JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

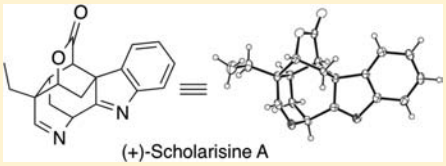
Access to the Akuammiline Family of Alkaloids: Total Synthesis of (+)-Scholarisine A

Gregory L. Adams, Patrick J. Carroll, and Amos B. Smith, III*

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

Supporting Information

ABSTRACT: The planning and implementation of an enantioselective total synthesis of (+)-scholarisine A is presented. Key tactics employed include a novel cyclization, consisting of a nitrile reduction coupled with concomitant addition of the resultant amine to an epoxide; a modified Fischer indolization; an oxidative lactonization of a diol in the presence of an indole ring; and a late-stage cyclization to complete the caged ring scaffold. The development of a possible "retro-biosynthetic" approach to other members of the akuammiline alkaloid family is also described.



INTRODUCTION

Scholarisine A (**1**), an akuammiline monoterpene indole alkaloid isolated from the leaves of *Alstonia scholaris* by Luo and co-workers, possesses an architecturally intricate cage-like scaffold containing a bridged lactone, an aliphatic imine, and an indolenine core (Figure 1).[1] From the outset, the intrinsic synthetic challenge involved in constructing this novel architecture attracted our attention. The possibility of devising a substrate that would also provide access to other members of the akuammiline alkaloid family via a late-stage "retro-biosynthetic" fragmentation further enhanced our interest in this alkaloid class. We therefore initiated synthetic studies toward the construction of (+)-scholarisine A (**1**) in 2008.

Alkaloids that derive biosynthetically via cyclization of geissoschizine (**5**), forming a bond between C-7 and C-16,[2] are considered members of the akuammiline alkaloid family (Figure 1).[3] Akuammiline (**7**),[4] the progenitor from which this class derives the name, was first characterized in 1932.[5] Acetate hydrolysis and deformylation is believed to give rise to the strictamine congener (**6**),[6] while hydrolysis of the amine moiety would permit formation of the furoindoline core, observed in aspidodasycarpine (**8**)[7] and aspidophylline A (**9**),[8] the latter the subject of a recent elegant total synthesis by the Garg group.[9] Akuammiline (**7**) could also give rise to picraline (**3**)[10] upon oxidation at C-5, while additional loss of the acetoxymethyl moiety from C-16 would lead to picrinine (**4**).[11] Further functionalization of the picrinine core would result in formation of lanciferine (**10**),[12] nareline (**11**),[13] and arbophylline (**12**),[14] while vincorine (**13**)[15] and echitamine (**14**)[16] consist of a scaffold containing a nitrogen shift.[17] A racemic synthesis of vincorine (**13**) was reported by Qin in 2009,[18] while more recently, in 2012, Ma reported an asymmetric total synthesis.[19]

Scholarisine A (**1**), the initial target of our efforts, is proposed to arise biosynthetically via rearrangement of picrinine (**4**) as illustrated in Figure 1. Opening of the hemiaminal ether oxygen bridge between C-2 and C-5 would provide an aldehyde at C-5. Double bond migration of the E-ethylidine could then furnish an enamine, which could undergo nucleophilic addition to the aldehyde. Finally, lactonization between the resultant hydroxyl group and the methyl ester would complete the caged scaffold of scholarisine A (**1**).[1]

Importantly, several members of the akuammiline alkaloid class are known to have bioactivity. Derivatives of picraline (**3**)[20] are reported to be selective inhibitors of the receptor SGLT2, a renal cortex membrane protein recently validated as a target for type II diabetes treatment,[21] while aspidophylline A (**9**) and echitamine (**14**) respectively reverse drug resistance in cancer cells[8] and display in vivo anti-tumor activity in rodents.[22]

Earlier this year, we reported the first total synthesis and assignment of the proposed absolute configuration of (+)-scholarisine A (**1**).[23] Herein we report a full account of the rationale behind the planning of this synthetic venture, in conjunction with implementation of the synthetic strategy, as well as initial experiments that hold the promise of providing access to other members of the akuammiline family via a "retro-biosynthetic" fragmentation.

Structural Insight into the Akuammiline Family of Alkaloids. After considering the proposed biosynthetic route to (+)-scholarisine A (**1**), with specific attention focused on aldehyde **2** (Figure 1), we began to view these alkaloids in a structurally open format (cf. **15** and **16**, Figure 2).

Inspired by indoline diol **15**, a degradation product of aspidodasycarpine (**8**) reported by the Djerassi group in 1964,[7] we reasoned that if such a carbon scaffold could be accessed, redox manipulation with functionalization might provide access to the entire akuammiline class. For example, ester indolenine aldehyde **16** could collapse to form picrinine (**4**). Reduction of the aldehyde in **16** would also provide alcohol **18**, which upon cyclization to a furoindoline core could furnish desformoaspi-

Received: November 13, 2012
Published: December 26, 2012

   dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

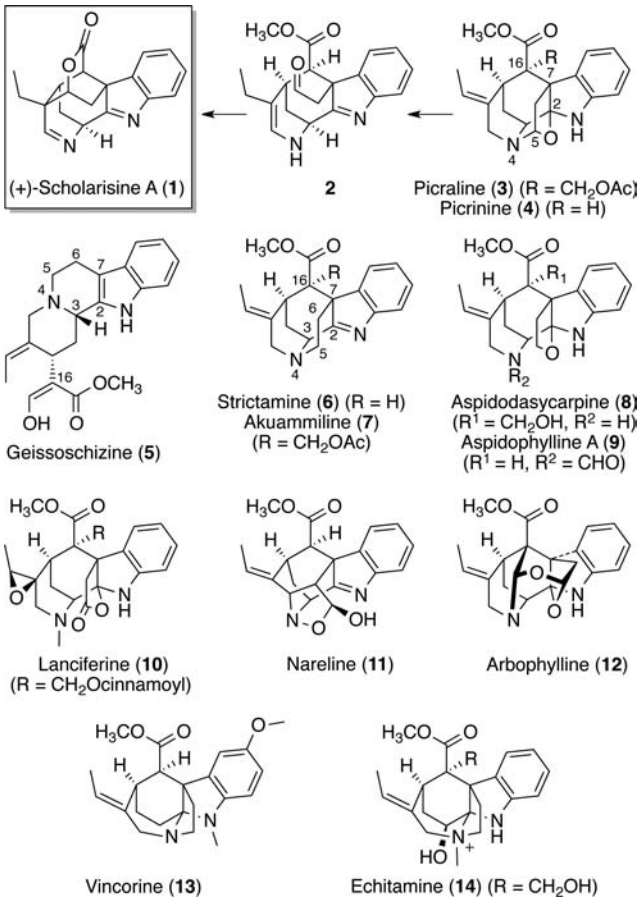


Figure 1. Representative akuammiline alkaloids.

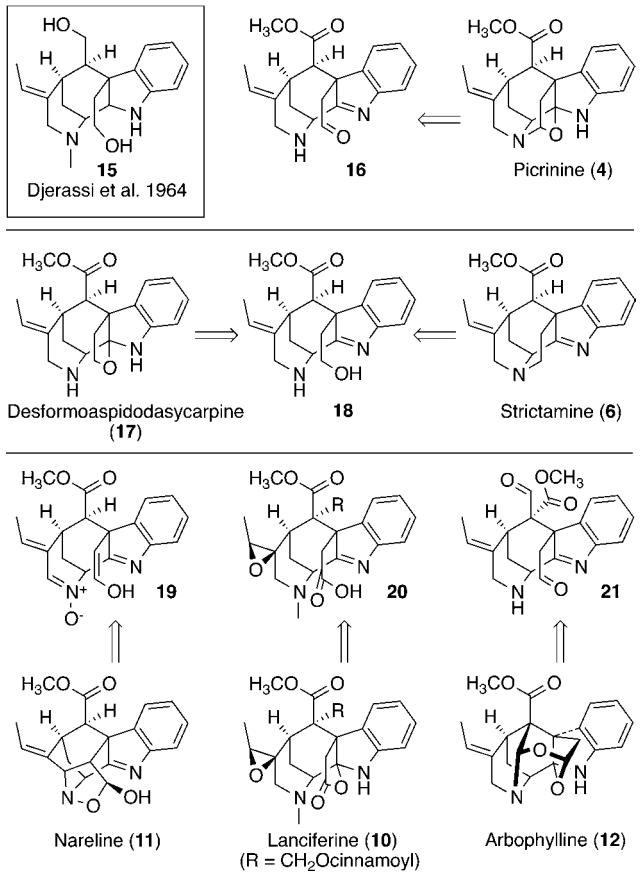


Figure 2. Open form view of akuammiline alkaloids.

