Total Synthesis

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Enantioselective Pd-Catalyzed Allylic Alkylation Reactions of Dihydropyrido[1,2-*a*]indolone Substrates: Efficient Syntheses of (−)-Goniomitine, (+)-Aspidospermidine, and (−)-Quebrachamine

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Dedicated to Professor K. C. Nicolaou on occasion of his 70th birthday

Abstract: *The successful application of dihydropyrido[1,2-a]indolone (DHPI) substrates in Pd-catalyzed asymmetric allylic alkylation chemistry facilitates rapid access to multiple alkaloid frameworks in an enantioselective fashion. Strategic bromination at the indole C3 position greatly improved the allylic alkylation chemistry and enabled a highly efficient Negishi cross-coupling downstream. The first catalytic enantioselective total synthesis of (−)-goniomitine, along with divergent formal syntheses of (+)-aspidospermidine and (−)-quebrachamine, are reported herein.*

Monoterpene indole alkaloids have been extensively studied by chemists and biologists alike due to their vast structural diversity and broad biological activity.[1] (−)-Goniomitine (**1**), isolated from the bark of *Gonioma malagasy*, is an *Aspidosperma* alkaloid with a unique octahydroindolo[1,2-*a*][1,8]naphthyridine core (Figure 1).[2]

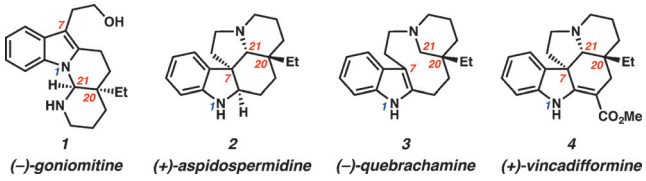
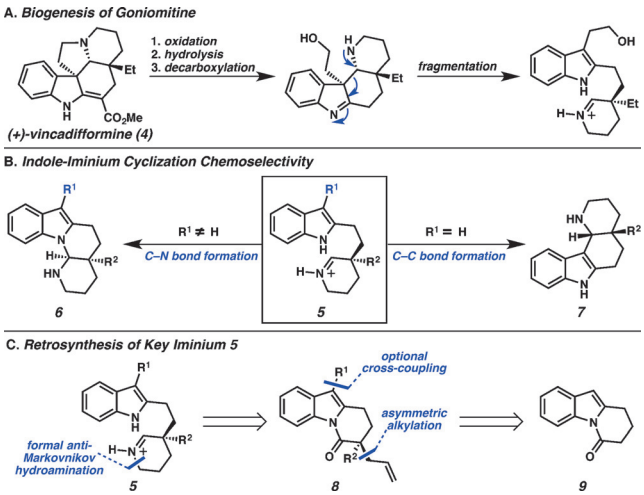


Figure 1. Skeletally diverse *Aspidosperma* alkaloids.

The key structural differences between goniomitine (**1**) and many *Aspidosperma* alkaloids (e.g., **2**–**4**, Figure 1)[3] are the aminal functional group at C21 and the vestigial (2-hydroxy)-ethyl moiety at C7.[4]

Biosynthetically, these features are believed to arise from oxidative degradation of the tryptamine fragment in vincadifformine (**4**, Scheme 1 A) followed by fragmentation and N1−C21 recombination.[5] Cyclizations between an indole and a C2-tethered iminium moiety (**5**, Scheme 1 B) are remarkably chemoselective. In the case of a C3-substituted indole fragment (e.g., **5**, $R^1 \neq H$), cyclization proceeds via C–N bond formation to furnish aminal-containing tetracycle **6**, as seen in previous syntheses of goniomitine (**1**).[5–7] Conversely, a C3-unsubstituted indole fragment (**5**, $R^1 = H$) undergoes C–C bond formation followed by rearomatization to arrive at alternative tetracycle **7**, a core that is present in numerous alkaloids (e.g., **2** and **4**).[8] We anticipated that iminium intermediates such as **5** could be accessed in straightforward fashion from compounds containing a dihydropyrido[1,2-*a*]indolone (DHPI) core (Scheme 1 C). Retrosynthetically, we envisioned that the propylamine fragment in **5** could arise from an anti-Markovnikov hydroamination of the allyl functionality in α-quaternary lactam **8**. Given our long-standing interest in the asymmetric synthesis of all-carbon quaternary centers, we believed that we could employ our Pd-catalyzed allylic alkylation chemistry to construct the quaternary stereocenter at C20 in an enantioselective fashion.[9,10] We expected that a cross-coupling reaction could enable optional substitution at the C3 position of the DHPI scaffold, thereby providing selective routes to tetracycles **6** and **7**. Therefore, development of this versatile substrate class in our Pd-catalyzed allylic alkylation chemistry would provide



