Natural Products

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

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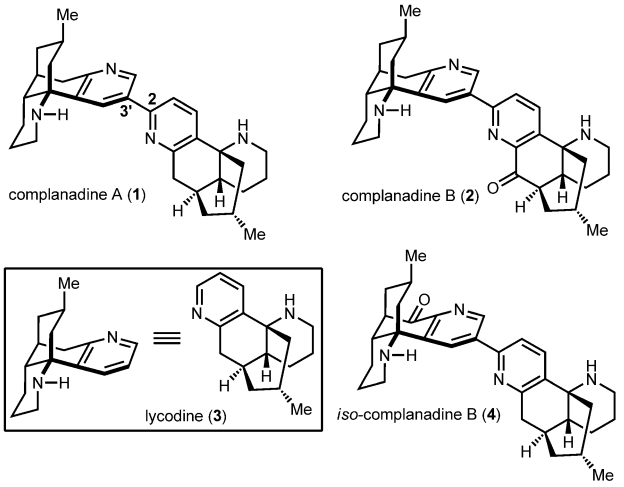
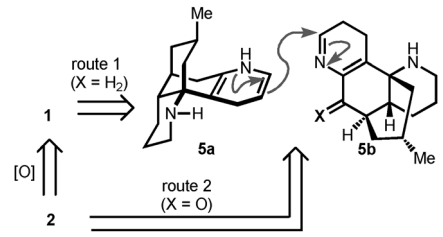
Complanadines A and B (**1** and **2**, Scheme 1) are dimeric Lycopodium alkaloids from the lycodine family that possess significant activity for stimulating nerve growth factor (NGF) production in human glial cells.[1,2] As such, **1** and **2** are of interest as potential small-molecule leads for 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]



Scheme 1. Complanadines A and B, lycodine, and *iso*-complanadine B.

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 $X = H_2$), as proposed by Morita, Kobayashi, and co-workers,[2] followed by a series of dehydrogenations.



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

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 Ir^I-catalyzed C–H borylation[8] of **8** to provide **6** (Scheme 3). 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 **2** commenced with the attempted oxygenation of Boc-protected complanadine A (**9**, Scheme 4). On the basis of literature precedent for the lateral oxygenation of picolines,[9] **9** was treated with SeO_2 (2.5 equiv, 1,4-dioxane, 150 °C, 3 h) and this led to the formation of **11** (dubbed Boc-*iso*-complanadine B) as the major product; none of the keto isomer that would correspond to **2** was observed. The observed selectivity for the oxygenation likely arises because of the greater accessibility of the nitrogen atom in the 2,3,5-substituted pyridine ring and the potential

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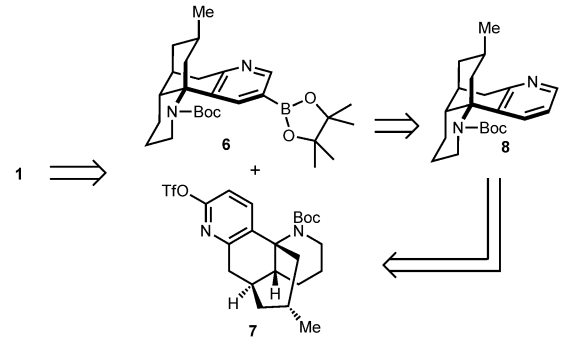
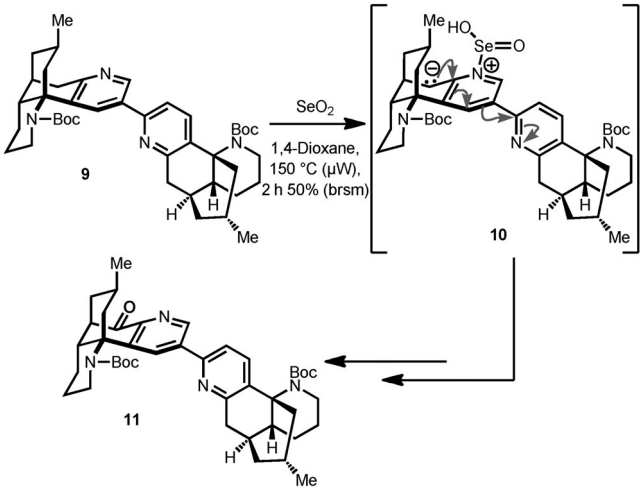


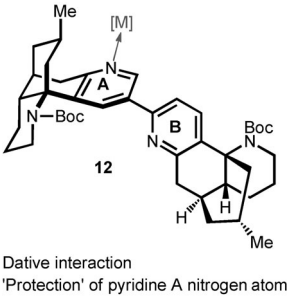
Scheme 3. Strategy for the synthesis of complanadine A. Boc = *tert*-butyloxycarbonyl.



