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Natural Products

Cascade Reactions: A Driving Force in Akuammiline Alkaloid Total Synthesis

*Joel M. Smith, Jesus Moreno, Ben W. Boal, and Neil K. Garg**

alkaloids · cascade reactions · heterocycles · natural products · total synthesis

The akuammiline alkaloids are a family of intricate natural products which have received considerable attention from scientists worldwide. Despite the fact that many members of this alkaloid class were discovered over 50 years ago, synthetic chemistry has been unable to address their architectures until recently. This minireview provides a brief overview of the rich history of the akuammiline alkaloids, including their isolation, structural features, biological activity, and proposed biosyntheses. Furthermore, several recently completed total syntheses are discussed in detail. These examples not only serve to highlight modern achievements in alkaloid total synthesis, but also demonstrate how the molecular scaffolds of the akuammilines have provided inspiration for the discovery and implementation of innovative cascade reactions for the rapid assembly of complex structures.

1. Introduction

Natural products belonging to the akuammiline family of alkaloids have provided a fruitful area of scientific discovery for over one century.[1] Initial interest in the akuammilines stemmed from their role in traditional medicine, where inhabitants of southern and southeastern Asia utilized the leaves of native plants such as *Alstonia scholaris* (Figure 1) to treat various ailments in humans and livestock.[2] As a result, scientists have investigated the pharmacological effects of akuammiline alkaloids and discovered their wide range of biological properties, which span from anticancer to analgesic effects. For example, (−)-echitamine (**1**), which was first isolated in 1875,[3] displays both in vitro and in vivo cytotoxicity,[4] whereas (+)-strictamine (**2**)[5] inhibits the transcription factor NF-κB (Figure 2).[6] Additionally, derivatives of (+)-picraline (**3**)[7] inhibit the renal cortex protein SGLT2,[8] while (−)-aspidophylline A [(−)-**4**] reverses drug resistance in cancerous cell lines.[9]

Figure 1. Francisco Manuel Blanco's depiction of the leaves of *Alstonia Scholaris.*10

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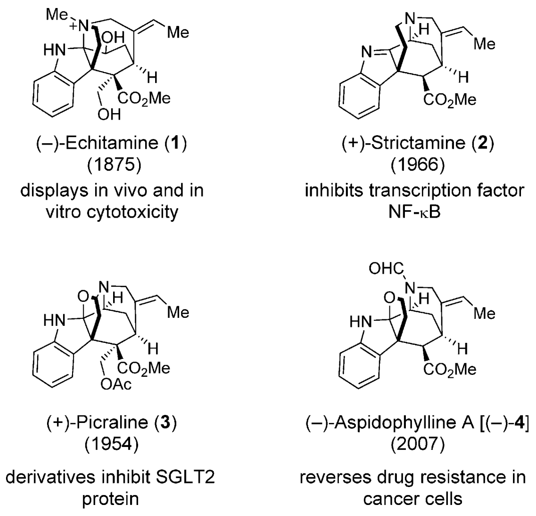
[*] J. M. Smith,[+] J. Moreno,[+] B. W. Boal, Prof. N. K. Garg
Department of Chemistry and Biochemistry, University of California
Los Angeles, CA 90095 (USA)
E-mail: neilgarg@chem.ucla.edu
Homepage: http://www.chem.ucla.edu/dept/Faculty/garg/Garg_Group/Home.html

[+] J.M.S. and J.M. contributed equally.



(−)-Echitamine (**1**)
(1875)
displays in vivo and in vitro cytotoxicity

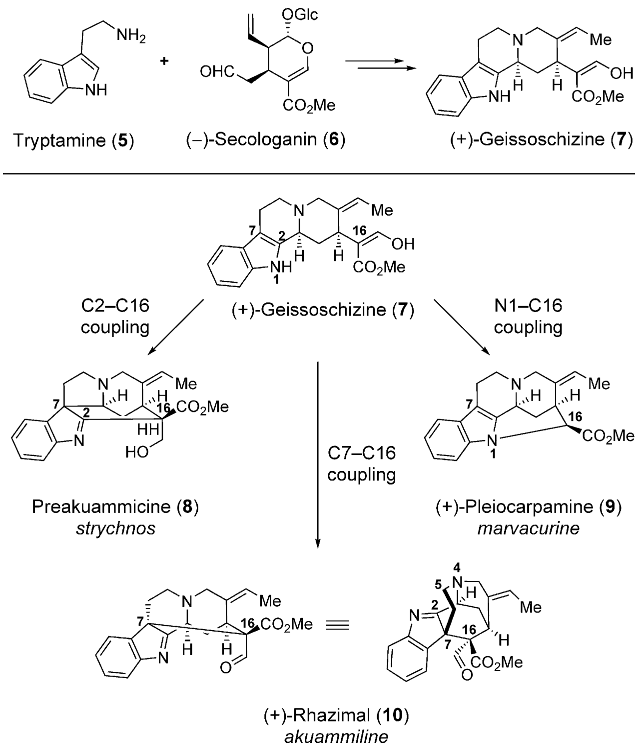
(+)-Strictamine (**2**)
(1966)
inhibits transcription factor NF-κB

(+)-Picraline (**3**)
(1954)
derivatives inhibit SGLT2 protein

(−)-Aspidophylline A [(−)-**4**]
(2007)
reverses drug resistance in cancer cells

Figure 2. Representative akuammilines **1**–**4**.

As is apparent from the representative family members shown in Figure 2, there is a great deal of complexity and structural diversity amongst the greater than 30 akuammiline alkaloids which have been isolated to date.[1] Although detailed biosynthetic studies have not been performed, the proposed biogenesis of various akuammilines sheds light on how nature likely assembles these intricate scaffolds. As shown in Figure 3, the union of tryptamine (**5**) and the monoterpenoid (−)-secologanin (**6**) first results in the formation of the natural product (+)-geissoschizine (**7**). In turn, **7** serves as the progenitor to many different alkaloid frameworks including the strychnos, marvacurine, and akuammiline varieties.[11] For example, the strychnos alkaloid preakuammicine (**8**) would arise from an intramolecular cyclization



Tryptamine (**5**)

(−)-Secologanin (**6**)

(+)-Geissoschizine (**7**)

Preakuammicine (**8**)
strychnos

(+)-Pleiocarpamine (**9**)
marvacurine

(+)-Rhazimal (**10**)
akuammiline

Figure 3. Biosynthesis of geissoschizine (**7**) and elaboration to other alkaloid families. Glc = glucosyl.

Joel M. Smith was born in Raleigh, NC, USA. He received his B.S. in Chemistry and Music from Furman University, where he performed undergraduate studies with Prof. Brian C. Goess on the synthesis of hibiscone C. He also performed research under the guidance of Prof. Fernando Coelho at UNICAMP in Campinas, Brazil studying heterocycle synthesis. Joel is currently a graduate student at the University of California, Los Angeles in Prof. Neil Garg's laboratory, pursuing the total synthesis of various akuammiline alkaloids.

