represent some of the most complex examples of Fischer indolizations to date. It is hoped that the lessons learned in the course of our total synthesis of **1** will help guide synthetic studies pertaining to akuammilines and other classes of complex indole alkaloids.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] and osmium tetroxide (OsO_4) were obtained from Strem. Phenylhydrazine (**18**) was purified by flash chromatography (4:1 hexanes/EtOAc) prior to use. Unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, and iodine staining. SiliCycle silica gel 60 (particle size 0.040−0.063 mm) was used for flash column chromatography. ^1H NMR spectra were recorded on 500 and 600 MHz spectrometers. Data for ^1H spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 77.16 ppm for $CDCl_3$. IR spectra are reported in terms of frequency absorption (cm^{-1}). High-resolution mass spectra were obtained using TOF or Orbitrap mass analyzers.

Experimental Procedures. *Note:* Experimental information for compounds **24** and **36**−**38** have been previously reported as part of the (±)-aspidophylline A synthesis.[23] Experimental information for compounds **1**, **55**−**61**, **66**, **68**, **70**, **74**−**75**, and **77**−**79** have been previously reported as part of the (±)-picrinine synthesis.[28]

*Hydrazone **27** and **SI-1**.* To a solution of ketone **24** (5.0 mg, 0.012 mmol) in 1,2-dichloroethane (DCE) (0.5 mL) was added phenylhydrazine (**18**) (1.8 μL, 0.018 mmol) and trifluoroacetic acid (TFA) (5.0 μL, 0.060 mmol). The reaction mixture was heated to 40 °C. After 24 h, the reaction was diluted with EtOAc (5 mL) and poured into a solution of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered,

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and evaporated under reduced pressure. Hydrazone **27** was the major product in the crude reaction mixture (3.5 mg, 57% crude yield). The crude residue was purified via preparative TLC (2:1 hexanes/EtOAc → 1:2 hexanes/EtOAc) to afford enone **SI-1** (1 mg, 35% yield) as an orange oil. Hydrazone **27**: R_f 0.55 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.79 (d, J = 8.3, 2H), 7.37−7.30 (m, 6H), 6.99 (tt, J = 7.2, 1.4, 1H), 6.01 (m, 1H), 5.49 (q, J = 6.9, 1H), 5.20 (dq, J = 17.1, 1.7, 1H), 5.03 (dq, J = 10.1, 1.7, 1H), 4.94 (t, J = 2.9, 1H), 4.18 (d, J = 16.0, 1H), 3.92−3.85 (m, J = 3H), 3.80 (dd, J = 13.4, 6.5, 1H), 3.77 (s, 3H), 2.49 (s, 3H), 1.70−1.62 (m, 4H), 1.17 (dt, J = 12.9, 3.2, 1H). **Enone SI-1**: R_f 0.70 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3, 2H), 7.27 (d, J = 8.3, 2H), 5.65 (q, J = 6.9, 1H), 5.27 (m, 1H), 4.78 (dq, J = 17.1, 1.7, 1H), 4.71 (dq, J = 10.1, 1.7, 1H), 4.55 (t, J = 3.3, 1H), 4.14 (d, J = 13.6, 1H), 3.98 (t, J = 3.2, 1H), 3.77 (s, 3H), 3.50 (dt, J = 13.6, 2.0, 1H), 3.09 (dd, J = 13.8, 6.7, 1H), 2.99 (dd, J = 13.8, 6.7, 1H), 2.41 (s, 3H), 2.34 (dt, J = 13.1, 3.3, 1H), 2.11 (dt, J = 13.1, 3.2, 1H), 1.69 (dd, J = 6.9, 1.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 167.2, 144.3, 143.6, 140.8, 135.4, 134.1, 129.5, 128.8, 128.2, 124.5, 116.5, 56.0, 52.5, 46.7, 33.9, 33.1, 30.5, 21.7, 12.9; IR (film) 2923, 2853, 1723, 1786, 1456, 1350, 1248, 1219, 1163, 1096; HRMS−ESI (m/z) [M + H]$^+$ calcd for $C_{22}H_{26}NO_5S^+$ 416.15262, found 416.15044.

Bicyclic Lactam ***39***. To a solution of ketal **38** (0.900 g, 4.92 mmol) in THF (117 mL) was added a solution of *n*-butyllithium (*n*-BuLi) (2.7 mL, 2.46 M in hexanes) at −50 °C. The solution was stirred for 30 min, and then a solution of 2-nitrobenzenesulfonyl chloride (NsCl) (1.634 g, 7.38 mmol) in THF (8 mL) was added. After being stirred for 30 min at −50 °C, the reaction was quenched by the addition of a solution of saturated aqueous NH_4Cl (10 mL) and warmed to room temperature. The reaction was then poured into brine (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc) to afford lactam **39** (1.630 g, 90% yield) as a white solid. Lactam **39**: mp 154−156 °C; R_f 0.52 (3:1 benzene/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (m, 1H), 7.76−7.72 (m, 3H), 6.74 (ddd, J = 7.6, 6.0, 1.6, 1H), 6.33 (ddd, J = 7.7, 6.2, 1.6, 1H), 5.25 (dd, J = 6.0, 1.7, 1H), 3.39 (s, 3H), 3.37 (m, 1H), 3.27 (s, 3H), 2.10 (dd, J = 13.2, 2.6, 1H), 1.85 (dd, 13.2, 3.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 148.0, 134.8, 134.6, 133.3, 132.5, 132.2, 130.6, 124.6, 105.5, 58.2, 49.8, 49.6, 45.2, 33.4; IR (film) 3102, 2950, 2839, 1726, 1541, 1441, 1367, 1264, 1229, 1177, 1135, 1117, 1092, 1061, 1040; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_7S^+$ 369.07510, found 369.07382.

Enoate ***41***. To a solution of lactam **39** (1.630 g, 4.43 mmol) in MeOH (70 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**40**) (0.739 g, 5.31 mmol) at room temperature. After 1 h, the reaction was diluted with EtOAc (50 mL) and poured into a solution of saturated aqueous NH_4Cl (75 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc) to afford enoate **41** (1.292 g, 73% yield) as a colorless oil. Enoate **41**: R_f 0.47 (3:1 benzene/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.6, 1.9, 1H), 7.92 (m, 1H), 7.75 (m, 2H), 6.68 (s, 1H), 5.57 (d, J = 7.0, 1H), 3.81 (m, 1H), 3.75 (s, 3H), 3.11 (s, 3H), 2.90 (s, 3H), 2.70 (d, J = 18.3, 1H), 2.60 (br. s, 2H), 2.35 (dq, J = 18.3, 2.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 147.8, 135.9, 135.1, 133.4, 132.9, 131.1, 127.0, 125.5, 99.4, 52.1, 51.5, 48.6, 48.1, 31.5, 29.4; IR (film) 3298, 3098, 2951, 2836, 1714, 1541, 1438, 1362, 1263, 1166, 1126, 1081, 1061; HRMS-ESI (m/z) [M − H]$^-$ calcd for $C_{16}H_{19}N_2O_8S^-$ 399.08676, found 399.08626.