Scheme 4. Direct oxygenation of Boc-protected complanadine A. brsm = based on recovered starting material.

stabilization of reactive intermediates[10] by both pyridine rings (see **10**).

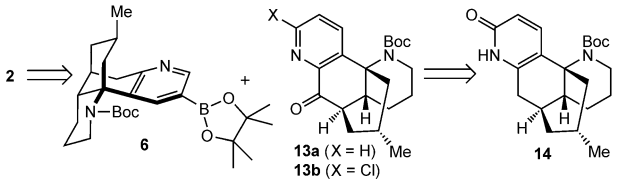
Despite the high selectivity for the formation of **11** from **9** upon treatment with SeO_2, we were hopeful that a strategy could be devised that would reverse the regioselectivity of the oxidation of **9**. Specifically, we sought to block and deactivate the more accessible pyridine ring (i.e., ring 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.



Scheme 5. A reversible blocking strategy.

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., $BF_3{\cdot}Et_2O$ or Ag_2CO_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 *m*CPBA) 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.[11]

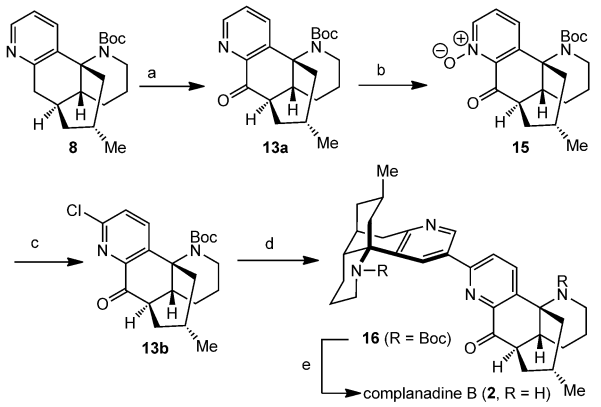
Given our lack of success in reversing the inherent selectivity for oxygenation of **9**, a revised strategy for the synthesis of **2** was devised; this strategy involved the oxygenation of the requisite monomer (see **13**; Scheme 6) prior to coupling with pinacolboronic ester **6**. Keto lycodine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



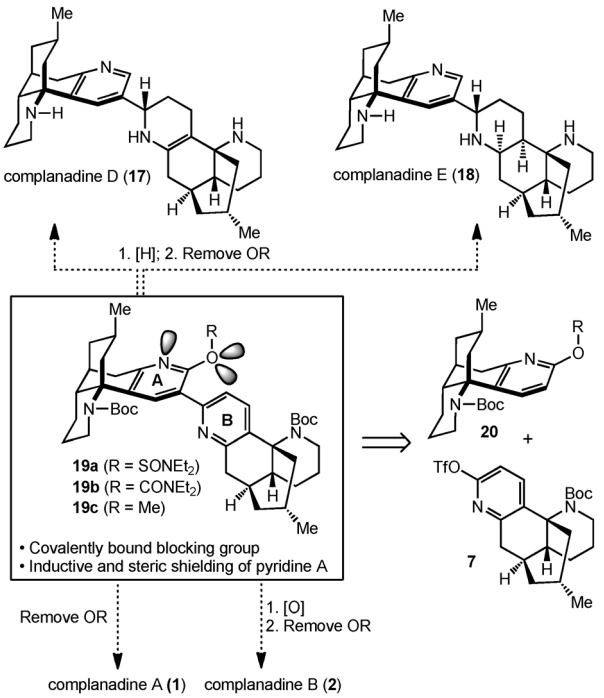
Scheme 6. Revised retrosynthetic analysis of **2**.