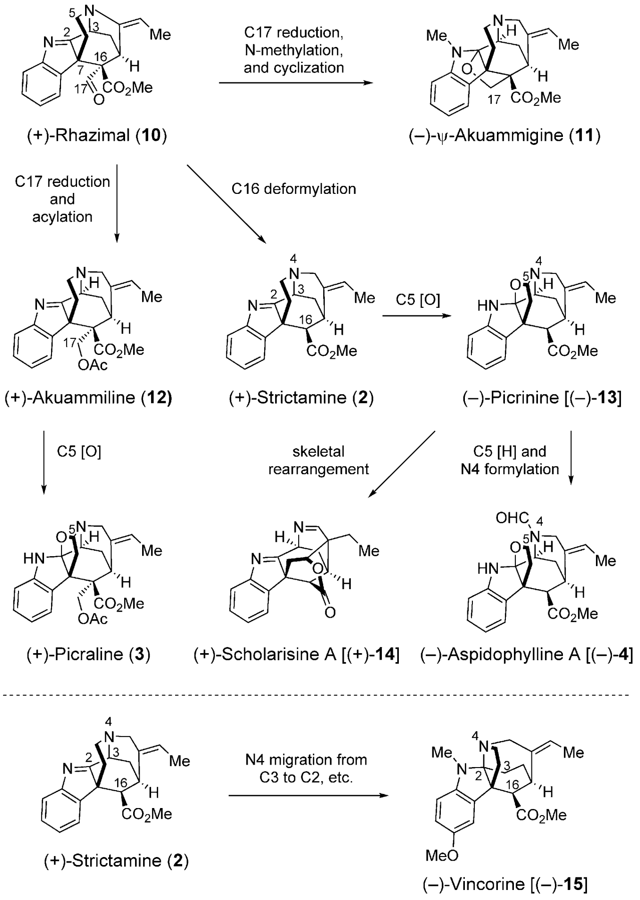
Ben Boal was born in Portland, Oregon, USA. He received his Bachelors degree in Chemistry from the University of Oregon. He recently completed his PhD at the University of California, Los Angeles in Prof. Neil Garg's laboratory, where he developed synthetic methods and pursued alkaloid total synthesis. Ben is currently a postdoctoral scholar at the California Institute of Technology working with Prof. Mark Davis laboratory.

Jesus Moreno was born in Los Angeles, CA, USA. He received a B.S. in Molecular Synthesis from the University of California, San Diego in 2012, where he pursued research with Prof. Thomas Hermann. In 2011, he performed research at the Scripps Research Institute in La Jolla with Prof. Ryan Shenvi. In the 2012, he worked as an intern at Vertex Pharmaceuticals, prior to beginning his graduate studies at the University of California, Los Angeles. Currently, Jesus is a graduate student working with Prof. Neil Garg on the total synthesis of akuammiline alkaloid natural products.

Neil Garg received a B.S. degree in Chemistry from New York University where he pursued research with Prof. Marc Walters. As an undergraduate he pursued research with Prof. Wais Hosseini at the Université Louis Pasteur as an NSF REU Fellow. He obtained his Ph.D. in 2005 from the California Institute of Technology under the direction of Prof. Brian Stoltz. He then spent two years as an NIH Postdoctoral Scholar with Prof. Larry Overman at the University of California, Irvine. Neil started his independent career at UCLA in 2007, where his group develops synthetic methodologies to enable the total synthesis of complex bioactive molecules.

between C2 and C16, whereas the marvacurine alkaloid (+)-pleiocarpamine (**9**) stems from a cyclization between N1 and C16. The akuammiline framework, in contrast, derives from an intramolecular oxidative coupling between C7 and C16 of **7**. This coupling constructs the caged indolenine framework of (+)-rhazimal (**10**).[12]

The polycycle **10** is thought to serve as a molecular platform to access to all the other akuammiline family members through either redox transformations, acylations, alkylations, or skeletal migrations (Scheme 1). For example, (−)-pseudoakuammigine (**11**)[13] is thought to arise from aldehyde reduction, N-methylation, and tetrahydrofuran-ring formation from **10**. Alternatively, (+)-akuammiline (**12**),[13] the namesake of the family, forms from reduction and acylation of the C17 carbonyl group. (+)-Strictamine (**2**), in contrast, forms from C16 deformylation.[5] Oxidation of **12** at C5 would provide (+)-picraline (**3**),[7,13b] while the analogous transformation from **2** would yield (−)-picrinine [(−)-**13**].[14] Both (+)-scholarisine A [(+)-**14**] and (−)-aspidophylline A [(−)-**4**] are believed to arise from (−)-**13**. (−)-Aspidophylline A [(−)-**4**][9] could be generated by reduction at C5 and N4 formylation, and (+)-**14** is proposed to come from a redox isomerization and skeletal reconfiguration.[15] Finally, the pyrrolidinoindoline scaffold of (−)-vincorine [(−)-**15**][16] is thought to stem from **2** through an N4 migration from C3 to C2.[5]



Scheme 1. Proposed akuammiline biosynthetic pathway and representative akuammiline alkaloids.

Research concerning the akuammilines has historically focused on isolation and pharmacological studies[1a] with relatively less emphasis on synthetic chemistry. However, synthetic studies by Dolby and co-workers in the 1970s brought some attention to the akuammilines and provided some noteworthy lessons on synthetic strategies for accessing these challenging natural products.[17] Since then, many research groups have reported promising strategies toward the akuammilines, including the groups of Sakai,[18] Toupet,[19] Bosch,[20] Takemoto,[21] Higuchi,[22] Shi,[23] and Zhu.[24]

Although many akuammiline alkaloids have yet to succumb to laboratory synthesis, synthetic efforts spanning the past five years have led to the completed total syntheses of four daunting akuammilines: (−)-vincorine [(−)-**15**],[25,26,27] (−)-aspidophylline A [(−)-**4**],[28,29,30] (−)-picrinine [(−)-**13**],[31] and (+)-scholarisine A [(+)-**14**].[32,33] Although the synthetic routes towards these alkaloids contain a variety of creative elements, one unifying theme is their utilization of innovative cascade reactions to elegantly and efficiently forge their intricate architectures. This minireview provides a perspective on the key transformations which construct multiple chemical bonds in one process, and how these cascades have fuelled achievements in akuammiline total synthesis. Additionally, other important bond formations are highlighted, specifically those that played instrumental roles in enabling the completed syntheses.

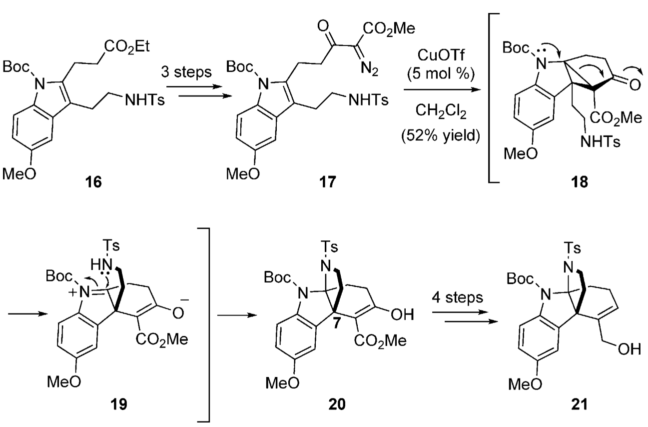
2. Total Syntheses of Vincorine

(−)-Vincorine [(−)-**15**; Scheme 1] was first isolated in 1962 from *Vinca minor* by Šefčovič and co-workers.[16] As mentioned above, this alkaloid contains a pyrrolidinoindoline core which arises from a nitrogen migration within the parent akuammiline architecture. This migration results in a pentacyclic scaffold which includes one seven-membered ring and four contiguous stereocenters, one of which is quaternary. This section highlights the three completed total syntheses of **15** which have been reported to date by the groups of Qin,[25] Ma,[26] and MacMillan.[27]

2.1. Qin's Cyclopropanation Approach

The first breakthrough in the total synthesis of akuammilines came from Qin and co-workers, who reported the total synthesis of (±)-vincorine [(±)-**15**] in 2009.[25] The group of Qin targeted two key challenges: assembly of the cyclohexyl-fused pyrrolidinoindoline framework and construction of the seven-membered ring. To address the former difficulty, Qin and co-workers employed an elegant cyclopropanation/fragmentation cascade sequence, which had earlier proven useful in their synthesis of the *strychnos* alkaloid minfiensine.[34]

