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Concise total synthesis of phidianidine A and B

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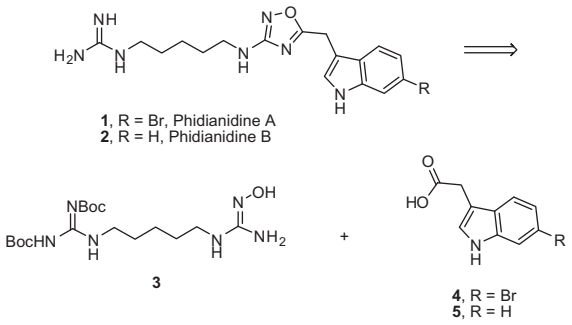
ABSTRACT

The shortest total synthesis of cytotoxic indole alkaloids phidianidine A and B is described. Rapid assembly of the 1,2,4-oxadiazole core from a novel *N*-hydroxyguanidine and the corresponding indole-3-acetic acid chloride led to formal syntheses of phidianidine A and B in only three steps from known compounds. Deprotection under standard conditions provided the trifluoroacetate salts of phidianidine A and B in quantitative yield.

Phidianidine A (**1**) and B (**2**) are cytotoxic indole alkaloids isolated from the marine ophisthobranch mollusk *Phidiana militaris* in 2011 and are believed to be the first natural products to contain a 1,2,4-oxadiazole ring.[1] Although compounds **1** and **2** are not toxic to normal human epithelial kidney (HEK293) cells, they are potent growth inhibitors of aggressive HeLa human epithelial cervical cancer and C6 rat glioma tumor cell lines (IC_{50} from 0.4 to 1.5 μM), as well as non-tumor H9c2 rat embryonic cardiac myoblasts and 3T3-L1 murine embryonic fibroblasts (IC_{50} from 0.1 to 5.4 μM).[1,2] Remarkably, phidianidine A and B also exhibit selective binding within two disparate classes of central nervous system (CNS) targets, such as the μ-opioid receptor (vs the δ- and κ-opioid receptors) and the dopamine transporter (vs the norepinephrine and serotonin transporters).[2] Selective inhibition of key CNS targets may also enable **1** and **2** to be used as analgesics for pain management and to treat certain CNS pathologies. Our laboratory was drawn to these natural products due to their intriguing architecture and activity toward diverse biological targets.

The novel structure and pharmacological profile of phidianidine A and B also inspired others to pursue their total synthesis, but drawbacks of these pioneering efforts prompted us to explore an alternative strategy.[2,3] For example, although 1,2,4-oxadiazole assembly was the key step in each synthesis, construction of the linear portion included extraneous nitrogen protecting group manipulations.[2,3] One approach enlisted an azide as an amine protecting group, but the preparation of low-molecular weight azides represents a significant safety concern when working with undergraduates.[3,4] In tandem with our safety concerns and our desire to achieve a rapid synthesis of phidianidine A and B, we seek to remedy discrepancies we found in the reported spectroscopic data.



Scheme 1. Retrosynthetic analysis of phidianidine A and B.

Despite the success of other synthetic efforts, we believed a shorter and safer route was possible. Specifically, our goal was to develop a synthetic strategy to prepare phidianidine A and B in a straightforward, convergent fashion in which the guanidine was installed first, eliminating unnecessary protecting group steps. We report a streamlined synthesis of compounds **1** and **2** that is two steps shorter than any known route, clarifies uncertainties in the assignment of ^{1}H and ^{13}C NMR peaks, addresses important safety issues, and was performed by undergraduates.

Our retrosynthesis was inspired by Gavagnin, Guo, and coworkers' proposed biosynthetic hypothesis and began with the preparation of novel *N*-hydroxyguanidine **3**, which contains the

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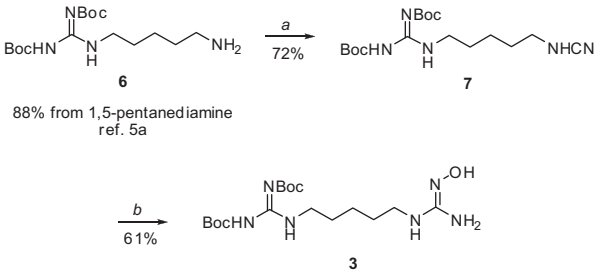
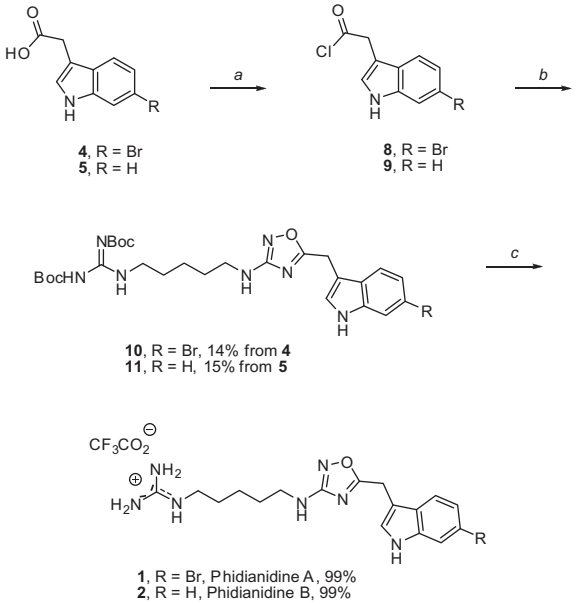