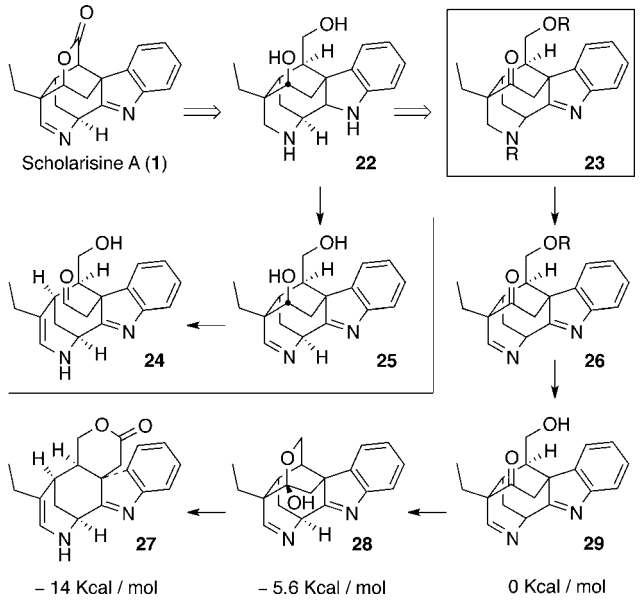


Figure 3. Fragmentation approach to the akuammiline core.

dodasycarpine (**17**).[7] Supporting this concept, Garg et al. recently demonstrated that the *N*-tosyl derivative of alcohol **18** spontaneously forms the furoindoline core during their synthesis of apspidophylline A (**9**).[9] Alternatively, activation of the hydroxyl present in **18** could lead, via cyclization, to strictamine (**6**). Furthermore, oxidation of the amine in **16** to nitrone **19** would provide a substrate that might undergo a [3+2] cycloaddition to provide nareline (**11**).[13] Alternative redox manipulation and functionalization could also provide the open substrates **20** and **21**, which upon collapse could lead to lanciferine (**10**) and arbophylline (**12**), respectively.

Total Synthesis of Scholarisine A: A Unified Route to the Akuammiline Alkaloids. With the above considerations in mind, we initially targeted indolenine ketone **23** (Figure 3) as a versatile late-stage intermediate to devise a unified approach to the akuammiline core. This substrate was envisioned to provide synthetic access to scholarisine A (**1**), as well as other members of the akuammiline family, via a series of fragmentations and cyclizations (Figure 3).

For example, indolenine ketone **23** was envisioned to undergo reduction followed by deprotection to provide indoline diol amine **22**, which could then be oxidized to either scholarisine A (**1**) or diimine **25**, that in turn might undergo an aza retroaldol-type fragmentation to furnish aldehyde enamine **24**, a scaffold reminiscent of the structures seen in Figure 2.

Alternatively, nitrogen deprotection and oxidation of the amine in **23** could lead to diimine **26**, which upon deprotection of the oxygen might elicit a fragmentation reaction consisting of the initially formed hydroxy ketone **29** collapsing to form lactol **28**, which could then undergo fragmentation to render lactone **27**.[24]

For each of the latter constitutional isomers, **27**, **28**, and **29**, the relative energies were calculated at the geometry-optimized B3LYP/6-31G(d) level. The computationally determined relative energies suggest lactone **27** to be the most energetically stable isomer.

dx.doi.org/10.1021/ja3111626 | *J. Am. Chem. Soc.* 2013, 135, 519–528

We consider the proposed fragmentation processes (**22** to **24** and **26** to **27**) to comprise a reversal of the biosynthetic path to scholarisine A (**1**) (Figure 1). Further manipulation of **24** and **27** to the oxidation states and functionalities illustrated in Figure 2 might provide access to the entire akuammiline family.

Central to our initial synthetic analysis (Figure 4), indolenine **23** was envisioned to arise via a cyclization involving the acidic

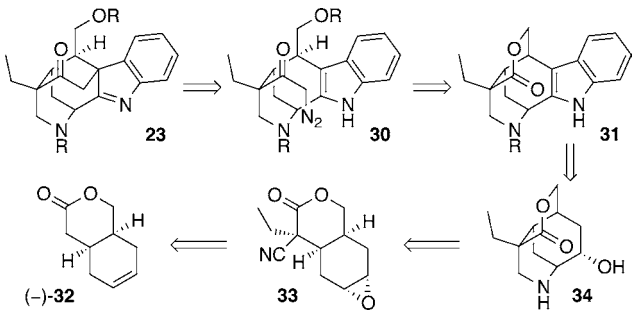


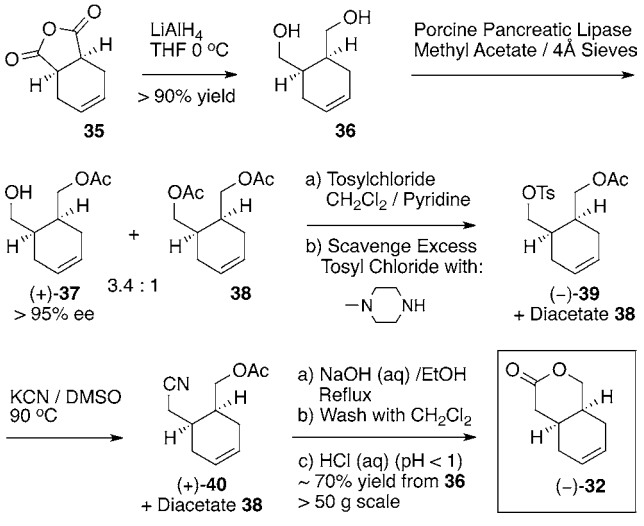
Figure 4. Initial retrosynthetic analysis.

decomposition of α-diazo ketone **30**[25] to install the quaternary center.[26] Cyclization substrate **30** in turn could be obtained via carboxylate activation and homologation of the protected seco acid of lactone **31**, which was envisioned to arise from tricyclic amine **34** after protection, oxidation, and Fischer indolization. Amine **34**, a central player in our proposed synthesis of (+)-scholarisine A (**1**), would result via a selective nitrile reductive cyclization of epoxide **33**, which would derive after functionalization from known lactone (−)-**32**.[27] Importantly, the convex−concave nature of lactone (−)-**32** would dictate the correct configuration at both the quaternary center and the oxirane ring in lactone **33**. Substrate control, once the correct stereogenicity of (−)-**32** was established, would thus dictate all of the remaining stereogenic centers required to access the (+)-scholarisine A (**1**) scaffold.

