ORGANIC LETTERS

2012
Vol. 14, No. 20
5350–5353

Synthesis of the Pentacyclic Skeleton of the Indole Alkaloid Arboflorine

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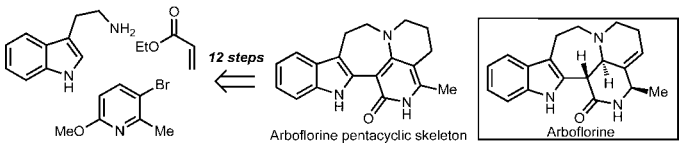
Received September 13, 2012

ABSTRACT



An effective synthesis of the pentacyclic core of the unusual *Kopsia* alkaloid arboflorine is reported. The success of the synthetic route rested on the use of a borylative C−H functionalization reaction, a convergent Suzuki cross-coupling to a C(2) halogenated indole, and an unprecedented transannular dehydrogenative C−N bond forming reaction.

Indole alkaloids isolated from the *Kopsia* genus of plants demonstrate a wide range of structural diversity as well as pharmacological activities.[1] In Southeast Asia, some of the traditional treatments for ailments including rheumatoid arthritis, edema, and tonsillitis rely on extracts from *Kopsia* plants. In 2006, Kam and co-workers reported the isolation of a *Kopsia* indole alkaloid of unusual structure from *K. arborea*, which was named arboflorine (**1**, Figure 1).[2] Arboflorine is one of a new subclass of *Kopsia* alkaloids that, unlike the majority of *Kopsia* congeners (which have two nitrogen atoms), possess three nitrogen atoms.[3] Although biological studies have not been conducted with **1**, it holds promise for interesting bioactivity given the established biological properties of other *Kopsia* alkaloids isolated from *K. arborea*.[4]

The atypical framework of **1** has spurred interest in its chemical synthesis, and to date two biomimetic approaches to arboflorine have been reported by the groups of Kerr[5] and Huang.[6] However, a total synthesis of **1** has yet to be achieved. In this Communication, we report our progress toward the synthesis of **1**, which has resulted in the assembly of the complete pentacyclic skeleton of the natural product.

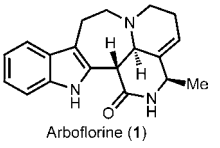


Figure 1. Structure of the *Kopsia* indole alkaloid arboflorine (**1**).

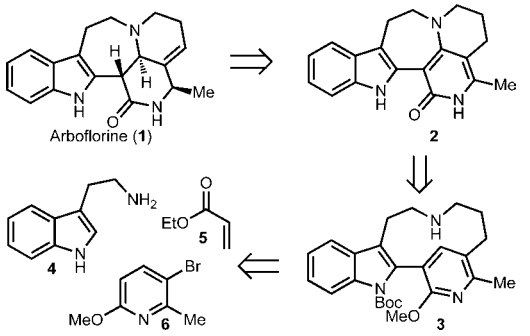
In our retrosynthetic analysis of **1**, we were drawn to the implementation of a modular strategy, which could provide opportunities to rapidly assemble the core of the natural product as well as related structural analogs. As shown in Scheme 1, we envisioned that the natural product would arise from pyridone **2**, whereby, in the forward direction, a formal hydrogenation and double bond transposition could be effected at a late stage. Pentacycle **2** was expected to be formed from macrocycle **3** using a formally dehydrogenative, transannular, carbon−nitrogen (C−N) bond construction as the key step. Although there is no

(1) Awang, K.; Svenet, T.; Pais, M. *Nat. Prod.* **1993**, *56*, 1134–1139.
(2) Lim, K.-H.; Kam, T.-S. *Org. Lett.* **2006**, *8*, 1733–1735.
(3) Other *Kopsia* indole alkaloids that possess three nitrogen atoms include the mersingines and lahadinines; see: (a) Kam, T. S.; Yoganathan, K.; Chen, W. *J. Nat. Prod.* **1996**, *59*, 1109–1112. (b) Kam, T. S.; Yoganathan, K. *Phytochemistry* **1997**, *46*, 785–787.
(4) Bioactivity including cytotoxicity toward KB and Jurkat cells and reversal of multidrug resistance of KB cells have been noted for other alkaloids isolated from *K. arborea*. For example, see: Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302–1307.
(5) Johansen, M. B. Part I: Synthesis of Pyrrolo[1,2-A]indoles Part II: Studies Towards Arboflorine. Ph.D. Dissertation, The University of Western Ontario, London, ON, Canada, 2010.
(6) Du, Y.; Huang, H.-Y.; Liu, H.; Ruan, Y.-P.; Huang, P.-Q. *SynLett* **2011**, 565–568.

