



# Total Synthesis of Leuconoxine, Melodinine E, and Mersicarpine through a Radical Translocation–Cyclization Cascade

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**Abstract:** The *Aspidosperma* alkaloids leuconoxine, melodinine E, and mersicarpine were synthesized. The approach features a key cascade radical reaction. A 1,5-hydrogen atom transfer is followed by spontaneous 5-*exo*-trig cyclization to construct the central indoline architecture. Late-stage differentiation of the radical cyclization product by chemoselective oxidation allows production of either the leuconoxine/melodinine E or mersicarpine structure.

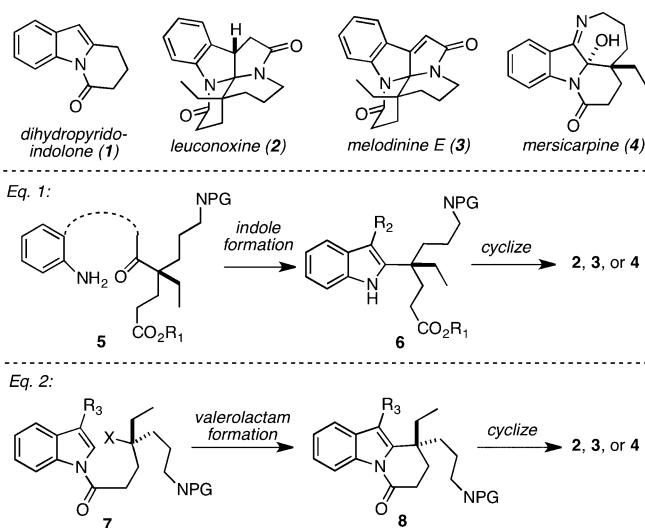
The *Aspidosperma* alkaloids are a large class of molecules isolated from dogbane trees native to Central and South America.<sup>[1]</sup> These alkaloids have attracted considerable attention due to their polycyclic structures, biological activities, and interesting biosyntheses.<sup>[2]</sup>

Rearranged *Aspidosperma* alkaloids have also attracted attention from the synthetic community. In particular, *Aspidosperma* congeners that share a common dihydropyridindolone substructure (1), such as leuconoxine (2), melodinine E (3), and mersicarpine (4) have received a flurry of recent investigations (Scheme 1).<sup>[3–5]</sup>

A common literature approach [Scheme 1, Eq. (1)] to such alkaloids involves starting materials that contain an aniline and substituted ketone exemplified by structure 5.<sup>[3,6]</sup> Heterocycle formation gives an indole substituted at C2 with a quaternary stereocenter (6). Sequential cyclization steps form the remaining rings to give the natural product architectures. This general strategy has been used by several groups for leuconoxine/melodinine E syntheses,<sup>[3a,b]</sup> mersicarpine synthesis,<sup>[3c,d]</sup> as well as in divergent syntheses of multiple *Aspidosperma* targets.<sup>[3e–i]</sup>

The other general strategy [Scheme 1, Eq. (2)] involves N-acylation of an indole starting material to give 7.<sup>[4]</sup> A functionalization of the indole C2 carbon forms the valerolactam substructure producing 8,<sup>[7]</sup> followed by cyclization leading to the target alkaloids. This strategy has been used in a divergent synthesis of 2, 3, and 4,<sup>[4a]</sup> however, it is particularly common for mersicarpine (4).<sup>[4b–e]</sup>

Our interest in these alkaloids stemmed from their dense polycyclic molecular architectures that housed a variety of different acidic or basic functional groups. Such acid-base active heteroatomic functional groups (for example, alcohols,



**Scheme 1.** Rearranged *Aspidosperma* alkaloids: Structure and synthesis.

amines, amides, etc.) conspire against synthetic strategies directed at formation of C–C bonds, which makes these structures challenging targets for synthesis. We have been developing approaches for the synthesis of alkaloids that focus on cascade reaction sequences that use alternatives to acid–base chemistry; specifically, strategies based on either radical<sup>[8]</sup> or pericyclic reactions.<sup>[9]</sup>

