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

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Complanadines A and B (1 and 2, Scheme 1) are dimeric Lycopodium alkaloids from the lycodeine family that possess significant activity for stimulating nerve growth factor (NGF) production in human glial cells.[1, 2] 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.[3]

Although the biogenesis of complanadine A (1) and complanadine B (2) has not been extensively studied,[4] it may be possible that 2 arises directly from 1 through an oxygenation (Scheme 2, route 1), which may be enzyme catalyzed. In turn, 1 may be formed by the union of enamine/imine tautomers (5a and 5b, respectively; where X = H2), as proposed by Morita, Kobayashi, and co-workers,[2] followed by a series of dehydrogenations.

The proposed dimerization event, which ultimately affords a 2,3′-conjoined pyridine dimer (the numbering for complanadine A, 1, see Scheme 1), is consistent with prior studies by Leete and Slattery.[5] However, the possible genesis of 2 from 1 by an oxygenation, although appealing, has not yet been explored. Given that 1 contains two pseudo-benzylic methylene groups that could potentially undergo oxygenation, a highly selective transformation would be required to obtain 2 (as opposed to iso-complanadine B: 4) from 1.

Herein, we describe the synthesis of complanadine B (2) and provide support for an assertion that if 2 does arise from 1, it likely occurs through an enzyme-mediated process. Alternatively, the possibility exists that 2 is biogenetically derived from a union of an oxygenated variant of 5b (where X = O, see Scheme 2) 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; this approach employs a strategy that not only enables the late-stage, site-selective, oxygenation of a complanadine A derivative to afford complanadine B (2), but could potentially be utilized in the synthesis of the other known members of the complanadine family.

In 2010, our group[6] and that of Siegel[7] reported syntheses of 1. Our strategy for the synthesis of 1 relied on a late-stage, site-selective IrI-catalyzed C–H borylation[8] of 8 (Scheme 3). Overall, distilling the synthesis of 1 to the preparation of lycodeine derivative 7 avoided costly double processing of many synthetic intermediates.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208571.
stabilization of reactive intermediates\cite{10} by both pyridine rings (see 10).

Despite the high selectivity for the formation of 11 from 9 upon treatment with SeO$_2$, we were hopeful that a strategy could be devised that would reverse the regioselectivity of the oxidation of 9. Specifically, we sought to block and deactivate the more accessible pyridine ring (i.e., ring A in 12; Scheme 5) 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 atom, the required interactions with the oxidants (e.g., SeO$_2$) could be effectively blocked. In this way, the selectivity for oxygenation could be reversed because the nitrogen atom of pyridine ring B would be more likely to interact with the oxidant.

Unfortunately, all of our attempts to put this strategy (Scheme 5) into practice have so far been unsuccessful. Thus, pretreatment of 9 with various Lewis acids (e.g., BF$_3$·Et$_2$O or Ag$_2$CO$_3$) prior to the introduction of the oxidant led only to the recovery of 11, whereas N-oxide formation on ring A of 9 (treatment with 1 equiv of mCPBA) and a subsequent attempted lateral oxygenation of ring B (with SeO$_2$) produced complex mixtures, in which the major product was 11, presumably arising from a Boekelheide-type rearrangement.\cite{11}

Given our lack of success in reversing the inherent selectivity for oxygenation of 9, a revised strategy for the synthesis of 2 was devised; this strategy involved the oxygenation of the requisite monomer (see 13; Scheme 6) 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.\cite{6}

Initial attempts to directly oxygenate the pseudo-benzylic methylene (“picolinic”) carbon of hydroxypyridine/pyridone 14 by using various oxidants that are known to oxidize benzylic methylene groups (PDC, IBX, Mn$_3$/TBHP, DDQ, CAN, and SeO$_2$) led either to decomposition, recovery of the starting material, or the formation of trace oxidation products, which were not fully characterized. Because the direct benzylic oxidation of pyridones to give a ketone has not been previously achieved,\cite{12} 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 SeO$_2$ were surveyed. Disappointingly, only the starting triflate 7 was isolated in the majority of cases. More-reactive oxidants such as DDQ led to 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 pulegone as previously described in our synthesis of 1. Gratifyingly, 8 was cleanly oxygenated using SeO$_2$ to provide 13a in 99% yield (Scheme 7). At this stage, treatment of keto pyridine 13a with mCPBA led to formation of N-oxide 15 in 85% yield. Treatment of 15 with POCl$_3$ in DMF led to a good yield of chloropyridine 13b, which was subjected to Suzuki cross-coupling with pinacolboronic ester 6 to yield

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Boc-protected complanadine B (16) in 72% yield. Removal of the Boc groups (HCl, heat) provided complanadine B (2) in quantitative yield.