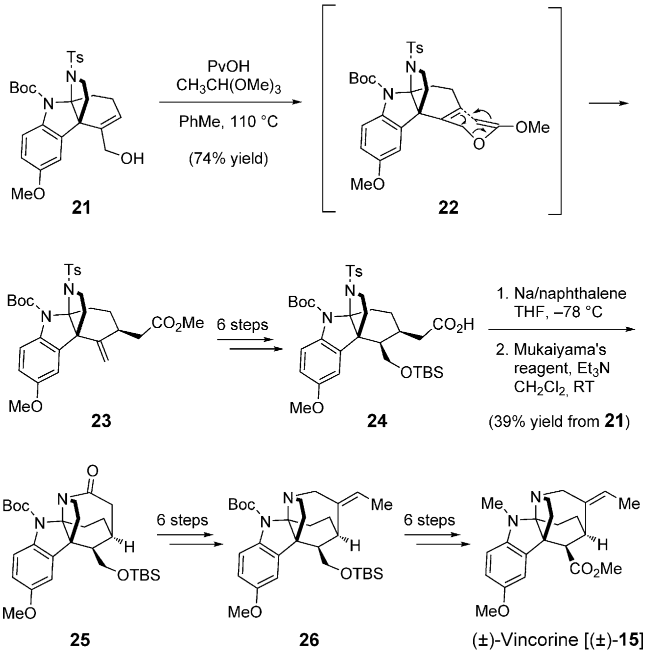
As depicted in Scheme 2, a three-step sequence was used to convert the ester **16**, a readily available intermediate,[35] into the α-diazoester **17**, the substrate for the key cascade reaction. Using 5 mol% of copper(I) triflate, **17** underwent



Scheme 2. Qin's cyclopropanation cascade towards (±)-vincorine [(±)-**15**]. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl, Tf = trifluoromethanesulfonyl.

the desired cyclopropanation/fragmentation sequence to furnish the tetracycle **20** in 52 % yield. The transformation is thought to proceed by initial cyclopropanation of the indole moiety. Subsequent fragmentation of the cyclopropane (**18**) to the corresponding indoleninium species presumably occurs rapidly by virtue of the indoline nitrogen atom. Subsequent trapping by the tosyl-protected amine (**19**) then delivers the tetracyclic product. Notably, this cascade reaction concisely builds one carbon–nitrogen bond and one carbon–carbon bond. Moreover, the key C7 quaternary stereocenter is introduced, in addition to the pyrrolidinoindoline scaffold. From **20**, four steps were used to access the allylic alcohol **21**.

An abbreviated sequence illustrating the endgame to the synthesis of (±)-**15** is shown in Scheme 3. Upon treatment with pivalic acid and trimethyl orthoacetate, **21** was converted into the ester **23** in a 74 % yield of the desired diastereomer by a Johnson–Claisen rearrangement (**22**).[36] The ester **23** was elaborated in six steps to the acid **24**, an important precursor towards constructing the natural product's seven-membered ring. The tosyl protecting group on the fused pyrrolidine was removed with Na/naphthalene, and thus set the stage for amide-bond formation using Mukaiyama's reagent. Impressively, the amide **25** was accessed in 39 % yield from **21** (nine steps). Further manipulation provided silyl ether **26** over six steps, which included introduction of the exocylic olefin. A final six-step sequence was used to convert **26** into (±)-**15** by deprotection and redox manipulations of the alcohol, and a deprotection and N-methylation of the indole nitrogen atom.



Scheme 3. Qin's seven-membered ring construction and total synthesis of (±)-**15**. Pv = *tert*-butylcarbonyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

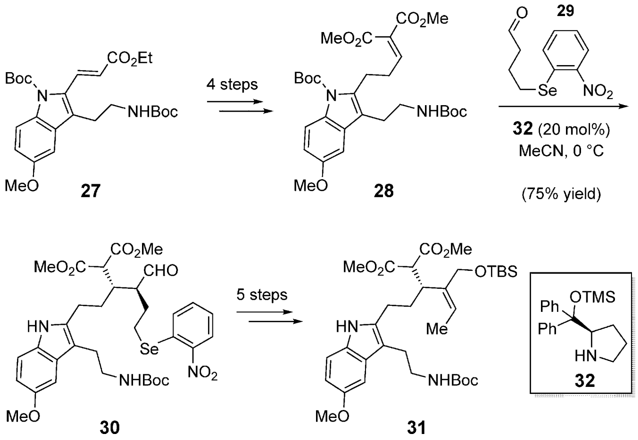
Qin's synthesis of (±)-**15** proceeded in 31 steps from the known intermediate **16**, in roughly 1 % overall yield. Of note, this was the first reported total synthesis of any akuammiline alkaloid, and marks a major achievement in the field. Qin's approach relied on the intermediate tetracycle **20**, which was synthesized using a copper-catalyzed cyclopropanation/fragmentation cascade. This sequence built an important quaternary center, part of the compound's distinct fused pyrrolidinoindoline scaffold. Qin's efforts toward (±)-**15** also served to reveal the many challenges associated with assembling the natural product's core, such as constructing the seven-membered ring of the natural product. These seminal studies provided significant groundwork for future syntheses of **15** and other akuammiline alkaloids.

2.2. Ma's Oxidative Coupling Approach

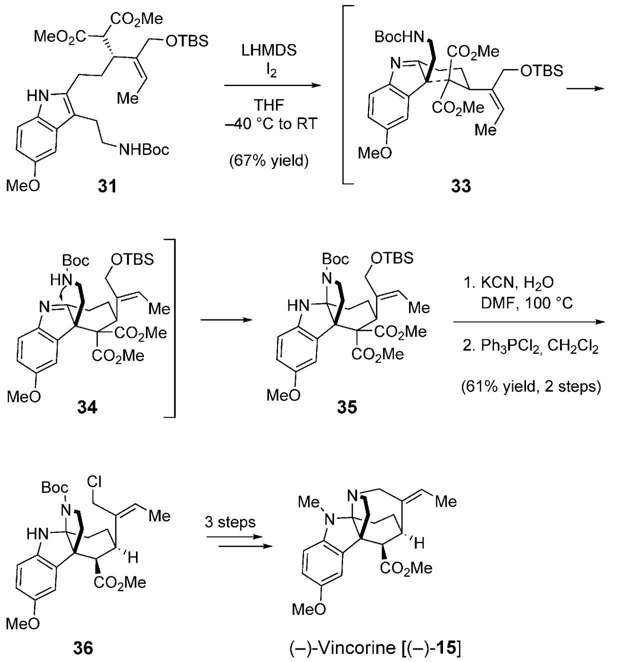
In 2012, Ma and co-workers reported the first enantioselective synthesis of (−)-vincorine [(−)-**15**].[26] Similar to the approach of Qin, Ma elected to forge the pyrrolidinoindoline scaffold early in the synthesis. Ma's approach utilizes a bioinspired intramolecular oxidative coupling to introduce all of the requisite carbon atoms of the natural product, prior to building the seven-membered ring. It should be noted that the group of Ma had previously developed a similar oxidative coupling strategy for their enantioselective synthesis of communesin F.[37]

Ma's synthesis of the key oxidative cyclization precursor, the diester **31**, is summarized in Scheme 4. The α,β-unsaturated ester **27**, an intermediate readily accessed from tryptophan, was elaborated to the malonate **28** in four steps. Toward installing the ethylidine unit, they implemented an organocatalyzed enantioselective Michael addition of **29** using a proline-derived catalyst, a reaction based of precedent.[38] Although both **29** and **28** were both more complex than substrates reported in the literature, the desired coupling proceeded smoothly to deliver the selenide **30** in 75 % yield as a 5:1 diastereomeric mixture. The selenide **30** was then converted into the oxidative intramolecular coupling substrate **31** over a five-step sequence.

