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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Concise Synthesis of Alkaloid (−)-205B

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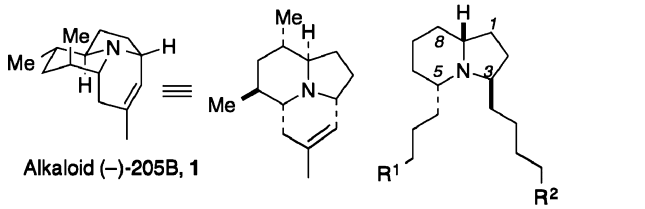
Supporting Information

ABSTRACT: Described herein is a short total synthesis of alkaloid (−)-205B (**1**) by means of an anti-selective S_N2' alkylation of an attractively functionalized cyclopropanol and diastereoselective cyclization of the resulting aminoallene adduct for bicyclic ring formation. The synthesis features a general route to *cis*- or *trans*-2,6-disubstituted piperidines by lithium aluminum hydride reduction of the imine intermediate by an appropriate choice of solvent and *cis*- or *trans*-2,5-disubstituted pyrrolidines by an exceptional level of chirality transfer from a pendant allene. Particularly noteworthy are the brevity and convergence made possible by a segment-coupling strategy.

Part of our research program has been directed at the development of a general synthetic method for indolizidines, pyrrolizidines, and related alkaloids with particular emphasis on selectivity, efficiency, and convergence. Neotropical poisonous frogs *Dendrobates* have been a rich source of a structurally diverse array of alkaloids, including indolizidines, pyrrolizidines, quinolizidines, and piperidines.[1] A subset of amphibian alkaloids are characterized by the presence of two alkyl substituents at C3 and C5, as exemplified by alkaloid (−)-205B (**1**) and indolizidines (−)-223AB (**2**), (−)-239AB (**3**), and (−)-239CD (**4**).[2] As a logical progression of our recently disclosed syntheses of **2**−**4**,[3] the structurally more complex tricylic alkaloid (−)-205B (**1**) was chosen as the next target for adaptation of a unified approach. The isolation and structure elucidation of **1** was reported by Daly and co-workers.[4] The first synthesis of the unnatural (+)-antipode of **1** by the Toyooka and Nemoto group in 2003 established its absolute configuration.[5] Interestingly, the unnatural (+)-**1** was reported to selectively inhibit α_7-nicotinic acetylcholine receptors (nAChRs).[6] There have been no complete pharmacological studies of (−)-**1**, probably because of its scarcity. The intricate structure of **1**, coupled with interest in biological evaluation, prompted three recent syntheses by the Smith, Comins, and Micalizio groups.[7−9] These syntheses utilized conceptually different approaches to streamline the overall synthetic operations. In view of the heightened interest in the design and development of selective nAChR modulators, especially α_7 receptors,[10] a practical gram-scale synthesis of **1** is highly desirable. We herein describe a concise synthesis of (−)-**1** by an efficient coupling of an attractively functionalized cyclopropanol and an (*R*)-propargylic tosylate.

Structurally, **1** is composed of a 2,6-*trans*-piperidine adorned with two methyl groups, a 2,6-*cis*-Δ^3-piperidine, and



Alkaloid (−)-205B, **1**

Indolizidine (−)-223AB, **2** (R^1, R^2=H)
Indolizidine (−)-239AB, **3** (R^1=OH, R^2=H)
Indolizidine (−)-239CD, **4** (R^1=H, R^2=OH)

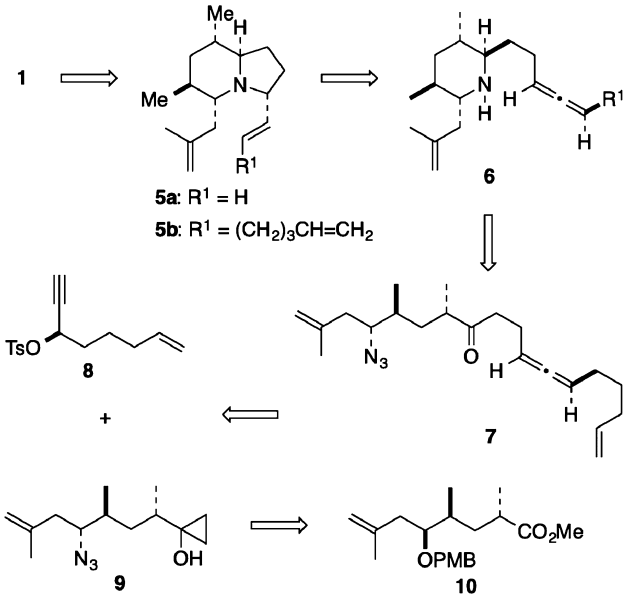
a 2,5-*trans*-pyrrolidine that are encased within the tricyclic skeleton. Our principal objective was to devise a convergent strategy that would be flexible enough to allow the stereoselective synthesis of **1** and other possible stereoisomers as well as *cis*- or *trans*- piperidines and pyrrolidines, common structural motifs in organic synthesis and medicinal chemistry.[11] An attractive solution was found in anti-selective S_N2' alkylation of attractively functionalized yet readily available cyclopropanols, one of the C−C bond-forming reactions of cyclopropanols recently developed in our group.[12,13] A point of departure from previous syntheses was easy preinstallation of the two methyl groups onto the cyclopropanol partner to obviate the need for their subsequent introduction. Thus, (−)-**1** was viewed as an excellent testing ground to highlight the utility of cyclopropanols as a versatile platform in natural product synthesis. Additionally, it should be emphasized that the use (e.g., alkylation) of cyclopropanols as homoenolate equivalents offers greater advantage than ester homoenolates in the rapid assembly of two large segments.