Iodide ***35***. To a solution of enoate **41** (0.349 g, 0.983 mmol) in MeCN (9.8 mL) were added tosylate **42** (1.300 g, 3.83 mmol)[42] and Cs_2CO_3 (0.417 g, 1.28 mmol). The reaction mixture was heated to 80 °C. After 3.5 h, the reaction was cooled to room temperature, and solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (50 mL) and poured into a solution of saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexanes/EtOAc → 2:1 hexanes/EtOAc) to afford iodide **35** (0.393 g, 75% yield) as a pale yellow oil. Iodide **35**: R_f 0.44 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.8, 1.3, 1H), 7.69−7.59 (m, 3H), 6.97 (m, 1H), 6.01 (qt, J = 6.4, 1.4, 1H), 4.47 (dt, J = 16.9, 1.4, 1H), 4.42 (t, J = 6.92, 1H), 4.37 (dt, J = 16.9, 1.7, 1H), 3.75 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 2.89−2.79 (m, 2H), 2.74 (m, 1H), 2.60 (dq, J = 18.1, 2.6, 1H), 1.62 (dt, J = 6.4, 1.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 147.9, 138.7, 135.5, 134.0, 133.3, 132.4, 131.5, 126.7, 124.4, 106.0, 100.0, 57.4, 56.6, 52.1, 51.0, 49.5, 30.8, 30.2, 22.0; IR (film) 2950, 2838, 1713, 1657, 1543, 1437, 1372, 1266, 1163, 1125, 1077; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{20}H_{26}IN_2O_8S^+$ 581.04491, found 581.04118.

Enoate ***34***. In the glovebox, tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] was added to a 500 mL round-bottom flask. The flask was removed from the glovebox, and a solution of iodide **35** (0.843 g, 1.45 mmol) in MeCN (104 mL) was added, followed by 1,2,2,6,6-pentamethylpiperidine (PMP) (0.676 g, 4.36 mmol). The reaction mixture was degassed with N_2 gas for 10 min and heated to 70 °C. After 16 h, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (40 mL) and poured into H_2O (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexanes/EtOAc → 2:1 hexanes/EtOAc) to afford enoate **34** (0.597 g, 91% yield) as a pale yellow oil. Enoate **34**: R_f 0.44 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5, 1H), 7.64 (m, 3H), 7.02 (s, 1H), 5.40 (q, J = 6.7, 1H), 4.40 (s, 1H), 3.92 (d, J = 14.8, 1H), 3.86 (d, J = 14.8, 1H), 3.83 (t, J = 2.8, 1H), 3.73 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.06 (dt, J = 13.1, 2.8, 1H), 1.79 (dt, J = 13.1, 2.8, 1H), 1.67 (d, J = 6.7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 148.1, 135.9, 134.5, 134.3, 133.3, 131.4, 131.1, 130.1, 124.2, 123.1, 96.3, 52.4, 52.2, 49.4, 49.3, 47.4, 30.7, 30.4, 12.8; IR (film) 2950, 2857, 1720, 1543, 1438, 1372, 1356, 1248, 1163, 1123, 1076, 1042; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{20}H_{25}N_2O_8S^+$ 453.13261, found 453.12936.

Enone ***43***. To a solution of enoate **34** (0.560 g, 1.24 mmol) in THF (8.3 mL) was added diisobutylaluminum hydride (*i*-Bu_2AlH) (4.95 mL, 1 M in hexanes) at −78 °C. After 4 h, the reaction was quenched with a solution of saturated aqueous NH_4Cl (10 mL) and warmed to room temperature. The mixture was then poured into a solution of saturated aqueous sodium potassium tartrate (Rochelle's salt) (10 mL) and stirred vigorously for 30 min. The mixture was extracted with EtOAc (3 × 50 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure afforded alcohol **SI-2**, which was used in the subsequent step without further purification.

To a solution of alcohol **SI-2** (0.526 g, 1.24 mmol) in acetone (13.6 mL) and H_2O (0.7 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (0.062 g, 0.248 mmol). The reaction mixture was heated to 40 °C. After 1.5 h, the reaction was poured into a solution of saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (1:2 hexanes/EtOAc) to afford enone **43** (0.431 g, 92% yield, two steps) as a colorless foam. Enone **43**: R_f 0.34 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 2.0, 7.3, 1H), 7.70 (m, 2H), 7.61 (dd, J = 2.0, 7.4, 1H), 6.28 (s, 1H), 5.68 (q, J = 7.0, 1H), 4.44 (br. s, 1H), 4.33 (d, J = 17.4, 1H), 4.20 (d, J = 15.2, 2H), 3.86 (dt, J = 2.2, 14.5, 1H), 3.56 (t, J = 3.2, 1H), 2.31 (dt, J = 13.2, 3.4, 1H), 2.20 (dt, J = 13.2, 3.0, 1H), 1.74 (dd, J = 1.9, 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 165.2, 148.2, 133.8, 133.4, 132.0, 131.9, 129.7, 124.3, 124.11, 124.10, 63.5, 56.7, 47.4, 34.1, 32.4, 13.0; IR (film) 3432, 2926, 1676, 1542, 1440, 1370, 1281, 1164, 1127, 1073; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_6S^+$ 379.09583, found 379.09474.

Hydroxy Ketone ***44***. To a solution of copper iodide (CuI) (0.500 g, 2.62 mmol) in hexamethylphosphoramide (HMPA) (1 mL) and THF

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(8 mL) was added diisobutylaluminum hydride (*i*-Bu_2AlH) (5.24 mL, 1 M in hexanes) at −78 °C. The solution was stirred for 30 min, at which point a solution of enone **43** (0.395 g, 1.05 mmol) in THF (3 mL) was added at −78 °C. After 2 h, the reaction was quenched with a solution of saturated aqueous NH_4Cl (10 mL) and allowed to warm to room temperature. The mixture was filtered over a pad of Celite and washed with EtOAc (5 × 30 mL). The mixture was then poured into a solution of saturated aqueous sodium potassium tartrate (Rochelle's salt) (100 mL) and stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc → 1:1 hexanes/EtOAc) to afford hydroxy ketone **44** (0.261 g, 66% yield) as a colorless foam. Hydroxy ketone **44**: R_f 0.12 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.71 (m, 2H), 7.63 (m, 1H), 5.72 (q, J = 7.0, 1H), 4.27 (d, J = 14.8, 1H), 4.26 (app. s, 1H), 4.13 (dt, J = 14.8, 2.1, 1H), 3.55 (m, 2H), 3.20 (q, J = 3.1, 1H), 2.56 (d, J = 13.2, 1H), 2.30 (m, 2H), 2.19 (dt, J = 14.0, 3.6, 1H), 2.01 (dt, J = 14.0, 3.0, 1H), 1.74 (dd, J = 7.0, 1.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 134.2, 134.1, 132.3, 132.2, 132.0, 130.8, 124.6, 124.3, 65.3, 59.0, 50.1, 44.2, 41.8, 33.9, 29.6, 13.1; IR (film) 3472, 2924, 1717, 1542, 1440, 1370, 1248, 1165, 1073, 1033; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_6S^+$ 381.11148, found 381.10923.

