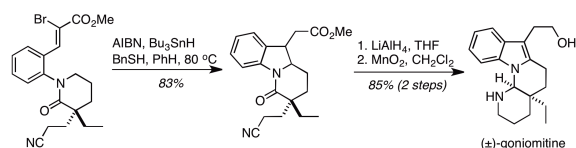


Total Synthesis of (±)-Goniomitine via Radical Translocation.

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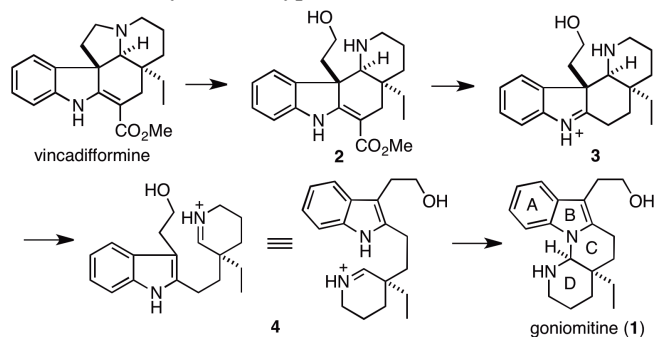
Supporting Information Placeholder



ABSTRACT: The aspidosperma alkaloid goniomitine was synthesized in six steps from 2-ethyl- δ -valerolactam. The convergent strategy features an Ullman coupling to assemble the required carbon atoms. A complexity-generating radical translocation reaction was used to build the indole architecture.

Goniomitine (**1**) is a monoterpene alkaloid that was isolated in 1987 by Husson and coworkers from the Madagascan tree *Gonioma malagasy*.¹ Goniomitine belongs to the family of aspidosperma alkaloids, but it has an unusual molecular architecture featuring four angularly fused rings and an aminal functional group. Husson and coworkers forwarded an insightful biogenetic hypothesis suggesting that goniomitine is derived from vincadifformine, which has a more typical aspidosperma alkaloid structure (Scheme 1).¹ Intermediate **2** was hypothesized to undergo ester hydrolysis and decarboxylation to arrive at tetracycle **3**. Retro-Mannich reaction would produce iminium **4**, which could be captured by the indole to produce goniomitine. This biosynthetic hypothesis was substantiated by subsequent investigations by Husson,² and by a biomimetic synthesis of goniomitine from vincadifformine following this strategy by Lewin and coworkers.³

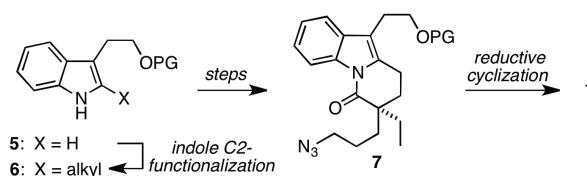
Scheme 1. Biosynthetic Hypothesis for Goniomitine.



The unusual molecular architecture of goniomitine and its micromolar antiproliferative activity on several cancer cell lines have captivated the attention of many synthetic chemists.^{4,5} In addition to the biosynthetic studies by Husson and Lewin, eight total syntheses of goniomitine have been reported. All of these total syntheses follow two general strategies. In the first strategy⁴ (Scheme 2), a protected tryptophol starting material (**5**) is functionalized at the C2 position of the indole in one or more steps. Additional synthetic transfor-

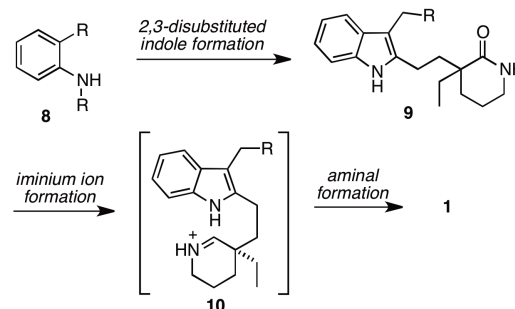
mations are used to build the δ -valerolactam C-ring found in goniomitine. Finally, reduction of a tethered azide and reductive cyclization with the lactam carbonyl gives the aminal structure and completes the synthesis of goniomitine.

Scheme 2. Tryptophol Functionalization Strategy.



The second general strategy for goniomitine⁵ is exemplified in Scheme 3. An *ortho*-substituted aniline **8** is used as a starting material for the construction of a 2,3-disubstituted indole **9**.⁶ Several steps are used to append a tethered D-ring in the form of a δ -valerolactam with the quaternary stereocenter in tact. Activation of the lactam carbonyl in **9** gives an iminium ion (**10**) that cyclizes to form the aminal functional group in goniomitine.

Scheme 3. Indole Functionalization Strategy.

