

Total Synthesis of (\pm) -Goniomitine via Radical Translocation

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Supporting Information

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.

oniomitine (1) is a monoterpene alkaloid that was isolated in 1987 by Husson and co-workers from the Madagascan tree *Gonioma malagasy*. 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 co-workers forwarded an insightful biogenetic hypothesis suggesting that goniomitine is derived from vincadifformine, which has a more typical aspidosperma alkaloid structure (Scheme 1). Intermediate 2 was hypothesized

Scheme 1. Biosynthetic Hypothesis for Goniomitine

$$\begin{array}{c} \text{HO} \\ \text{HN} \\ \text{HO} \\$$

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 co-workers.³

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 strategy (Scheme 2), a protected tryptophol starting material (5) is functionalized at the C2 position of the indole in one or more steps. Additional synthetic transformations are used to build the δ -valerolactam C-ring found in goniomitine. Finally, reduction of a tethered azide and reductive cyclization with the lactam

Scheme 2. Tryptophol Functionalization Strategy

carbonyl gives the aminal structure and completes the synthesis of goniomitine.

The second general strategy for goniomitine⁵ is exemplified in Scheme 3. An *ortho*-substituted aniline 8 is used as a starting

Scheme 3. Indole Functionalization Strategy

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 intact. Activation of the lactam carbonyl in 9 gives an iminium ion (10) that cyclizes to form the aminal functional group in goniomitine.

Our interest in aminal-containing molecules led us to goniomitine. 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

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reactivity of the nitrogen atom. However, our initial efforts were ultimately unsuccessful because of a general paucity of methods for the preparation of aminals incorporating indole nitrogen atoms. 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

Scheme 4. Retrosynthetic Analysis of Goniomitine

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.

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 four-step sequence) of 14 would give 15, which contains the requisite quaternary carbon (Scheme 5, top). Sb We were able to optimize

Scheme 5. Preparation of Radical Reaction Substrate

$$\begin{array}{c} \text{ZnCl}_2, \, \text{Et}_3 \text{N} \\ \text{TMSOTf, CH}_2 \text{Cl}_2 \\ 0 \, ^{\circ} \text{C to rt} \\ \text{O} \\ \text{O} \\ \text{CN} \\ \text{I5: R = Bn} \\ \text{I3: R = H} \\ \text{NH}_3 \\ \text{I3: R = H} \\ \text{NH}_3 \\ \text{I7% (from 15)} \\ \text{I6, PhMe, } \\ \text{A} \\ \text{O} \\ \text{O} \\ \text{CO}_2 \text{Me} \\ \text{I. ZnCl}_2, \, \text{Et}_3 \text{N} \\ \text{TMSOTf, CH}_2 \text{Cl}_2 \\ \text{O} \, ^{\circ} \text{C to rt} \\ \text{CN} \\ \text{O} \\ \text{O} \\ \text{CI} \\ \text{NC} \\ \text{II} \\ \text{II} \\ \text{II} \\ \text{II} \\ \text{CI} \\ \text{CI} \\ \text{CI} \\ \text{CI} \\ \text{CI} \\ \text{CI} \\ \text{II} \\ \text{CI} \\ \text{CI} \\ \text{CI} \\ \text{II} \\ \text{CI} \\ \text{CI} \\ \text{II} \\ \text{II} \\ \text{CI} \\ \text{CI} \\ \text{II} \\ \text{CI} \\ \text{CI} \\ \text{II} \\ \text{CI} \\ \text{II} \\ \text{CI} \\ \text{C$$

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 hydrogenolysis 10 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.

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 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.

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 led 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

Scheme 6. Radical Translocation

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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 oxidation ¹⁴ were ineffective, returning unreacted starting materials. More forcing conditions using CAN (Scheme 7, eq 1) or NBS (eq 2) gave overoxidation 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 (Scheme 8). Previous goniomitine syntheses utilized a reductive

Scheme 8. Completion of the Goniomitine Synthesis

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 h, 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 MnO_2 to give the natural product as the only isolable product. The combined yield of goniomitine from radical translocation products 19 and 20 was 51%.

In summary, we have completed a synthesis of the aspidosperma 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

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02277.

Experimental procedures, spectroscopic data, depiction of ¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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