Chemical Synthesis of Aspidosperma Alkaloids Inspired by the Reverse of the Biosynthesis of the Rhazinilam Family of Natural Products**

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Pyrrole and pyrroldine heterocycles are ubiquitous structural features in natural products. Nature's biosynthetic machinery often synthesizes the pyrrole functionality in these molecules from a saturated pyrrolidine as part of its metabolic degradation pathway.^[1] Interestingly, the chemical synthesis of substituted pyrroles is usually more straightforward in comparison to that of the corresponding pyrrolidines; the saturated hydrocarbon framework of pyrrolidine is relatively unreactive,^[2] usually requiring the presence of additional functional groups to install a particular substituent, thus rendering the synthesis of such compounds difficult in comparison to their aromatic congeners. Therefore, the transformation of a highly substituted pyrrole into an architecturally complex pyrrolidine becomes an attractive and potentially powerful strategy for total synthesis (Figure 1 A). $^{[3,4]}$

Herein, we report the realization of this ideal through a reductive transannular cascade strategy that transforms the pyrrole-containing aromatic metabolite, rhazinilam (1a), directly into aspidospermidine (2), a more complex pyrrolidine-containing natural product possessing a core molecular architecture that is common to a large number of terpeneindole alkaloids (Figure 1B).^[5] This strategy exploits the reactivity of the substituted pyrrole ring by triggering a cascade reaction that results in a dramatic structural rearrangement; pyrrole-containing metabolites are transformed into pyrrolidine-containing natural products. Key to the implementation of this synthesis is the use of metalcatalyzed C-H bond functionalization^[6] to introduce the desired substituents selectively and sequentially around the pyrrole ring,^[7] thereby allowing rapid assembly of the core framework of rhazinilam.^[8,9] The confluence of this concise pyrrole functionalization tactic with the complexity-generating cascade delivers a powerful synthetic process capable of converting planar heteroarenes into architecturally complex alkaloid natural products.^[10] Moreover, this approach could

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have great potential in drug-discovery programs because the structural diversification would generate a completely different scaffold that may have biological properties that are different from those of the parent pyrrole compound.^[11]

Implementing total-synthesis strategies using multiple metal-catalyzed C-H bond functionalizations is still a significant challenge.^[12] Controlling which C-H bond transforms becomes more difficult as the complexity of the molecular environment increase. Accordingly, we envisioned that a metal-catalyzed C-H arylation process at the C3 position of a simple pyrrole derivative would give the central biaryl motif, a position that is not normally reactive in conventional pyrrole chemistry (Scheme 1A). Functionalization of the C2 position was planned through a C-H alkenylation process that not only builds the all-carbon quaternary center, but also installs the topological features that define the structure of the natural product. Furthermore, commencing our synthesis using 2-carbomethoxypyrrole derivative 5 could provide a handle to control the site selectivity of the two metalcatalyzed C-H bond functionalizations on the heteroarene, and also engage a divergent endgame that would deliver rhazinilam (1a),^[8] kopsiyunnanine C3 (1b)^[13] and other natural-product congeners.

We employed the first of our proposed metal-catalyzed C-H bond functionalization reactions to build the heterobiaryl fragment (Scheme 1B). While we had used this tactic in our synthesis of rhazinicine,^[12a] our divergent strategy for the synthesis of rhazinilam and kopsiyunnanine C3 required us to start from a different pyrrole, 8. Pleasingly, application of the Ir^I-catalyzed C-H borylation methodology, developed by the research groups of Smith and Maleczka^[14a] and the research groups of Hartwig, Miyaura, and Ishiyama,^[14b,c] enabled exploitation of the synergistic steric effects of the N-Boc and 2-carbomethoxy groups and led to borylation of the pyrrole at the C4 position-the only C-H bond not adjacent to any other substituent. Immediate addition of orthoiodonitrobenzene (6), catalytic Pd(OAc)₂, S-Phos, and K_3PO_4 in *n*BuOH to the reaction mixture facilitated a Suzuki coupling reaction,^[15] which completed the C-H arylation process, as well as removal of the Boc group, thus affording the heterobiaryl compound 9 in 63% yield from 8. The process required only one purification step and was amenable to being conducted on multigram scale. In common with our synthesis of rhazinicine,^[12a] 11 was available in 3 steps from 10, in 79% overall yield (Scheme 1 C). Reduction of carboxylic acid 11 with sodium borohydride, via the mixed acylcarbonate, afforded the primary alcohol, which was converted into iodide 12. Fragment union of 9 and 12