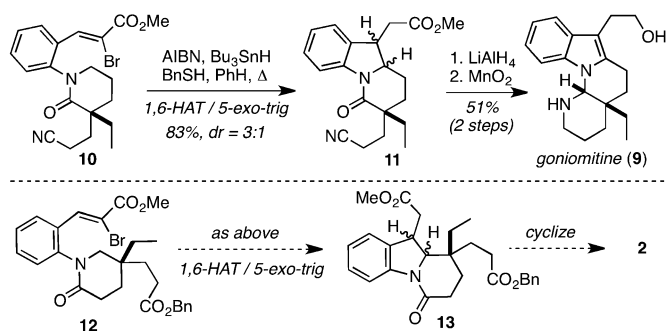
As is evidenced by previous approaches in this area [Scheme 1, Eq. (1),(2)], the key to building these *Aspidosperma* alkaloids is the creation of the indole bearing a C2-quaternary carbon. Our approach to such structures delays the formation of the substituted indole until after the *N*-aryl valerolactam has been assembled. Additionally, it uses radical reactions to form (rather than substitute) the 5-membered azole ring of the indole. These aspects make our strategy distinct from previous approaches to these targets.

For example, we synthesized the related *Aspidosperma* alkaloid goniomitine (9) from precursor 10 (Scheme 2, top).<sup>[10]</sup> Homolysis of the C–Br bond gives a vinyl radical, which undergoes a 1,6-hydrogen atom transfer (1,6-HAT, also called radical translocation) and spontaneous 5-*exo*-trig cyclization<sup>[11]</sup> to give indoline 11 as an inconsequential mixture of diastereomers in good yield. Goniomitine was prepared in two additional steps. This strategy benefits from the convergent union of valerolactam and cinnamate building blocks to make the radical substrate (10). Moreover, requisite functional groups to complete the target are tolerated by the radical cyclization, and endgame functional group manipulations are minimized.

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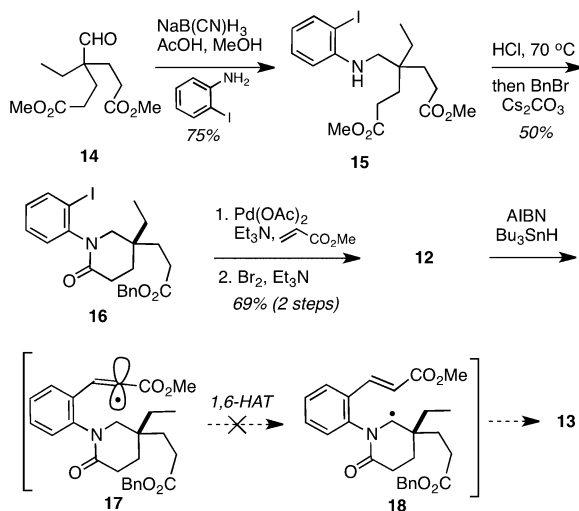


**Scheme 2.** Goniomitine synthesis and strategy for leuconoxine.

Application of our strategy was envisioned for leuconoxine (**2**, Scheme 2, bottom). Specifically, 1,6-HAT–5-*exo*-trig cyclization of **12** would give **13**. The ester functional groups would provide functional handles for cyclizations to give **2**. The envisioned leuconoxine radical cascade of **12** would be similar to the reaction of **10**; however, the radical translocation would occur adjacent to the quaternary carbon. Radical reactions are capable of constructing sterically hindered motifs, and the planned cascade would address the challenge of preparing the vicinal fully substituted quaternary and aminal carbons in the target.

The leuconoxine synthesis began with aldehyde **14**, which was prepared from butanal and two equivalents of methyl acrylate following literature precedent (Scheme 3).<sup>[12]</sup> Reductive amination of **14** with 2-iodoaniline gave **15**. Treatment of **15** with acid induced lactamization, with concomitant methyl ester hydrolysis. The carboxylic acid was protected as the benzyl ester (**16**). Heck coupling and subsequent bromination gave radical substrate **12**.

