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Total Synthesis of the *Lycopodium* Alkaloid (+)-Serratezomine A

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The *Lycopodium* alkaloids have provided some of the most intricately structured and stereochemically dense specimens among naturally occurring small molecules.[1] The attendant challenge for chemical synthesis, often combined with their promise as potential therapeutics, has led to broad interest in their total chemical synthesis.[2] Recent reports have detailed rather concise preparations of (−)-fawcettimine,[3] (+)-fawcettidine,[4] (−)-lycopodine,[5] lyconadin A and B,[6] and (−)-cernuine.[7,8] Importantly, valuable new chemical methods have been developed in nearly every case to solve specific synthetic challenges while also avoiding synthetic routes that would not address the important issue of supply.

Kobayashi and co-workers[9] isolated (+)-serratezomine A (**1**) (as its trifluoroacetic acid salt) as part of a search for new therapeutics from the club moss *L. serratum*, from which the huperzine alkaloids were isolated. The polycyclic structure merges a 5,6-fused ring system (an indolizidine) with a 6,6-spirocyclic ring and a bridging lactone. Morita and Kobayashi[10] found that the lactone is subject to isomerization from O13 to O8, resulting in the thermodynamically favored fused γ-lactone. Among the six contiguous stereogenic carbons, the

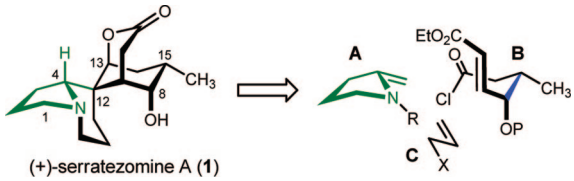


Figure 1. Convergent construction strategy for (+)-serratezomine A.

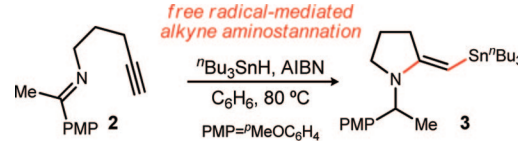
axial alcohol at C8, which is absent from the natural products listed above, sterically impinges upon the spirocyclic piperidine through a 1,3-diaxial interaction. Finally, all but two of the stereochemical elements overlap with a bridgehead or bicyclic union. We anticipated that these challenges might provide an opportunity to develop new chemistry to meet the goal of a convergent synthesis. In this communication, we describe these developments in the context of the first total synthesis of **1**.

Our solution to the problem of convergency rested on the hypothesis that an exocyclic enamine of general type **A** (Figure 1), an unsaturated 2-methylpyrrolidine, could provide a multiply nucleophilic C12 and serve as the synthesis lynchpin. The first step toward annulation would involve acylation of the enamine with a structure of type **B**, and subsequent enamine conjugate addition would complete the cyclohexannulation. Preparation of acid chloride **B** could be similarly convergent through the application of a Brown crotylation to establish the proper relative and absolute configuration at C15/C8. Finally, we intended to annulate the spirocyclic piperidine by alkylation sequentially at carbon and nitrogen with a functional equivalent to **C**.

We targeted β-stannyl enamine **3** (Scheme 1) to serve the role of **A** (Figure 1), as the terminal stannyl group would presumably facilitate the first carbon−carbon bond-forming step to regenerate the enamine. Alkynyl imine **2** was prepared by condensation of *p*-methoxyacetophenone with the known 5-amino-1-pentyne.[11] Application of radical-generating conditions (^{n}Bu$_3$SnH, AIBN, 90 °C) provided the desired β-stannyl enamine **3** through a sequence of stannyl radical addition to the terminal alkynyl carbon followed by addition of the nascent vinyl radical to the nitrogen of the azomethine.[12] Regiocontrol in this addition step was achieved through the use of a ketimine that electronically encourages the formation of the α-amino methyl radical and sterically retards addition to the azomethine carbon through disubstitution.[13]

Fragment **B** (Figure 1) was prepared from commercially available aldehyde **5**, which can also be obtained directly from ozonolysis of inexpensive ethyl sorbate in 93% yield (Scheme 2).[14] Application of Brown's crotylation reagent[15] and silylation of the secondary alcohol delivered the unsaturated ester in 76% yield (two steps). The Mosher ester of **6** was prepared in order to assign the absolute configuration as shown.[16] Hydroboration/oxidation of the terminal olefin provided the primary alcohol in 82% yield, and this was immediately oxidized to **8** using a two-step method (92% overall). The acid chloride generated from **8** was then treated with freshly prepared β-stannyl enamine **3**, resulting in the desired vinylogous amide (**9**) isolated in 65% yield (two steps from acid **8**). Our efforts to coerce this *N*-alkyl vinylogous amide to engage the unsaturated ester were uniformly unsuccessful. However, oxidative dealkylation at nitrogen using $Ce(NH_4)_4(NO_2)_6$ (CAN) resulted in the desired cyclization to **10**. We anticipated that the tetrasubstituted alkene would provide sufficient A^{1,3}-strain[17] to favor the axial orientation of the ethyl acetate ($-CH_2CO_2Et$) substituent at C7. Indeed, measured coupling constants and NOESY