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A. New strategies for the synthesis of substituted pyrrole and pyrrolidines



Figure 1. Synthesis blueprint.

proceeded smoothly through treatment of pyrrole **9** with NaH in DMF before addition of iodide **12**, thus forming the key alkyl pyrrole **13** in 85% yield.

With the entire acyclic backbone of rhazinilam in place, the remaining steps focused on "zipping up" the linear system 13 to the natural products 1a and 1b. Construction of the allcarbon quaternary center was initially planned through an intramolecular Pd^{II}-catalyzed C-H bond alkenylation (Scheme 1D), a strategic disconnection similar to that deployed in our rhazinicine synthesis. We first applied the reaction conditions adapted from the rhazincine synthesis to the transformation of compound 13, but disappointingly, even with a stoichiometric amount of Pd(OTFA)₂, a low yield of 14 was observed (Scheme 1D, entry 1). This reaction is thought to proceed through electrophilic palladation of the pyrrole, a pathway favored for electron-rich arenes. However, the nucleophilicity of pyrrole 13 is relatively low owing to the presence of the 2-carbomethoxy substituent and therefore palladation may be suppressed, thus resulting in poor reactivity.

While considering this problem, we reasoned that palladation proceeding through concerted metalation-deprotonation (CMD) C-H bond cleavage would be more suited to the electron-deficient pyrrole 13,^[16] because this pathway is facilitated by the acidity of the C-H bond. We were, however, conscious that the relatively acidic C-H bond ortho to the nitro group on the other arene might undergo competitive palladation, or that the carbomethoxy substitutent would potentially direct the reaction to the position adjacent to the ester group. Pleasingly, we found that under reaction conditions reported by Liégault and Fagnou for the Pd^{II}-catalyzed alkylation of pyrroles,^[17] the desired intramolecular catalytic C-H alkenylation reaction to give 14 proceeded in a low but encouraging 15% yield (Scheme 1D, entry 4). Only trace byproducts were observed and the remaining mass balance was starting material. Subsequent investigations of this intramolecular oxidative Heck reaction led to optimal reaction conditions (Scheme 1D, entry 6) requiring treatment of 13 with 10 mol% Pd(OAc)₂, 20 mol% NaOtBu, and 10 mol% DMF in pivalic acid at 110°C under a balloon of oxygen to afford the desired product **14** in 60% yield (78% based on recovered starting material). Notably, the use of oxygen as a terminal oxidant reinforces the efficiency of this C–H alkenylation process, through which we have introduced an extremely sterically hindered structural feature of the rhazinilam natural products from the readily assembled pyrrole **13**.

Having installed the key architectural features of rhazinilam, the remaining steps, comprising global hydrogenation, cleavage of the TSE ester, and macrolactamization, proceeded smoothly to give methyl ester **15** in 70% yield over three steps. The presence of the C2 ester group in **15** provided an ideal handle to implement our divergent endgame strategy. Saponification, followed by decarboxylation of the C2 ester group, afforded rhazinilam (**1a**) in 68% yield; on the other hand, DIBAL-H reduction of the same C2 ester group delivered kopsiyunnanine C3 (**1b**), thus completing the first total synthesis of this natural product (Scheme 1E). The longest linear sequence in the divergent synthesis of both rhazinilam and kopsiyunnanine C3 is 11 steps with 15% and 16% overall yields, respectively.

With an expedient method for the functionalization of pyrroles established, we were then able to return to our initial question: can these substituted pyrroles be converted directly into architecturally more-complex pyrrolidines? We reasoned that the inherent nucleophilicity of the pyrrole moiety could be used to induce an alkylation reaction on the heteroarene at a position bearing a substituent, a transformation that would be followed by interception of the consequent pyrrolium ion with a reducing agent, thus completing an alkylative–reductive dearomatization event (Figure 2). The resulting pyrrolidine would display a quaternary carbon center as part of the intricate array of new stereogenic centers, installed directly from the planar pyrrole.