Having established an efficient synthesis of **31**, the focus turned to forming the fused pyrrolidinoindoline core of the natural product. As shown in Scheme 5, **31** underwent



Scheme 4. Ma's organocatalytic asymmetric synthesis of the oxidative coupling substrate **31**. TMS = trimethylsilyl.



Scheme 5. Ma's oxidative coupling cascade and seven-membered ring formation. DMF = *N*,*N*-dimethylformamide, LHMDS = lithium hexamethyldisilazide.

oxidative cyclization in the presence of two equivalents of lithium hexamethyldisilazide (LiHMDS) and iodine to give the indoline **35**. This key cascade sequence presumably proceeds through formation of a tricyclic indolenine intermediate, followed by subsequent trapping by the Boc-protected amine (**34**). The stereochemical outcome of this transformation can be attributed to the chairlike transition-structure **33** shown in Scheme 5. In this orientation, the axial ester avoids repulsive interactions with the indole moiety, thus resulting in the desired stereochemical outcome. It should be noted that initial attempts at −78 °C gave minor amounts of the desired **35**, but when the reaction was started at −40 °C and then warmed to room temperature, the yield improved to an impressive 67 %. Starting the reaction at a higher temperature did not improve the yield. It should also be noted that the use of other oxidants such as iron(III) salts, copper(II) salts, or *N*-iodosuccinimide in place of iodine,[39] had detrimental effects on the reaction. Nonetheless, this bioinspired cascade transformation resulted in the construction of the key C7 quaternary center and three of the natural product's four stereogenic centers. In addition, the oxidative coupling was highly diastereoselective, thus translating the stereoselectivity of the organocatalyzed Michael addition into the enantioenriched pyrrolidinoindoline product.

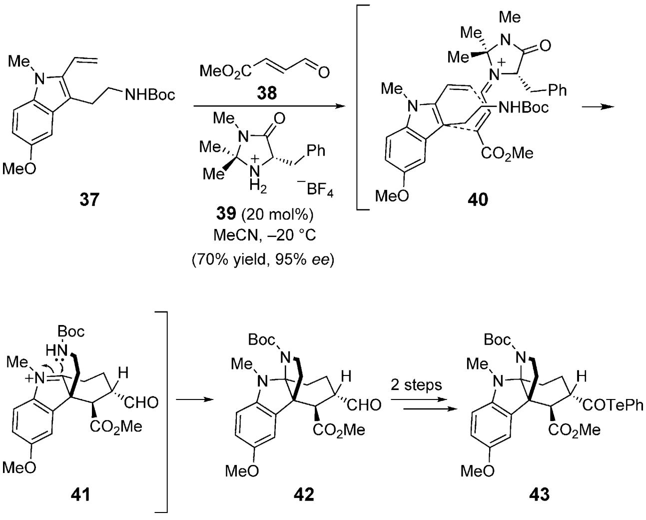
To complete the total synthesis, Krapcho decarboxylation[40] of **35**, followed by treatment with triphenylphosphine dichloride[41] delivered the alkyl chloride **36** in 61 % yield over two steps. This intermediate was then quickly elaborated to (−)-**15** after a final three-step sequence involving deprotection, cyclization to forge the seven-membered ring, and methylation.

Ma's total synthesis of (−)-**15** stands as the first asymmetric route to this complex natural product. A key feature of the synthesis is the use of an oxidative cyclization to construct the quaternary center of (−)-**15** and two of its complex rings. Of note, this cascade also builds the compound's carbon framework, which greatly facilitated late-stage transformations. Ma's approach to (−)-**15** proceeds in 18 steps from commercially available starting materials in a striking overall yield of 5 %.

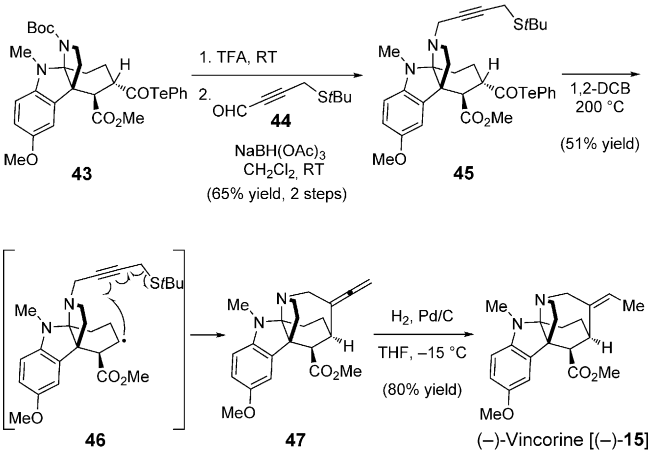
2.3. MacMillan's Organocatalytic Approach

Most recently, the group of MacMillan successfully completed a concise enantioselective total synthesis of (−)-vincorine [(−)-**15**].[27] Similar to the overall bond construction strategy pursued by the groups of Qin and Ma, MacMillan opted to first assemble the pyrrolidinoindoline framework of the natural product before building the seven-membered ring. However, in the interest of creating a general strategy toward (−)-**15** and related natural products, MacMillan and coworkers designed an enantioselective organocatalytic Diels–Alder/iminium ion cyclization cascade sequence[42] to construct the fused pyrrolidinoindoline tetracyclic core, which, in turn enabled the efficient introduction of the seven-membered ring.

The details of the key cascade reaction are presented in Scheme 6. The vinyl tryptamine **37**, a readily accessible intermediate from 5-methoxy-*N*′-Boc tryptamine, was combined with the enal **38** and treated with catalyst **39** at −20 °C to afford the tetracycle **42** in 70 % yield and 95 % *ee*. It is proposed that the activated iminium species approaches the vinyl tryptamine as depicted in transition-structure **40** in an *endo* fashion with the facial selectivity controlled by the catalyst's steric environment. Following tandem catalyst dissociation and acid-promoted protonation, an indoleninium is formed. Trapping of this ion by the tethered carbamate (**41**) affords the tetracyclic product **42**. It should be emphasized that this remarkable cascade reaction establishes the relative and absolute configuration of four stereocenters, three of which reside in the natural products' architecture. From there,



Scheme 6. MacMillan's organocatalytic asymmetric Diels–Alder/iminium ion trapping cascade.



Scheme 7. MacMillan's 7-*exo*-dig radical cyclization and completion of (−)-vincorine [(−)-**15**]. DCB = dichlorobenzene, TFA = trifluoroacetic acid.

42 was transformed into the telluride **43** over two steps in preparation of constructing the seven-membered ring.

The elaboration of **43** to the natural product is depicted in Scheme 7. Removal of the N-Boc group was effected with TFA and the resultant pyrrolidine nitrogen atom was alkylated under reductive amination conditions with the aldehyde **44** to furnish **45** in 65% yield over two steps. Upon heating this substrate to 200 °C for 10 h, the desired 7-*exo*-dig cyclization (**46**) took place, thus furnishing the exocyclic allene product **47**.[43] The authors propose that homolysis of the C–Te bond leads to extrusion of carbon monoxide and formation of a putative secondary radical. This radical is then poised to undergo the desired cyclization with the pendant π acceptor to form the final ring system of the natural product. The authors noted that the corresponding transformation was less effective using other radical precursors, such as thiohydroxamic acids and acyl selenides, under a variety of radical initiation conditions. Nonetheless, the successful conversion of **43** into **45** represents the first example of an acyl telluride being used as an alkyl radical precursor, and provides a bold and creative solution to the formation of the challenging seven-membered ring. With **47** in hand, selective hydrogenation of the allene terminus delivered (−)-**15** in 80% yield.

MacMillan's synthesis of (−)-**15**, which is just nine steps beginning from commercially available starting materials, is the most concise route to (−)-**15** reported to date. Furthermore, it proceeds in the highest overall yield, an impressive 9%. The brevity of the synthesis can be attributed to the elegant cascade reaction employed: the enantioselective organocatalytic Diels–Alder/iminium ion cyclization, which generates almost all of the natural product's framework with control of relative and absolute stereochemistry. This reaction is a testament to the power of asymmetric organocatalysis for the generation of high molecular complexity in a single synthetic step from achiral starting materials.