In our synthetic planning, the only double bond of **1** was the obvious site for ring-closing metathesis (RCM) to unveil **5**, an indolizidine having two side chains at the C3 and C5 positions (Scheme 1). As was the case in our recent syntheses of **2**−**4**,[3] anti-S_N2' alkylation of cyclopropanol **9** with propargylic tosylate **8** and subsequent electrophilic allene cyclization of **6** could offer a short route to **1**. Exceptional chirality transfer from the tethered allene in the stereoselective cyclization of each aminoallene antipode was demonstrated in the total syntheses of **2** and its 3-epimer.[3] An enantiopure allene was a prerequisite for the stereoselective formation of a 2,5-*trans* (or, when desired, *cis*)-disubstituted pyrrolidine, which in turn prompted us to prepare **5b** (over **5a**) to set the stage for a relay RCM.[14] Impressive recent advances in gold- or silver-catalyzed elaboration of allenes notwithstanding,[15] there are surprisingly only a handful of applications in

Received: January 8, 2015
Published: January 30, 2015

DOI: 10.1021/jacs.5b00243
J. Am. Chem. Soc. 2015, 137, 2243−2246

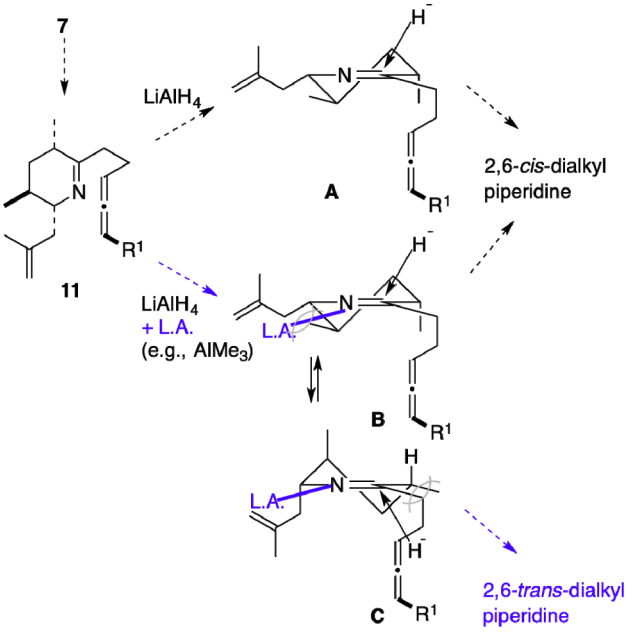
Scheme 1. Retrosynthetic Analysis of (−)-1



alkaloid synthesis, and known examples are limited primarily to monocyclic ring formation.[16,17]

The key intermediate **5b** contains a highly decorated 2,6-*trans*-piperidine subunit, which contrasts with the 2,6-*cis*-counterpart present in **2**−**4**. The latter stereochemical arrangement is known to be readily accessible by the stereoelectronically controlled addition of a hydride nucleophile to the six-membered cyclic imine (see **A**) or iminium ion (Scheme 2).[18,19] In contrast, stereoselective formation of 2,6-*trans*-piperidines presents a challenge but might be possible by adaptation of Yamamoto's method, which exploits the minimization of $A^{1,2}$ steric interactions.[19] A careful analysis of plausible transition states related to imine **11** under Yamamoto's conditions raised serious concerns: there may be only a small difference in energy between the two limiting