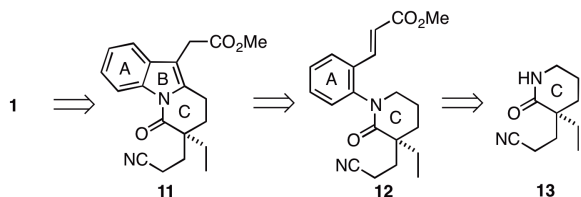


Our interest in aminal-containing molecules led us to goniomitine.⁷ Initially, we explored strategies to use aminal radical intermediates for the construction of the goniomitine structure. Radical chemistry is well suited for the synthesis of nitrogenous molecules, as carbon-centered radicals are generally

tolerant of the nitrogen lone pair and the rich acid-base reactivity of the nitrogen atom.⁸ However, our initial efforts were ultimately unsuccessful because of a general paucity of methods for the preparation of aminals incorporating indole nitrogen atoms.⁹ However, we continued to consider radical-based approaches toward the goniomitine structure.

Goniomitine may arise from intermediate **11**, which was envisioned to be an immediate precursor to the natural product by way of global hydride reduction (Scheme 4). In a departure from all previous synthetic strategies, we chose to unravel the indole B-ring to give intermediate **12**. Intermediate **12** could be prepared from substituted δ -valerolactam **13** using standard cross-coupling methods.

Scheme 4. Retrosynthetic Analysis of Goniomitine.

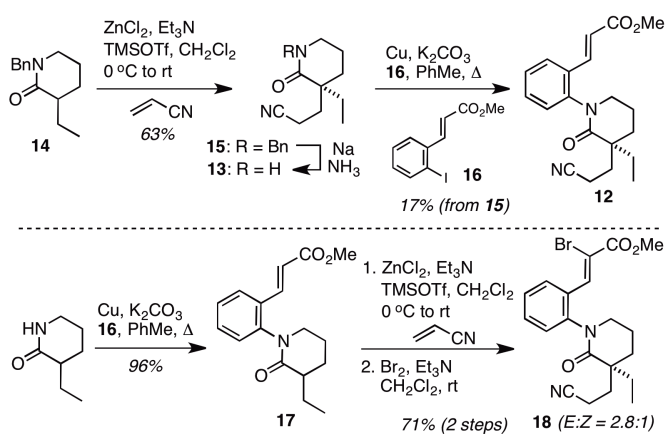


The previous syntheses of goniomitine involved 8–28 synthetic steps, and many of the transformations were devoted to preparing the central C-ring of the target molecule. In fact, all previous syntheses of goniomitine required construction of the central C-ring. We suspected that beginning our synthesis with a readily available δ -valerolactam starting material (as the C-ring) could result in an expeditious synthesis of the target molecule.

A key consideration in the synthesis of goniomitine is creating the quaternary stereocenter. We initially followed Pagenkopf's report that a one step alkylation (or a more robust 4 step sequence) of **14** would give **15**, which contains the requisite quaternary carbon (Scheme 5, top).^{5b} We were able to optimize the one step conversion to a synthetically useful 63% yield. However, we had substantial difficulty removing the benzyl protecting group to give lactam **13**. After many failed attempts at this transformation with hydrogenolysis¹⁰ and other conditions,¹¹ we found that dissolving metal reduction cleanly removed the benzyl group to give **13**, which proved to be a sensitive intermediate. Lactam **13** could be taken into the subsequent coupling with iodide **16**¹² without purification, but the Ullmann coupling to give **12** was low yielding. Ultimately, although we were able to forge the desired bonds, the chemical yields were disappointing, and an alternative route was investigated.

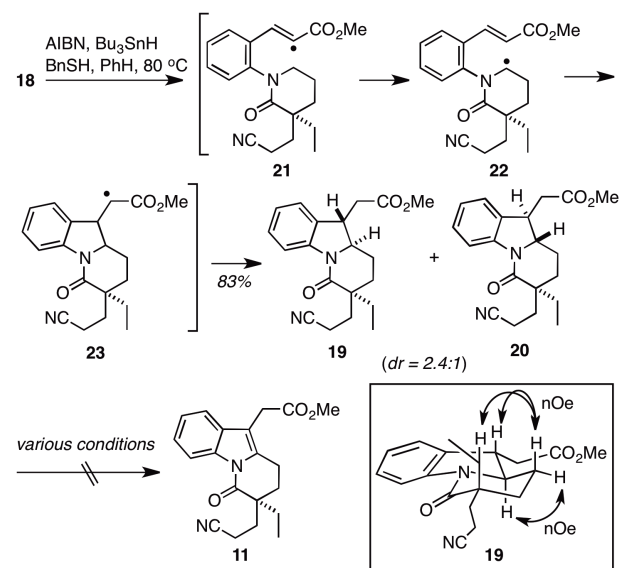
Changing the order of steps proved to be auspicious and more step-economical (Scheme 5, bottom). We found that the Ullmann coupling of ethyl δ -valerolactam with **16** was a high-yielding reaction producing *N*-aryl lactam **17**. Moreover, the installation of the quaternary carbon proceeded smoothly to give **12** in high yield, which avoided the use of the benzyl protecting group altogether. Finally, bromination of the alkene gave key cyclization intermediate **18** as a 2.8:1 mixture of alkene isomers. Notably, this sequence begins from ethyl δ -valerolactam and assembles **18** in just three high-yielding operations, and **18** is complete with all the carbons of goniomitine and a functional handle for the radical cyclization reaction.