Rhazinilam (1a) and aspidospermidine $(2)^{[18]}$ display a number of congruent features including a common quaternary stereogenic center (C9), as well as pyrrole and pyrrolidine rings at the heart of their respective structures (Figure 1B). The crucial difference between the framework connectivity of rhazinilam and aspidospermidine was the presence or absence of a C–C bond between the C12 and C4

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substituted dearomatized structurally arene nplex molecule Figure 2. Propagation of structural complexity: pyrroles to pyrrolidines.

reduction

H(-)

alkylative

dearomatization

of transforming one class of natural product into a structurally different natural product, we analyzed the three-dimensional structure of rhazinilam and noted that the C12-amide carbonyl group, a moderately electrophilic functionality, was located in close proximity to the C4 position of the pyrrole motif. Therefore, conversion of this C12 amide into a more reactive iminium functionality would potentially trigger a transannular nucleophilic attack of the pyrrole onto this electrophilic species, thereby generating the C-C bond essential for the connectivity of aspidospermidine. Accordingly, addition of a Boc group to the nitrogen atom of the C12 amide gave 16, which was reduction using LiBHEt₃ (Scheme 2). Immediate treatment of the reaction mixture with acetic anhydride and DMAP allowed in situ acylation, thus furnishing the desired acetylated hemiaminal 16a, which was directly treated with trifluoroacetic acid, thus generating the desired iminium species 16b and initiating the planned cascade reaction. Gratifyingly, this iminium intermediate underwent C4-C12 transannular bond formation, forming 16c. After two hours, NaCNBH₃ was added, stereoselectively reducing the pyrrolium ion, as well as the enamine motif to give 17. Treatment with trifluoroacetic acid afforded aspidospermidine (2), thus completing the synthesis of the natural product in just three steps from rhazinilam (1b) in 47% yield. The complexity-generating transannular cascade process forms two new stereocenters and two new rings, which are present in aspidospermidine, the core structure of which is prevalent in the indole-terpene alkaloid family of natural products. Furthermore, this remarkable transformation is the reverse of a proposed biosynthesis that oxidatively degrades the aspidosperma alkaloids to rhazinilam.^[19]

The pyrrole and pyrrolidine heterocyclic motifs, present at the heart of rhazinilam and aspidospermidine, impart the conformational restrictions that most likely define the structure and biological properties of these natural products. Our bioinspired transformation, which converts a rapidly assembled pyrrole into a complex pyrrolidine, therefore leads to a dramatic change in the structural, functional, and physical properties of the parent molecule and generates a completely different natural product scaffold. It is this diversification that we believe could have great potential in the search for molecules with novel therapeutic properties.

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Scheme 1. Divergent and modular synthesis of rhazinilam alkaloids.

Ac = acetyl, Boc = t-butoxycarbonyl, cod = 1,5-cyclooctadiene, DCE = dichloroethane, DIBAL-H = diisobutylaluminum hydride, DMF = N, N-dimethylformamide, pin = pinacolate, Piv = pivalyl,

S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl,

TFA = trifluoroacetyl, TSE = trimethylsilylethyl.

rhazinilam 1a 11 steps. 15% overall vield

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kopsiyunnanine C3 1b

11 steps. 16% overall vield

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Scheme 2. Transformation of rhazinilam to aspidospermidine. DMAP=4-(dimethylamino)pyridine, TFA=trifluoroacetic acid.

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Natural Product Synthesis

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Chemical Synthesis of Aspidosperma Alkaloids Inspired by the Reverse of the Biosynthesis of the Rhazinilam Family of Natural Products



Pyrrole reduction: Iterative metal-catalyzed C–H functionalization reactions facilitated the preparation of a highly substituted pyrrole derivative. This derivative could be transformed into the pyrrole-containing secondary metabolite, rhazinilam, which could in turn be transformed through a reductive transannular cascade process into the structurally complex pyrrolidine-containing alkaloid natural product, aspidospermidine.