10.1021/ol302535r
Published on Web 09/28/2012

direct precedent for this step, we anticipated that such a process would be favorable because of its transannular nature. Specifically, a variant of the Chichibabin reaction[7] or an *N*-haloamine cyclization[8] could be enlisted to convert **3** to **2**. Macrocycle **3** would be formed from the readily available components of tryptamine (**4**), ethyl acrylate (**5**), and bromomethoxypicoline **6**, which was first reported by Langlois.[9]

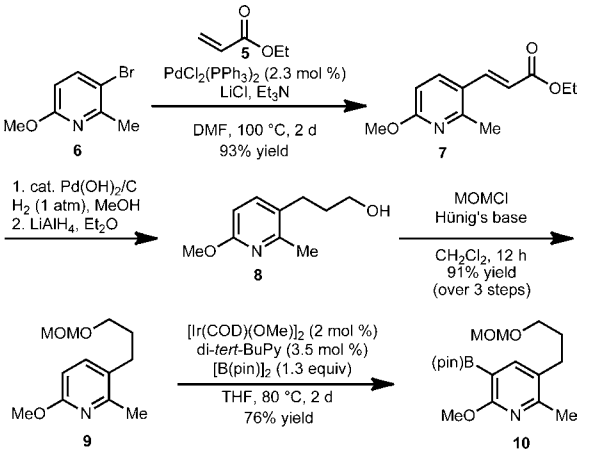
Scheme 1. Retrosynthetic Analysis of Arboflorine



Our research group has implemented bromomethoxypicoline **6** in various complex molecule syntheses.[10] For example, we have previously employed **6** in the total syntheses of the natural products lyconadin A,[11] alkaloid G.B. 13,[12] and lycoposerramine R.[13] Therefore, our approach to arboflorine would provide another opportunity to further investigate the reactivity of **6** in a complex setting and would further demonstrate its utility in complex molecule synthesis.

Our synthetic studies commenced with the preparation of borylated methoxypicoline **10** (Scheme 2), which would serve as a surrogate for the lactam and dehydropiperidine portion of **1**. First, Heck cross-coupling of **6** with ethyl acrylate (**5**) gave adduct **7** in 93% yield. In the course of our optimization studies, it was found that LiCl was important as an additive to obtain consistently high yields of **7**.[14] A two-stage reduction of **7** by hydrogenation of the enoate double bond and lithium aluminum hydride reduction of the ester group gave alcohol **8**. Protection of the primary hydroxyl group as a MOM ether set the stage for a borylative C−H functionalization using the conditions of Hartwig and Miyaura.[15] The reaction proceeded to give **10** in 76% yield with excellent selectivity for C(3) of the pyridine over C(4). The observed selectivity likely reflects a stereoelectronic bias that comprises the influence of the C(2) and C(5) substituents as well as the innate reactivity of the pyridine nucleus.

Scheme 2. Synthesis of Borylated Methoxypicoline **10**



With boronic ester **10** in hand, we proceeded with its Suzuki cross-coupling to nosyl-protected[16] 2-bromotryptamine derivative **4a** (Scheme 3), which was prepared in two steps from tryptamine using the protocol for the preparation of the tosylamide derivative by Stewart and co-workers.[17] Following the conditions of Wyvratt et al.,[18] we found that the Suzuki coupling product (**11**) could be obtained in a reproducible 51% yield by employing a solvent mixture of dimethoxymethane and water. At this stage, deprotection of the primary hydroxyl by removal of the MOM group and macrocyclization under modified Mitsunobu conditions gave macrocycle **12**. Of note, high dilution of the Mitsunobu reaction mixture was necessary to suppress competing polymerization of the starting material. Protection of the indole nitrogen of **12** with a Boc group and selective cleavage of the nosyl group proceeded without event to provide amine **3**.

As shown in Table 1, our initial attempts to convert **3** to the pentacyclic core of arboflorine (see **14**) sought to achieve a transannular addition of the amine group to C(4) of the pyridine moiety using a variant of the Chichibabin

(7) For a review, see: McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1–79.

(8) For example, an *N*-centered radical addition into an arene could be utilized. For a related precedent, see: Stella, L. *Angew. Chem., Int. Ed.* **1983**, *22*, 337–422.

(9) Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron* **2000**, *56*, 3181–3187. (b) Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367–1379.

(10) For a use of **6** and a closely related derivative by others in synthesis, see: (a) Tun, M. K. M.; Wüstmann, D.-J.; Herzon, S. B. *Chem. Sci.* **2011**, *2*, 2251–2253. (b) Ding, R.; Sun, B.-F.; Lin, G.-Q. *Org. Lett.* **2012**, *14*, 4446–4449.