3. Total Syntheses of Aspidophylline A and Picrinine

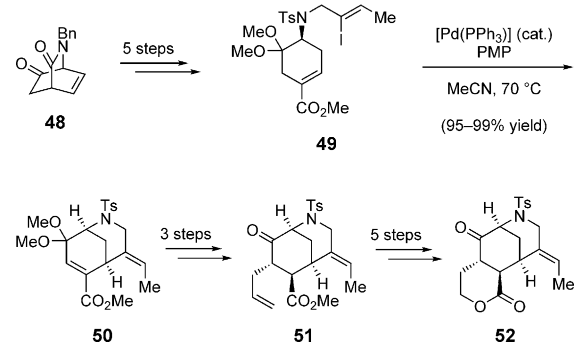
The akuammiline alkaloids (−)-aspidophylline A [(−)-**4**] and (−)-picrinine [(−)-**13**] were isolated in 2007[9] and 1965,[14] respectively (Scheme 1). (−)-Aspidophylline A [(−)-**4**] was found to reverse drug resistance in cancer cells, while (−)-picrinine [(−)-**13**] has been shown to have mild analgesic activity.[44] Each natural product contains a furoindoline motif embedded within a polycyclic framework. Additionally, both compounds contain multiple stereogenic centers, including quaternary centers at C7, thus rendering them daunting synthetic targets. This section includes a summary of total syntheses of (−)-**4** reported by the groups of Garg,[28] Zhu,[29] and Ma,[30] as well as Garg's total synthesis of (−)-**13**.[31]

3.1. Garg's Interrupted Fischer Indolization Approach

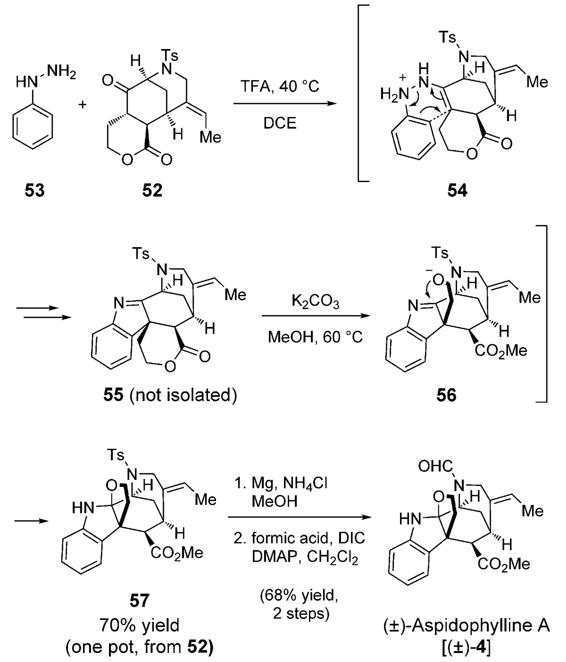
In 2011, the group of Garg reported the first synthesis of (±)-aspidophylline A [(±)-**4**].[28] Central to their strategy for building the pentacyclic framework of the natural product was the construction of the fused indoline moiety through an interrupted Fischer indolization cascade reaction.[45] Of note, the authors were able to execute this challenging approach at a late stage in the total synthesis.

The synthesis of the substrate for the aforementioned cascade reaction is illustrated in Scheme 8. The [2.2.2] bicyclic lactam **48** was elaborated over five steps to the vinyl iodide **49**, which, upon treatment with palladium(0) and pentamethylpiperidine, cleanly underwent a regioselective Heck cyclization[46] to forge the [3.3.1] azabicycle and furnish **50** in excellent yield. Next, in a series of transformations, **50** was converted into the hydroxy ester **51** in three steps, and it was subsequently carried forward to the tricyclic lactone **52** in five steps.

As previously mentioned, **52** was identified as a suitable substrate for the intended key interrupted Fischer indolization cascade reaction, the details of which are shown in Scheme 9. The tricyclic lactone **52** was treated with phenyl-



Scheme 8. Garg's synthesis of tricyclic lactone **52**. PMP = 1,2,2,6,6-pentamethylpiperidine.



Scheme 9. Garg's interrupted Fischer indolization and endgame to (±)-aspidophylline A [(±)-**4**]. DCE = 1,2-dichloroethane, DIC = diisopropylcarbodiimide, DMAP = 4-dimethylaminopyridine.

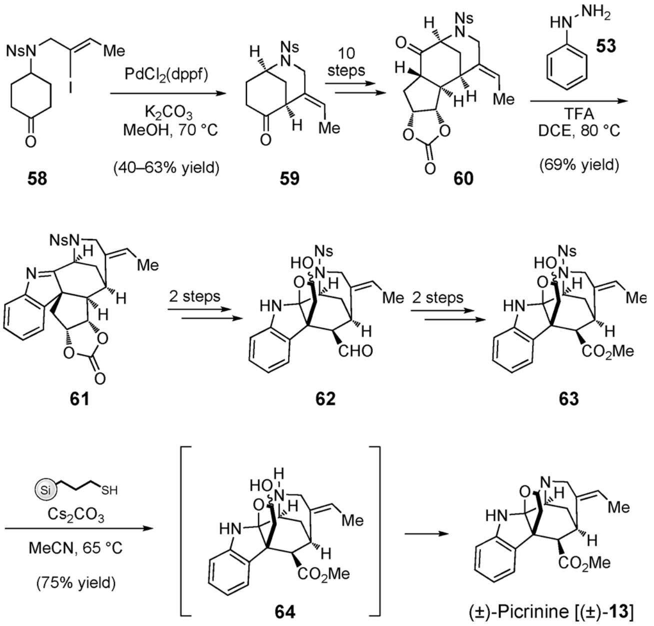
hydrazine (**53**) and trifluoroacetic acid in 1,2-dichloroethane at 40 °C. The resulting ene-hydrazine underwent a charge-accelerated [3,3] sigmatropic rearrangement (**54**) and subsequent extrusion of ammonia to furnish the indolenine **55**. This intermediate was not isolated, but rather was subjected to base-promoted methanolysis to generate an alkoxide intermediate. In situ cyclization (**56**) gave **57** in 70 % yield, which contains the pentacyclic framework of (±)-**4**. Notably, this cascade reaction assembles two new carbon–heteroatom bonds, one new C–C bond, and one quaternary center, and also proceeds with complete diastereoselectivity. Following construction of the pentacycle **57**, removal of the tosyl protecting group and N-formylation delivered (±)-**4**.

Garg's synthesis of (±)-**4** marked the second total synthesis of any akuammiline alkaloid, preceded only by Qin's synthesis of (±)-**15**. The synthesis proceeds in 7.5 % overall yield, and requires 20 steps from commercially available starting materials. In particular, the hallmark of the synthesis is the use of the interrupted Fischer indolization cascade at a late stage to assemble the compound's complex pentacyclic architecture and introduce two stereogenic centers. This late-stage reaction demonstrates the efficiency of cascade reactions for swiftly generating and manipulating high molecular complexity, while also highlighting the virtues of the venerable Fischer indolization reaction.

3.2. Garg's Synthesis of Picrinine

In a related effort, Garg and co-workers have recently completed the first total synthesis of (±)-picrinine [(±)-**13**].[31] Although structurally similar to **4**, **13** possesses a challenging bis(N,O-acetal) linkage. Inspired by the interrupted Fischer indolization cascade of their (±)-aspidophylline A synthesis, they designed a related substrate to subsequently access the indoline scaffold of picrinine. Additionally, a late-stage deprotection/cyclization sequence was implemented to build the caged structure of the natural product.