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^{III}/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,[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 **7** 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 *m*CPBA 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



Scheme 7. Completion of the synthesis of complanadine B. Reaction conditions: a) SeO_2 (2.5 equiv), 1,4-dioxane, 150 °C, μW, 2 h, 99%; b) *m*CPBA (1.5 equiv), CH_2Cl_2, 23 °C, 4 h, 85%; c) $POCl_3$ (1.5 equiv), DMF, 0 °C to 23 °C, 4 h, 61%; d) **6**, $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (12.5 mol%), Et_3SiH (25 mol%), K_3PO_4 (3 equiv), DMF, 80 °C, 8 h, 72%; d) 6 N HCl(aq), 70 °C, 2 h, quantitative. *m*CPBA = *meta*-chloro perbenzoic acid, DMF = dimethylformamide, dppf = diphenylphosphino ferrocene.



Scheme 8. Proposed strategies for controlling pyridine reactivity.

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

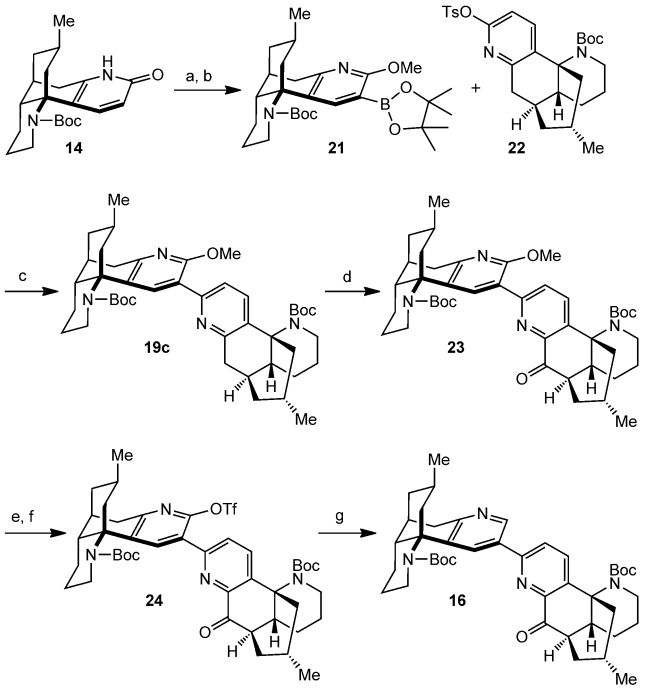
The physical properties and spectral data (^{1}H NMR and ^{13}C NMR spectra) for synthetic complanadine B were fully consistent with the data, which had been previously reported by Kobayashi and co-workers, obtained from the isolated product.[2]

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 oxygenation, whereas syntheses of complanadines D (**17**) and E (**18**) would require selective reduction of the B ring.[13]

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 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 Snieckus, Garg, and co-workers[14] recently reported their stability toward Pd^0-catalyzed cross-coupling conditions and their removal using Ni^0-catalyzed reduction conditions. However, the requisite substrates (i.e., **19a** and **19b**) failed to undergo Ir^I-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 η_2 fashion to the metal center before the C–H activation step.[15] 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.[8] Cross-coupling of boronic ester **21** with tosylate **22** under the conditions previously identified by us[6] 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 SeO_2 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**.



Scheme 9. Alternative synthesis of **16**. Reaction conditions: a) Ag_2CO_3 (1. 3 equiv), MeI (10 equiv), $CHCl_3$, 23 °C, 1 d, 58%; b) [Ir(cod)(OMe)$_2$] (10 mol%), di-*t*Bu-dipy (21 mol%), B_2pin_2 (1.8 equiv), THF, 100 °C, 3 d, 94%; c) [$PdCl_2$(dppf)]·CH_2Cl_2 (10 mol%), Et_3SiH (12 mol%), K_3PO_4 (3 equiv), CH_2Cl_2, 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), CH_2Cl_2, −78 °C to 23 °C, 2 h, 53% over 2 steps; g) [$PdCl_2$(dppf)]·CH_2Cl_2 (10 mol%), NH_4O_2CH (10 equiv), then Et_3N (5 equiv), DMF, 100 °C, 6 h, 70%. cod = cyclooctadiene, dipy = dipyridine, pin = pinacol, Tf = trifluoromethanesulfonyl.