RESULTS AND DISCUSSION

Lactone (−)-32. At the outset, a synthetic route permitting access to large amounts of lactone (−)-**32** was developed and implemented (Scheme 1). To this end, meso diol **36**, obtained via lithium aluminum hydride reduction of commercially

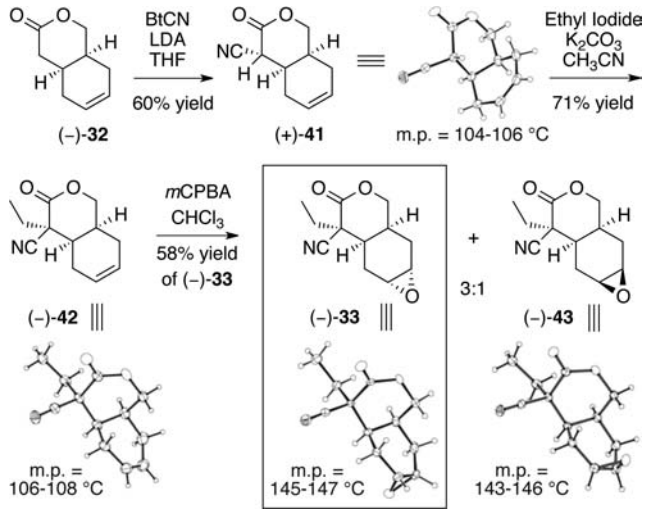
Scheme 1. Synthesis of Lactone (−)-32



available anhydride **35** in cold tetrahydrofuran,[28] was subjected to a modification of a known[27] enzymatic asymmetrization employing porcine pancreatic lipase in a reaction medium of methyl acetate containing 4 Å sieves; the latter were introduced to scavenge the methanol byproduct of enzyme acylation, thus permitting a manageable amount of methyl acetate to be employed as solvent upon reaction scale-up.[29] Without separation, the resultant mixture of monoacetate (+)-**37** and diacetate **38** (3.4:1) was directly treated with toluenesulfonyl chloride in pyridine and dichloromethane (1:1 v/v) at room temperature to furnish tosylate (−)-**39**. The reaction mixture was then subjected to an aqueous workup after quenching the excess tosyl chloride with *N*-methylpiperazine to create a water-soluble sulfonamide.[30] After workup, treatment of the product mixture with potassium cyanide[31] in hot dimethyl sulfoxide furnished nitrile (+)-**40**. Basic hydrolysis was followed by extraction with dichloromethane to remove impurities and diol **36**, which formed upon saponification of diacetate **38**, the latter proving inert to the previous two reactions. Lactone (−)-**32**, in turn, was obtained upon acidification in approximately 70% yield from diol **36**.

Epoxide (−)-33. With lactone (−)-**32** in hand, the focus shifted to the preparation of the cyclization substrate, epoxide **33**. Toward this end, the anion of lactone (−)-**32**, derived by reaction with 2.2 equiv of lithium diisopropyl amide in tetrahydrofuran, was treated with cyanobenzotriazole[32] at 0 °C to furnish nitrile (+)-**41**[33] in 60% yield, after a workup involving aqueous extraction (Scheme 2).

Scheme 2. Synthesis of Epoxide (−)-33



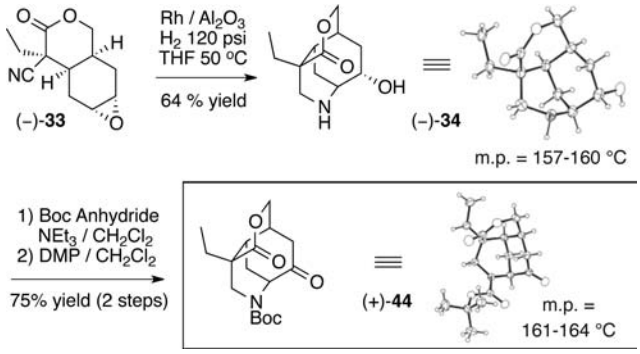
Next, ethyl cyanolactone (−)-**42**[33] was generated in 71% yield upon addition of ethyl iodide in a warm slurry of potassium carbonate and acetonitrile. As anticipated, alkylation occurred from the convex face of cyanolactone (+)-**41** to deliver the requisite configuration at the quaternary center. Epoxidation to prepare the scaffold for reductive cyclization was then achieved via use of *m*CPBA in chloroform; a mixture of diastereomeric epoxides, consistent with expectations based on literature precedent, resulted.[34] The desired epoxide (−)-**33**[33] was formed in preference to (−)-**43**[33] in a ratio of 3:1. Crystallization from toluene provided pure (−)-**33** in 58% yield.

Construction of Ketones (+)-44 and (+)-45: Fischer Indole Substrates. Orchestration of what proved to be a

dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

novel reductive cyclization of epoxide (−)-**33** to access (+)-**44**[33] (Scheme 3) was achieved via nitrile hydrogenation, followed by *in situ* epoxide ring-opening to generate tricylic amine (−)-**34**.[33,35] The reaction was performed employing a

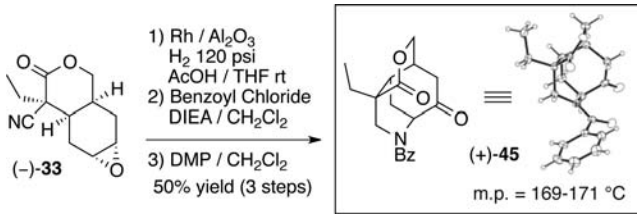
Scheme 3. Synthesis of Ketone (+)-44



pressure bomb at ca. 100 psi of hydrogen, with rhodium on alumina as the catalyst. The commonly employed nitrile hydrogenation medium of alcoholic ammonia could not be used in this case due to decomposition of lactone (−)-**33**. Tetrahydrofuran was thus employed as the solvent, but heating was required, since the reaction did not progress at room temperature. Even with heating, the reaction proved to be slow.

Ketone (+)-**44**, employed as the initial substrate for the Fischer indole synthesis, was prepared via protection of amine (−)-**34** with di-*tert*-butyl dicarbonate followed by Dess−Martin oxidation.[36] Improved cyclization conditions were subsequently discovered (Scheme 4), wherein a mixture of acetic acid and

Scheme 4. Synthesis of Ketone (+)-45

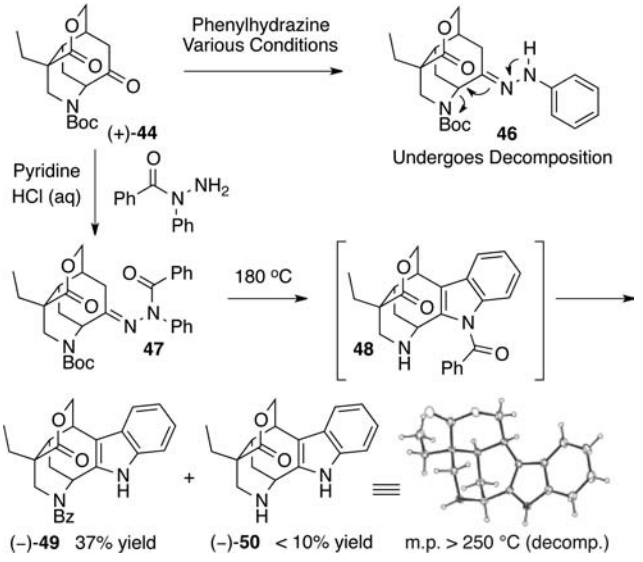


tetrahydrofuran (1:1) was employed.[37] Under these conditions the reaction proceeds at room temperature at a reasonable rate. Tetrahydrofuran, which is known to suppress epoxide hydrogenolysis when used as a solvent for catalytic hydrogenation of alkenes, is required in this case as a co-solvent to achieve a clean reaction product.[38] Uncharacterized side products were observed when pure acetic acid was used as the solvent.

The product from this hydrogenation was next subjected, without purification, directly to protection of the secondary amine in this case with benzoyl chloride, employing diisopropylethylamine (DIEA) as an acid scavenger (Scheme 4). After an aqueous workup, oxidation with Dess−Martin periodinane furnished ketone (+)-**45**,[33] which was sufficiently pure to use directly in the next step.

