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Synthesis of the Pentacyclic Skeleton of the Indole Alkaloid Arboflorine

Raul A. Leal, Danial R. Beaudry, Saeed K. Alzghari, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720

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 coworkers 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 Kerr⁵ 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.

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 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 reaction⁷ or an *N*-

*rsarpong@berkeley.edu.

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>.

haloamine cyclization⁸ could be enlisted to convert **3** to **2**. Macrocyclic **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

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. 13¹² 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 stereo-electronic bias that comprises the influence of the C(2) and C(5) substituents as well as the innate reactivity of the pyridine nucleus.

With boronic ester **10** in hand, we proceeded with its Suzuki cross-coupling to nosyl-protected¹⁶ 2-bromo-tryptamine derivative **4a**, which was prepared in two steps from tryptamine using the protocol for the preparation of the tosylamide derivative by Stewart and coworkers.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 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(sp²)-N coupling between dialkyl *N*-haloamines and benzene rings under Hoffman-Löffler-Freytag (HLF) type conditions, we subjected the *N*-chloro derivative²⁰ of **3** to H₂SO₄ and 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 a 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

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 reduction²⁴ 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 alkoxy pyridine 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, super-hydride and Gribble reduction conditions.²⁶ While the majority of these attempts have simply returned the starting material or led to non-specific decomposition, the use of Zn dust in concentrated HCl led, surprisingly, to the formation of **20**, which may arise via **19**.

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-bromo tryptamine derivative. Furthermore, we report the first example of a direct oxidative C(sp²)-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 on-going.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

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. [PubMed: 16597153]
3. Other Kopsia indole alkaloids that possess three nitrogen atoms include the mersingines and lahadinines, see: Kam TS, Yoganathan K, Chen WJ. *Nat. Prod.* 1996; 59:1109–1112. Kam TS, Yoganathan K. *Phytochemistry.* 1997; 46:785–787.
4. Bioactivity including cytotoxicity toward KB and Jurkat cells and reversal of multi-drug 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. [PubMed: 17665953]
5. Johansen, MB. Ph.D. Dissertation. The University of Western Ontario; London, ON, Canada: 2010. Part I: Synthesis of Pyrrolo[1,2-A]indoles Part II: Studies Towards Arboflorine.
6. Du Y, Huang H-Y, Liu H, Ruan Y-P, Huang P-Q. *SynLett.* 2011:565–568.
7. For a review, see: McGill CK, Rappa A. *Adv. Heterocycl. Chem.* 1988; 44:1–79.
8. For example, an N-centered radical addition into an arene could be utilized. For 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 MA, 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: Tun MKM, Wüstmann D-J, Herzon SB. *Chem. Sci.* 2011; 2:2251–2253. Ding R, Sun B-F, Lin G-Q. *Org. Lett.* 2012; 14:4446–4449. [PubMed: 22900755]
11. (a) Bisai A, West SP, Sarpong R. *J. Am. Chem. Soc.* 2008; 130:7222–7223. [PubMed: 18479095] (b) West SP, Bisai A, Lim AD, Narayan RR, Sarpong R. *J. Am. Chem. Soc.* 2009; 131:11187–11194. [PubMed: 19591469]
12. Larson KK, Sarpong R. *J. Am. Chem. Soc.* 2009; 131:13244–13245. [PubMed: 19754185]
13. Bisai V, Sarpong R. *Org. Lett.* 2010; 12:2551–2553. [PubMed: 20441180]
14. For a discussion of the role of chloride anion in oxidative addition to zero-valent palladium complexes, see: Amatore C, Jutand A. *Acc. Chem. Res.* 2000; 33:314–321. [PubMed: 10813876] Amatore C, Azzabi M, Jutand A. *J. Am. Chem. Soc.* 1991; 113:8375–8384.
15. Ishyama T, Takagi J, Ishida K, Miyaura N, Anastasi NR, Hartwig JF. *J. Am. Chem. Soc.* 2002; 124:390–391. [PubMed: 11792205] For a related reaction, see: Cho J-Y, Tse MK, Holmes D, Maleczka RE Jr, Smith MR. *Science.* 2002; 295:305–308. [PubMed: 11719693] For a recent review, see: Mkhali IAI, Barnard JH, Marder TB, Murphy JM, Hartwig JF. *Chem. Rev.* 2010; 110:890–931. [PubMed: 20028025]
16. Nosyl is defined as 2-nitrobenzenesulfonyl.
17. Priebbenow DL, Henderson LC, Pfeffer FM, Stewart SG. *J. Org. Chem.* 2010; 75:1787–1790. [PubMed: 20131765]
18. Chu L, Fisher MH, Goulet MT, Wyvrat MJ. *Tetrahedron Lett.* 1997; 38:3871–3874.
19. Anderson PS, Lundell GF, Cias JL, Robinson FM. *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(sp²)-N bond formations, see: Mei T-S, Wang X, Yu J-Q. *J. Am. Chem. Soc.* 2009; 131:10806–10807. [PubMed: 19606861] Jordan-Hore JA, Johansson CCC, Gulias M, beck EM, Gaunt MJ. *J. Am. Chem. Soc.* 2008; 130:16184–16186. [PubMed: 18998652]
24. Donohoe TJ, McRiner AJ, Helliwell M, Sheldrake PJ. *Chem. Soc. Perkin Trans 1*. 2001:1435–1445.
25. Hook JM, Mander LN. *Nat. Prod. Rep.* 1986; 3:35–85.
26. Gribble GW. *Chem. Soc. Rev.* 1998; 27:395–404.

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

Scheme 1.
Retrosynthetic analysis of arboflorine

Scheme 2.
Synthesis of borylated methoxypicoline **10**

Scheme 3.
Synthesis of macrocycle **3**

Scheme 4.
Attempted reduction of methoxypicoline moiety of **14**

Table 1

Formal dehydrogenative C–N bond formation

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