Scheme 1. A) Biogenesis of goniomitine from vincadifformine. B) Effects of C3 substitution on indole–iminium cyclization. C) Retrosynthetic analysis of **5**.

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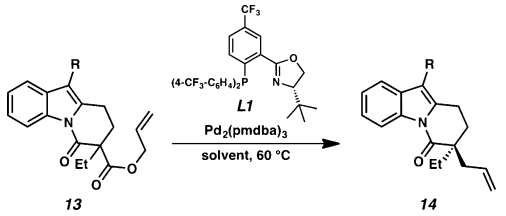
a powerful tool for divergent enantioselective syntheses of multiple *Aspidosperma* alkaloids.

Owing to its antiproliferative activity and unusual structure, several groups have targeted goniomitine (**1**) for total synthesis.[6,7] While modern approaches to this molecule have improved upon the seminal report by Takano and co-workers,[7a] a synthesis of goniomitine (**1**) that employs asymmetric catalysis to achieve stereocontrol has not yet been demonstrated. To date, asymmetric syntheses of goniomitine (**1**) have relied on either enzymatic resolutions or chiral pool materials.[7] Furthermore, in previous syntheses of goniomitine, unless the (2-hydroxy)ethyl moiety was incorporated using a tryptophol-derived starting material, a multi-step sequence from an unsubstituted C7 position was required. We instead anticipated that a cross-coupling reaction between a C3-brominated DHPI and a suitable organometallic reagent would enable efficient access to the (2-hydroxy)ethyl fragment in the natural product. Realization of this synthetic plan would deliver the first catalytic enantioselective total synthesis of (−)-goniomitine (**1**).

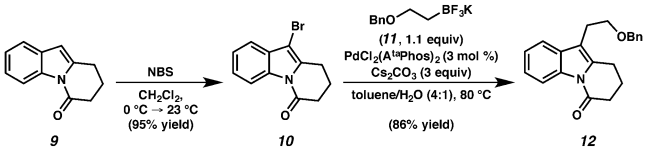
Table 1: Pd-catalyzed asymmetric allylic alkylation of DHPI substrates.[a]



Entry	R (*13*→*14*)	Solvent	$Pd_2(pmdba)_3$ [mol%]	Ligand [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	CH_2CH_2OBn (*13a*→*14a*)	toluene	10	25	72	38	89
2	CH_2CH_2OBn (*13a*→14a)	TBME	10	25	24	59	87
3	Br (13b→14b)	toluene	5	12.5	24	21	93
4	Br (*13b*→*14b*)	TBME	5	12.5	8	83	96
5	H (*13c*→*14c*)	toluene	10	25	48	54	92
6	H (*13c*→*14c*)	TBME	5	12.5	24	71	94

[a] Reactions were performed in stated solvent (0.033 M) at 60 °C. [b] Yield of isolated product. [c] Determined by chiral SFC. [d] pmdba = 4,4′-dimethoxydibenzylideneacetone.