Shown in Scheme 10 is a summary of the total synthesis of (±)-**13** beginning with sulfonamide **58**, which could be accessed in one step from known precursors. Initially, a concise synthesis of the [3.3.1] azabicyclic scaffold was performed by treating **58** with catalytic [PdCl$_2$(dppf)] in the presence of K$_2$CO$_3$ and MeOH to forge the bicyclic ketone **59** in 40–63 % yield.[47] Following this key palladium-catalyzed cyclization, **59** was elaborated over 10 steps to the tetracyclic carbonate **60**, which was to be the substrate for the key Fischer indolization. Treatment of **60** with **53** and trifluoroacetic acid in 1,2-dichloroethane at 80 °C promoted the Fischer indolization,[48] thus leading to the indolenine **61** in 69 % yield. Of note, the reaction proceeds with complete diastereoselectivity



Scheme 10. Garg's synthesis of (±)-picrinine [(±)-**13**]. dppf = 1,1′-(diphenylphosphino) ferrocene, Ns = 2-nitrobenzenesulfonyl.

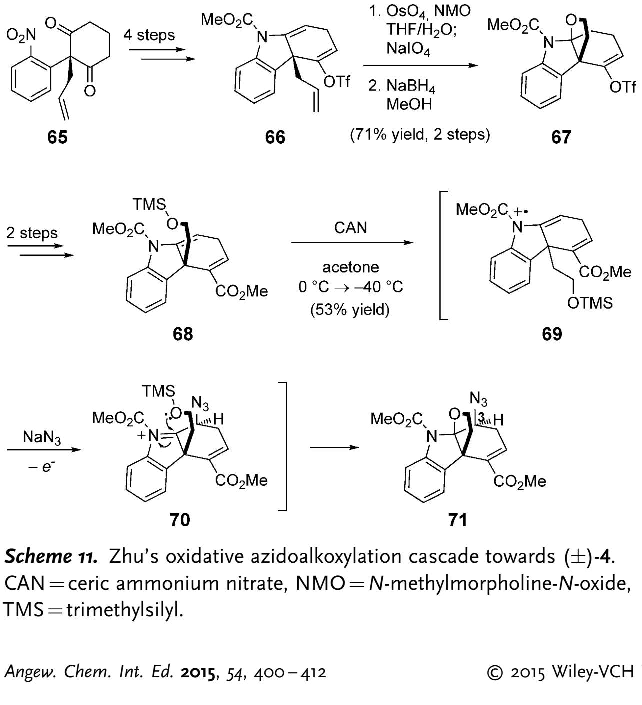
and introduces the natural product's quaternary stereocenter. In the following two steps, carbonate cleavage and oxidative C−C bond cleavage provided the fused lactol indoline **62** in 81% yield over two steps. Chemoselective oxidation of the aldehyde in two more steps provided the ester **63**, which set the stage for assembly of the bis(N,O-acetal) linkage. Treatment of **63** with a solid-supported thiol resin[49] and base led to cleavage of the nosyl protecting group to presumably furnish the transient intermediate **64**. In situ cyclization onto the proximal lactol gave (±)-**13**. The favorability of the final cleavage/condensation cascade was hypothesized to be proximity-driven.

Garg's 18-step total synthesis is still the only reported route to (±)-**13** to date. The rapid construction of the [3.3.1] azabicycle through a palladium-catalyzed vinylation reaction greatly differed from the authors' synthesis of (±)-**4**. A similar late-stage Fischer indolization reaction constructed the natural product's carbon framework, including the key quaternary stereocenter, whereas a nosyl cleavage/cyclization cascade enabled access to the heptacyclic scaffold of the natural product.

3.3. Zhu's Oxidative Azidoalkoxylation Approach

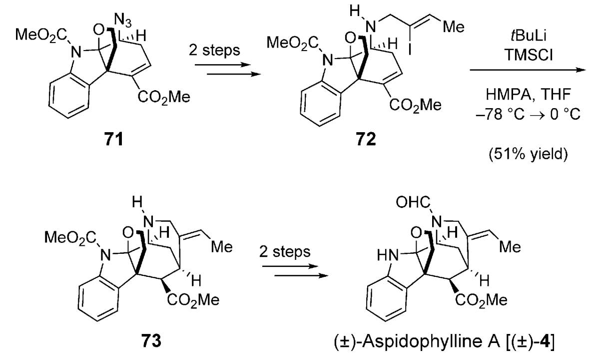
Earlier this year, Zhu and co-workers reported the second synthesis of (±)-aspidophylline [(±)-**4**].[29] Zhu's synthesis hinged upon an oxidative azidoalkoxylation reaction[50] to install N2 of the alkaloid's scaffold while concurrently establishing the furoindoline moiety.[51] This contrasted with Garg's strategy described earlier, where installation of the [3.3.1] azabicycle was accomplished early in the synthesis, followed by late-stage introduction of the furoindoline.

As shown in Scheme 11, Zhu's synthesis commenced from the readily available cyclohexanedione **65**,[52] which was elaborated to the tricycle **66** through a triflation,[53] reduction,[54] and carbamoylation sequence. Next, chemoselective oxidation of the terminal olefin with osmium tetroxide and sodium periodate,[55] followed by sodium borohydride reduction, provided the furoindoline **67** in 71% yield over two steps. This intermediate was then elaborated to the silyl ether **68**, the substrate for the key oxidative cyclization cascade. In the event, treatment of **68** with ceric ammonium nitrate and sodium azide in acetone delivered the azidofuroindoline **71** in 53% yield. Mechanistically, it is thought that ceric ammonium nitrate serves as a mild oxidant to first promote single-electron transfer and putatively form the radical cation **69**. Then, this radical cation is trapped by azide, with tandem loss of another electron, to afford an indoleninium species, which undergoes in situ cyclization (**70**). This umpolung cascade transformation efficiently forges the tetracyclic furoindoline core of the natural product. Additionally, it successfully installs three contiguous stereocenters and the important nitrogen substituent at C3 of the natural product.



Scheme 11. Zhu's oxidative azidoalkoxylation cascade towards (±)-**4**. CAN = ceric ammonium nitrate, NMO = *N*-methylmorpholine-*N*-oxide, TMS = trimethylsilyl.

The remainder of Zhu's synthesis is depicted in Scheme 12. In a two-step azide reduction and alkylation sequence,[56] the furoindoline **71** was elaborated to the iodide **72**, which was the utilized as the substrate for a challenging intramolecular Michael addition into the embedded enoate. After much optimization, the authors found that treatment of **72** with *t*BuLi and TMSCl in HMPA and THF at low temperature delivered the adduct **73** in 51% yield, thus forging the pentacyclic scaffold of the natural product.[57] Subsequent formylation and cleavage of the methyl carbamate delivered (±)-**4**.



Scheme 12. Zhu's completion of (±)-**4**. HMPA = hexamethylphosphoramide.

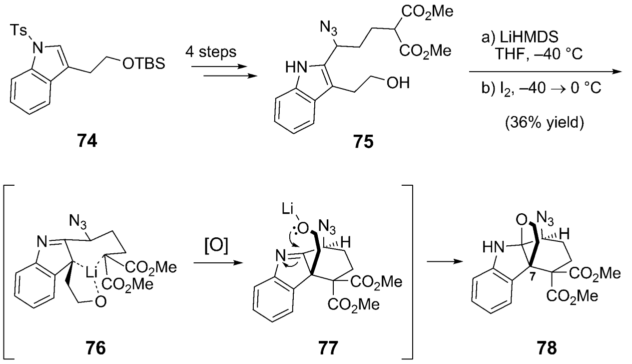
Zhu's impressive total synthesis of (±)-**4** proceeds in just 14 steps from the known cyclohexanedione **65**. The key oxidative azidoalkoxylation cascade reaction employed in the synthesis provides an elegant means to construct the natural product's densely substituted cyclohexane ring. Additionally, Zhu's swift approach demonstrates the enabling power of umpolung reactivity as a functionalization strategy in complex molecule synthesis.

