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Synthetic Studies on Pseudo-Dimeric Lycopodium Alkaloids: Total Synthesis of Complanadine B

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Complanadines A and B (**1** and **2**, Figure 1) are dimeric *Lycopodium* alkaloids in the lycodine family that possess significant activity for nerve growth factor (NGF) production from human glial cells.^{i, ii} As such, **1** and **2** are of interest as potential small molecule leads for the treatment of neurodegenerative diseases such as Alzheimer's disease as well as adjuvants for the regeneration of nerve cells in, for example, spinal cord injury treatment.ⁱⁱⁱ

Although the biogeneses of **1** and **2** have not been extensively studied,^{iv} it may be possible that complanadine B (**2**) arises directly from complanadine A (**1**) by an oxygenation process (Route 1, Scheme 1) that could be enzyme catalyzed. In turn, **1** may be formed by the union of enamine/imine tautomers **5a** and **5b** (where X = H₂), respectively, as proposed by Morita, Kobayashi and their coworkers,ⁱⁱ followed by a series of dehydrogenations.

The proposed dimerization event, which ultimately affords a 2,3 –conjoined pyridine dimer (the numbering for complanadine A is adopted, see **1**), is consistent with prior studies by Leete and Slattery.^v However, the possible genesis of complanadine B (**2**) from complanadine A (**1**) by an oxygenation event, while appealing, is an open question. Given the presence of two pseudo-benzylic methylene groups in **1** that could potentially undergo oxygenation, exquisite selectivity to provide **2** (as opposed to iso-complanadine B, **4**) would have to be effected were **1** to be the precursor to **2**.

In this manuscript, we detail our studies on the laboratory synthesis of complanadine B (**2**) and provide support for an assertion that complanadine B, were it to arise from **1**, likely occurs through an enzyme-mediated process. As an alternative, the possibility exists that **2** is biogenetically derived from a union of an oxygenated variant of **5b** (where X = O, see Scheme 1) with **5a** (i.e., Route 2). This latter hypothesis has formed the basis of our first approach to **2**. We also present a second approach to **2**, which employs a strategy that not only enables a late stage, site-selective, oxygenation of a complanadine A derivative to afford **2**, but could potentially be utilized in the synthesis of the other known members of the complanadine family.

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In 2010, our group,^{vi} as well as the group of Siegel,^{vii} reported syntheses of complanadine A (**1**). A summary of our strategy for the synthesis of **1**, which relied on a late-stage, site-selective Ir(I)-catalyzed C-H borylation^{viii} of **8** to provide **6** is shown in Scheme 2. Overall, distilling the synthesis of **1** to the preparation of lycodine derivative **7** avoided costly double processing of many synthetic intermediates.

Our synthetic studies of complanadine B commenced with the attempted oxygenation of Boc-complanadine A (**9**, Scheme 3). On the basis of literature precedent for the lateral oxygenation of picolines,^{ix} treatment of **9** with SeO₂ (2.5 equiv, 1,4-dioxane, 150 °C, 3 h) led to the formation of **11** (dubbed Boc-*iso*-complanadine B) as the major product. The observed selectivity for oxygenation likely arises because of the higher accessibility of the nitrogen in the 2,3,5-substituted pyridine ring as well as the potential stabilization of reactive intermediates^x by both pyridine rings (see **10**).

Despite the overwhelming selectivity for the formation of Boc-*iso*-complanadine B (**11**) from **9** upon exposure to SeO₂, we were hopeful that a strategy could be devised that would reverse the regioselectivity of Boc-complanadine A oxidation. Specifically, we sought to block and deactivate the more accessible pyridine ring (i.e., ring A, see **12**, Figure 2) in order to achieve lateral ('picolinic') oxygenation of pyridine ring B. We theorized that if a dative bond could be achieved between an appropriate Lewis acid and the more accessible pyridine nitrogen, interactions with oxidants (e.g., SeO₂) that would be required for oxygenation could be effectively blocked. In this way, the pattern for oxygenation could be reversed because the nitrogen of pyridine ring B would be more likely to be engaged.

Unfortunately, all of our attempts to put into practice the logic proposed in Figure 2 have so far been unsuccessful. Thus, pre-treatment of **9** with various Lewis acids (e.g., BF₃•Et₂O or Ag₂CO₃) prior to the introduction of the oxidant led only to the recovery of Boc-*iso*-complanadine B (**11**), whereas N-oxide formation on ring A of **9** (using 1 equiv of *m*CPBA) and a subsequent attempted lateral oxygenation of ring B (with SeO₂) produced complex mixtures where the major product was Boc-*iso*-complanadine B (**11**), presumably arising from a Boekelheide-type rearrangement.^{xi}

Given our lack of success in reversing the inherent selectivity for oxygenation of **9**, a revised strategy for the synthesis of **2** was devised, which called for oxygenation of the requisite monomer (see **13**, Scheme 4) prior to coupling with pinacolboronic ester **6**. Keto-lycodine derivative **13** could in turn arise from pyridone **14**, which we had previously prepared from pulegone in the context of our complanadine A synthesis.^{vi}