Pivaloate ***45***. To a solution of ketone **44** (59 mg, 0.16 mmol) in MeCN (1 mL) were added pivalic anhydride (Piv_2O) (86 mg, 0.47 mmol) and scandium triflate $[Sc(OTf)_3]$ (8.0 mg, 0.016 mmol). After 10 min, the solvent was removed under reduced pressure. The resulting residue was redissolved in CH_2Cl_2 (20 mL) and poured into a solution of saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (5:1 hexanes/EtOAc → 1:1 hexanes/EtOAc) to afford pivaloate **45** (54 mg, 73% yield) as a colorless foam. Pivaloate **45**: R_f 0.62 (3:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.71 (m, 2H), 7.64 (m, 1H), 5.73 (q, J = 6.95, 1H), 4.27 (m, 2H), 4.15 (dt, J = 15.2, 2.2, 1H), 3.98 (dd, J = 11.2, 6.9, 1H), 3.91 (dd, J = 11.2, 6.5, 1H), 3.12 (app. q, J = 3.6, 1H), 2.58 (dd, J = 15.9, 5.9, 1H) 2.46 (m, 1H), 2.32 (dd, J = 15.9, 12.9, 1H), 2.20 (dt, J = 14.0, 3.6, 1H), 2.02 (dt, J = 14.0, 3.1, 1H), 1.68 (dd, J = 6.9, 1.7, 3H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): (19 of 20 observed) δ 204.4, 178.4, 148.1, 134.1, 132.2, 132.0, 129.8, 124.9, 124.3, 66.2, 58.7, 49.9, 42.0, 41.1, 38.9, 33.7, 29.8, 27.3, 13.2; IR (film) 2959, 2928, 1721, 1543, 1367, 1282, 1164, 1128; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_7S^+$ 465.16900, found 465.16831.

Ketone ***46***. To a solution of pivaloate **45** (78 mg, 0.167 mmol) in THF (2 mL) was added a solution of lithium hexamethyldisilazide (LHMDS) (0.028 g, 0.167 mmol) in THF (1.3 mL) at −78 °C. After 30 min, the solution was warmed to 0 °C and stirred for 1 h. Allyl iodide (15.2 μL, 0.167 mmol) was then added at 0 °C, and the reaction mixture was allowed to warm to room temperature. After 3 h, the reaction mixture was poured into a solution of saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexanes/EtOAc → 2:1 hexanes/EtOAc) to afford ketone **46** (25 mg, 30% yield) as a colorless foam and recovered pivaloate **45** (47 mg, 60% yield). Ketone **46**: R_f 0.68 (3:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.70 (m, 2H), 7.61 (m, 2H), 5.69 (q, J = 6.6, 1H), 5.58 (m, 1H), 4.98 (dq, J = 17.2, 1.5, 1H), 4.95 (d, J = 10.2, 1H), 4.31 (t, J = 3.3, 1H), 4.30 (d, J = 14.5, 1H), 4.21 (dt, J = 14.5, 2.2, 1H), 4.20 (dd, J = 11.5, 2.4, 1H), 3.94 (dd, J = 11.5, 7.3, 1H), 3.17 (app. q, J = 3.4, 1H), 2.57 (ddd, J = 12.1, 6.4, 3.2, 1H), 2.45 (dq, J = 14.5, 1.6, 1H), 2.30 (m, 1H), 2.20, (m, 1H), 2.14 (dt, J = 14.0. 3.6, 1H), 1.97 (dt, J = 14.0, 3.1, 1H), 1.68 (dd, J = 6.9, 1.9, 3H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 178.4, 148.1, 135.0, 134.1, 132.24, 132.20, 132.0, 130.6, 124.4, 124.2, 117.6, 64.7, 59.1, 50.3, 49.1, 44.9, 38.9, 33.8, 31.5, 31.1, 27.3, 13.0; IR (film) 3077, 2974, 1721, 1545, 1370, 1283, 1165, 1071; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_7S^+$ 505.20030, found 505.20001.

Indolenine ***50***. To a solution of ketone **46** (14 mg, 0.028 mmol) in 1,2-dichloroethane (DCE) (0.5 mL) were added phenylhydrazine (**18**) (16.4 μL, 0.17 mmol) and trifluoroacetic acid (TFA) (43 μL, 0.56 mmol). The reaction mixture was heated to 40 °C. After 24 h, the reaction was diluted with EtOAc (5 mL) and poured into a solution of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc → 1:2 hexanes/EtOAc) to afford indolenine **50** (11 mg, 65% yield) as an orange oil. Indolenine **50**: R_f 0.70 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (m, 1H), 7.74 (m, 2H), 7.68 (d, J = 7.7, 1H), 7.63 (m, 1H), 7.45 (d, J = 7.4, 1H), 7.36 (td, J = 7.7, 1.1, 1H), 7.27 (td, J = 7.4, 1.1, 1H), 5.80 (q, J = 7.2, 1H), 5.25 (t, J = 3.2, 1H), 5.10 (m, 1H), 4.83 (dd, J = 11.3, 2.5, 1H), 4.71 (d, J = 16.8, 1H), 4.62 (d, J = 10.1, 1H), 4.43 (d, J = 15.1, 1H), 4.22 (t, J = 11.2, 1H), 4.05 (dt, J = 15.1, 2.6, 1H), 3.21 (s, 1H), 3.11 (dd, J = 14.0, 4.6, 1H), 2.50 (dd, J = 14.0, 8.9, 1H), 2.46 (dt, J = 14.0, 3.6, 1H), 1.85 (dt, J = 14.0, 3.0, 1H), 1.74 (dd, J = 7.0, 1.9, 1H), 1.68 (dt, J = 11.1, 3.0, 1H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 178.3, 154.1, 148.9, 143.3, 134.1, 131.9, 131.82, 131.77, 131.6, 131.3, 128.4, 126.1, 125.1, 124.3, 123.6, 121.8, 118.4, 62.7, 61.4, 54.8, 51.8, 47.7, 38.9, 36.0, 35.2, 29.0, 27.4, 13.9; IR (film) 2975, 1727, 1545, 1480, 1456, 1441, 1371, 1282, 1164, 1074; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{31}H_{36}N_3O_6S^+$ 578.23193, found 578.23111.