3.4. Ma's Oxidative Coupling Approach

Very recently, Ma and co-workers were also successful in completing a total synthesis of (±)-aspidophylline A [(±)-

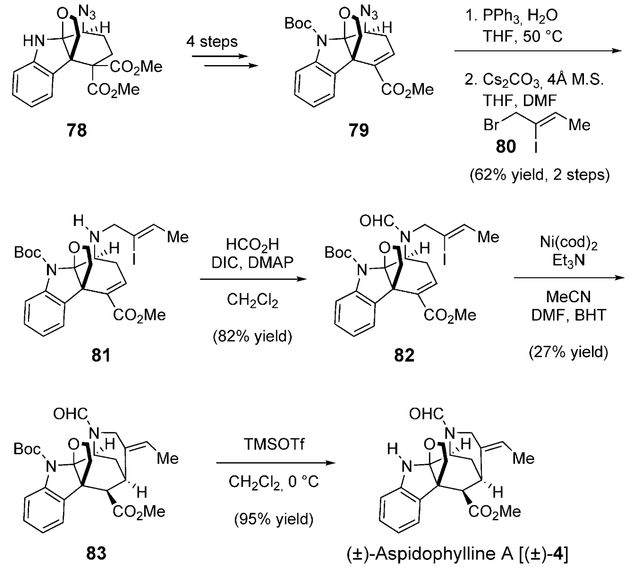
4].[30] Similar to their completed synthesis of (−)-vincorine [(−)-**15**], the authors sought to employ an intramolecular oxidative coupling[37] to build the core tetracyclic furoindoline scaffold of the natural product. Then, analogous to the overall strategy executed by Zhu, Ma envisioned construction of the piperidine ring through a late-stage cyclization strategy.

The synthesis began by elaborating the indole **74** to azide **75**, which was the substrate for the key intermolecular oxidative coupling cascade reaction (Scheme 13). Although the substrate for this coupling appeared less complex than the coupling substrate in the authors' synthesis of (−)-**15**, the transformation proved to be quite challenging.[58] After optimization, it was discovered that treatment of **75** with LHMDS in THF at −40 °C promoted formation of the putative lithium complex **76**. Quenching with iodine and warming to 0 °C led to oxidative C−C bond formation, thus furnishing an indolenine intermediate. In turn, this underwent in situ imine trapping (**77**) to deliver the furoindoline **78** in 36 % yield. Ma and co-workers noted that the addition of additives to this reaction, such as HMPA, resulted mostly in oxidative coupling of the diester to the indole nitrogen atom, presumably as a result of HMPA disrupting the formation of **76**. Although the oxidative coupling was not as high yielding as the analogous reaction in Ma's synthesis of (−)-**15**, the transformation is quite impressive in that it provides the furoindoline scaffold of the natural product, with three contiguous stereocenters including the quaternary center at C7.



Scheme 13. Ma's oxidative coupling cascade towards (±)-**4**.

Ma's synthetic endgame is shown in Scheme 14. The furoindoline **78** was converted into the tetracyclic enoate **79** through a protection, decarboxylation, and oxidation sequence. Similar to the approach taken by Zhu, the vinyl iodide **81** was synthesized from **79** in two steps, including Staudinger reduction and alkylation with the bromide **80**. Next, formylation of the secondary nitrogen atom with formic acid and *N,N'*-diisopropylcarbodiimide delivered the formamide **82**. Following this acylation event, cyclization of the iodide with the pendant enoate was mediated by [Ni(cod)$_2$] in the presence of triethylamine and BHT to deliver the pentacycle **83** in 27 % yield.[59] Following this difficult cyclization, cleavage of the Boc group was achieved in nearly quantitative yield to afford (±)-**4**.



Scheme 14. Ma's completion of (±)-**4**. BHT = 2,6-di-*tert*-butyl-4-methylphenol, cod = 1,5-cyclooctadiene, M.S. = molecular sieves.

Ma's total synthesis of (±)-**4** requires only 15 steps. Critical to the brevity of the synthesis is the use of an innovative intramolecular oxidative cascade coupling to rapidly assemble the furoindoline core of the natural product. This unique strategy, along with the concise construction of the piperidine ring, provides useful synthetic tools that should prove useful in assembling other complex molecules.

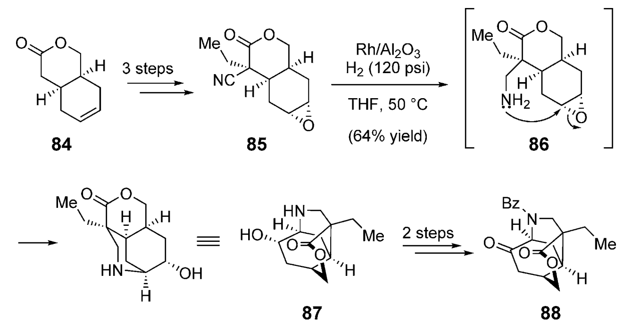
4. Total Syntheses of (+)-Scholarisine A

The natural product (+)-scholarisine A [(+)-**14**] is one of the most recently discovered akuammilines. Reported in 2008, Luo and co-workers isolated (+)-**14** from the tree *Alstonia scholaris*.[15] (+)-Scholarisine A [(+)-**14**] contains a rearranged akuammiline skeleton with six fused rings and six stereogenic centers, including two quaternary centers. In addition, its unusual [2.2.2] bicyclic lactone moiety provides a unique synthetic challenge in akuammiline alkaloid total synthesis. The valiant efforts of the groups of Smith[32] and Snyder[33] have recently led to two completed total syntheses, both of which harness the power of cascade reactions to access (+)-**14**.

4.1. Smith's Reductive Cyclization Approach

In 2012, the Smith laboratory reported the first total synthesis of (+)-scholarisine A [(+)-**14**].[32] Their route relied on the use of a reductive cyclization cascade to introduce three rings of the natural product. In addition, the authors utilized a late-stage Fischer indolization reaction to install the indole nucleus en route to forging the [2.2.2] bicyclic lactone of the natural product.

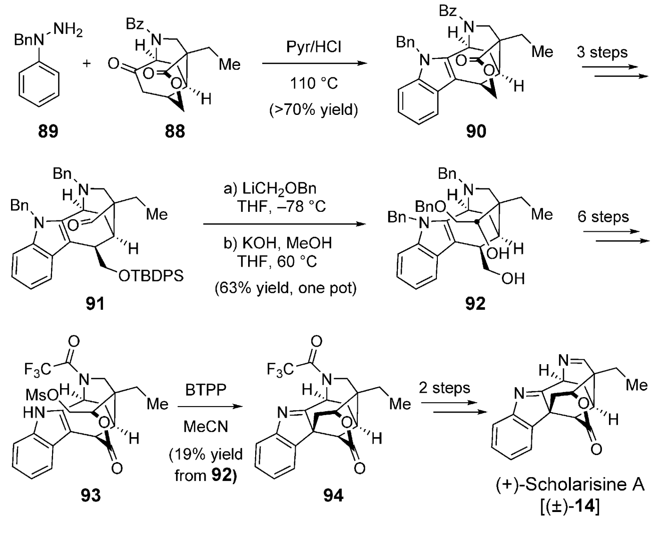
The synthesis of the ketone **88** is depicted in Scheme 15. The lactone **84**, a known compound synthesized from



Scheme 15. Smith’s reductive cyclization cascade. Bz = benzoyl.

commercially available cis-4-cyclohexene-1,2-dicarboxylic anhydride,[60] was elaborated to the nitrile **85** in three steps. Upon treatment of **85** with H_2 and rhodium on alumina, the desired reductive cyclization cascade occurred to deliver the tricyclic amine **87** in 64 % yield. This cascade sequence presumably proceeds by reduction of the nitrile,[61] followed by intramolecular epoxide opening by the resulting amine.[62] Of note, the authors observed that this cyclization is the first of its kind and, importantly, forges the [3.3.1] bicyclic moiety contained within the natural product’s structure. In addition, the opening of the epoxide elegantly provided a secondary alcohol functional group handle that could be used to later install the indole nucleus. The authors performed two additional steps to convert the amine **87** into ketone **88**, a step which involved amine protection and alcohol oxidation.

