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A Synthesis of Alsmaphorazine B Demonstrates the Chemical Feasibility of a New Biogenetic Hypothesis

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Supporting Information

ABSTRACT: An *N*-oxide fragmentation/hydroxylamine oxidation/intramolecular 1,3-dipolar cycloaddition cascade efficiently converted an oxidized congener of akuammicine into the complex, hexacyclic architecture of the alsmaphorazine alkaloids. This dramatic structural change shows the chemical feasibility of our novel proposal for alsmaphorazine biogenesis. Critical to these endeavors was a marked improvement in our previously reported Zincke aldehyde cycloaddition approach to indole alkaloids, which permitted the gram-scale synthesis of akuammicine. The chemoselective oxidations of akuammicine leading up to the key rearrangement also generated several biogenetically related alkaloids of the alstolucine and alpneumine families.

Inspiration from presumed biogeneses has led to compelling outcomes in numerous alkaloid syntheses.[1] In one historically fascinating example, Woodward patterned aspects of his landmark strychnine synthesis[2] on a hypothesis that its biosynthesis might involve an arene oxidative cleavage event.[3] While this attractive idea turned out to be incorrect, his thoughts about strychnine's biogenesis were likely critical to the design of the successful approach. Here, we put forth a new biogenetic hypothesis for the origins of the hexacyclic alsmaphorazine alkaloids—one that might or might not be correct—and demonstrate how this way of thinking enabled the first synthesis of alsmaphorazine B.

Alsmaphorazines A and B (**1** and **2**, Figure 1) feature a stereochemically dense, highly oxidized, and cage-like hexacyclic skeleton with an endocyclic N−O bond that is rarely encountered in indole alkaloids. In their report on the isolation and structural elucidation of these compounds,[4] the Morita group put forth a proposed biosynthesis via akuammicine-type intermediates involving multiple stepwise oxidations and rearrangements to access the alsmaphorazines. Our analysis of the structural relationship between the almaphorazines, which were isolated from the tree *Alstonia pneumatophora*, and other well-known alkaloids from *Alstonia* led us to propose a new biogenesis of **1** and **2**.

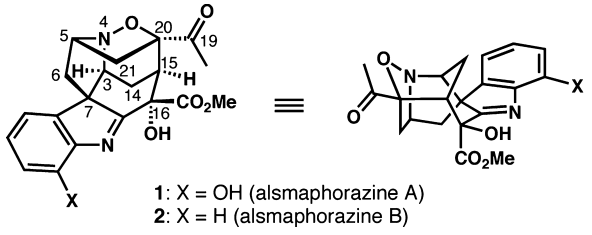
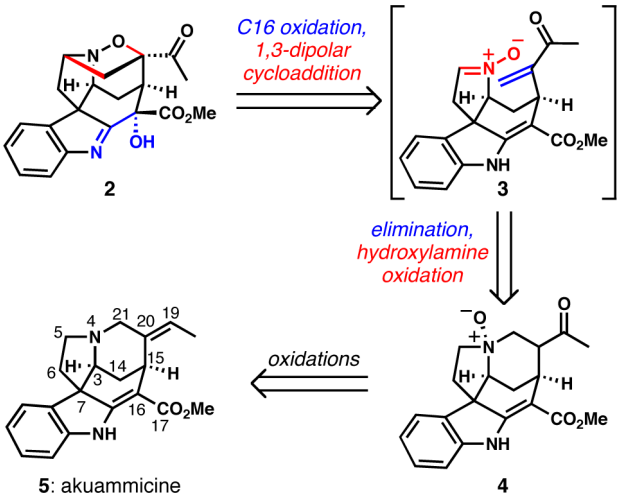


Figure 1. Alsmaphorazines A and B.

Our alternative biogenetic hypothesis also centered on the idea of performing multiple oxidations of akuammicine.[5,6] Of course, 1,2-oxazolidines are retrons for application of the nitrone-alkene 1,3-dipolar cycloaddition,[7] and we viewed nitrone/enone **3** (Scheme 1) as a key progenitor of the alsmaphorazine framework. This fleeting intermediate might be formed by *β*-elimination of a tertiary amine *N*-oxide and *in situ* hydroxylamine oxidation starting from intermediates of type **4**, one diastereoisomer of which corresponds to the enantiomeric natural products alstolucine C and alpneumine C.[8] The requisite C19 and N4-oxidations of akuammicine (**5**) to **4** appeared straightforward, and during the course of our investigations, Andrade et al. reported just these types of transformations.[6i] Numerous syntheses of akuammicine have been reported, with Andrade's six-step synthesis of (±)-**5** currently standing as the most concise.[6f] The directness of our previously described Zincke aldehyde-based approach to *Strychnos*-type alkaloids was also attractive.[9] We recognized that the alsmaphorazine challenge provided an excellent opportunity for optimization and extension of our chemistry