Alcohol ***51***. To a solution of indolenine **50** (15 mg, 0.026 mmol) in MeOH (2 mL) was added potassium carbonate (K_2CO_3) (20 mg, 0.14 mmol). The reaction mixture was heated to 65 °C. After 4 h, the reaction was diluted with EtOAc (10 mL) and poured into a solution of aqueous $NaHSO_4$ (10 mL, 0.5 M). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (1:3 hexanes/EtOAc) to afford alcohol **51** (8 mg, 65% yield) as colorless oil. Alcohol **51**: R_f 0.21 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.72 (m, 2H), 7.67 (d, J = 7.6, 1H), 7.61 (m, 1H), 7.38 (d, J = 7.6, 1H), 7.35 (dt, J = 7.6, 1.2, 1H), 7.23 (dt, J = 7.6, 1.2, 1H), 5.78 (q, J = 7.1, 1H), 5.23 (t, J = 3.4, 1H), 5.10 (m, 1H), 4.70 (d, J = 16.7, 1H), 4.61 (d, J = 10.2, 1H), 4.41 (d, J = 15.1, 1H), 4.07−3.95 (m, 2H), 3.37 (br. s, 1H), 3.10 (ddt, J = 14.1, 4.8, 1.5, 1H), 2.43 (m, 2H), 1.88 (dd, J = 7.1, 2.1, 3H), 1.82 (dt, J = 14.1, 3.1, 1H), 1.48 (dt, J = 10.4, 3.3, 1H), 1.36 (dd, J = 6.4, 3.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 154.2, 148.9, 143.7, 134.0, 132.3, 131.8, 131.7, 131.6, 131.3, 128.3, 125.7, 125.2, 124.2, 123.6, 121.8, 118.2, 61.9, 60.6, 55.9, 55.0, 47.8, 35.9, 35.5, 28.2, 14.3; IR (film) 3422, 3070, 2924, 2840, 1542, 1441, 1371, 1173, 1127, 1074; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_5S^+$ 494.17442, found 494.17214.

Ester ***52***. To a solution of alcohol **51** (4 mg, 0.008 mmol) in CH_2Cl_2 (0.30 mL) was added pyridinium chlorochromate (PCC) (6 mg, 0.028 mmol). After 1 h, Celite (0.5 g) was added followed by Et_2O (3 mL). The hetereogenous mixture was filtered over a pad of basic alumina and Celite and washed with EtOAc (20 mL). Evaporation of the filtrate under reduced pressure afforded a crude residue of aldehyde **SI-3** that was used in the subsequent step without further purification.

To a solution of crude aldehyde **SI-3** (4 mg) and 2-methyl-2-butene (0.10 mL) in *t*-BuOH (0.150 mL) at 0 °C was added a solution of sodium chlorite ($NaClO_2$) (4 mg, 0.040 mmol) and monobasic sodium phosphate (NaH_2PO_4) (6 mg, 0.047 mmol) in H_2O (0.150 mL). After 15 min, the reaction mixture was quenched with AcOH (0.25 mL), diluted with EtOAc (mL), and poured into a brine solution (4 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue of acid **SI-4** was used in the subsequent step without purification.

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To a solution of acid **SI-4** (4 mg) in MeOH (0.15 mL) and CH_2Cl_2 (0.25 mL) was added (trimethylsilyl)diazomethane (Me_3SiCHN_2) (5 μL, 2 M in hexanes). After 15 min, the reaction mixture was quenched with acetic acid (AcOH) (0.25 mL) and concentrated under reduced pressure. The crude residue was purified by preparative TLC (1:1 hexanes/EtOAc) to afford ester **52** (2.5 mg, 60% yield over three steps) as a colorless oil. Ester **52**: R_f 0.42 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): 8.17−8.13 (m, 1H), 7.75−7.71 (m, 2H), 7.64 (d, J = 7.7, 1H), 7.64−7.61 (m, 1H), 7.35 (d, J = 7.5, 1H), 7.33 (t, J = 7.7, 1H), 7.21 (t, J = 7.5, 1H), 5.76 (q, J = 7.2, 1H), 5.29 (t, J = 3.1, 1H), 5.12−5.02 (m, 1H), 4.71 (d, J = 17.2, 1H), 4.57 (d, J = 10.2, 1H), 4.41 (d, J = 15.1, 1H), 4.00 (d, J = 15.1, 1H), 3.74 (s, 3H), 3.64 (dd, J = 14.4, 9.4, 1H), 3.53 (br s, 1H), 3.33 (dt, J = 14.4, 4.9 1H), 2.47 (dt, J = 13.9, 3.4, 1H), 2.15 (d, J = 3.0, 1H), 1.85 (dt, J = 13.9, 3.41, 1H), 1.61 (d, J = 7.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 171.5, 154.0, 144.1, 134.1, 132.6, 132.5, 131.8, 131.4, 130.9, 128.4, 126.3, 125.7, 124.3, 123.4, 121.5, 118.1, 61.1, 54.7, 54.5, 52.0, 47.8, 35.7, 35.4, 31.5, 13.8; IR (film) 2950, 1738, 1543, 1441, 1372, 1169, 1126, 1073; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{27}H_{28}N_3O_6S^+$ 522.16933, found 522.16656.