Initial attempts to directly oxygenate the pseudo-benzylic methylene ('picolinic') carbon of hydroxypyridine/pyridone **14** using various oxidants that are known to oxidize benzylic methylene groups (PDC, IBX, Mn(III)/TBHP, DDQ, CAN and SeO₂) led either to decomposition, recovery of the starting material, or the formation of trace oxidation products that were not fully characterized. Because the direct benzylic oxidation of pyridones is not general for ketone formation,^{xii} we chose to focus on variants of **14** that exist solely in the pyridine form. Thus, several conditions for the picolinic oxygenation of triflate **7** with oxidants including IBX and SeO₂ were surveyed. Disappointingly, only the starting triflate (**7**) was isolated in the majority of cases. More reactive oxidants such as DDQ led to non-specific decomposition of **7** at higher temperatures. On the basis of a hypothesis that the lack of reactivity of **7** was a result of the electron withdrawing effect of the triflate substituent, pyridine **8** (i.e., Boc-lycodine), lacking the triflate group, was prepared from **7** as previously described in our synthesis of **1**.

Gratifyingly, **8** was cleanly oxygenated in 99% yield using SeO₂ to provide **13a** (Scheme 5). At this stage, treatment of keto-pyridine **13a** with *m*CPBA led to formation of N-oxide **15** in 85% yield. Treatment of **15** with POCl₃ in DMF led to a good yield of chloropyridine **13b**, which was subjected to Suzuki cross-coupling with pinacolboronic ester **6** to yield Boc-complanadine B (**16**) in 72% yield. Removal of the Boc groups (HCl, heat) provided complanadine B in quantitative yield.

The physical properties and spectral data (¹H NMR and ¹³C NMR) for synthetic complanadine B were fully consistent with the isolation data that had been previously reported by Kobayashi and coworkers.ⁱⁱ

Although the approach detailed in Scheme 5 led to an effective synthesis of complanadine B, we recognized that our initial blocking strategy (Figure 2), if executed from an isolable intermediate, could yield a late-stage compound that could be employed universally in the preparation of all the known members of the complanadine family. Such an intermediate would have to enable selective late-stage manipulations of the pyridine B ring (see Figure 3). For example, the synthesis of **2** would require selective lateral oxygenation, whereas syntheses of complanadines D (**17**) and E (**18**) would require selective reduction of the B ring.^{xiii}

Schematically, we envisioned that an intermediate with the abovementioned capabilities would possess an electron-withdrawing group to the nitrogen on ring A, which would serve to mitigate the reactivity of this pyridine toward oxidants and reductants, particularly those reagents that require coordination to the nitrogen atom. Importantly, we desired an electron-withdrawing group that could be removed directly in order to limit late stage manipulations. Finally, the ideal group would have to be compatible with Ir(I)-catalyzed borylation and Pd(0)-catalyzed cross-coupling conditions, which would be required for the preparation of this versatile late-stage synthetic intermediate.

We were initially drawn to carbamate and sulfamate derivatives of **9** (see **19a** and **19b**) because of recent reports from Sneickus and Garg^{xiv} demonstrating their stability toward Pd(0)-catalyzed cross-coupling conditions and their removal using Ni(0)-catalyzed reduction conditions. However, in our hands, the requisite substrates (i.e., **19a** and **19b**) failed to undergo Ir(I)-catalyzed borylation using the conditions of Hartwig and Miyaura, most likely due to a reduced capability to bind in an η² fashion to the metal center before the C-H activation step.^{xv} As an alternative to the carbamate and sulfamate derivatives, we turned to a methoxy derivative (**19c**). Methoxy substitution on pyridines, as has been previously proposed by us^{xvi} and by Corey and Chein,^{xvii} is also *inductively* electron-withdrawing and, additionally, accomplishes steric shielding of the pyridine nitrogen (as a result of minimized dipoles of the lone pair on the pyridine nitrogen and oxygen substituent). We were also hopeful that we could directly remove the methoxy group utilizing the Ni-catalyzed strong bond activation methods introduced by Martin,^{xviii} Garg,^{xix} Hartwig^{xx} and Agapie.^{xxi} On this basis, we envisioned **19c** as a versatile intermediate to the complanadines. We selected complanadine B as a challenging test case for this strategy since we would have to overcome the inherent unfavorable selectivity for oxygenation of the 2,3 bipyridine core.

The synthesis of **19c** (illustrated in Scheme 6) parallels our synthesis of **9** and began with O-alkylation of pyridone **14** using the conditions of Langlois^{xxii} followed by borylation using the conditions of Hartwig and Miyaura.^{viii} Cross-coupling of boronic ester **21** with *tosylate* **22** under the conditions previously identified by us^{vi} gave **19c** in 67% yield. Of note, the analogous cross-coupling of boronic ester **21** with *triflate* **7** proceeded in dramatically lower yields because of the competing hydrolysis of the triflate group under the reaction conditions. Gratifyingly, exposure of **19c** to SeO₂ oxidation conditions produced **23** in 63%

yield. At this stage, what remained, in order to intercept our established route to complanadine B (see Scheme 5) was the removal of the methoxy group to afford **16**.