Scheme 1. Proposed Biogenesis of Alsmaphorazine B



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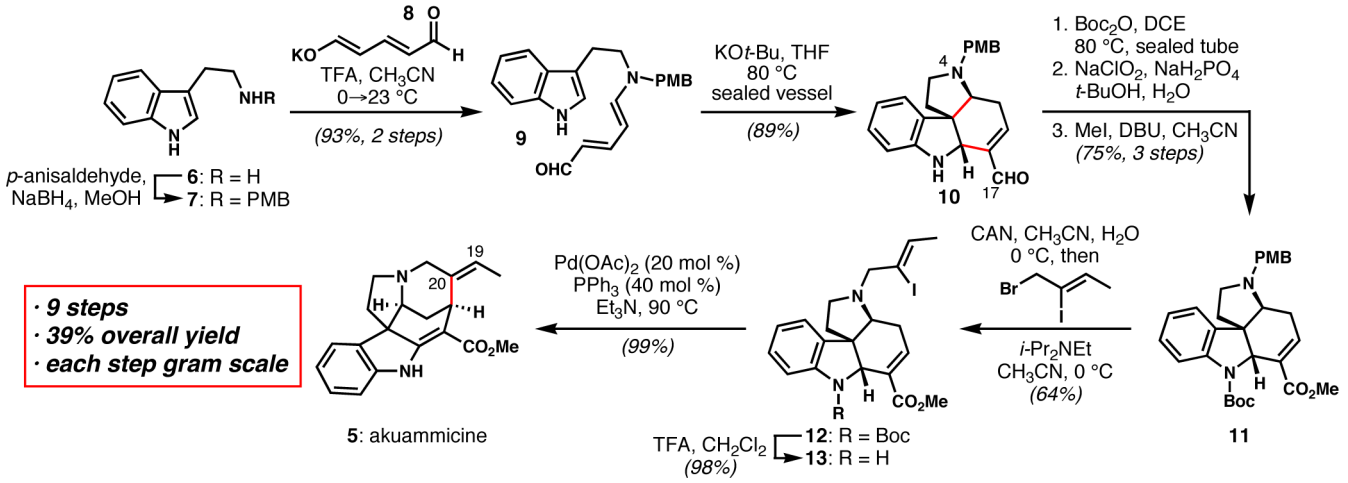
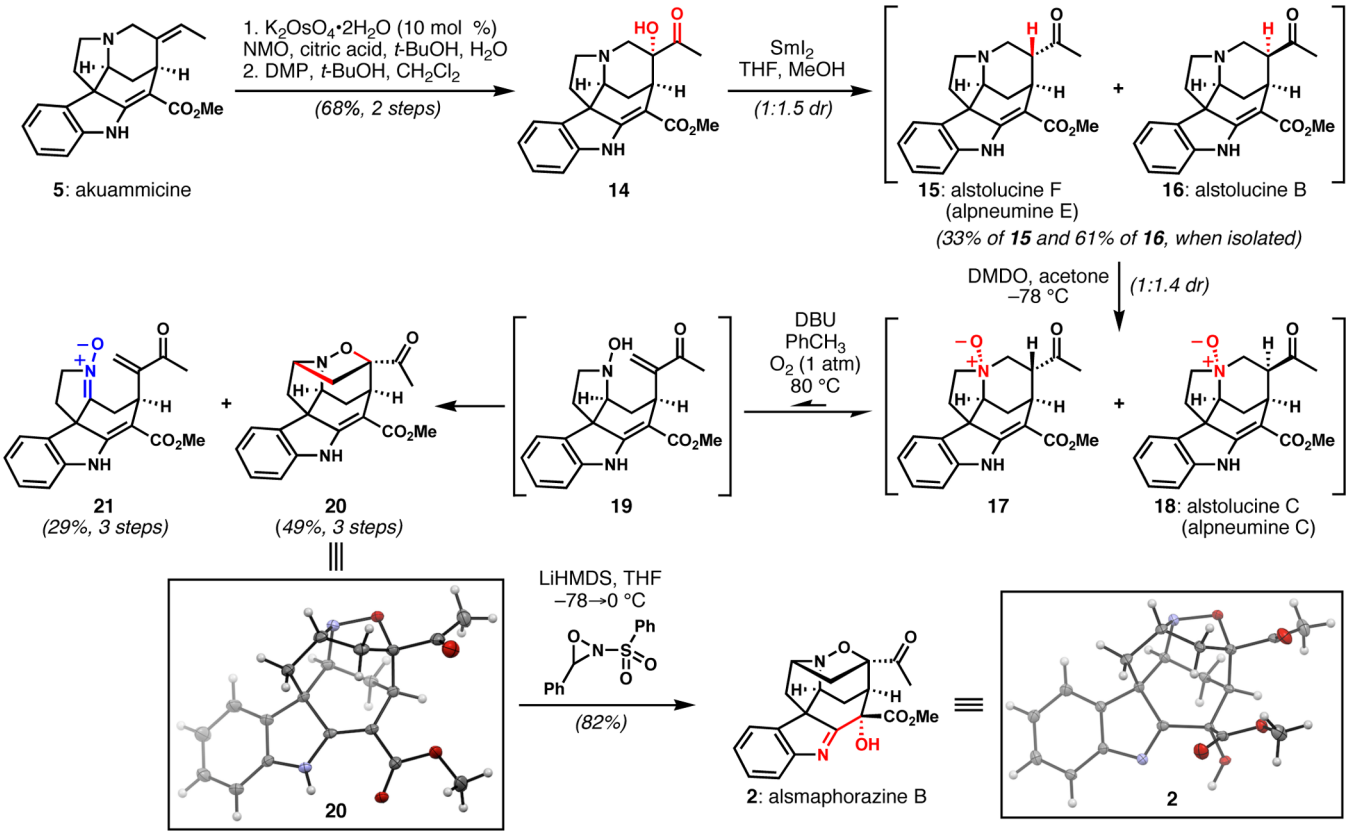
Scheme 2. A Nine-Step Synthesis of Akuammicine Amenable to the Production of Gram Quantities