Scheme 2. Reagents and conditions: (a) BrCN (1.2 equiv), $NaHCO_3$ (6.0 equiv), H_2O/CH_2Cl_2, 0 °C, 0.5 h, then, rt, 1 h; (b) $NH_2OH{\cdot}HCl$ (1.2 equiv), K_2CO_3 (3.0 equiv), EtOH, rt, 3 h.

terminal guanidine in a protected form (Scheme 1).[1] Exposure of known *N*,*N*′-di-Boc guanidine[5] **6** to cyanogen bromide under biphasic conditions provided cyanamide **7**, which was converted to *N*-hydroxyguanidine **3** using hydroxylamine hydrochloride (Scheme 2).[6] To our knowledge, a similarly functionalized *N*-hydroxyguanidine has not been prepared previously.

With *N*-hydroxyguanidine **3** in hand, the 1,2,4-oxadiazole core of phidianidine A and B was then constructed by joining the acid chloride derived from the known 6-bromoindole-3-acetic acid[7] (**4**) or indole-3-acetic acid (**5**), respectively, with compound **3** (Scheme 3). Acid chlorides **8** and **9** were generated from their respective indole-3-acetic acids by treatment with oxalyl chloride at 0 °C. Each acid chloride was then condensed with *N*-hydroxyguanidine **3** to afford the respective 1,2,4-oxadiazoles **10** and **11**, which constituted formal total synthesis of phidianidine A and B.[3a,8,9] Completion of each total synthesis was achieved by deprotection with TFA under standard conditions. The ^1H and ^{13}C NMR spectra in CD_3OD and DMSO-d_6 of synthetic phidianidine A (**1**) and B (**2**) are identical to those reported for the natural products.[1]

Although our ^1H and ^{13}C NMR spectra matched the reported data,[1] we discovered that some specific peak assignments disagreed with our 2D-NMR data. After close examination of our 2D-NMR data (COSY, HSQC, and HMBC) in CD_3OD, we suggest reassignment of certain ^1H and ^{13}C NMR peaks in compounds **1** and **2** in



Scheme 3. Reagents and conditions: (a) $(COCl)_2$ (3.0 equiv), DMF (cat.), CH_2Cl_2, 0 °C, 1.5 h; (b) (i) **3** (1.1 equiv), CH_2Cl_2, rt, 3 h; (ii) $ClCH_2CH_2Cl$, 83 °C, 2 h; (c) TFA/CH_2Cl_2 (1:10 v/v), rt, 8 h.

that solvent.[9] We also normalized ^1H and ^{13}C NMR chemical shift data in CD_3OD and DMSO-d_6 for natural and synthetic phidianidine A and B to tetramethylsilane to correct for variation in both the spectral reference peak and chemical shift value chosen by each author.[1–3,10]

In conclusion, we have completed the shortest total synthesis of phidianidine A (**1**) and B (**2**) to date (4 steps, longest linear sequence from known amine **6**, 6% and 7% overall yield, respectively). Overall yields are 5.4% and 5.7%, respectively, if the synthesis begins with commercially available 1,5-pentanediamine (cadaverine). Our convergent strategy featured direct introduction of an *N*,*N*′-di-Boc guanidine that was carried through the synthesis. This simplified approach circumvented the cumbersome protected amine-to-amine-to-guanidine sequence characteristic of all prior syntheses of compounds **1** and **2**, and should enable the rapid preparation of analogs for biological evaluation. By avoiding the preparation of low-molecular weight azides and diazides, we provide a safer and more direct route to terminal-guanidine containing compounds, which is a primary concern of undergraduate researchers amid the changing safety culture in academia. We plan to apply our direct guanidinylation approach to the preparation of other bioactive, guanidine-containing natural products, and will report our results in due course.

Acknowledgments

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Supplementary data

Supplementary data (complete experimental procedures, copies of all spectral data, tables of normalized ^1H and ^{13}C NMR peak data, 2D NMR data to support corrected peak assignments, and full characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.063.

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8. The change in solvents from CH_2Cl_2 to $ClCH_2CH_2Cl$ was necessary because acid chlorides **8** and **9**, as well as *N*-hydroxyguanidine **3**, are insoluble in $ClCH_2CH_2Cl$; however, heating above 80 °C was required for 1,2,4-oxadiazole formation.

9. After workup, we obtained quantitative mass balance for each 1,2,4-oxadiazole-forming reaction; however, the isolated yield of pure compounds **10** and **11** was low. Compounds **10** and **11** were stable during silica-gel column chromatography (3:2 hexanes/ethyl acetate), which was confirmed by 2D-TLC. Snider and Lin (Ref. 3a) also prepared compounds **10** and **11** from acid chlorides **8** and **9**, respectively, confirming their stability to silica gel. Methanol quenching experiments indicated that acid chlorides **8** and **9** were formed cleanly, suggesting that the 1,2,4-oxadiazole formation step was problematic in each case. We deemed it unnecessary to determine the structures of polar reaction products obtained from column chromatography, so at this time, we cannot speculate as to the cause of the reduced yield of our 1,2,4-oxadiazole-forming reaction.
10. See Supplementary data.