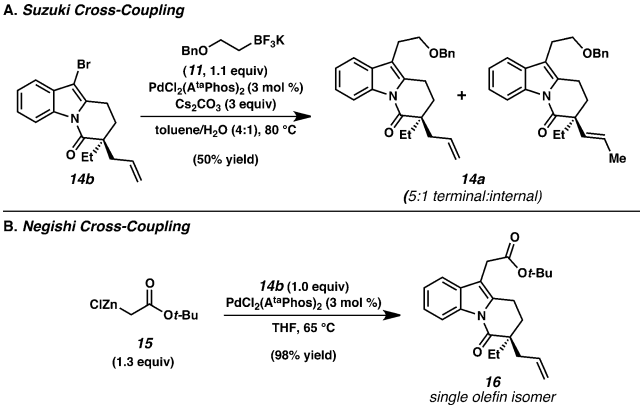
Our synthesis of (−)-goniomitine (**1**) commenced from known *N*-acyl indole **9**,[11] which underwent regioselective bromination to give heteroaryl bromide **10** in 95% yield (Scheme 2). Treatment of **10** with potassium (2-benzyloxy)ethyl trifluoroborate (**11**) and catalytic $PdCl_2(A^{ta}Phos)_2$ afforded cross-coupled product **12** in 86% yield.[12,13] Facile C-acylation and -alkylation of tricycles **9**, **10**, and **12** positioned us to investigate the heretofore untested asymmetric allylic alkylation of the dihydropyrido[1,2-*a*]indolone (DHPI) substrate class.[14]



Scheme 2. Suzuki cross-coupling of a 3-bromoindole fragment. [a] $A^{ta}Phos$ = di-*tert*-butyl(4-dimethylamino)phenylphosphine.

Exposure of (2-benzyloxy)ethyl-substituted DHPI **13a** to standard Pd-catalyzed decarboxylative allylic alkylation conditions yielded the α-quaternary product **14a** in 38% yield and 89% enantiomeric excess (Table 1, Entry 1). Switching from toluene to TBME as solvent greatly improved the reaction rate and yield, albeit with a minor decrease in enantioselectivity (Entry 2). Previous studies by our group have revealed that electron-withdrawing substituents on the lactam nitrogen atom provide the best results in the allylic alkylation chemistry.[9b] As the enolate intermediate would be in cross-conjugation with the arene π-system, we postulated that a bromide at the C3 position could provide both a beneficial electronic effect and a handle for cross-coupling downstream. While there are numerous reports of aryl bromides withstanding the conditions of Pd-catalyzed allylic alkylation reactions, their strategic implementation for cross-coupling events following the allylic alkylation is comparatively limited.[15] Gratifyingly, brominated β-amidoester **13b** reacted to give the desired quaternary alkylated product **14b** (Entries 3 and 4), which in TBME was afforded in 83% yield and 96% *ee* with no observable interference from the C3 bromide (Entry 4). Given that the successful inclusion of a C3–H substrate in our allylic alkylation chemistry would enable divergent construction of additional alkaloids (see Scheme 1B), we were pleased to find that β-amidoester **13c** could deliver α-quaternary lactam **14c** in 71% yield and 94% *ee* (Entry 6).

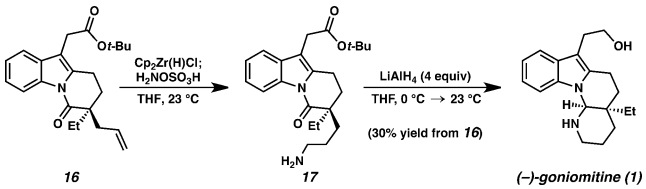
We next turned our attention toward the cross-coupling of brominated α-quaternary lactam **14b** with a suitable hydroxyethyl surrogate. Unfortunately, we found that the Suzuki reaction between **14b** and trifluoroborate **11** could not be improved beyond a 50% yield of inseparable olefin isomers **14a** in a 5:1 ratio (Scheme 3A). We hypothesized that a Pd–H species was responsible for this undesired isomerization pathway, and sought to identify an alternative C_{sp^3} nucleo-



Scheme 3. Cross-coupling reactivity of α-quaternary DHPI **14b**.