Furanoindoline ***54***. To a solution of ester **54** (6 mg, 0.012 mmol) in THF (0.40 mL) and H_2O (0.20 mL) were added 2,6-lutidine (5.4 μL, 0.046 mmol) and sodium periodate ($NaIO_4$) (10 mg, 0.046 mmol) followed by aqueous osmium tetraoxide (OsO_4) (25 μL, 0.079 M in H_2O). After 16 h, the reaction was poured into a brine solution (5 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via preparative TLC (1:1 hexanes/EtOAc) to afford furanoindoline **54** (11 mg, 20% yield) as a colorless oil. Furanoindoline **54**: R_f 0.45 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.72 (m, 3H), 7.14 (d, J = 7.3, 1H), 7.07 (t, J = 8.0, 1H), 6.75 (t, J = 7.3, 1H), 6.61 (d, J = 8.0, 1H), 5.35 (q, J = 6.8, 1H), 4.52 (s, 1H), 4.44 (t, J = 3.0, 1H), 4.30 (d, J = 14.6, 1H), 4.02 (d, J = 13.1, 1H), 3.77 (d, J = 11.1, 1H), 3.71 (s, 3H), 3.46 (d, J = 14.6, 1H), 3.45 (d, J = 12.4, 1H) 3.28 (m, 1H), 3.10 (d, J = 5.1, 1H), 3.02 (t, J = 12.2, 1H), 2.31 (dd, J = 13.1, 4.1, 1H), 2.04 (dt, J = 13.7, 3.7, 1H), 2.01 (dt, J = 13.7, 2.8, 1H), 1.54 (d, J = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 147.8, 146.7, 137.0, 133.8, 133.2, 132.2, 132.0, 129.7, 128.6, 125.2, 125.0, 123.3, 119.9, 108.6, 100.7, 80.5, 61.6, 54.7, 54.6, 54.2, 51.8, 48.7, 37.6, 30.4, 30.0, 12.9; IR (film) 3372, 2917, 2849, 2338, 1734, 1608, 1541, 1472, 1319, 1155, 1100; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{27}H_{30}N_3O_8S^+$ 556.1748, found 556.1754.

Alcohol ***62***. To a solution of $CH_3OCH_2OCH_2SnBu_3$ (39 mg, 0.11 mmol)[76] in THF (1 mL) was added a solution of *n*-butyllithium (*n*-BuLi) (0.046 mL, 2.05 M in hexanes) at −78 °C. The reaction mixture was stirred for 20 min, at which point a solution of enone **61** (25 mg, 0.072 mmol) in THF (1 mL) was added dropwise over 1 min at −78 °C. After 1 h, the reaction mixture was quenched with a solution of saturated aqueous NH_4Cl (3 mL) and allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc) to afford alcohol **62** (9 mg, 30% yield) as a pale yellow oil. Alcohol **62**: R_f 0.28 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.68 (m, 2H), 7.62, (m, 1H), 5.86 (dd, J = 10.0, 1.3, 1H), 5.73 (ddd, J = 10.0, 5.7, 1.3, 1H), 5.66 (q, J = 6.9, 1H), 4.68−4.48 (m, 3H), 3.97 (d, J = 14.1, 1H), 3.90 (dt, J = 14.1, 2.0, 1H), 3.58 (d, J = 10.4, 1H), 3.48 (d, J = 10.4, 1H), 3.38 (s, 3H), 3.23 (t, J = 3.8, 1H), 2.49 (s, 1H), 1.99 (dt, J = 13.4, 3.0, 1H), 1.82 (dt, J = 13.4, 3.4, 1H), 1.66 (dd, J = 6.9, 2.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 136.2, 133.7, 133.6, 131.8, 131.2, 130.8, 125.6, 124.8, 124.4, 97.3, 72.8, 71.5, 55.7, 47.9, 47.7, 35.0, 30.9, 12.9; IR (film) 3526, 2931, 1543, 1442, 1372, 1352, 1213, 1164, 1108, 1036; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_7S^+$ 425.13770, found 425.13565.

Epoxide ***64***. To a suspension of trimethylsulfonium iodide ($Me_3S^+I^-$) (39 mg, 0.19 mmol) in THF (1 mL) was added *n*-butyllithium (*n*-BuLi) (65 μL, 2.65 M in hexanes) at 0 °C. After 5 min, a solution of enone **61** (56 mg, 0.16 mmol) in THF (0.6 mL) was added dropwise over 1 min at 0 °C. After 30 min, the reaction was warmed to room temperature and poured into a brine solution (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc) to afford epoxide **64** (30 mg, 52% yield) as a pale yellow oil. Epoxide **64**: R_f 0.58 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (m, 1H), 7.69 (m, 2H), 7.63 (m, 1H), 5.94 (ddd, J = 1.5, 5.9, 9.9, 1H), 5.56 (q, J = 6.8, 12), 5.55 (dd, J = 1.2, 9.9, 1H), 4.61(dt, J = 3.0, 5.9, 1H), 4.00(m, 2H), 2.96 (d, J = 5.2, 1H), 2.85 (d, J = 5.2, 1H), 2.73 (br. s, 1H), 2.16 (dt, J = 3.1, 12.9, 1H), 1.99 (ddt, J = 1.6, 3.4, 12.9, 1H), 1.56 (dd, J = 1.5, 6.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 135.8, 133.6, 133.7, 131.9, 131.0, 130.8, 129.1, 124.4, 123.5, 58.3, 56.4, 47.6, 47.3, 34.9, 32.3, 12.7; IR (film) 2924, 1543, 1440, 1372, 1165, 1127, 1075; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_5S^+$ 363.10090, found 363.10024.

Enal ***65***. To a solution of tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$ (1 mg, 0.00030 mmol) and acetic acid (AcOH) (2 μL, 0.033 mmol) in THF (0.25 mL) was added a solution of epoxide **64** (0.011 g, 0.030 mmol) dropwise over 1 min. After 30 min, the reaction was filtered over a plug of SiO_2, washed with EtOAc (25 mL), and the filtrate was concentrated under reduced pressure. The resulting residue was purified via preparative TLC (2:1 hexanes/EtOAc) to afford enal **65** (7 mg, 62% yield) as a colorless oil.

Enal ***65***. To a solution of epoxide **64** (11 mg, 0.030 mmol) in THF (0.30 mL) was added an aqueous solution of sulfuric acid (H_2SO_4) (0.2 mL, 2% w/w). After 5 min, the reaction mixture was diluted with EtOAc (5 mL) and poured into a solution of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc) to afford enal **65** (10 mg, 91% yield) as a colorless oil. Enal **65**: R_f 0.38 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.05 (m, 1H), 7.74−7.63 (m, 3H), 6.91 (t, J = 3.7, 1H), 5.43 (q, J = 6.9, 1H), 4.45 (br. s, 1H), 3.96 (br. s, 1H), 3.85 (d, J = 14.3, 1H), 3.71 (d, J = 14.3, 1H), 2.82 (ddd, J = 3.4, 5.9, 21.5, 1H), 2.59 (dd, J = 3.9, 21.5, 1H), 1.92 (dt, J = 3.4, 12.8, 1H), 1.78 (dd, J = 1.8, 6.8, 3H), 1.69 (dt, J = 3.1, 12.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 149.1, 148.0, 142.5, 133.7, 133.6, 131.9, 131.0, 130.7, 124.5, 122.7, 48.0, 47.0, 33.2, 30.9, 26.6, 12.9; IR (film) 2923, 1682, 1542, 1440, 1371, 1340, 1164, 1126, 1081; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_5S^+$ 363.10090, found 363.10022.