Treatment of **12** with radical conditions did not deliver the desired indoline products (**13**). Only the product of radical dehalogenation was observed. Bromide **12** differs from the goniomitine cyclization substrate **10** by the location of the quaternary center. Vinylic radicals such as **17** bearing  $sp^2$ -hybridized substituents are linear ( $\pi$ -type),<sup>[13]</sup> and this geom-

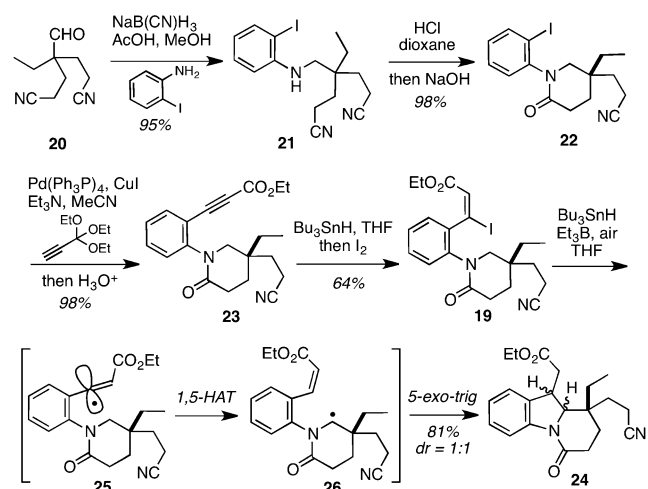


**Scheme 3.** 1,6-HAT Strategy for leuconoxine.

etry requires the ester to project directly into the sterically hindered quaternary carbon during the desired 1,6-HAT step. Steric hindrance of the quaternary carbon in **17** likely disfavors this reactive conformation leading to **18**, allowing hydrogen atom transfer from the reagent (that is, reduction) to kinetically outcompete translocation.

1,5-HAT reactions are far more common<sup>[14]</sup> than 1,6-HATs because the optimal linear geometry of  $R^{\bullet}\cdots H-C$  and the distance between reacting atoms is optimal in 1,5-HATs.<sup>[15]</sup> Moreover, it was anticipated that positioning the reactive radical at the benzylic position would relieve steric crowding in the HAT step (see below).<sup>[16]</sup>

The corresponding 1,5-HAT starting material (**19**) was prepared (Scheme 4). Dinitrile **20** (prepared from butanal and acrylonitrile)<sup>[12]</sup> participated in reductive amination to give **21**. It was found that treatment of **21** with acid led to an

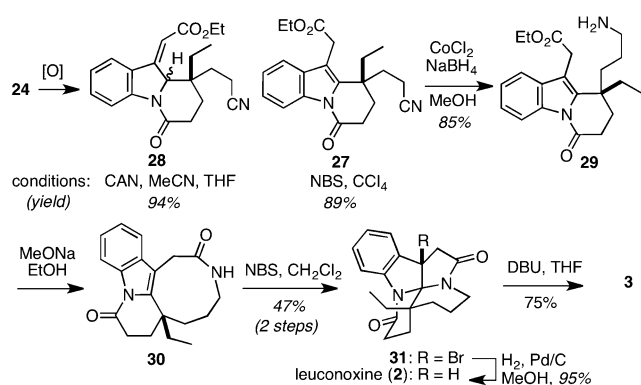


**Scheme 4.** 1,5-HAT Strategy for leuconoxine.

amidine, which could be hydrolyzed with base to *N*-iodophenyl lactam **22**, leaving the cyanoethyl group intact. Iodide **22** underwent Sonogashira coupling and hydrolytic workup to give alkyne **23**. Hydrostannylation-iodination gave **19** as a single regioisomer.<sup>[17]</sup> The alkene geometry and regiochemistry were confirmed by 2D-NOE correlations. Gratifyingly, **19** successfully cyclized to indolines **24** in good yield, as an inconsequential 1:1 mixture of *trans*-indoline diastereomers.

Homolysis of the C–I bond in **19** leads to radical **25**. In **25**, the linear  $\pi$ -type vinylic radical is located at the benzylic position, and the adjacent  $sp^2$ -hybridized (trigonal) carbon positions the ester group away from the quaternary carbon. This accommodates a reactive conformation for the 1,5-HAT step that out-competes reductive dehalogenation and gives the desired  $\alpha$ -amino radical **26**. Subsequent 5-*exo*-trig cyclization forms desired indolines **24**.