Scheme 5. Preparation of Radical Reaction Substrate.



With **18** in hand, the key radical cyclization reaction was investigated.¹³ Treatment of **18** with standard radical conditions led to the formation of desired indolines **19** and **20** as a 2.4:1 mixture of *cis*-indoline diastereomers. Presumably, the initial radical species **21** arises from the homolytic cleavage of the C–Br bond. Radical translocation then gives α -amino radical **22**. Intramolecular cyclization gives radical **23**, which abstracts a hydrogen atom from Bu₃SnH to give the products.

Scheme 6. Radical Translocation.

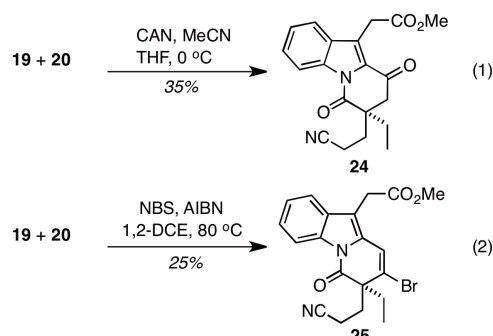


The combined chemical yield of **19** and **20** in the reaction was quite good, and the production of two diastereomeric indolines was acceptable because these stereocenters will be destroyed upon oxidation to the corresponding indole. The pure geometric alkene isomers of **18** were isolated and individually subjected to the radical reaction; they gave an identical mixture of **19** and **20**. This result indicated there is no stereospecificity in this reaction, and the alkene geometry of **18** is inconsequential.

The stereochemistry of **19** and **20** is also inconsequential for the goniomitine synthesis; however, the stereochemistry of the major product diastereomer (**19**) was determined using NOESY methods (see key correlations in Scheme 6). The similarity of the coupling pattern in **19** and **20** lead us to tentatively assign **20** as a *trans* indoline as well.

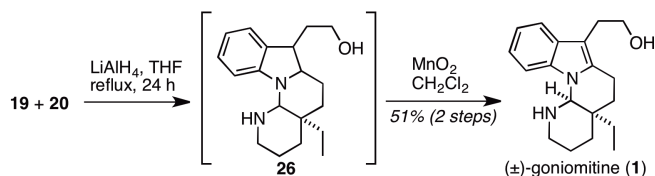
Oxidation of **19** and **20** to indole **11** would convert both diastereomers to one racemic product, and it would make characterizing intermediates from the final steps of the synthesis more convenient. However, the *N*-acyl group, substitution at both C2 and C3, and the inductively withdrawing carbomethoxy group in **19** and **20** conspired against this transformation, and no conditions for the indoline oxidation to **11** were found. Most standard reagents (MnO₂, DDQ, Pd/C, S₈, KMnO₄) for indoline oxidation¹⁴ were ineffective, returning unreacted starting materials. More forcing conditions using CAN (Scheme 7, eq 1) or NBS (eq 2) gave over-oxidation of the indole producing **24** and **25**, respectively.

Scheme 7. Attempted Indoline Oxidation.



Of course, the goniomitine structure does not possess an *N*-acyl indole, so we decided to postpone the indoline oxidation step and perform the required hydride reduction first. Previous goniomitine syntheses utilized a reductive cyclization sequence of compounds with structure **7** (Scheme 1) that was promoted by LiAlH₄. Treatment of **19** and **20** with LiAlH₄ in hot THF for 12 hours, followed by an aqueous workup gave a mixture of compounds with spectroscopic characteristics consistent with the desired reduction products **26** as a complex mixture of diastereomers. Gratifyingly, intermediates **26** underwent smooth oxidation with MnO₂ to give the natural product as the only isolable product. The combined yield of goniomitine from radical translocation products **19** and **20** was 51%.

Scheme 8. Completion of the Goniomitine Synthesis.



In summary, we have completed a synthesis of the aspido-sperma alkaloid goniomitine. The synthesis requires six synthetic transformations from ethyl δ -valerolactam and has an overall yield of 29%, which makes it the most efficient synthesis of (\pm) -goniomitine to date. Key features of this synthesis are the strategic use of a δ -valerolactam starting material and a radical translocation reaction to build the indole B-ring. Efforts to extend this strategy in other alkaloid targets are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, depiction of ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors.

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