Enal ***71***. To a solution of enal **68** (25 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (0.046 mL, 0.40 mmol) and chlorotriethylsilane (TESCl) (33 μL, 0.20 mmol). After being stirred for 17 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and poured into H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via preparative TLC (1:1 hexanes/EtOAc) to afford enal **71** (27 mg, 83% yield) as a colorless oil. Enal **71**: R_f 0.31 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.06 (m, 1H), 7.73−7.65 (m, 3H), 6.75 (dd, J = 4.0, 1.2, 1H), 5.41 (q, J = 6.7, 1H), 4.41 (d, J = 4.0, 1H), 4.06 (br. s, 1H), 2.90 (t, J = 2.9, 1H), 3.81 (d, J = 14.5, 1H), 3.67 (dt, J = 14.5, 1.9, 1H), 1.95 (dt, J = 13.0, 3.1, 1H), 1.76 (dd, J = 6.8, 1.9, 3H), 1.66 (dt, J = 13.0, 3.2, 1H), 0.96 (t, J = 8.1, 9H), 0.66 (q, J = 8.1, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 148.0 (2 carbons), 142.1, 133.8, 133.4, 131.9, 131.1, 129.7, 124.7, 122.9, 67.9, 55.1, 47.2, 27.1, 26.2, 12.8, 6.9, 4.7; IR (film) 2957, 2877, 1690, 1543, 1457, 1440, 1370, 1343, 1240, 1164, 1126, 1071, 1009; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{23}H_{32}N_2O_6SSi^+$ 493.18231, found 493.17800.

Aldehyde ***73*** *and Aldehyde* ***SI-5***. In the glovebox, a vial was charged with tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$ (2 mg, 0.0016 mmol) and zinc chloride ($ZnCl_2$) (17 mg, 0.125 mmol). The flask was removed from the glovebox and placed under N_2 pressure, and THF (1.5 mL) was added. To this solution was added a

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solution of enal **68** (27 mg, 0.054 mmol) in THF (1.2 mL). The resulting mixture was sparged with N_2 for 10 min, at which point tributyltin hydride (Bu_3SnH) (0.029 mL, 0.11 mmol) was added. After 20 h, the reaction mixture was diluted with EtOAc (10 mL) and poured into H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting diastereomeric mixture was purified via preparative TLC (18:1:1 benzene/Et_2O/CH_2Cl_2) to afford aldehyde **73** (14 mg, 52% yield) and aldehyde **SI-5** (3 mg, 10% yield) as colorless oils. The stereochemical assignment of **73** and **SI-5** were determined by analysis of ^{1}H NMR coupling constants. Aldehyde **73**: R_f 0.48 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.96 (m, 1H), 7.70 (m, 2H), 7.61 (m, 1H), 5.48 (q, J = 7.0, 1H), 4.14 (app. q, J = 3.1, 1H), 4.06 (d, J = 14.1, 1H), 3.75 (m, 2H), 3.36 (br. s, 1H), 2.35 (ddd, J = 14.8, 6.8, 2.5, 1H), 2.30 (dt, J = 14.2, 2.7, 1H), 2.25 (d, J = 6.8, 1H), 2.03 (d, J = 14.8, 1H), 1.57 (d, J = 7.0, 3H), 1.50 (dt, J = 14.2, 3.7, 1H), 0.96 (t, J = 8.1, 9H), 0.62 (q, J = 8.1, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 148.7, 134.4, 133.8, 131.61, 131.57, 131.2, 124.4, 121.9, 68.9, 54.3, 48.61, 48.60, 27.19, 27.17, 20.4, 13.2, 6.9, 4.7; IR (film) 2955, 2921, 2876, 1720, 1544, 1467, 1439, 1373, 1356, 1242, 1168, 1105, 1082, 1069; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{23}H_{34}N_2O_6SSi^+$ 495.19796, found 495.19705. Aldehyde **SI-5**: R_f 0.48 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.04 (m, 1H), 7.69 (m, 3H), 5.45 (q, J = 6.9, 1H), 4.19 (app. q, J = 2.7, 1H), 4.13 (dt, J = 15.3, 2.4, 1H), 3.90 (d, J = 15.3, 1H), 3.85 (app. q, J = 3.5, 1H), 3.35 (app. q, J = 3.5, 1H), 3.02 (dt, J = 12.7, 4.4, 1H), 2.41 (dt, J = 13.2, 3.1, 1H), 2.10 (ddd, J = 15.7, 13.0, 3.4, 1H), 1.85 (dd, J = 15.7, 4.8, 1H), 1.60 (dd, J = 6.9, 1.6, 3H), 1.56 (dt, J = 13.2, 3.6, 1H), 0.95 (t, J = 8.1, 9H), 0.61 (q, J = 8.1, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 148.1, 133.7, 133.0, 131.8, 131.3, 130.7, 124.7, 122.5, 68.5, 53.3, 49.7, 48.7, 29.0, 28.8, 26.7, 13.2, 7.0, 4.7; IR (film) 2955, 2920, 2876, 1723, 1543, 1459, 1440, 1369, 1243, 1164, 1127, 1099, 1067, 1045, 1006; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{23}H_{34}N_2O_6SSi^+$ 495.19796, found 495.19642.

*Aldehyde **70** and Aldehyde **SI-6**.* In a glovebox, a round-bottom flask was charged with tetrakis(triphenylphosphine)palladium [Pd(PPh_3)$_4$] (68.0 mg, 0.059 mmol) and zinc chloride ($ZnCl_2$) (370 mg, 2.71 mmol). The flask was removed from the glovebox and placed under N_2 pressure, and THF (11 mL) was added. To this solution was added a solution of enal **11** (430 mg, 1.17 mmol) in THF (11 mL). The resulting mixture was sparged with N_2 for 10 min, at which point tributyltin hydride (Bu_3SnH) (0.63 mL, 2.35 mmol) was added. After being stirred for 12 h, the reaction was quenched with a solution of saturated aqueous NH_4Cl (30 mL). The resulting mixture was diluted with EtOAc (65 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 65 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (30 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting diastereomeric mixture was purified via flash chromatography (1.5:1 hexanes/EtOAc → 1:1.5 hexanes/EtOAc) to afford aldehyde **70** (0.341 g, 79% yield) as a yellow solid and aldehyde **SI-6** (0.049 g, 0.13 mmol) as a colorless foam. The stereochemical assignments of **70** and **SI-6** were determined by analysis of ^{1}H NMR coupling constants. Characterization data for aldehyde **70** has been previously reported as part of the (±)-picrinine synthesis.[28] Aldehyde **SI-6**: R_f 0.12 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.01 (m, 1H), 7.71 (m, 2H), 7.61 (m, 1H), 5.53 (q, J = 6.9, 1H), 4.16 (t, J = 3.0, 1H), 4.11 (d, J = 14.2, 1H), 3.88 (app. q, J = 3.4, 1H), 3.82 (d, J = 14.2, 1H), 3.35 (br. s, 1H), 2.45 (d, J = 6.9, 1H), 2.37 (d, J = 4.1, 1H), 2.30 (ddd, J = 15.3, 6.9, 3.2, 1H), 2.16 (dt, J = 14.9, 2.9, 1H), 2.13 (d, J = 15.3, 1H), 1.62 (d, J = 6.9, 3H), 1.55 (dt, J = 14.9, 3.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 148.7, 134.0, 133.9, 131.7, 131.5, 131.3, 124.3, 122.4, 68.0, 53.8, 49.1, 48.6, 27.2, 25.5, 20.5, 13.2; IR (film) 3516, 2926, 2854, 1716, 1542, 1467, 1440, 1373, 1352, 1165, 1127, 1102, 1078, 1066; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{17}H_{20}N_2O_6S^+$ 381.11148, found 381.11041.