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 that involve removing methoxy groups from the C2 or C6 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 to yield **24**. Upon exposure of triflate **24** to Pd-catalyzed reduction conditions, Boc-protected complanadine B (**16**) was obtained in 70% yield, thus completing a formal synthesis of the natural product. The data for **16** exactly matched the data for the product of the coupling of **13b** and **6** (Scheme 7).

In conclusion, we have reported 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 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 picolinic 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.[23]

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[1] J. Kobayashi, Y. Hirasawa, N. Yoshida, H. Morita, *Tetrahedron Lett.* **2000**, *41*, 9069 – 9073.
[2] H. Morita, K. Ishiuchi, A. Haganuma, T. Hoshino, Y. Obara, N. Nakahata, J. Kobayashi, *Tetrahedron* **2005**, *61*, 1955 – 1960.
[3] H. L. Jiang, X. M. Luo, D. L. Bai, *Curr. Med. Chem.* **2003**, *10*, 2231 – 2252.
[4] For biosynthesis of lycodine (**3**) and other Lycopodium alkaloids, see: a) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 2911 – 2918; b) M. Castillo, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 1893 – 1903; c) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, J. T. Wrobel, *J. Am. Chem. Soc.* **1968**, *90*, 1360 – 1361.
[5] E. Leete, S. A. Slattery, *J. Am. Chem. Soc.* **1976**, *98*, 6326 – 6330.
[6] D. F. Fischer, R. Sarpong, *J. Am. Chem. Soc.* **2010**, *132*, 5926 – 5927.
[7] C. Yuan, C.-T. Chang, A. Axelrod, D. Siegel, *J. Am. Chem. Soc.* **2010**, *132*, 5924 – 5925.
[8] a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390 – 391; b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, *Science* **2002**, *295*, 305 – 308; c) I. A. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890 – 931; d) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864 – 873.
[9] D. Jerchel, E. Bauer, H. Hippchen, *Chem. Ber.* **1955**, *88*, 156 – 163.
[10] For a general review on the mechanism of SeO_2 oxidations, see: a) N. Rabjohn, *Org. React.* **1976**, *24*, 261 – 415; for a discussion of potential mechanisms for SeO_2 oxidation of benzylic methylic groups, see: b) E. L. Trump, M. X. Zhou, *Trans. Kans. Acad. Sci.* **1993**, *96*, 167 – 180.
[11] a) V. Boekelheide, W. J. Linn, *J. Am. Chem. Soc.* **1954**, *76*, 1286 – 1291; b) V. Boekelheide, W. L. Lehn, *J. Org. Chem.* **1961**, *26*, 428 – 430.
[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,

Bioorg. Med. Chem. **2007**, *15*, 413 – 417; for the isolation of complanadine E, see: b) K. Ishiuchi, T. Kubota, H. Ishiyama, S. Hayashi, T. Shibata, K. Mori, Y. Obara, N. Nakahata, J. Kobayashi, *Bioorg. Med. Chem.* **2011**, *19*, 749 – 753.

[14] K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 6352 – 6363.

[15] For a discussion of the mechanism for borylative C–H functionalization, see: T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263 – 14278.

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

[17] R.-J. Chein, E. J. Corey, *Org. Lett.* **2010**, *12*, 132 – 135. The computations reported in this manuscript, which appeared two years prior to Ref. [16], simulated the gas phase.

[18] P. Álvarez-Bercedo, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 17352 – 17353.

[19] T. Mesganaw, N. F. Fine Nathel, N. K. Garg, *Org. Lett.* **2012**, *14*, 2918 – 2921.

[20] A. G. Sergeev, J. F. Hartwig, *Science* **2011**, *332*, 439 – 443.

[21] P. Kelley, S. Lin, G. Edouard, M. W. Day, T. Agapie, *J. Am. Chem. Soc.* **2012**, *134*, 5480 – 5483.

[22] A. Haudrechy, C. Chassaing, C. Riche, Y. Langlois, *Tetrahedron* **2000**, *56*, 3181 – 3187.

[23] During the preparation of this manuscript, we became aware of the elegant synthesis of complanadines A and B by Tsukano et al.: L. Zhao, C. Tsukano, E. Kwon, Y. Takemoto, M. Hirama, Angew. Chem., DOI: 10.1002/ange.201208297; Angew. Chem. Int. Ed., DOI: 10.1002/anie.201208297.

