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Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C−H Functionalization

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The *Lycopodium* alkaloids are among the most skeletally diverse families of natural products that have been isolated to date.[1] In addition to their complex architecture, many of the alkaloids in this family possess potentially useful biological activity, which includes acetylcholinesterase (AChE) inhibition.[2] The utility of known AChE inhibitors, such as the *Lycopodium* alkaloid huperzine A (**1**, Figure 1),[3] to partially address the treatment of Alzheimer's disease is supported by the observation of increased memory and learning in rats upon administration of **1**.[4] Furthermore, several AChE inhibitors, including galanthamine[5] and Aricept,[6] are commercial pharmaceuticals that are used to treat Alzheimer's disease indications. However, because AChE inhibition appears to treat only the symptoms of neurodegenerative diseases, there continues to be a need to identify other natural products that promote the growth of new neural networks. In this regard, *Lycopodium* alkaloids, such as the lyconadins (e.g., **3**)[7] and complanadine A (**4**),[8] are especially interesting because they enhance mRNA expression for nerve growth factor (NGF) and the production of NGF in human glial cells.[9]

As a first step in a program aimed at the biological evaluation of *Lycopodium* alkaloids and their analogues as neurotrophic factors, we have undertaken the synthesis of several of these compounds. We recently reported the total synthesis of lyconadin A (**3**).[10] In this manuscript, we present the details of our total synthesis of complanadine A (**4**), which is a dimer of the well-known phlegmarine-derived alkaloid lycodine (**5**).[11] The synthetic challenge posed by **4** stems primarily from the fact that it is an *unsymmetrical* dimer of lycodine (C2−C3′ linkage; see **4**) and therefore requires the introduction of position-control elements prior to merging of the two halves (see **6** and **7**, Scheme 1). A powerful simplification of the synthesis would entail formation of **6** and **7** from the same intermediate (e.g., tricyclic enamide **8**). Enamide **8** was in turn envisioned to arise from an acid-promoted formal cycloaddition of **9** and **10** following the precedent of Schumann for the synthesis of racemic *N*-desmethyl-α-obscurine (**17**, Scheme 2).

The synthesis of complanadine A commenced with the preparation of ketal **12** (eq 1), which is available from (+)-pulegone using

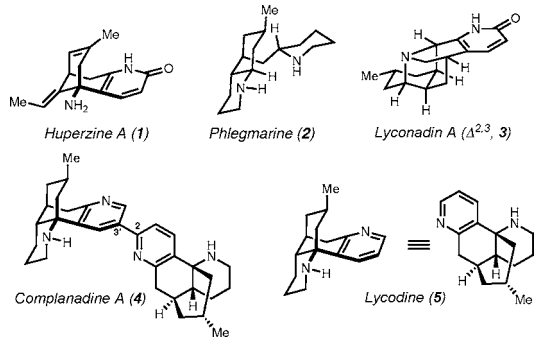
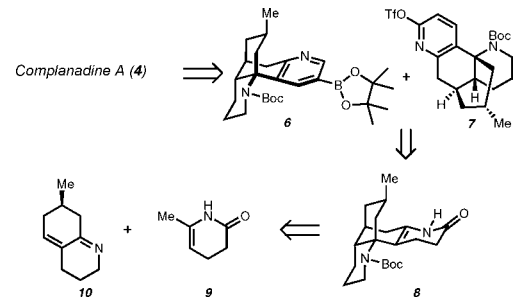
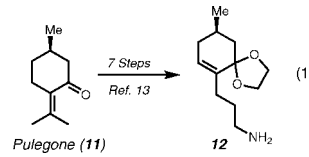


Figure 1. Selected *Lycopodium* alkaloids.

Scheme 1

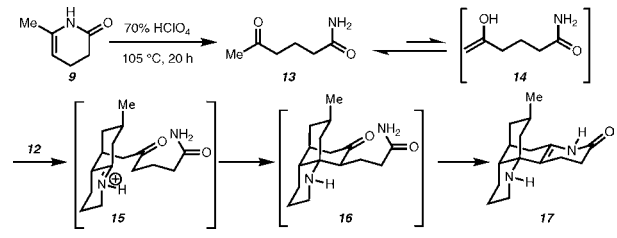


literature procedures.[13] Aminoketal **12** was used as a direct precursor to oxygen-sensitive α,β-unsaturated imine **10**.[14]



Enamide **9** was prepared from commercially available 5-ketohexanenitrile[15] via Zn(II)-catalyzed hydrolysis of the cyano group and subsequent dehydrative cyclization upon distillation.[16] Interestingly, our empirical observations suggest that under the conditions identified by Schumann for the formation of **17** (Scheme 2) from **9** and **10** (70% $HClO_4$(aq), dioxane, 105 °C, 20 h), enamide **9** undergoes hydrolysis to **13**.[17] Ketoamide **13** likely forms reactive enol tautomer **14**, which in turn reacts with protonated **10** (generated in situ from **12**) to yield *N*-desmethyl α-obscurine **17** following a series of cyclizations (i.e., via **15** and **16**).