(11) (a) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223. (b) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187–11194.

(12) Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244–13245.

(13) Bisai, V.; Sarpong, R. *Org. Lett.* **2010**, *12*, 2551–2553.

(14) For a discussion of the role of the chloride anion in oxidative addition to zerovalent palladium complexes, see: (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.

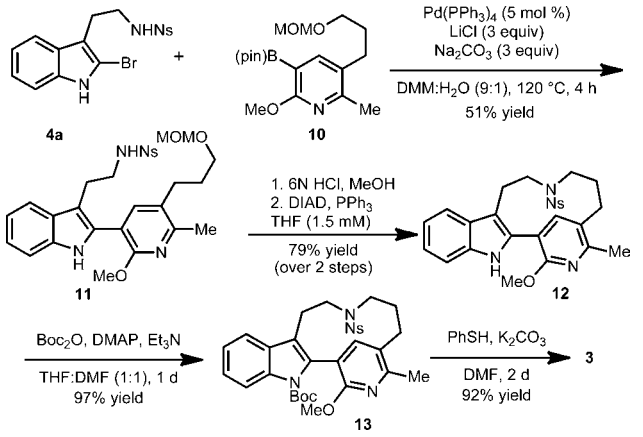
(15) (a) Ishyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (b) For a related reaction, see: Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R. *Science* **2002**, *295*, 305–308. (c) For a recent review, see: Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.

(16) Nosyl is defined as 2-nitrobenzenesulfonyl.

(17) Priebbenow, D. L.; Henderson, L. C.; Pfeffer, F. M.; Stewart, S. G. *J. Org. Chem.* **2010**, *75*, 1787–1790.

(18) Chu, L.; Fisher, M. H.; Goulet, M. T.; Wyvratt, M. J. *Tetrahedron Lett.* **1997**, *38*, 3871–3874.

Scheme 3. Synthesis of Macrocycle **3**



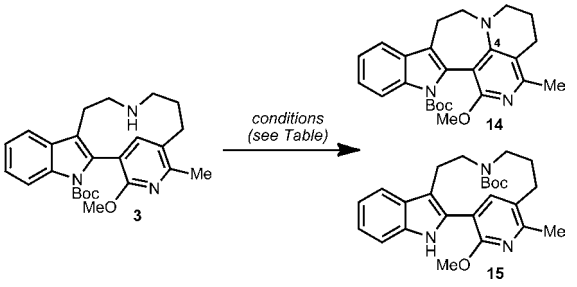
reaction. Exposure of **3** to *n*-BuLi (which likely generates the lithium amide) followed by heating in toluene at 140 °C for 1 day led only to the transfer of the Boc group (probably intermolecularly) from the indole nitrogen to the secondary amine group (see **15**; entry 1 of Table 1). Additional trials using sodium amide as the base simply led to the recovery of the starting material.

Alternatively, following conditions from a previous report by Robinson et al.[19] on the formal dehydrogenative intramolecular C(sp^2)–N coupling between dialkyl *N*-haloamines and benzene rings under Hoffman–Löffler–Freytag (HLF) type conditions, we subjected the *N*-chloro derivative[20] of **3** to H_2SO_4 and irradiation with a medium pressure (MP) mercury lamp but only recovered the reduced product (i.e., **3**). After several additional unsuccessful attempts, we discovered that an acid-free variant of the HLF conditions (entry 2) described by Oishi et al.[21] led to the desired product (**14**), albeit in only 8% yield. Ultimately, the use of *N*-iodosuccinimide (1 equiv), triethylamine (6 equiv), and irradiation using an MP mercury lamp were found to be optimal.[22] To our delight, these conditions led to a 81% yield of **14** (entry 4).

Several insights emerged from this optimization campaign. First, the *N*-Cl and *N*-Br derivatives of **3** (not shown), while competent in the transannular C–N bond formation, gave diminished yields of **14** accompanied by significant formation of imine byproducts presumably arising from the loss of HCl or HBr, respectively. However, the reaction solvent had the largest discernible effect on the yield of product. Dichloromethane and benzene led to good yields whereas tetrahydrofuran and carbon tetrachloride gave poor yields (compare entries 3 and 4).