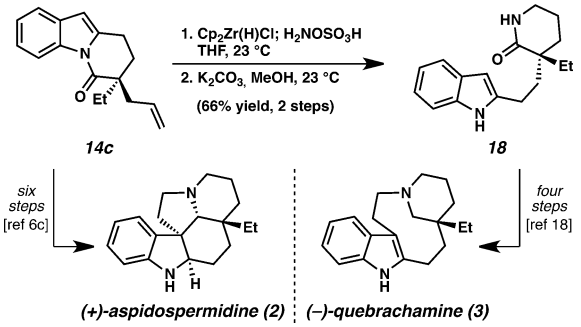
philic coupling partner that would not allow for facile β-hydride elimination. Recognizing that a reduction would ultimately be required to convert the amide present in **14b** to the aminal present in goniomitine (**1**), we decided to incorporate a substituent in a higher oxidation state via the cross-coupling, thereby allowing concomitant unveiling of the (2-hydroxy)ethyl moiety at a later stage. After investigating a multitude of Negishi conditions, we were thrilled to find that Reformatsky reagent **15** could be efficiently coupled with heteroaryl bromide **14b** using catalytic $PdCl_2(A^{ta}Phos)_2$ to deliver arylated product **16** in 98% yield without any detectable amount of undesired olefin isomers (Scheme 3B).[16]

With the requisite carbon–carbon bonds established, we began investigating methods to effect an anti-Markovnikov hydroamination of the terminal olefin of **16**. To this end, we employed a one-pot hydrozirconation/amination sequence reported by Hartwig and co-workers.[17] To our knowledge, this is the first implementation of Hartwig's hydrozirconation/amination procedure in the context of natural product synthesis. Following this formal hydroamination, we were pleased to find that complete reduction of the *tert*-butyl ester of **17** could be achieved alongside partial reduction of the amide carbonyl in one pot using a single reductant. In the event, primary amine **17** was subjected to $LiAlH_4$ in THF, followed by acidic workup, to afford (−)-goniomitine (**1**) in 30% yield from **16** (Scheme 4).



Scheme 4. Completion of the synthesis of (−)-goniomitine.

Having completed the total synthesis of (−)-goniomitine (**1**), we sought to leverage the flexibility of the DHPI scaffold by exploiting the chemoselectivity in cyclizations of an indole with a C2-tethered iminium functionality (Scheme 1B). Indeed, the synthesis of **14c** completes an enantioselective formal synthesis of (+)-aspidospermidine (**2**, Scheme 5).[6c]



Scheme 5. Asymmetric formal syntheses of other *Aspidosperma* alkaloids.

Furthermore, treatment of **14c** with the aforementioned hydroamination conditions followed by a mild amide exchange furnishes free N–H α-quaternary δ-lactam **18** in 66% yield over two steps, constituting an asymmetric formal synthesis of (−)-quebrachamine (**3**).[18]

In summary, we have completed the first catalytic enantioselective total synthesis of (−)-goniomitine (**1**) in 11 steps and 8% overall yield from indole, or 7 steps and 17% overall yield from known DHPI **9**. The redox efficiency and freedom from protecting-group manipulations is a marked improvement from previous nonracemic syntheses, which deliver the target in 10–28 steps and 0.25–3.2% overall yield from commercial materials. Rationally designed heteroaryl bromide **13b** underwent Pd-catalyzed allylic alkylation to deliver the α-quaternary product (**14b**) in 83% yield and 96% *ee*. The surprisingly robust C_{aryl}–Br bond served as a handle for a subsequent Negishi cross-coupling. The compatibility of aryl bromides in our allylic alkylation reactions, along with the identification of cross-coupling conditions that do not isomerize the allyl group, provide a powerful platform for the convergent synthesis of complex organic molecules. Additionally, by completing formal syntheses of (+)-aspidospermidine (**2**) and (−)-quebrachamine (**3**), we demonstrate the ability of the DHPI scaffold to provide divergent, enantioselective access to structurally diverse alkaloid frameworks. Efforts to expand upon the capabilities of allylic alkylation/cross-coupling sequences and to further exploit the utility of DHPIs in the context of alkaloid total synthesis will be reported in due course.

Acknowledgements

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