The physical properties and spectral data (1H NMR and 13C NMR spectra) for synthetic complanadine B were fully consistent with the data, which had been previously reported by Kobayashi and co-workers, obtained from the isolated product. [2]

Although the approach detailed in Scheme 7 led to an effective synthesis of complanadine B (2), we recognized that our initial blocking strategy (Scheme 5), 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 be amenable to selective late-stage manipulations of the pyridine B ring (see Scheme 8). For example, the synthesis of 2 would require selective lateral oxidation, whereas syntheses of complanadines D (17) and E (18) would require selective reduction of the B ring. [10]

We envisioned that an intermediate with the above-mentioned capabilities would possess an electron-withdrawing group α to the nitrogen atom on ring A. This electron-withdrawing group 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 to limit the number of late stage manipulations. Finally, the ideal group would have to be compatible with IrI-catalyzed borylation and Pd0-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 Snieckus, Garg, and co-workers [14] recently reported their stability toward Pd0-catalyzed cross-coupling reactions and their removal using Ni2+-catalyzed reduction conditions. However, the requisite substrates (i.e., 19a and 19b) failed to undergo IrI-catalyzed borylation when the conditions of Hartwig, Miyaura, and co-workers were used, most likely because of the reduced capability of these substrates to bind in an η1 fashion to the metal center before the C–H activation step. As an alternative to the carbamate and sulfamate derivatives, we turned to a methoxy derivative (19c). A methoxy substituent on pyridines, as has been previously proposed by us [16] and by Corey and Chein, [17] is inductively electron-withdrawing and, additionally, sterically shields the pyridine nitrogen atom (as a result of minimized dipoles of the lone pairs on the pyridine nitrogen and oxygen substituent). We were also hopeful that we could directly remove the methoxy group by utilizing the Ni-catalyzed bond-activation methods introduced by the groups of Martin, [18] Garg, [19] Hartwig, [20] and Agapie. [21] On this basis, we envisioned 19c as a versatile intermediate to the complanadines. We selected complanadine B (2) as a challenging test case for this strategy, as we would have to overcome the inherent unfavorable selectivity for oxygenation of the 2,3′-bipyridine core.

The synthesis of 19c (Scheme 9) parallels our synthesis of 9 and began with O-alkylation of pyridone 14 by using the conditions of Langlois and co-workers, [22] with a subsequent borylation under the conditions of Hartwig, Miyaura, and co-workers. [23] Cross-coupling of boronic ester 21 with tosylate 22 under the conditions previously identified by us [24] 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, oxidation of 19c with SeO2 produced 23 in 63% yield. At this stage, all that remained to intercept our established route to complanadine B (see Scheme 7), was the removal of the methoxy group to afford 16.
Unfortunately, all of our attempts to remove the methoxy group in 23 directly by using Ni-catalyzed bond-activation methods failed. Notably, 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 of the oxygenation of the corresponding methoxy arenes to ketones. There are no general methods for the direct lateral oxygenation of methylene groups at C6 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 picoline position that is counter to what may be expected in nature given the existence of complanadine B. Thus, it would seem 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 hypotheses for how 2 arises. Our future studies are aimed at the synthesis of analogues 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.

Keywords: alkaloids · borylative C-H functionalization · complanadine · pyridine oxidation · total synthesis

Received: October 24, 2012
Published online: January 10, 2013

Scheme 9. Alternative synthesis of 16. Reaction conditions: a) Ag2CO3 (1. 3 equiv), Mel (10 equiv), CHCl3, 23 °C, 1 d, 58%; b) [Ir(cod)(OMe)2] (10 mol%), di-8Bu-dipty (21 mol%), Bp, pin (1.8 equiv), THF, 100 °C, 3 d, 94%; c) [PdCl2(dpdpf)]·CH2Cl2 (10 mol%), Et3SiH (12 mol %), K3PO4 (3 equiv), CH2Cl2, 100 °C, 150 h, 81%; d) SeO2 (2.5 equiv), 1,4-dioxane, 150 °C, 12 h, 63%; e) NaH (10 equiv), ETS (20 equiv), DMF, 140 °C, 2 h; f) Tf2O (1.5 equiv), pyridine (10 equiv), CH2Cl2, = 78 °C to 23 °C, 2 h, 53 % over 2 steps; g) [PdCl2(dpdpf)]·CH2Cl2 (10 mol%), NH4O2CH (10 equiv), then Et3N (5 equiv), DMF, 100 °C, 6 h, 70%. cod = cyclooctadiene, dpf = dipyrine, pin = pinacol, Tf = trifluoromethanesulfonyl.

12) Although many examples describing the oxidation of the pyridone methyl substituents to aldehydes are known, there are no examples of the oxygenation of the corresponding methylene groups to ketones.
13) For the isolation of complanadine D, see: a) K. Ishiuchi, T. Kubota, Y. Mikami, Y. Obara, N. Nakahata, J. Kobayashi,


[16] R. A. Murphy, R. Sarpong, Org. Lett. 2012, 14, 632–635. The computations reported in this manuscript simulated the reaction solvent.