Scheme 2



The synthetic sequence up to this point is easily amenable to scale-up, which has provided **17** on a multigram scale. At this stage, we proceeded to address the major challenge of the synthesis, which was to advance **17** to triflate **7** as well as boronic ester **6**. To set the stage for these tasks, selective Boc protection of **17** (Scheme 3) afforded **8** (65% yield over two steps).[18] This was followed by oxidation of **8** with lead tetraacetate to provide pyridone **18** in 84% yield. Triflation of the pyridone using triflic anhydride in pyridine proved optimal, giving **7** in 72% yield.

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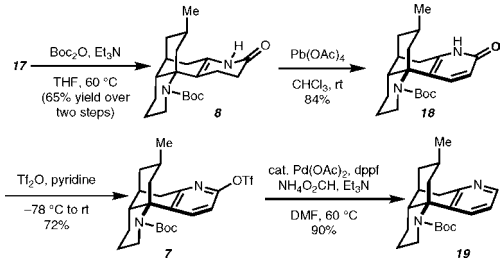
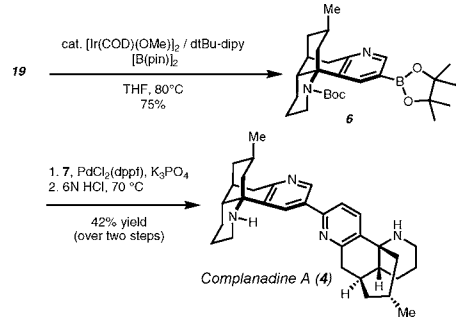
With one of the desired coupling partners in hand, we looked to address the synthesis of the other (i.e., boronic ester **6**).[19] The triflate group in **7** was removed under Pd-catalyzed reducing conditions to provide Boc-protected lycodine (**19**).

Scheme 3



The conversion of **19** to boronic ester **6** was achieved in a single step, as illustrated in Scheme 4. Our approach to the remarkable direct C−H functionalization of **19** rested on the uniquely effective Ir(I)-catalyzed borylation chemistry developed by Hartwig and Miyaura.[20] In the event, treatment of **19** with 4 mol % [Ir(OMe)-(cod)]$_2$, 8 mol % di-*tert*-butylbipyridine (dtpy), and diboron pinacolato ester (0.75 equiv) in THF at 80 °C gave **6** in 75% yield after 5.5 h. The observed site selectivity is consistent with that noted by Hartwig for pyridine functionalization and appears to be guided mainly by steric factors. Suzuki cross-coupling of boronic ester **6** and triflate **7** followed by cleavage of the Boc protecting groups gave complanadine A (**4**) in 42% yield over two steps.

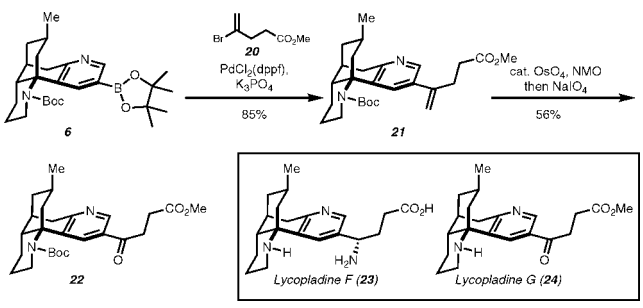
Scheme 4



Synthetic complanadine A gave spectral data (^{1}H and ^{13}C NMR) consistent with that reported by Kobayashi and co-workers during its isolation.[21]

Access to boronic ester **6** should prove highly significant as a starting point for the synthesis of congeners and analogues of complanadine A and lycodine. For example, coupling of boronic ester **6** (Scheme 5) to vinyl bromide **20**[22] followed by dihydroxylation using the Upjohn method[23] and periodate cleavage yields **22**, which is a direct precursor to lycopladines G and F.[24]

Scheme 5



In summary, we have reported the total synthesis of the unsymmetrical lycodine dimer complanadine A. Our synthetic sequence proceeds in eight steps from enamide **9** and acetal **12**. The synthetic strategy also provides potential access to the natural products lycodine, lycopladine F, and lycopladine G. Highlights of the complanadine synthesis include a Hartwig−Miyaura Ir(I)-catalyzed site-selective borylation and a late-stage Suzuki cross-coupling to form the C2−C3′ bipyridine. The application of the strategy to the multigram scale production of **4** and congeners, as well as the synthesis of other *Lycopodium* alkaloids, is underway and will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Preliminary results indicated that **13** may be used instead of **9** in the formation of **17**.
(18) Because of its high polarity, **17** was taken directly into the next step without purification.
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