The conditions that we have identified for the conversion of **3** to **14** provide an effective solution to this unique C–N bond forming problem, which we failed to solve using a multitude of tactics including transition metal mediated processes.[23]

Table 1. Formal Dehydrogenative C–N Bond Formation

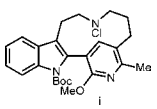


entry	conditions	result
1	*n*-BuLi (1 equiv), PhMe, 140 °C, 1 d	**15** (10%) + complex mixture
2	NCS (1 equiv), THF; Et_3N (6 equiv), hν, 12 h	**14** (8%)
3	NIS (1 equiv), THF; Et_3N (6 equiv), hν, 12 h	**14** (15%)
4	NIS (1 equiv), PhH; hν, 10 min; Et_3N (6 equiv), hν, 5 h	**14** (81%)

The availability of pentacycle **14** from our approach has provided opportunities to try to advance this compound to arboflorine. In our efforts to advance pentacycle **14**, several important insights, especially pertaining to the reactivity of fully substituted methoxy pyridines and *N*-alkyl pyridones, have emerged from our studies. For example, attempts to directly reduce the methoxypicoline moiety of **14** using hydrogenation or dissolving metal reduction[24] conditions have thus far proved fruitless. These observations are not entirely surprising given the well recognized disinclination of highly substituted arenes to undergo dissolving metal reduction.[25] Similarly, our attempts to reduce pyridone **17** (Scheme 4; prepared from **14** using ethane thiolate demethylation conditions) have also met with little success. This may be attributed, partially, to the tautomeric alkoxypyridine form that **17** likely adopts. To obviate this possibility, we prepared *N*-methyl pyridone derivative **18** from **17** and subjected it to a plethora of reduction conditions including selectrides, superhydride, and Gribble reduction conditions.[26] While

(19) Anderson, P. S.; Lundell, G. F.; Cias, J. L.; Robinson, F. M. *Tetrahedron Lett.* **1971**, *12*, 2787–2790.

(20) *N*-Chloro derivative (**i**) of **3**.



(21) Ban, Y.; Kimura, M.; Oishi, T. *Heterocycles* **1974**, *2*, 323–328.

(22) Quartz tubes were used as reaction vessels.

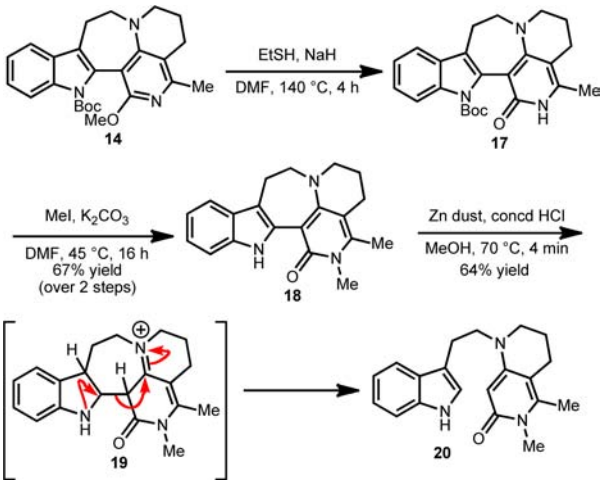
(23) For some recent examples of metal-mediated oxidative C(sp^2)–N bond formations, see: (a) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807. (b) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186.

(24) Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435–1445.

(25) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35–85.

the majority of these attempts have simply returned the starting material or led to nonspecific decomposition, the use of Zn dust in concentrated HCl led, surprisingly, to the formation of **20**, which may arise via **19**.

Scheme 4. Attempted Reduction of Methoxypicoline Moiety of **14**



In conclusion, we have developed an effective synthetic sequence to the pentacyclic core of the unusual *Kopsia* alkaloid arboflorine. Our synthetic sequence features a highly regioselective borylative C−H functionalization of a highly substituted methoxypicoline derivative and a convergent Suzuki cross-coupling of a 2-bromotryptamine derivative. Furthermore, we report the first example of a direct oxidative C(sp^2)−N bond formation involving an *N*,*N*-dialkylamine and a pyridine group, which proceeds in a transannular fashion. This powerful transformation, should it emerge to be general, may afford new opportunities for alkaloid synthesis. These directions form the basis of future studies in our laboratory. Finally, even though our synthetic plan has not as yet culminated in a total synthesis of arboflorine, primarily because of difficulties associated with the late-stage reduction of the pyridine and pyridone moieties, several important insights into the reactivity of highly substituted pyridines and pyridones have been gained. Efforts to advance **17** to arboflorine are ongoing.

Acknowledgment. The authors are grateful to Prof. John F. Hartwig (UC Berkeley) for insightful discussions related to the borylation chemistry. The authors thank the NIH (NIGMS RO1 08637) for financial support of this work. R.A.L. is grateful for a National Science Foundation graduate research fellowship and a Berkeley EDGE summer fellowship. S.K.A. thanks UC Berkeley for a Chancellor's Fellowship. We are indebted to Eli Lilly, Abbott, Amgen, Dupont, and Astra Zeneca for unrestricted funds to support our research.

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

(26) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395–404.

The authors declare no competing financial interest.