*Indolenine **79** and Indoline **80**.* To a solution of carbonate **78** (14.7 mg, 0.033 mmol) in 1,2-dichloroethane (DCE) (1.1 mL) was added phenylhydrazine (**18**) (10 μL, 0.098 mmol) followed by trifluoroacetic acid (TFA) (20 μL, 0.26 mmol). The reaction was heated to 80 °C. After being stirred for 2 h, the reaction mixture was cooled to room temperature and quenched with a solution of saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was diluted with EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc → 1:2 hexanes/EtOAc) to afford indolenine **79** and indoline **80** (12.0 mg, 69% yield) as a red oil. Characterization data for indolenine **79** has been previously reported as part of the (±)-picrinine synthesis.[28] Indoline **80**: R_f 0.77 (3:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6): 7.71 (dd, J = 7.9, 1.3, 1H), 7.06 (td, J = 7.6, 1.1, 1H), 6.68–6.61 (m, 3H), 6.45 (td, J = 7.7, 1.3, 1H), 6.38 (d, J = 7.6, 1H), 6.1 (d, J = 7.5, 1H), 5.35 (q, J = 7.7, 1H), 4.39–4.34 (m, 3H), 4.23 (t, J = 3.1, 1H), 3.80 (d, J = 15.4, 1H), 3.09 (s, br, 1H), 3.05 (s, br, J = 1H), 2.90 (dd, J = 16.0, 2.9, 1H), 2.49 (dd, J = 3.5, 3.0, 1H), 2.17 (m, 1H), 1.91 (dt, J = 13.4, 3.1, 1H), 1.76 (dt, J = 13.4, 3.5, 1H), 1.55–1.53 (m, 1H) 1.65 (dd, J = 7.7, 2.1, 3H); ^{13}C NMR (500 MHz, C_6D_6) δ 154.7, 147.8, 145.1, 138.7, 133.3, 133.2, 131.5, 131.2, 129.4, 129.1, 127.5, 124.1, 121.4, 119.5, 109.9, 94.2, 81.1, 80.3, 55.7, 55.3, 53.7, 50.5, 37.1, 32.3, 27.2, 13.4; IR (film) 3475, 3359, 1803, 1731, 1599, 1542, 1372, 1163; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{26}H_{25}N_3O_8SNa^+$ 562.1255, found 562.1262.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00872.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Baliga, M. S. *Chin. J. Integr. Med.* **2012**, DOI: 10.1007/s11655-011-0947-0.

(2) Chatterjee, A.; Mukherjee, B.; Ray, A. B.; Das, B. *Tetrahedron Lett.* **1965**, *6*, 3633–3637.

(3) For the X-ray structure of **1**, see: (a) Ghosh, R.; Roychowdhury, P.; Chattopadhyay, D.; Iitaka, Y. *Acta Crystallogr., Sect. C: Cryst. Struct.*