Scheme 3. Synthesis of (±)-Alsmaphorazine B by Successive Oxidations of Akuammicine



to procure the quantities of akuammicine needed to study our hypothesis for biogenesis of the alsmaphorazines.

Our synthesis of akuammicine began with reductive amination of tryptamine with *p*-anisaldehyde to give secondary amine **7** (Scheme 2), which was treated with potassium glutaconate salt **8** according to modified Marazano conditions[10] (in lieu of Zincke pyridinium ring opening[9,11]) to deliver Zincke aldehyde **9** in 93% yield from tryptamine. Notably, this improved procedure greatly simplifies the purification of the key Zincke aldehyde, requiring only trituration of the crude material. Subsequent base-mediated formal cycloaddition[9] provided tetracyclic enal **10** in 89% yield. Numerous attempts were made at direct C17 oxidation; however, the free indoline proved to be a liability. In the end, several steps were needed to reliably change the C17 oxidation state and to refunctionalize N4; however, each of these reactions proved efficient even on multigram scales, and the intramolecular Heck reaction precursor **13** could be reliably accessed. This final ring closure, patterned on the work of Rawal,[6e,12] MacMillan,[6g] and Andrade,[6f,h,i] was remarkably efficient. The nine-step sequence to akuammicine proceeded in nearly 40% overall yield and procured gram quantities of the racemic alkaloid for our alsmaphorazine studies.

For the next stage of our plan, we sought to perform selective oxidations of akuammicine to arrive at the ketone natural products of the alstolucine and alpneumine series (Scheme

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3).[13] Our efforts to engage the C19−C20 alkene with Wacker and peracid oxidations, as well as thiol-ene, oxymercuration, and hydroboration reactions, were met either with outright failure or undesired regioselectivity. Inspired by the precedent of Brown and Djerassi,[14] in which stoichiometric osmium tetroxide was used to dihydroxylate akuammicine, we evaluated catalytic variants, eventually settling on the conditions developed by Fokin and Sharpless[15] owing to the relative ease of extractive removal of osmium remnants. Attempts to extend this oxidation process to an alkene ketohydroxylation by employing the conditions of DuBois[16] proved unsuccessful, and only starting material and minor products of dihydroxylation were observed. We made many attempts to effect a hydride shift of the intermediate diol directly to the C19 ketone with no success. We performed the oxidation of crude diol with CrO_3 as prescribed by Brown and Djerassi,[14] but only obtained 27% yield (two steps) of α-hydroxyketone **14**. Oxidation by the Dess−Martin periodinane proved sluggish depending on the batch of diol. Careful evaluation of the reaction conditions led to the identification of *t*-BuOH as a critical accelerant,[17] providing product **14** in 68% yield over two steps. SmI_2 reduction of the α-ketol[18] provided an inconsequential 1:1.5 mixture of alstolucine F/alpneumine E (**15**) and alstolucine B (**16**). The components can be separated by chromatography, providing the former in 33% yield and the latter in 61% yield; however, we typically use the crude mixture of ketones in subsequent operations. Exposure of the diastereomeric mixture of methyl ketones to DMDO at −78 °C led to quantitative conversion to the corresponding *N*-oxides, **17** and **18**, the latter of which is the racemate of the enantiomeric natural products alstolucine C and alpneumine C. Minimal C20 epimerization was observed during this reaction, as determined by ^{1}H NMR (1:1.4 dr).