Unfortunately, all of our attempts to remove the methoxy group in **23** directly using Ni-catalyzed strong bond activation methods have failed. It is important to note that despite the extensive studies on the cross-coupling of methoxy arenes that have recently appeared, to the best of our knowledge, there are no examples that describe removing methoxy groups from the C(2) or C(6) position of the pyridine heterocycle. A solution, albeit indirect, to this synthetic impasse, was to cleave the methyl ether in **23** and effect triflation of the resulting pyridone under standard conditions, which yielded **24**. Upon exposure of triflate **24** to Pd-catalyzed reduction conditions, Boc-protected complanadine B (**16**) was obtained in 70% yield, completing a formal synthesis of the natural product. The data for **16** matched exactly that which was obtained from the coupling of **13b** and **6** (Scheme 5).

In conclusion, we report two strategies for the synthesis of the dimeric *Lycopodium* natural product complanadine B. Several aspects of our syntheses of complanadine B serve to highlight some remaining unsolved challenges pertaining to functionalization of pyridines and pyridine derivatives (e.g., pyridones). For example, there are no general methods for the direct lateral oxygenation of methylene groups at C(6) of pyridones or for the demethoxylation of 2- or 6-methoxy pyridines. Development of methods to accomplish these goals will undoubtedly streamline the syntheses of not only the complanadines, but other pyridine-based molecules as well. Furthermore, our studies indicate that there is a preference for oxygenation of the complanadine A skeleton (albeit the Boc-protected form) at the picolinic position that is counter to what may be expected in Nature given the existence of complanadine B. Thus, it would seem likely that lateral oxygenation of a lycodine unit (to form keto-lycodine) prior to coupling with another lycodine may be operative in the biosynthesis of complanadine B. However, keto-lycodine natural products (related to **13a**) or iso-complanadine B (**4**) have yet to be isolated to support either biogenetic hypothesis for how **2** arises. Our future studies are aimed at the synthesis of analogs of the complanadines by taking advantage of triflate **24**, as well as continuing to expand the utility of **19c** in the synthesis of other members of the complanadine family.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Complandines A and B and lycodine.

Figure 2.
A reversible blocking strategy

Figure 3.
Proposed strategies for controlling pyridine reactivity

Scheme 1.
Possible biogenesis of **1** and **2**

Scheme 2.
Strategy for the synthesis of complanadine A

Scheme 3.
Direct oxygenation of Boc-complanadine A

Scheme 4.
Revised retrosynthetic analysis of **2**

Scheme 5.

Completion of the synthesis of complanadine B. Reagents and conditions: a) SeO_2 (2.5 equiv), 1,4-dioxane, 150 °C, μW , 2 h, 99%; b) *m*CPBA (1.5 equiv), DCM, 23 °C, 4 h, 85%; c) POCl_3 (1.5 equiv), DMF, 0 °C to 23 °C, 4 h, 61%; d) **6**, $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (12.5 mol %), Et_3SiH (25 mol %), K_3PO_4 (3 equiv), DMF, 80 °C, 8 h, 72%; e) 6 N $\text{HCl}(\text{aq})$, 70 °C, 2 h, quantitative. *m*CPBA = *meta*-Chloro perbenzoic acid, DCM = dichloromethane, DMF = dimethylformamide, dppf = diphenylphosphino ferrocene.

Scheme 6.

Alternative synthesis of **16**. Reagents and conditions: a) Ag_2CO_3 (1.3 equiv), MeI (10 equiv), CHCl_3 , 23 °C, 1 d, 58%; b) $[\text{Ir}(\text{COD})(\text{OMe})_2]$ (10 mol %), di-*t*-Bu-dipy (21 mol %), B_2Pin_2 (1.8 equiv), THF, 100 °C, 3 d, 94%; c) $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (12 mol %), cat. Et_3SiH , K_3PO_4 (3 equiv), DCM, 100 °C, 7 h, 63%; d) SeO_2 (2.5 equiv), 1,4-dioxane, 150 °C, 12 h, 63%; e) NaH (10 equiv), EtSH (20 equiv), DMF, 140 °C, 2 h; f) Tf_2O (1.5 equiv), pyridine (10 equiv), DCM, -78 °C to 23 °C, 2 h, 53% over 2 steps; g) $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (10 mol %), $\text{NH}_4\text{O}_2\text{CH}$ (10 equiv), then Et_3N (5 equiv), DMF, 100 °C, 6 h, 70%. COD = cyclooctadiene, dipy = dipyrindine, pin = pinacol, DCM = dichloromethane, dppf = diphenylphosphino ferrocene, DMF = dimethylformamide, Tf = Trifluoromethanesulfonyl