DOI: 10.1021/acs.joc.5b00872
J. Org. Chem. 2015, 80, 8954–8967

Commun. **1988**, *C44*, 2151−2154. (b) The 3D representation was prepared from the X-ray data of **1** using CYLview. For CYLview, see:. (c) Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Québec, 2009; http://www.cylview.org.
(4) Shang, J.-H.; Cai, X.-H.; Feng, T.; Zhao, Y.-L.; Wang, J.-K.; Zhang, L.-Y.; Yan, M.; Luo, X.-D. *J. Ethnopharmacol.* **2010**, *129*, 174−181.
(5) Shang, J.-H.; Cai, X.-H.; Zhao, Y.-L.; Feng, T.; Luo, X.-D. *J. Ethnopharmacol.* **2010**, *129*, 293−298.
(6) For reviews on the akuammiline alkaloids, see: (a) Ramírez, A.; García−Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891−1915. (b) Eckermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813−2823. (c) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 400−412.
(7) (a) Battersby, A. R.; Thompson, M.; Glüsenkamp, K.-H.; Tietze, L.-F. *Chem. Ber.* **1981**, *114*, 3430−3438. (b) Battersby, A. R.; Westcoltt, N. D.; Glüsenkamp, K.-H.; Tietze, L.-F. *Chem. Ber.* **1981**, *114*, 3439−3447. (c) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151−157. (d) Stöckigt, J.; Barleben, L.; Panjikar, S.; Loris, E. A. *Plant Physiol. Biochem.* **2008**, *46*, 340−355.
(8) Ahmad, Y.; Fatima, K.; Le Quesne, P. W.; Atta-Ur-Rahman. *Phytochemistry* **1983**, *22*, 1017−1019.
(9) Schnoes, H. K.; Biemann, K.; Mokrý, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1641−1642.
(10) (a) Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1144−1149. (b) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455−3482. (c) Mori, M. *Heterocycles* **2010**, *81*, 259−292. (d) Roth, K. *Chem. Unserer Zeit* **2011**, *45*, 202−218. (e) Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288−4311.
(11) (a) Henry, T. A. *J. Chem. Soc.* **1932**, 2759−2768. (b) Olivier, L.; Lévy, J.; Le Men, J.; Janot, M. M.; Budzikiewicz, H.; Djerassi, C. *Bull. Soc. Chim. Fr* **1965**, 868−876.
(12) For the isolation of **10**, see: Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783−1789.
(13) Ohashi, M.; Joule, J. A.; Djerassi, C. *Tetrahedron Lett.* **1964**, *5*, 3899−3905.
(14) Subramaniam, G.; Kam, T.-S. *Helv. Chim. Acta* **2008**, *91*, 930−937.
(15) For initial isolation, see: (a) Thomas, A. F. D. Phil. Thesis, Oxford, England, 1954. (b) For a subsequent isolation, see Britten, A. Z.; Smith, G. F. *J. Chem. Soc.* **1963**, 3850−3854.
(16) Lim, K.-H.; Kam, T.-S. *Tetrahedron Lett.* **2006**, *47*, 8653−8655.
(17) For the initial isolation of **15**, see: Group-Besanez, v. *Justus Liebigs Ann. Chem.* **1875**, *176*, 88−89.
(18) Mokrý, J.; Dúbravková, L.; Šefčovič, P. *Experientia* **1962**, *18*, 564−565.
(19) Cai, X.-H.; Tan, Q.-G.; Liu, Y.-P.; Feng, T.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D. *Org. Lett.* **2008**, *10*, 577−580.
(20) (a) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013−6020. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447−457.
(21) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126−9129.
(22) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442−6445.
(23) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877−8879.
(24) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1818−1821.
(25) Teng, M.; Zi, W.; Ma, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 1814−1817.
(26) (a) Adams, G. L.; Carroll, P. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **2012**, *134*, 4037−4040. (b) Adams, G. L.; Carroll, P. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **2013**, *135*, 519−528.
(27) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964−12967.
(28) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 4504−4507.
(29) For the classic Fischer indole synthesis, see: (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241−2245. (b) Fischer, E.; Hess, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559−568.
(30) For related examples, see: (a) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458−3461. (b) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687−4695. (c) Schammel, A. W.; Chiou, G.; Garg, N. K. *J. Org. Chem.* **2012**, *77*, 725−728. (d) Schammel, A. W.; Chiou, G.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4556−4559. (e) Bunders, C.; Cavanaugh, J.; Melander, C. *Org. Biomol. Chem.* **2011**, *9*, 5476−5481.
(31) Liu, P.; Wang, J.; Zhang, J.; Qiu, F. G. *Org. Lett.* **2011**, *13*, 6426−6428.
(32) Zu, L.; Boal, B. W.; Garg, N. K. Unpublished results.
(33) For a study on N−N bond cleavage in Fischer indolization reactions, see: Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752−5755.
(34) For a review on the nosyl protecting group, see: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353−359.
(35) For examples of the Fischer indolization being employed in the late-stage total synthesis of complex alkaloids, see refs 23 and 26, in addition to the following: (a) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, *6*, 2261−2268. (b) Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 7600−7603. (c) Satoh, H.; Ueda, H.; Tokuyama, H. *Tetrahedron* **2013**, *69*, 89−95.
(36) For reviews of the Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (c) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. (d) Heravi, M. M.; Hashemi, E.; Ghobadi, N. *Curr. Org. Chem.* **2013**, *17*, 2192−2224.
(37) For the use of the Heck reaction in the synthesis of Strychnos alkaloids, see: (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686. (c) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472−3473.
(38) Herdeis, C.; Hartke, C. *Heterocycles* **1989**, *29*, 287−296.
(39) (a) Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626−4642. (b) Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, *17*, 4447−4450.
(40) See the Materials and Methods in the Supporting Information for microwave reactor details.
(41) For an example of aminolysis using TBD, see: Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863−3866.
(42) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695−1698.
(43) Nagata, H.; Kawamura, M.; Ogasawara, K. *Synthesis* **2000**, 1825−1834.
(44) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825−4830.
(45) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317−4320.
(46) Hypervalent iodine reagents such as $PhI(OAc)_2$ and periodic acid were ineffective for this transformation.
(47) For an example of an oxidative cleavage cascade, see: Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102−15108.
(48) Sulfonamide **60** is commercially available from Aurora Fine Chemicals LLC (CAS No. 115462-23-0) or can be readily prepared in two steps from *trans*-4-aminocyclohexanol·HCl.
(49) For related Pd-catalyzed cyclizations, see: (a) Sole, D.; Piedro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228. (b) Liao, X.; Zhou, H.; Yu, J.; Cook, J. M. *J. Org. Chem.* **2006**, *71*, 8884−8890. (c) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368−5377.
(50) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996.

DOI: 10.1021/acs.joc.5b00872
J. Org. Chem. 2015, 80, 8954−8967

(51) For preparation of the stannane, see: (a) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medlich, J. R. *Org. Synth.* **1993**, *71*, 133−139. For use of the reagent, see: (b) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027−7039.
(52) For the original Dauben oxidation, see: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682−685.
(53) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303−4306.
(54) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750−4752.
(55) Nagaoka, H.; Kobayashi, K.; Matsui, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 2021−2023.
(56) Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550−12551.
(57) Campagnole, M.; Delmond, B. *Synth. Commun.* **2007**, *37*, 1077−1090.
(58) Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synth. Commun.* **1989**, *19*, 3579−3587.
(59) Newton, R. F.; Wadsworth, A. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 823−830.
(60) For a review, see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. *Chem. Rev.* **2008**, *108*, 2916−2927. For examples, see: (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293. (c) Baker, B. A.; Bošković, Ž. V.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289−292. See also ref 43.
(61) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390−1399.
(62) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477−480.
(63) For the effect of silyl groups on controlling diastereoselective protonation, see: (a) Bouzide, A. *Org. Lett.* **2002**, *4*, 1347−1350. (b) Rodrigues, M. T., Jr.; Gomes, J. C.; Smith, J.; Coelho, F. *Tetrahedron Lett.* **2010**, *51*, 4988−4990.
(64) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122−9124.
(65) (a) Jabri, S. Y.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 8766−8788. (b) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771−6772.
(66) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814−4818.
(67) Akbutina, F. A.; Torosyan, S. A.; Vyrypaev, E. M.; Furlei, I. I.; Miftakhov, M. S. *Russ. J. Org. Chem.* **1999**, *35*, 1386−1387.
(68) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.
(69) Burk, R. M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395−398.
(70) Indolenine **79** and hydrate **80** readily interconverted in $CDCl_3$ or upon prolonged exposure to silica gel.
(71) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matsuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. *J. Org. Chem.* **2003**, *68*, 1216−1224.
(72) Foos, J.; Steel, F.; Rizvi, S. Q. A.; Fraenkel, G. *J. Org. Chem.* **1979**, *44*, 2522−2529.
(73) (a) For the removal of nosyl groups using a solid-supported thiol reagent, see: Cardullo, F.; Donati, D.; Merlo, G.; Paio, A.; Salaris, M.; Taddei, M. *Synlett* **2005**, 2996−2998. (b) The thiol resin was obtained from SiliCycle, Inc. (product no. R51030B).
(74) Mass spectral analysis of the crude reaction mixture suggests that nosyl cleavage occurred. However, efforts to purify products formed in the reaction were unsuccessful.
(75) Although the MetSThiol reagent is typically used as a metal scavenger, this is the first example of this resin being used for the cleavage of a nosyl group.
(76) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806−810.

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J. Org. Chem. 2015, 80, 8954−8967