Construction of the Indole Ring. With ketones (+)-**44** and (+)-**45**, possessing the 2-azabicyclo[3.3.1]nonan-8-one ring system, in hand, we explored installation of the indole. Initial attempts at Fischer annulation, employing phenylhydrazine and ketone (+)-**44**, proved unsuccessful (Scheme 5). Following the reaction by LCMS, however, indicated that the hydrazone was

Scheme 5. Initial Indole Synthesis



formed, but only decomposition followed. Although the products of decomposition were not isolated, a possible route for the decomposition of **46** was envisioned to entail proton abstraction, coupled with the protected nitrogen acting as a leaving group, as illustrated in Scheme 5.

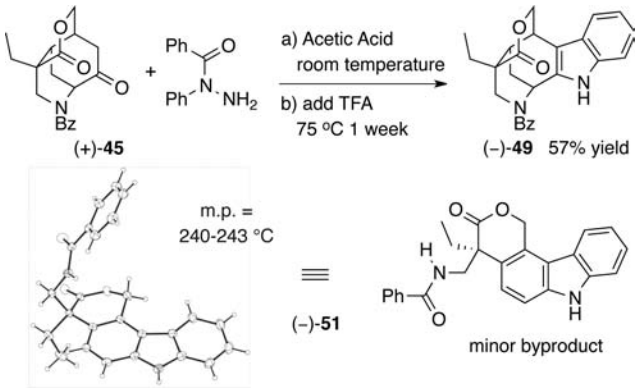
To determine if this decomposition pathway pertained, the possibility of proton abstraction was removed via substitution of the involved hydrogen with a benzoyl group. A stable hydrazone **47** could then be obtained upon subjecting (+)-**44** to benzoylphenylhydrazine[39] in pyridine containing aqueous hydrochloric acid (Scheme 5).[40] The weakly acidic reaction medium of pyridine/hydrochloric acid was chosen to retain the nitrogen protection. Under these conditions the hydrazone proved stable, even upon heating at 100 °C for 5 days. However, upon raising the temperature to 180 °C for 5 h, employing microwave radiation, two different indole products were obtained; indole amide (−)-**49** resulted in a 37% yield, with indole (−)-**50**[33] isolated as a minor product. We reason that during the course of this reaction, the secondary alkyl nitrogen undergoes exchange of protection via thermal decomposition of the carbamate, concurrent with the Fischer annulation process, to form first the benzoyl indole **48** as a transient intermediate[41] that then undergoes benzoyl transfer either bimolecularly or in an intramolecular fashion.[42] Indole (−)-**50** results via competing hydrolysis of benzoyl indole **48**.[43]

After we demonstrated that indole (−)-**49** was a viable synthetic intermediate (*vide infra*), an alternate route to (−)-**49** more amenable to scale-up was devised, which directly introduced benzoyl protection by employing ketone (+)-**45**. Subjecting this ketone to benzoyl phenylhydrazine in a solution of acetic acid and trifluoroacetic acid (TFA) (1:1) for 1 week at 75 °C furnished (−)-**49** in 57% yield (Scheme 6).[44]

While this route provided sufficient indole (−)-**49** to advance the synthesis, the acidic conditions and long reaction time appeared to cause partial degradation of the product as the reaction progressed. Carbazole (−)-**51**,[33] observed as a minor byproduct, probably forms via protonation of the amide moiety, followed by an E1 elimination and oxidation. Involvement of the nitrogen atom in this elimination pathway lends further support to the proposed hydrazone decomposition pathway outlined in Scheme 5. Later studies established that benzyl

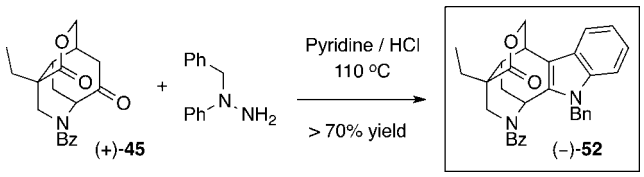
dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

Scheme 6. Synthesis of Indole (−)-49



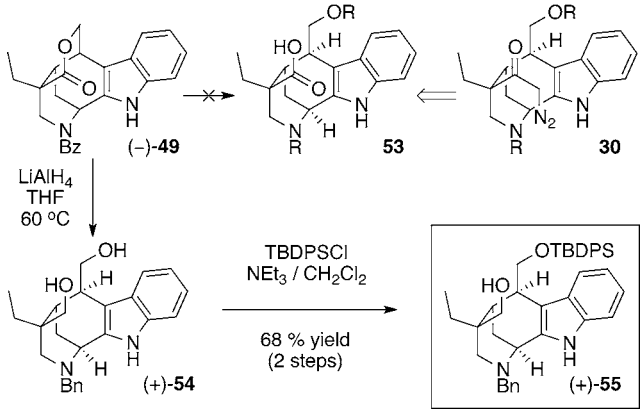
instead of benzoyl protection of the phenylhydrazine would prove beneficial. To this end, treatment of ketone (+)-**45** with benzyl phenylhydrazine[45] employing the slightly acidic medium of pyridine/hydrochloric acid at 110 °C overnight furnished the benzyl-protected indole (−)-**52** in greater than 70% yield (Scheme 7).

Scheme 7. Synthesis of Indole (−)-52



Lactone Ring-Opening and Hydroxyl Protection: A Difficult Transformation. Once indole (−)-**49** was obtained, attempts were made to construct seco acid **53** (Scheme 8).

Scheme 8. Lactone Opening and Hydroxyl Protection



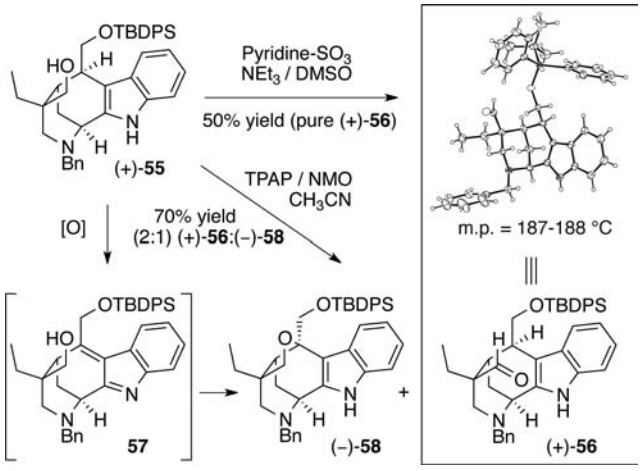
Carboxylate activation in **53** followed by reaction with diazomethane would provide α-diazoketone **30**, a central intermediate in our synthetic analysis (see Figure 4). To achieve this transformation, opening of the lactone ring in (−)-**49** with selective protection of the resulting hydroxyl group would be required.

Unfortunately, all efforts to achieve this transformation failed. Upon treatment with aqueous sodium hydroxide, lactone ring-opening could be observed by LCMS, but all further manipulations of the resultant hydroxy carboxylate, including addition of trialkyl silyl chlorides to capture the free hydroxyl group, resulted only in lactone ring closure. Attempts to convert the lactone directly to the corresponding Weinreb amide using either basic or acidic conditions, or treatment of the lactone with potassium trimethylsilanol in tetrahydrofuran, also proved unproductive.

Lactone (−)-**49** could however be reduced with lithium aluminum hydride to furnish diol (+)-**54**. Equally important, the less hindered hydroxyl of the resultant diol (+)-**54** could be protected selectively as the TBDPS ether[46] to furnish (+)-**55**.

Oxidation of Alcohol (+)-55 to the Carboxylic Acid: Another Difficult Transformation. Indole alcohol (+)-**55** was next subjected to oxidation with tetrapropylammonium perruthenate, employing *N*-methylmorpholine *N*-oxide as the co-oxidant (TPAP/NMO);[47] a mixture of products resulted (Scheme 9).

