Enantioselective Syntheses of Both Enantiomers of Noranabasamine
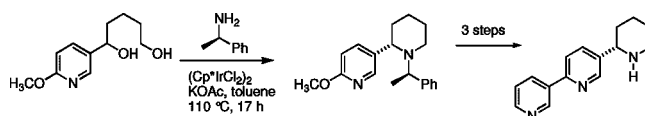
Lei Miao, Stassi C. DiMaggio, Hong Shu, and Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

mtrudell@uno.edu

ABSTRACT

Both the *R* and *S* enantiomers of the amphibian alkaloid noranabasamine were prepared in >30% overall yield with 80% ee and 86% ee, respectively. An enantioselective iridium-catalyzed *N*-heterocyclization reaction with either (*R*)- or (*S*)-1-phenylethylamine and 1-(5-methoxypyridin-3-yl)-1,5-pentanediol was employed to generate the 2-(pyridin-3-yl)-piperidine ring system in 69−72% yield.

The pharmacology of amphibian alkaloids has generated significant interest in these molecules over the past decade. Many of these compounds have aided in the elucidation of biological mechanisms and the development of lead compounds for the treatment of a wide variety of pathologies mediated by nicotinic acetylcholine receptors (nAChRs) and corresponding ion channels.[1] However, the paucity of useful quantities of isolated amphibian alkaloids has led to a flurry of synthetic activity to make these compounds available for biological study. While many of the amphibian alkaloids possess unique chemical structures,[1] the similarity between noranabasamine (**1**) isolated from the columbian poison dart frog *Phyllobates terribilis*[2] and plant alkaloids isolated from the tobacco species *Nicotian tabacum* [e.g., nicotine (**2**), anabasine (**3**)],[3] as well as the central asian shrub *Anabasis aphylla [anabasamine (4)]*,[4] is noteworthy. The plant-derived piperidine alkaloids **2** and **3** are widely known to elicit their pharmacological effects via nAChRs.[5] Anabasamine (**4**) has been much less studied but has been reported to inhibit acetylcholine esterase and exhibit anti-inflammatory activity.[6]
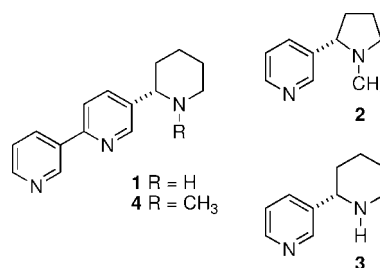

Figure 1. Noranabasamine (**1**) and related plant alkaloids.

Our interests in the development of new pharmacotherapies for nAChR mediated disorders and disease states[7] prompted an investigation into the synthesis of the enantiomers of noranabasamine (**1**). It was our aim to develop an efficient synthesis of **1**, that would provide sufficient quantities for

(1) For a review see: (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556. (b) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445. (c) Gomes, A.; Giri, B.; Saha, A.; Mirsha, R.; Dasgupta, S. C.; Debnath, A.; Gomes, A. *Indian J. Exp. Biol.* **2007**, *45*, 579. (d) *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*; Arneric, S. P., Brioni, J. D., Eds.; Wiley-Liss Inc.: New York, 1999.

(2) Tokuyama, T.; Daly, J. W. *Tetrahedron* **1983**, *39*, 41.

(3) Leete, E.; Mueller, M. E. *J. Am. Chem. Soc.* **1982**, *104*, 6440.

(4) Lovkova, M. Y.; Nurimov, E. *Isv. Akad. Nauk. SSSR Ser. Biol.* **1978**, 545.

(5) Crooks, P. A.; Dwoskin, L. P. *Biochem. Pharmacol.* **1997**, *54*, 743.

(6) (a) Tilyabaev, Z.; Abduvakhabov, A. A. *Chem. Nat. Compd.* **1998**, *34*, 295. (b) Tilyabaev, Z.; Aabd Mukhamedzhanova, Kh. S. *Dokl. Akad. Nauk UzSSR* **1984**, *8*, 45. (c) Mukhamedzhanova, Kh. S. *Dokl. Akad. Nauk UzSSR* **1983**, *7*, 47.

(7) (a) Cheng, J.; Izenwasser, S.; Zhang, C.; Zhang, S.; Wade, D.; Trudell, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1775. (b) Nishiyama, T.; Gyermek, L.; Trudell, M. L.; Hanaoka, K. *Eur. J. Pharmacol.* **2003**, *470*, 27. (c) Cheng, J.; Zhang, C.; Stevens, E. D.; Izenwasser, S.; Wade, D.; Chen, S.; Paul, D.; Trudell, M. L. *J. Med. Chem.* **2002**, *45*, 3041. (d) Cheng, J.; Izenwasser, S.; Wade, D.; Trudell, M. L. *Med. Chem. Res.* **2001**, *10*, 356.

biological evaluation. In addition, it was envisaged that the preparation of both antipodes of **1** would aid in the confirmation of the absolute configuration of the natural product which has yet to be unequivocally established.[4] Herein we describe the first enantioselective syntheses of both enantiomeric forms of noranabasamine.