The final and key stage in our plan was also the riskiest. We needed to initiate a base-mediated elimination or thermal Cope elimination to liberate an enone and a hydroxylamine (see **19**), the latter of which needed to be oxidized *in situ* to a reactive nitrone for 1,3-dipolar cycloaddition. The precedent of Ciganek[19] showed that it is indeed possible to execute $E1_{cb}$ eliminations of cyclic piperidine *N*-oxides with adjacent electron-accepting groups, but the hydroxylamines thus formed readily recyclize by conjugate addition upon standing. We reasoned that the intermediate hydroxylamine might be intercepted by air oxidation[20] to selectively generate the desired nitrone intermediate, which would participate in the intramolecular cycloaddition. With this idea in mind, we heated the mixture of *N*-oxides[21] in toluene in the presence of DBU under an atmosphere of air. After complete consumption of starting material, we painstakingly separated the complex mixture of cycloadduct **20**, nitrone isomer **21**, and amines **15** and **16** along with other unidentified side products. The structure of cycloadduct **20** was confirmed by single crystal X-ray diffraction. The formation of amines **15** and **16** might be explained by a disproportionation process[22] in which the intermediate hydroxylamine **19** might shuffle oxidation states to give amines and nitrones.

On the basis of this result, we reasoned that a more strongly oxidizing atmosphere might facilitate complete oxidation to the desired nitrone and mitigate the presumed disproportionation. Indeed, conducting the same reaction under an oxygen balloon led to an isolated yield of cycloadduct **19** in 49% yield over three steps along with fully substituted nitrone **20** in 29% yield.

Only oxidation of the vinylogous carbamate, which was expected to be highly stereoselective by virtue of the cage-like ring system, separated **20** from alsmaphorazine B. On the basis of numerous studies toward *Vinca* alkaloids,[23] we treated the cycloadduct with *m*-CPBA in the presence of various additives; however, only decomposition was observed. DMDO and peroxide reagents also proved ineffective. It appeared that N4 underwent competitive oxidation, and Baeyer−Villiger oxidation of the ketone might also have occurred under some conditions. Furthermore, the indolenine of alsmaphorazine B could potentially undergo oxidation, further complicating our efforts at a selective reaction. We reasoned that deprotonation of the vinylogous carbamate moiety could increase its relative reactivity and facilitate oxidation to the tertiary alcohol. Indeed, metallation of the vinylogous carbamate of **20** followed by treatment with Davis oxaziridine provided alsmaphorazine B in 82% yield. The structure of our synthetic sample was confirmed by single crystal X-ray diffraction, and the accumulated spectral data were in agreement with those reported by Morita.[4]

We have completed the first synthesis of alsmaphorazine B in 15 steps and 10.6% overall yield by recognizing its potential biosynthetic connection to akuammicine via oxidation-induced fragmentation and nitrone/alkene dipolar cycloaddition. To achieve this goal, we improved and extended our Zincke aldehyde methodology to facilitate the gram-scale synthesis of akuammicine. Subsequent chemoselective oxidation of the pentacyclic framework provided several alkaloids of intermediate levels of oxidation. Although our synthesis produces racemic material, we recognize that many of the intermediate alkaloids have been isolated in both enantiomeric forms,[8] with representatives in each series demonstrating interesting biological activities; resolutions of synthetic **15** and **18**, for example, will each yield two natural products. In our key fragmentation/oxidation/dipolar cycloaddition step, the cogeneration of the two complementary reactive functionalities for the dipolar cycloaddition is noteworthy. Our synthetic work provides a meaningful biosynthetic oxidation pathway that connects all of these *Alstonia* alkaloids and provides strong support for our biogenetic proposal that features a nitrone/alkene 1,3-dipolar cycloaddition, adding to the current literature of such dipolar cycloadditions in complex alkaloid biosynthesis.[24,25]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, X-ray crystallographic structures, and information for **2** and **20** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04686.

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Notes

The authors declare no competing financial interest.

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