Scheme 9. Synthesis of Aldehyde (+)-56



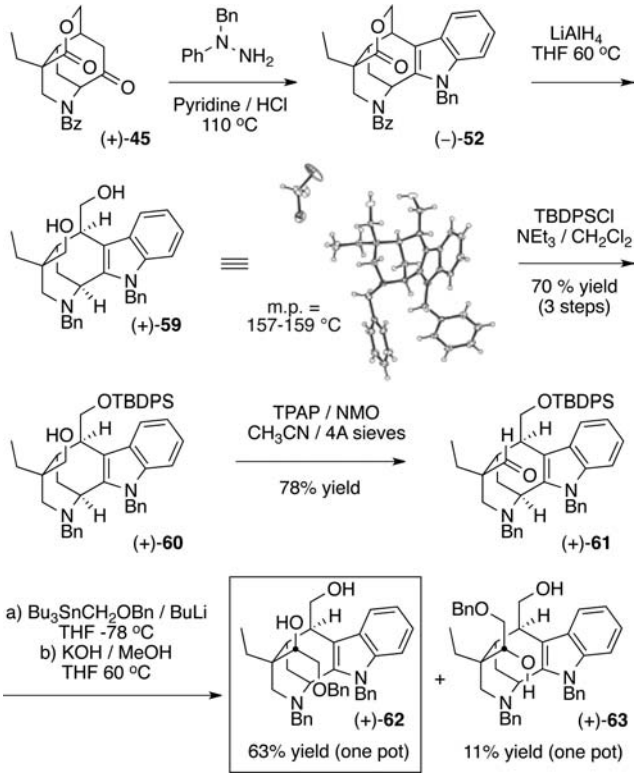
The desired aldehyde (+)-**56** was obtained along with cyclic ether (−)-**58**; the ratio was 2:1. The mixture however proved very difficult to separate by chromatography. We envision that cyclic ether (−)-**58** arises via competing indole oxidation as illustrated in Scheme 9.[48] Fortunately, pure aldehyde (+)-**56**[33] could be obtained via Parikh−Doering oxidation[49] in a moderate yield of 50%.

Multiple conditions were next employed to oxidize aldehyde (+)-**56**, but the desired carboxylate product **53** (Scheme 8) was not observed. The only products that could be observed resulted from indole oxidation in a fashion similar to that illustrated in Scheme 9 [cf. (−)-**58**].[48c]

We reasoned that the sterically encumbered environment of the aldehyde carbonyl in (+)-**56** led to our inability to obtain the carboxylic acid. Presumably, formation of the requisite aldehyde hydrate required for oxidation was unfavorable due to an increase in steric interactions. In support of this scenario, aldehyde (+)-**56** did not form a cyanohydrin or bisulfite adduct. Attempts at methylenation of aldehyde (+)-**56** also proved unsuccessful. Aldehyde (+)-**56** did however react readily with alkyllithium reagents. A decision was thus made to define the stereochemical outcome of this reaction. Obtaining the correct stereogenicity upon addition of a carbon nucleophile to the aldehyde would orchestrate the same oxidation state and configuration required for (+)-scholarisine A (**1**). To explore this stereochemical issue we selected aldehyde **61** (Scheme 10), where both nitrogens were similarly protected with benzyl groups.

dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

Scheme 10. Synthesis of Diol (+)-62



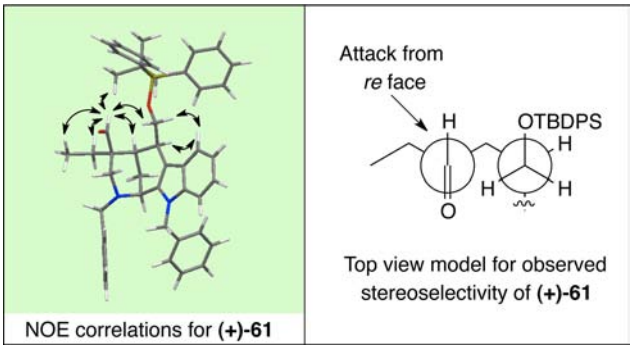


Figure 5. NOE-derived model of the reactivity of (+)-**61**.

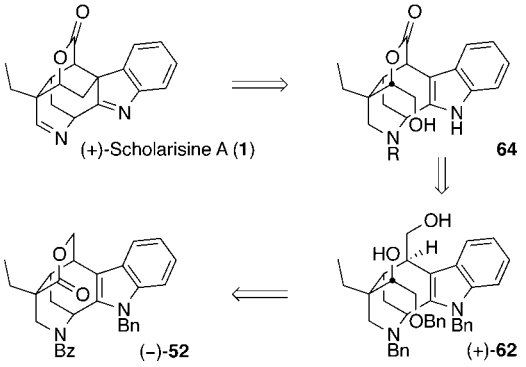


Figure 6. A new plan forward.

Reaction of Aldehyde (+)-61 with Benzyloxymethyllithium. To arrive at aldehyde (+)-**61**, indole (−)-**52** was reduced employing lithium aluminum hydride to furnish diol (+)-**59**;[33] the nitrogen benzoyl group was also reduced to the benzyl amine. Diol (+)-**59** was then selectively protected as the TBDPS ether to furnish (+)-**60**. This three-step sequence proved highly effective, proceeding in a 70% yield. Oxidation of alcohol (+)-**60** with TPAP/NMO completed construction of aldehyde (+)-**61**. In this case protection of the indole nitrogen in (+)-**60** blocks competing indole ring oxidation.

With aldehyde (+)-**61** in hand, we examined the stereochemical outcome upon addition of an alkyllithium species. Pleasingly, in situ generation of benzyloxymethyllithium in tetrahydrofuran at −78 °C employing the Still protocol,[50] followed by addition of aldehyde (+)-**61** to the solution, afforded diol (+)-**62** in 63% yield after hydrolytic workup to remove the TBDPS group. The undesired diastereomer, diol (+)-**63**, was also obtained in 11% yield. That the required stereogenicity of (+)-**62** for (+)-scholarisine A (**1**) was obtained, was initially based on NOESY NMR studies that indicated that the average conformation of the aldehyde carbonyl in (+)-**61** is as depicted in Figure 5. Nucleophilic attack occurring from the external face of the carbonyl would lead to the formation of diol (+)-**62**. The NMR-defined aldehyde conformation was also observed in the X-ray structure of the unprotected indole (+)-**56** (see Scheme 9). Confirmation of this stereochemical assignment was subsequently achieved both by NMR NOE correlations observed in lactone (−)-**65** and by X-ray analysis of (+)-**74** (*vide infra*).

A Plan Forward. The discovery that diol (+)-**62** could be obtained in good yield with the appropriate stereogenicity led rapidly to a path forward, as outlined in retrospective fashion in Figure 6. Indole (−)-**52** would first be converted to diol (+)-**62** as described above. Oxidative lactonization would then be performed, followed by protecting group exchange, to yield indole alcohol **64** (Figure 6). Activation of the hydroxyl group would permit cyclization to form the indolenine quaternary center. Deprotection followed by amine oxidation would then complete the total synthesis of (+)-scholarisine A (**1**).

Lactonization of Diol (+)-62. Although initial attempts to oxidize diol (+)-**62**, employing TPAP/NMO as the oxidant, proved successful to furnish the desired lactone (−)-**65**, the yield (36%) was only modest (Scheme 11).