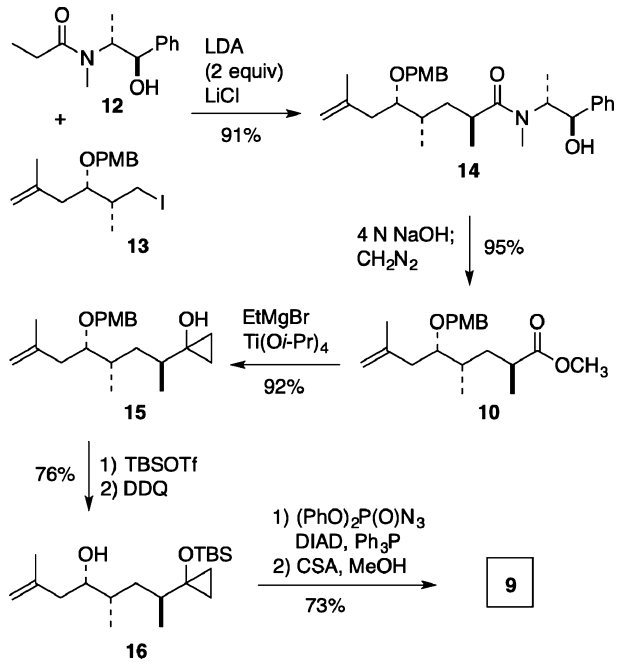
Scheme 2. Formation and Reduction of Imine 11



half-chair conformers **B** and **C** due to competing $A^{1,2}$ strain, and the presence of a Lewis acid could promote the formation of the corresponding metalloenamine, leading to epimerization of the adjacent stereocenter. Unfortunately, there is a dearth of literature precedents on the applicability of Yamamoto's protocol to *substituted* piperidinium ions. If successful, however, the imine reduction strategy would provide a divergent route to both 2,6-*cis*- and -*trans*-piperidines from common imine intermediates. Because of the potential impact, we decided to forge ahead with the identification of suitable conditions for stereoselective reduction of cyclic imine **11**.

Our segment coupling approach to (−)-**1** entailed the preparation of two segments **8** and **9**. The synthesis of cyclopropanol **9** commenced with Myers' asymmetric alkylation[20] of commercially available **12** with iodide **13** (readily available from the corresponding diol)[21] to afford **14** in 91% yield (with >20:1 ds) (Scheme 3). The latter

Scheme 3. Preparation of Cyclopropanol 9

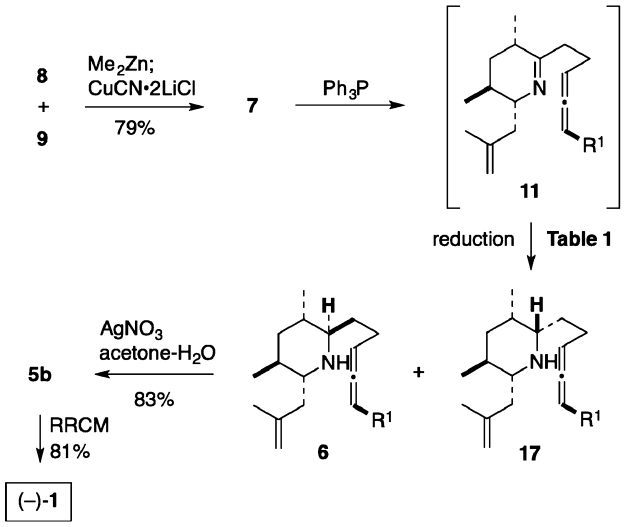


compound was then converted to the corresponding methyl ester **10** in 95% yield by standard methods. The Kulinkovich cyclopropanation of ester **10** proceeded cleanly to deliver cyclopropanol **15** in 92% yield.[22] Straightforward functional group manipulation gave alcohol **16** in 76% yield. Stereoselective displacement of the secondary alcohol of **16** with diphenylphosphoryl azide, followed by desilylation, furnished azide **9** in 73% yield. The coupling partner **8** was easily prepared in two steps from a known compound.[23]

The key cross-coupling reaction of **8** and **9** at room temperature under previously reported conditions[3,12] afforded **7** in 79% yield (Scheme 4). With **7** in hand, the remaining tasks called for the sequential construction of the three heterocycles by stereoselective elaboration of two sp^2 carbons to the respective sp^3 stereocenters. Aza-olefination of **7** by the action of Ph_3P gave imine **11** cleanly to set the stage for in situ reduction to prepare piperidine **6** in preference to **17**. According to a screening of common reducing agents, our initial concern that the imine intermediate could be prone to