Scheme 1. Use of Free-Radical-Mediated Alkyne Aminostannation to Prepare β-Stannyl Enamine **3**

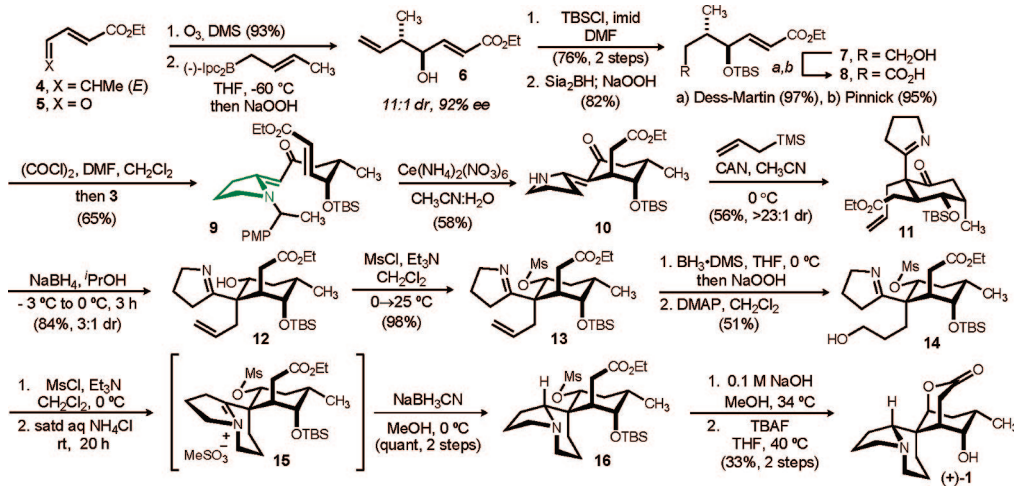


measurements were consistent with the diaxial conformer and *Z* alkene depicted for vinylogous amide **10** in Scheme 2. A range of alkylations were evaluated next in an attempt to establish the proper configuration at the central carbon of the β-imino ketone, as this hindered position is the common link (C12) between the two rings of the spirocycles. Unfortunately, nearly all of the activation methods simply promoted intramolecular lactamization with the terminal ester. We found one exception in the form of an oxidative allylation developed by Hwu,[18] in which Ce(IV) and allyltrimethylsilane combine with the vinylogous amide to deliver β-imino ketone **11** in 56% yield and 23:1 dr. Coupling-constant and NOESY analyses were consistent with the chair conformer depicted for **11**.[19] From this intermediate containing all of the backbone carbons needed for the natural product, a series of final bond-forming reactions commenced.

Borohydride reduction of **11** provided the equatorial alcohol **12** in 84% yield (3:1 dr), and this was readily converted to its mesylate **13**

10.1021/ja900536d CCC: $40.75

Scheme 2. Completion of the Total Synthesis of (+)-Serratezomine A



in 98% yield. Hydroboration/oxidation of the terminal olefin was notably sluggish but led to the desired primary alcohol **14** (51% yield, 86% conversion). This was converted to its mesylate, which cyclized slowly upon standing. Treatment of the iminium ion **15** with ammonium chloride was necessary to prevent its tautomerization to the corresponding enamine, as the latter undergoes efficient cyclization to the *C*-acyl enamide (C3, pyrroline numbering). Moreover, this undesired reaction could be avoided almost completely so long as iminium reduction by sodium cyanoborohydride commenced once cyclization to the iminium was complete. Inspection of models suggested that hydride approach to **15** might be less hindered from the β-face, but perhaps more important is that the interactions between the pyrrolidine and cyclohexane rings in **16** are considerably less than in *epi*-16 (at C4). The final two steps of the synthesis involved a tandem saponification/intramolecular S_N2 cyclization to form the bridging lactone[20] and careful desilylation to avoid formation of the fused lactone.[10,21] Synthetic (+)-serratezomine A, so formed, was spectroscopically identical (^{1}H and ^{13}C NMR)[22] to reported values. Optical rotation {$[\alpha]_D$ +9.5 (*c* 0.3, MeOH)} was also consistent with the literature value {$[\alpha]_D$ +13 (*c* 0.5, MeOH)}, thereby providing further confirmation of the absolute configuration.

In summary, the first total synthesis of (+)-serratezomine A is described. The use of β-stannyl enamine **3** as a synthesis lynchpin, the stereocontrolled, strategically convergent assembly of fragments (**3**, **8**, and allyltrimethylsilane), and the minimal use of protecting groups combined to provide a reasonably short chemical synthesis of one of the most structurally and stereochemically complex members of the *Lycopodium* alkaloid family. The challenges posed by serratezomine A inspired the development of free radical-mediated vinyl amination (**2** → **3**) and led to the application of cerium(IV) oxidative allylation (**10** → **11**) as a means to establish the congested all-carbon quaternary center with the proper configuration needed for serratezomine A.

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Supporting Information Available: Preparations, spectral data, and structure elucidation for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) See the Supporting Information for comparisons.

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