The remainder of Smith’s synthetic efforts are highlighted in Scheme 16. Treatment of **88** with benzyl-protected phenylhydrazine (**89**) and HCl in pyridine[63] facilitated the key Fischer indolization to provide the indole **90** in 70 % yield. Of note, **90** possesses most of the (+)-scholarisine A framework. A three-step sequence was used to elaborate **90** to the aldehyde **91**, which in turn, was treated with in situ generated benzyloxy-methyllithium.[64] Subsequent base-mediated desilylation in the same pot afforded the diol **92**. The diol **92** was carried forward to the mesylate **93** over six steps and subjected to *tert*-butyliminotri(pyrrolidino)-phosphorane (BTPP).[65] This resulted in cyclization to provide the indolenine **94** in 19 % yield from **92**. The indolenine **94** was quickly elaborated to (+)-**14** using a two-step sequence.



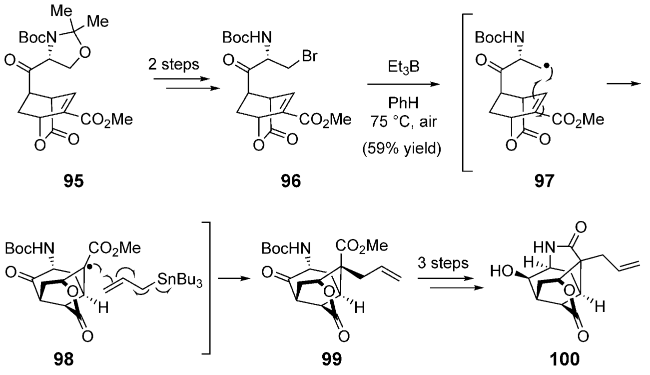
Scheme 16. Smith’s Fischer indolization and completion of the synthesis. BTPP = *t*-butyliminotri(pyrrolidino)-phosphorane, Ms = methanesulfonyl, Pyr = pyridine, TBDPS = *tert*-butyldiphenylsilyl.

Smith’s elegant synthesis of (+)-**14** marked the first asymmetric synthesis of an akuammiline alkaloid. The longest linear reaction sequence to arrive at the intricate natural product structure is just 20 steps from the known **84**. A major highlight of the synthesis is Smith’s use of a reductive cyclization cascade of **85** to smoothly construct the [3.3.1] bicycle of the natural product. This key reaction provided the groundwork for the late-stage efforts, thus illustrating the importance of cascade reactions not solely for generating complexity, but also for providing properly functionalized synthetic intermediates for subsequent manipulations.

4.2. Snyder’s Radical Functionalization Approach

The group of Snyder reported the most recent synthesis of (+)-scholarisine A [(+)-**14**] in 2013.[33] Their strategy differed greatly from that of Smith’s and relied heavily on radical cascade processes to forge the natural product’s polycyclic skeleton. In particular, two cascade reactions were utilized to construct the two quaternary centers and, in turn, the important indolenine moiety.

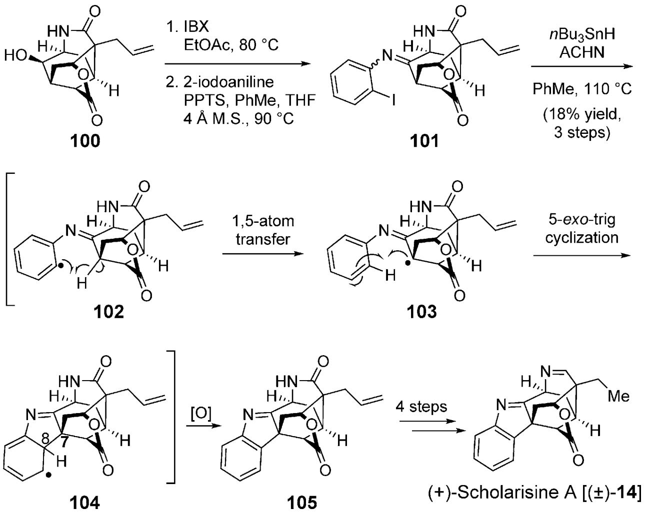
Shown in Scheme 17 is the key radical cascade used to construct the tetracyclic lactam **100**. Starting from the bicyclic lactone **95**, the substrate for the radical cascade (**96**) was synthesized in two steps by an acetonide hydrolysis[66] and bromination sequence. Subsequent treatment of **96** with triethyl borane in the presence of air at 75 °C promoted homolysis of the carbon–bromine bond which putatively revealed a primary radical.[67] This radical then underwent a 6-*exo*-trig cyclization (**97**), thus resulting in the tertiary radical compound **98**, which was trapped in situ with allyltributylstannane to give the tricycle **99** with full diastereoselectivity. Notably, this cyclization/trapping cascade sequence forged two key carbon–carbon bonds with remarkable stereocontrol,



Scheme 17. Snyder’s radical conjugate addition/Keck allylation cascade.

and allowed swift access to the natural product's core. This tricyclic intermediate was further elaborated over three steps to the lactam **100** through a redox epimerization of the nitrogen substituent and intramolecular amide formation.

The construction of **100** allowed the second radical cascade to be executed en route to (+)-**14**, as shown in Scheme 18. First, oxidation of the alcohol at C2 gave the corresponding ketone. Subsequent condensation with 2-iodoaniline provided the imine **101** as a mixture of geometrical isomers. Upon heating **101** with tributylstannane and 1,1′-azobis(cyclohexane-carbonitrile) in toluene, the authors obtained the indolenine **105**[68] (18% over the three steps from lactam **100**). The transformation is thought to proceed by initial homolysis of the C–I bond to give an aryl radical. 1,5-Hydrogen-atom transfer (**102**) then yields an isomeric bridgehead radical intermediate, and 5-*exo*-trig homolytic aromatic substitution on the pendant aryl ring, as suggested in transition-structure **103**, would then forge the C7–C8 linkage and deliver the intermediate **104**. Oxidation of the cyclohexadienyl radical provides **105**. This key synthetic intermediate was then used to complete the synthesis of (+)-**14**.



Scheme 18. Snyder's radical C–H functionalization and synthesis endgame. ACHN = 1,1′-azobis(cyclohexanecarbonitrile), IBX = 2-iodoxybenzoic acid, PPTS = pyridinium *p*-toluenesulfonic acid.

Snyder's approach to (+)-**14** is currently the most concise approach to this complex alkaloid (14 steps). The synthesis was enabled by the daring use of two challenging radical cascades, which highlights their importance and utility in building complex molecular architectures.

5. Conclusions

In summary, the akuammiline alkaloid natural products have been the subject of many recent synthetic endeavors, despite being known for many decades. Their intricate structures, along with their promising biological activities, have made them attractive targets amongst the chemical community. Various approaches towards making these natural products have been reported, of which the successful routes are highlighted herein. These successful routes have utilized cascade reactions to construct the cores of these compounds, thus demonstrating that these innovative techniques are useful in building exceedingly complex structural manifolds. The collective efforts of the many labs involved in this area has not only provided a solid groundwork for making other akuammilines and their derivatives, but has also set the stage for using modern cascade reactions in the synthesis of other intricate molecular scaffolds.

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