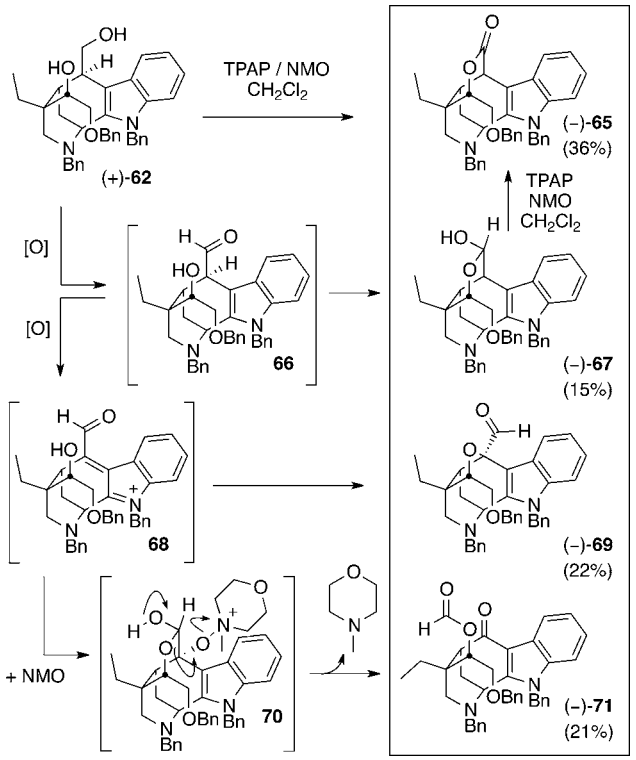
To understand this oxidation, the reaction was interrupted after 1 h, and the products were isolated via preparative TLC. Lactol (−)-**67** (15%) and lactone (−)-**65** (36%) were isolated as the expected products that would occur if the reaction progressed as desired. Also present, however, was aldehyde ether (−)-**69** (22%), possessing an internal ether linkage, along with formate (−)-**71** (21%). When pure lactol (−)-**67** was treated with TPAP/NMO, only lactone (−)-**65** was observed by LCMS; none of the other byproducts were observed. We reason that byproducts (−)-**69** and (−)-**71** were likely the result of oxidation of indole aldehyde **66** prior to lactol formation, as shown in Scheme 11.[51]

A two-step protocol was therefore developed (Scheme 12) that employed first a Corey–Palani[52] oxidation to arrive at lactol (−)-**67**, employing 2-iodoxybenzoic acid (IBX) in tetrahydrofuran and dimethyl sulfoxide (1:1); TPAP/NMO oxidation then led to desired lactone (−)-**65** in 57% yield for the two steps, along with lactol (−)-**72** (11%). Lactol (−)-**72**, the only observed side product, presumably results from oxidation of the more hindered secondary hydroxyl group in the first step.

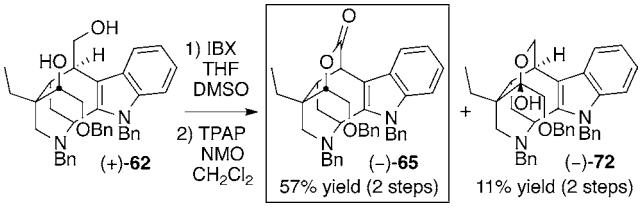
Completion of the Total Synthesis of (+)-Scholarisine A (1). With ample quantities of lactone (−)-**65** available, treatment with aluminum chloride in toluene,[53] employing

dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

Scheme 11. Initial Oxidative Lactonization



Scheme 12. Two-Step Oxidative Lactonization

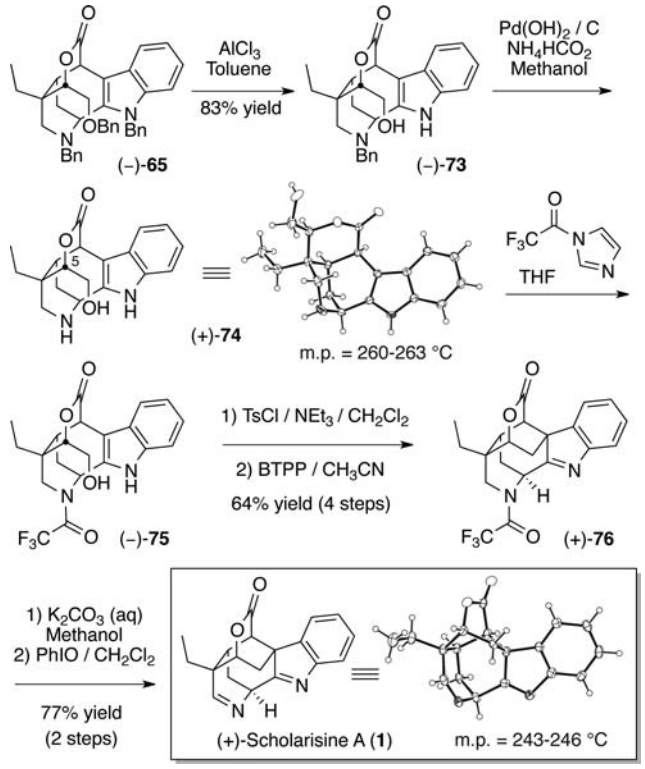


sonication, selectively led to release of the oxygen and indole nitrogen benzyl groups to furnish alcohol (−)-**73** in 83% yield (Scheme 13). Multiple attempts however at hydroxyl activation in (−)-**73** resulted only in scaffold degradation. Cyclization involving nucleophilic attack by the tertiary alkyl amine, as opposed to the indole ring, was suspected. Exchange of nitrogen protection was therefore explored as a means to remove the basicity of the aliphatic nitrogen.

The required protecting group exchange was achieved via transfer hydrogenolysis first to render amine (+)-**74**;[33] acylation employing trifluoroacetylimidazole[54] in tetrahydrofuran then furnished trifluoroacetamide (−)-**75**. Pleasingly, single-crystal X-ray analysis of (+)-**74** confirmed the C(5)-stereogenicity, previously assigned on the basis of NMR NOE correlations in lactone (−)-**65**.

Activation of the hydroxyl in (−)-**75** with toluenesulfonyl chloride, followed by treatment of the stable sulfonate ester with *tert*-butyliminotri(pyrrolidino)phosphorane (BTPP),[55] effected the strategically planned cyclization involving indole deprotonation to furnish indolenine (+)-**76** in a 64% yield over the four steps. On the other hand, direct treatment of amine (+)-**74** with a variety of sulfonyl chlorides resulted only in selective substitution at both the oxygen and secondary amine to furnish the corresponding sulfonate ester sulfonamide. Deprotonation of the indole nitrogen, which was inert in the

Scheme 13. Total Synthesis of (+)-Scholarisine A (1)



previous step, then furnished a sulfonamide indolenine substrate. The trifluoroacetyl moiety, however, proved preferable to sulfonamide protection of the nitrogen due to superior lability during subsequent removal.

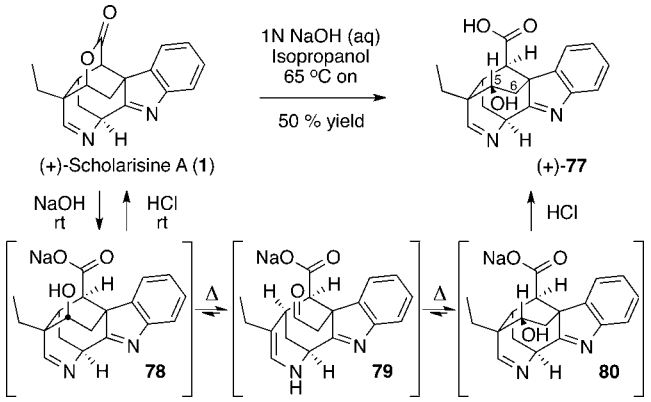
Removal of the trifluoroacetyl group in (+)-**76** was then readily achieved employing a mixture of saturated aqueous K_2CO_3 and methanol (1:2) to furnish the corresponding free amine. Oxidation with iodosobenzene (PhIO)[56] in methylene chloride completed the synthesis of (+)-scholarisine A (**1**);[33] the yield for the final two steps was 77%. Totally synthetic (+)-scholarisine A (**1**) was identical in all respects to the natural product [i.e., ^1H and ^{13}C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].[1] The structure of synthetic (+)-scholarisine A (**1**) was also defined via X-ray analysis. Taken together, these results confirmed the structure and absolute configuration of (+)-scholarisine A (**1**). Approximately 70 mg of totally synthetic (+)-scholarisine A (**1**) has been prepared to date.