DOI: 10.1021/jacs.5b00243
J. Am. Chem. Soc. 2015, 137, 2243−2246

Scheme 4. Total Synthesis of Alkaloid (−)-205B (1)



tautomerization and the accompanying epimerization at the methyl stereocenter appeared to be well-founded (Table 1). Tautomerization/epimerization, not surprisingly, was more pronounced in a protic solvent (entry 1). Similarly, the use of a sterically hindered Lewis acid (e.g., Me_3Al or Et_3Al), the salient feature of Yamamoto's elegant tactic, also appeared to promote tautomerization (entries 2−6). Despite a recent renaissance in asymmetric reduction of imines and derivatives,[24] there were very few examples involving imines having α-stereocenters in the literature.[25] Instead of searching for different hydride reagents and Lewis acids, we were intrigued by the uncommon solvent effects in lithium aluminum hydride (LAH) reduction of the penultimate imine intermediate reported in the synthesis of solenopsin A, a prototype 2,6-*trans*-piperidine. The degree of selectivity was modest, but the reversal (in Et_2O vs THF or CH_2Cl_2) was striking.[19a,b] If the diastereomeric ratio could be improved, this simple tactic based on a judicious choice of solvent would provide an attractive route to either 2,6-*cis*- or -*trans*-piperidines. Ultimately, LAH reduction of **11** in Et_2O gave a satisfactory solution to afford **6** in 67−70% yield in a 15−19:1 ratio (entry 8 vs 9). The combined use of *n*-BuLi and diisobutylaluminum hydride (DIBAL-H) (entry 7) exclusively formed **17**. Piperidine **6** is easily distinguishable from **17** by thin-layer chromatography (TLC), with a large difference in R_f values (0.2 and 0.5, respectively, on neutral alumina TLC plates using 5% EtOAc/hexanes as the eluent). The stereochemical determination of **6** and **17** was secured by their eventual conversion to (−)-**1** and its epimer.[26] An investigation of this extraordinary solvent effect in imine reduction is warranted to shed light on its origin and assess its scope and limitations.

Once reliable access to **6** was secured, the remaining two steps were uneventful (Scheme 4). Silver nitrate-mediated cyclization of aminoallene **6** proceeded cleanly to deliver **5b** in 83% yield as a single isomer.[27] Finally, a short synthesis of alkaloid (−)-205B (**1**) was completed by a relay RCM using the second-generation Grubbs catalyst.[28] Spectroscopic data and optical rotation of (−)-**1** were in excellent accord with literature values.[5,7−9]

In conclusion, we have reported a concise synthesis of alkaloid (−)-205B (**1**) that punctuates the simplicity and brevity of the synthetic sequence. The expedient synthesis of (−)-**1** is made possible by anti-S_N2' alkylation of attractively functionalized cyclopropanols. This work also delineates a general strategy for preparing 2,6-*cis*- or 2,6-*trans*-piperidines by stereoselective reduction of imines and 2,5-*cis*- or 2,5-*trans*-pyrrolidines by diastereoselective cyclization of aminoallenes. These new synthetic methods hold promise in the stereoselective syntheses of pyrrole, pyrrolizidine, and indolizidine alkaloids along with other natural products containing aza- and oxygen heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSF (CHE-1265843) for generous financial support.

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Table 1. Formation and Reduction of Imine 11

entry	hydrides, *T*	imine[f]; reduction[f]	**6**:**17**:epimer[g]
1	$NaBH_4$ (3 equiv), 0 °C	THF; MeOH	1:1:1
2	Me_3Al + $LiAlH_4$, −78 °C[a]	toluene; THF	∼2:1:1
3	Et_2AlCl + $LiAlH_4$, −78 °C[b]	toluene; THF	∼1:1:1
4	$(iPrO)_3TiCl$ + $LiAlH_4$, −78 °C[b]	THF; THF	1:1:1
5	Me_3Al + DIBAL-H, −78 °C[c]	toluene; toluene	∼1:4:1
6	DIBAL-H, −78 °C[d]	THF; THF	∼1:4:1
7	*n*BuLi + DIBAL-H, −78 °C[c]	Et_2O; Et_2O	0:1:0
8	$LiAlH_4$, 0 °C[d]	THF; THF	∼1:1:0.1
9	$LiAlH_4$, 0 °C[d,e]	Et_2O; Et_2O	∼15:1:0

[a]10 equiv each. [b]Lewis acid (10 equiv) + $LiAlH_4$ (5 equiv). [c]5 equiv each. [d]5 equiv. [e]Comparable results were obtained at −78 °C. [f]Solvents for imine formation and reduction are given. [g]The product ratios were determined by analysis of NMR spectra of crude reaction mixtures. The stereochemical assignment of the methyl epimer, which was obtained as one isomer, was not made.

DOI: 10.1021/jacs.5b00243
J. Am. Chem. Soc. 2015, 137, 2243−2246

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(26) There are unmistakable differences between the ^{1}H NMR spectra of **1** and its epimer. Particularly diagnostic is the (equatorial) proton at 3.86 ppm in **1**, which is absent in the epimer.

(27) Stereoselective cyclization of aminoallene **6** required an enantiopure allene subunit (i.e., **5b** where $R^1 \neq H$). Our preliminary study during the total synthesis of **4** (see ref 3) guided us to rely on a relay RCM strategy.

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DOI: 10.1021/jacs.5b00243
J. Am. Chem. Soc. 2015, 137, 2243−2246