A variety of common oxidants were evaluated for the conversion of indolines **24** to the corresponding indole **27** (Scheme 5). Surprisingly, common oxidants (such as CAN) resulted in formation of unsaturated ester **28**. Ultimately, we found that oxidation of **24** with NBS<sup>[18]</sup> gave indole **27** in good yield. Presumably, this reaction occurs by a benzylic bromi-



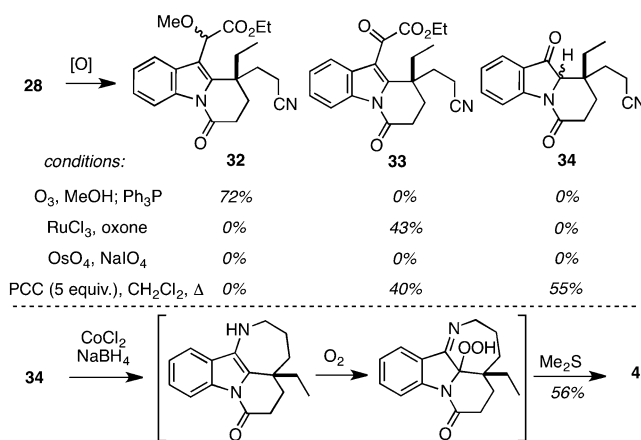
Scheme 5. Synthesis of leuconoxine and melodinine E.

nation–elimination sequence. Reduction of the nitrile gave amine **29**.

At this point, we envisioned a protonation of the indole in **29** to give an acyl imminium ion, which would be trapped by the tethered amine to form the central aminal. However, acid-mediated activation of indole **29** was unsuccessful, likely because of the presence of the basic amine functional group.

Serendipitously, it was discovered that treatment of **29** with NaOMe in ethanol gave smooth formation of the 9-membered lactam **30**. Interestingly, other combinations of alkoxide and alcohol (NaOMe/MeOH, NaOEt/EtOH, or NaOEt/MeOH) did not induce this transformation.<sup>[19]</sup> We suspect the reaction involves formation of a ketene intermediate, but at this time we cannot explain why this set of reaction conditions is superior to others. In any event, lactam **30** underwent transannular bromolactamization to give **31**. Hydrogenolysis of **31** gave leuconoxine (**2**), and elimination of bromide **31** gave melodinine E (**3**).

The production of the unanticipated CAN oxidation product **28** opened the possibility of a divergent synthetic route to mersicarpine (**4**). This required oxidative cleavage of the unsaturated ester in **28** (Scheme 6). However, treatment of **28** with a variety of standard oxidants (such as, O<sub>3</sub>, RuO<sub>4</sub>) routinely used for alkene cleavage<sup>[20]</sup> gave products of alkene oxidation (**32** and **33**), or no reaction (OsO<sub>4</sub>). We began to



Scheme 6. Synthesis of mersicarpine.

explore oxidants less commonly associated with oxidative cleavage reactions. Chromium-based reagents are known to effect alkene oxidations.<sup>[21]</sup> In particular, PCC is known to cleave electron-rich alkenes such as enol ethers,<sup>[22]</sup> and substituted styrenes.<sup>[23]</sup> However, we are unaware of examples of PCC mediating the cleavage of cinnamates. Nevertheless, subjecting of **28** to PCC gave the desired ketone **34** as the major product along with some indole glyoxylate **33**.<sup>[24]</sup> Selective reduction of the nitrile in **34** presumably gave the amine, which underwent spontaneous cyclization to the corresponding enamine, oxidation by air, and peroxide reduction to give mersicarpine (**4**).<sup>[3e]</sup>

In summary, we have synthesized leuconoxine, melodinine E, and mersicarpine. Our synthesis features a 1,5-HAT–5-*exo*-trig radical cascade reaction to give a substituted indoline product (**24**). The indoline intermediate was a common precursor to the three title natural products. Leuconoxine and melodinine E were accessed using a transannular bromo-lactamization. Mersicarpine was prepared using an unusual PCC oxidative cleavage of an unsaturated ester. Efforts to apply the key radical reaction in other alkaloid architectures are currently underway in our laboratory.

## Acknowledgements

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** leuconoxine · melodinine E · mersicarpine · radical reactions · total synthesis

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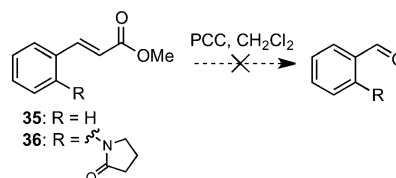
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