"Retrobiosynthetic" Fragmentation of Scholarisine A (1)—A First Step To Access Other Members of the Akuammiline Alkaloid Family. Having achieved the total synthesis of (+)-scholarisine A (**1**), we turned our attention to devising a substrate that would hold the promise of providing access to other members of the akuammiline alkaloid family via a late-stage "retro-biosynthetic" strategy. We focused on utilizing synthetic (+)-scholarisine A (**1**) to access aldehyde **79** (Scheme 14), a carboxylate congener of aldehyde **2** (Figure 1).

Toward this end, synthetic (+)-scholarisine A (**1**) was treated overnight at 65 °C with aqueous sodium hydroxide (1 N) in isopropanol (Scheme 14). The solution was then acidified with aqueous hydrochloric acid (1 N), the solvent removed in vacuo, and the residue purified via supercritical fluid chromatography (SFC) to afford (+)-**77** in approximately 50% yield. The

dx.doi.org/10.1021/ja3111626 | J. Am. Chem. Soc. 2013, 135, 519−528

Scheme 14. "Retro-biosynthetic" Fragmentation



assigned structure was confirmed employing multiple 1D and 2D NMR experiments. Particularly diagnostic was the similarity of the ^{1}HNMR spectra of (+)-scholarisine A (**1**) and the scaffold hydrogens in (+)-**77**, except for the differences in the chemical shifts and coupling constants for the hydrogens on C-5 and C-6, the epimerized carbon and the vicinal hydrogens, respectively.

The observed reaction pathway is presumed to proceed by initial formation of alcohol **78** via hydrolytic opening of the scholarisine A lactone bridge. The protonated form of **78** was readily observed by LCMS upon treatment of scholarisine A (**1**) with alcoholic aqueous sodium hydroxide at room temperature. Acidification of the sample at room temperature resulted in immediate reversion to scholarisine A (**1**), again observed by LCMS. However upon heating, the hydroxy imine carboxylate (**78**) likely undergoes an aza retroaldol fragmentation to provide enamine aldehyde **79** as a transient reaction intermediate that can then undergo cyclization via enamine attack at the aldehyde carbonyl to re-form **78**, or alternatively to form hydroxy imine **80**, where the hydroxyl carbon has undergone epimerization. Under the basic reaction conditions, **80** appears to be thermodynamically more stable than **78**, as complete conversion to **80** was observed to occur by LCMS. Acidification at room temperature provided carboxylic acid (+)-**77**. Formation of carboxylic acid (+)-**77** demonstrates that in fact a "retro-biosynthetic" fragmentation of this system is possible. Exploration of this dynamic system, we believe, holds the promise of access to other members of the akuammiline alkaloid family.

Summary. The first total synthesis of (+)-scholarisine A (**1**) has been achieved, employing a longest linear reaction sequence of 25 steps from commercially available anhydride **35**. Key synthetic tactics include a novel cyclization, comprising nitrile reduction coupled with concomitant addition of the resultant amine to an epoxide; a modified Fischer synthetic protocol; an oxidative lactonization of a diol in the presence of an indole ring; and a late-stage cyclization to complete the caged ring scaffold of (+)-scholarisine A (**1**). A "retro-biosynthetic" fragmentation of totally synthetic (+)-scholarisine A (**1**) has also been achieved. Studies are currently underway to exploit this fragmentation to gain access to related members of the akuammiline family.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectra, and X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

smithab@sas.upenn.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors dedicate this article to Professor Carl Djerassi on the occasion of his upcoming 90th birthday, friend, scholar, and gentleman. Financial support was provided by the National Institutes of Health (National Cancer Institute) through CA-19033. We also thank Drs. George Furst and Rakesh Kohli for help respectively obtaining the high-resolution NMR and mass spectral data. Prof. William Dailey is also thanked for his guidance while we performed the computational studies.

■ REFERENCES

(1) 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.

(2) (a) Smith, G. F. *Chem. Ind.* **1961**, 1120. (b) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580−1589.

(3) For an overview of the akuammiline alkaloid family, see: (a) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891−1915. (b) Llopart, C. C.; Joule, J. A. *Arkivoc* **2004**, *x*, 20−38. For a review of the alkaloids found in *Alstonia* species, see: (c) Rahman, A. U.; Qureshi, M. M.; Ali, S. S. *J. Chem. Soc. Pak.* **1990**, *12*, 355−406.

(4) Olivier, L.; Levy, J.; Le Men, J.; Janot, M. M.; Budzikiewicz, H.; Djerassi, C. *Bull. Soc. Chim. Fr.* **1965**, 868−876.

(5) Henry, T. A. *J. Chem. Soc.* **1932**, 2759−2768.

(6) (a) Schnoes, H.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1641−1642. (b) Ahmad, Y.; Fatima, K.; Rahman, A.; Occolowitz, J.; Solheim, B.; Clardy, J.; Garnick, R.; Le Quesne, P. *J. Am. Chem. Soc.* **1977**, *99*, 1943−1946.

(7) (a) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717−1734. (b) Ohashi, M.; Joule, J. A.; Djerassi, C. *Tetrahedron Lett.* **1964**, *5*, 3899−3905.

(8) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T. S. *J. Nat. Prod.* **2007**, *70*, 1783−1789.

(9) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877−8879.

(10) (a) Britten, A. Z.; Smith, G. F. *J. Chem. Soc.* **1963**, 3850−3854. (b) Britten, A.; Smith, G.; Spiteller, G. *Chem. Ind.* **1963**, 1492−1493.

(11) (a) Chatterjee, A.; Mukherjee, B.; Ray, A. B.; Das, B. *Tetrahedron Lett.* **1965**, *6*, 3633−3637. (b) Ghosh, R.; Roychowdhury, P.; Chattopadhyay, D.; Iitaka, Y. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988**, *44*, 2151−2154.

(12) Lewin, G.; Poisson. *J. Bull. Soc. Chim. Fr.* **1980**, II-400−II-404.

(13) Morita, Y.; Hesse, M.; Schmid, H.; Banerji, A.; Banerji, J.; Chatterjee, A.; Oberhansli, W. E. *Helv. Chim. Acta* **1977**, *60*, 1419−1434.

(14) Lim, K. H.; Kam, T. S. *Tetrahedron Lett.* **2006**, *47*, 8653−8655.

(15) (a) Mokry, J.; Dubravkova, L.; Sefcovic, P. *Experientia* **1962**, *18*, 564−565. (b) Das, B. C.; Cosson, J. P.; Lukacs, G.; Potier, P. *Tetrahedron Lett.* **1974**, *15*, 4229−4302. (c) Mamatas-Kalamaras, S.; Sevenet, T.; Thal, C.; Potier, P. *Phytochemistry* **1975**, *14*, 1637−1639.

(16) (a) Goodson, J. A.; Henry, T. A. *J. Chem. Soc.* **1925**, *127*, 1640−1648. (b) Manohar, H.; Ramaseshan, S. *Tetrahedron Lett.* **1961**, *2*, 814−816.

(17) The echitamine core has been proposed to arise directly from geissoschizine (**5**) (see ref 2a). This core has also been shown to

derive from strictamine (**6**), via reduction with zinc in methanolic sulfuric acid (see ref 6a).
(18) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013−6020.
(19) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126−9129.
(20) Arai, H.; Hirasawa, Y.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Sato, S.; Aoyama, C.; Takeo, J.; Morita, H. *Bioorg. Med. Chem.* **2010**, *18*, 2152−2158.
(21) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145−1149.
(22) (a) Kamarajan, P.; Sekar, N.; Mathuram, V.; Govindasamy, S. *Biochem. Int.* **1991**, *25*, 491−498. (b) Jagetia, G. C.; Baliga, M. S.; Venkatesh, P.; Ulloor, J. N.; Mantena, S. K.; Genebriera, J.; Mathuram, V. *J. Pharm. Pharmacol.* **2005**, *57*, 1213−1219.
(23) Adams, G. L.; Carroll, P. J.; Smith, A. B., III *J. Am. Chem. Soc.* **2012**, *134*, 4037−4040.
(24) Garg recently reported the use of a similar lactone (see ref 9). We initially considered lactone (**27**) while contemplating a Fischer annulation approach inspired by the work of Levy and Dolby. See: (a) Laronze, J. Y.; Laronze, J.; Patigny, D.; Levy, J. *Terahedron Lett* **1986**, *27*, 489−492. (b) Dolby, L. J.; Esfandiari, Z. *J. Org. Chem.* **1972**, *37*, 43−46. (c) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882−2887.
(25) For an overview on acid-promoted decomposition of unsaturated α-diazo ketones, see: Smith, A. B., III; Dieter, R. K. *Tetrahedron* **1981**, *37*, 2407−2439.
(26) Attempts to form the indolenine quaternary center of the akuammiline family have proven difficult. See: (a) Bennasar, M. L.; Zulaica, E.; Lopez, M.; Bosch, J. *Tetrahedron Lett.* **1988**, *29*, 2361−2364. (b) Bosch, J.; Bennasar, M. L. *Synlett* **1995**, 587−596. (c) Bennasar, M. L.; Zulaica, E.; Ramirez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239−1251 Also see refs 24b and 24c..
(27) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506−2513. Also see: Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837−8852. Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron: Asymmetry* **1990**, *1*, 793−800.
(28) Ochiai, H.; Ohtani, T.; Ishida, A.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Nakai, H.; Toda, M. *Eur. J. Med. Chem.* **2004**, *39*, 555−571.
(29) For use of 4 Å sieves during lipase transesterification with methyl ester solvent, see: Ottolina, G.; Carrea, G.; Riva, S. *J. Org. Chem.* **1990**, *55*, 2366−2369. For an overview of enzymatic asymmetrization of *meso*-compounds, see: Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. Chiral Synthons via Enzyme-Mediated Asymmetrization of *Meso*-Compounds. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press Inc.: Greenwich, CT, 1993; Vol. *1*, pp 143−219.
(30) For use of a diamine to quench the reaction of tosyl chloride, see: Morita, J.; Nakatsuji, H.; Misaki, T.; Tanabe, Y. *Green Chem.* **2005**, *7*, 711−715.
(31) Extreme caution should be employed when using potassium cyanide, especially when in a DMSO solution. See: Potassium Cyanide. *e-EROS Encyclopedia of Reagents for Organic Synthesis* [Online]; Wiley & Sons, Posted April 15, 2001; http://onlinelibrary.wiley.com/o/eros/articles/rp208/frame.html (accessed November 5, 2012).
(32) (a) Hughes, T. V.; Hammond, S. D.; Cava, M. P. *J. Org. Chem.* **1998**, *63*, 401−402. (b) Katritzky, A. R.; Akue-Gedu, R.; Vakulenko, A. V. *Arkivoc* **2007**, *iii*, 5−12. (c) Katritzky, A. R.; Brzezinski, J. Z.; Lam, J. N. *Rev. Roum. Chim.* **1991**, *36*, 573−580.
(33) The structures of (−)-**33**, (−)-**34**, (+)-**41**, (−)-**42**, (−)-**43**, (+)-**44**, (+)-**45**, (−)-**50**, (−)-**51**, (+)-**56**, (+)-**59**, (+)-**74**, and totally synthetic (+)-scholarisine A (**1**) were confirmed by single-crystal X-ray analysis. Crystallization of (+)-**59** with chloroform led to co-crystallization of chloroform in the unit cell, which in turn permitted confirmation of the absolute configuration of (+)-**59** by X-ray analysis, exploiting the heavy-atom anomalous dispersion of chlorine. See the Supporting Information for CIF files of (+)-**44**, (−)-**50**, (−)-**51**, and (+)-**56**. See ref 23 for CIF files of (−)-**33**, (−)-**34**, (+)-**41**, (−)-**42**, (−)-**43**, (+)-**45**, (+)-**59**, (+)-**74**, and totally synthetic (+)-scholarisine A (**1**).
(34) (a) Kasai, T.; Watanabe, H.; Mori, K. *Bioorg. Med. Chem.* **1993**, *1*, 67−70. (b) OBrien, P.; Tournayre, J. *Tetrahedron* **1997**, *53*, 17527−17542.
(35) Rhodium on alumina has been shown to tolerate the oxirane moiety. See: (a) Tarbell, D. S.; West, R. L.; McNally, J. G.; McCorkindale, N. J.; Kunstmann, M.; Carman, R. M.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Varino, H. L.; Rosowsky, A.; Chapman, D. D. *J. Am. Chem. Soc.* **1961**, *83*, 3096−3113. For reduction of nitriles to primary amines using rhodium on alumina, see: (b) Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386−2389. Bridged azapolycyclic alcohols have been constructed via intramolecular expoxide opening by an amide. See: (c) Schultz, R.; Staas, W.; Spurlock, L. *J. Org. Chem.* **1973**, *38*, 3091−3093. Also see ref 24c.
(36) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(37) For use of acetic acid as a solvent for nitrile hydrogenation employing rhodium on alumina, see: Galan, A.; De Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 452−454.
(38) Sajiki, H.; Hattori, K.; Hirota, K. *Chem.—Eur. J.* **2000**, *6*, 2200−2204.
(39) Benzoyl phenylhydrazine has been used in an attempt to avoid pyrazole or pyrazolone formation during Fischer indole syntheses with acyclic 1,3-dicarbonyl compounds. See: Mills, K.; Alkhawaja, K.; Alsaleh, F.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 636−641.
(40) Welch, W. M. *Synthesis* **1977**, 645−646.
(41) *N*-Aroylindoles have been isolated upon Fischer syntheses with aroyl phenylhydrazines. See: Yamamoto, H. *J. Org. Chem.* **1967**, *32*, 3693−3695.
(42) For similar acyl migration, see: Kardos-Balogh, Z.; Soti, F.; Incze, M.; Kajtar-Peredy, M.; Radics, L.; Szantay, C. *Heterocycles* **1989**, *28*, 303−312.
(43) Possible benzoyl migration involving formation and decomposition of a 1,3-benzodiazapine has not been ruled out. See: Plieninger, H.; Nogradi, I. *Chem. Ber* **1955**, *88*, 1965−1967. Chen, F. M. F.; Forrest, T. P. *Can. J. Chem.* **1973**, *51*, 881−884.
(44) It is possible that the corresponding benzoyl indole forms and then undergoes hydrolysis under the reaction conditions. Unprotected indole products were observed by Joule and co-workers during their Fischer indole studies with benzoyl phenylhydrazine (see ref 39).
(45) Perni, R. B.; Gribble, G. W. *Org. Prep. Proced. Int.* **1982**, *14*, 343−346.
(46) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975−2977.
(47) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.
(48) For reports of similar oxidations, see: (a) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213−1216. (b) Pinchon, T. M.; Nuzillard, J. M.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Sevenet, T. *Phytochemistry* **1990**, *29*, 3341−3344. (c) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett.* **2001**, *3*, 345−348. (d) Yu, J.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4681−4684.
(49) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(50) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487.
(51) *N*-Methylmorpholine *N*-oxide is known to oxidize activated halides to the carbonyl oxidation state. See: Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D. *Synth. Commun.* **1992**, *22*, 1967−1971.
(52) (a) Corey, E.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945−7948. (b) Corey, E.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485−3488.

(53) (a) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152−1156. (b) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738−740.
(54) Staab, H.; Walther, G. *Chem. Ber.* **1962**, *95*, 2070−2072.
(55) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.
(56) (a) Muller, P.; Gilabert, D. *Tetrahedron* **1988**, *44*, 7171−7175. (b) Larsen, J.; Jorgensen, K. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1213−1217.