Our retrosynthetic analysis illustrated in Scheme 1 focused on the disconnection of the terminal pyridyl group (ring C)
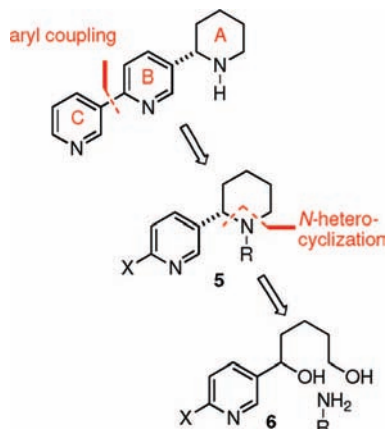
to afford a 2-substituted piperidine fragment **5** as our initial target. There are a variety methods for the enantioselective construction of 2-substituted piperidines,[8] but the iridium-complex-catalyzed *N*-heterocyclization of primary amines with diols recently reported by Yamaguchi and co-workers seemed to be exceptionally well suited for the construction of the AB-ring system of **5** and has not been explored for the preparation of natural products.[9] A diastereoselective *N*-heterocyclization with the appropriate chiral primary amine was envisaged for introduction of the single stereogenic carbon atom of the noranabasamine skeleton. The approach not only was deemed straightforward but also offered the flexibility for the preparation of various derivatives and analogues if structure–activity studies were warranted in the future.

As illustrated in Scheme 2, the required diol **9** was prepared from 5-bromo-2-methoxypyridine (**7**). Treatment
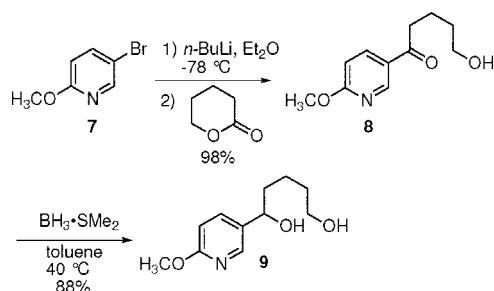
of **7** with *n*-butyllithium followed by addition of δ-valero-lactone to the lithiated pyridine solution afforded the ketone **8** in 98% yield. The ring-opening reaction proceeded regioselectively to give **8** without further nucleophilic addition to the carbonyl. The carbonyl group of **8** was then reduced to the hydroxyl moiety with $BH_3 \cdot SMe_2$ to furnish the diol **9** in 88% yield.

With the diol **9** in hand, our attention focused on the enantioselective construction of the piperidine ring using *N*-heterocyclization chemistry (Scheme 3). The diol **9** was
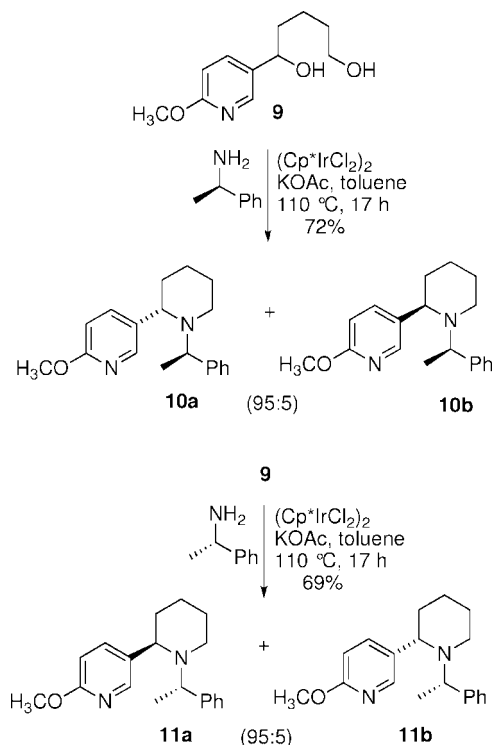
heated at 110 °C in toluene with (*R*)-1-phenylethylamine[10] in the presence of a catalytic amount (1.5 mol%) of $(Cp*IrCl_2)_2$ in a sealed reaction tube. The *N*-heterocyclization then proceeded diastereoselectively to provide the 2-substituted piperidine **10ab** in 72% (**10a**:**10b**, dr, 95:5). The diastereoisomers were easily separated by column chromatography. The 2-substituted piperidine **11ab** was prepared in similar fashion from diol **9** using (*S*)-1-phenylethylamine (Scheme 3). The piperidine **11ab** was obtained in 69% yield with a diastereomeric ratio of **11a**:**11b** equal to 95:5. On the basis of the work of Fujita and co-workers, we initially assigned the stereochemistry at C2 of **10a** as possessing an *S*-configuration and **11a** as having an *R*-configuration.

Presumably *N*-heterocyclization proceeds through the formation of various imine and enamine intermediates.[9] To ensure ourselves that epimerization/racemization of the two stereogenic centers had not occurred during the ring-generating process, it would be necessary to establish the enantiomeric integrity of the piperidine ring. Crooks and co-

workers recently reported a procedure for the determination of the enantiopurity of anabasine and related alkaloids using NMR spectroscopy and the chiral shift reagent 1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPPA).[11] With this technique in mind, it was envisaged that the issue of the enantiopurity of the piperidine ring system would be more easily resolved with **1**, due to the similar secondary amine structure of noranabasamine to the anabasine.

With the piperidine ring system **10a** in hand, our attention was directed toward completing the synthesis of noranabasamine (**1**). On the basis of the initial stereochemical assignment of **1**,[2] it was assumed that the *N*-heterocyclization product **10a** possessed the correct stereochemistry at C2. However, the conversion of **10a** into **1** would require the manipulation of the methoxy group into a more suitable moiety to facilitate an aryl cross-coupling reaction. To this end, treatment of **10a** with POCl$_3$ furnished the 5-chloro-pyridin-3-yl derivative **12** in 92% yield (Scheme 4). The

Scheme 4
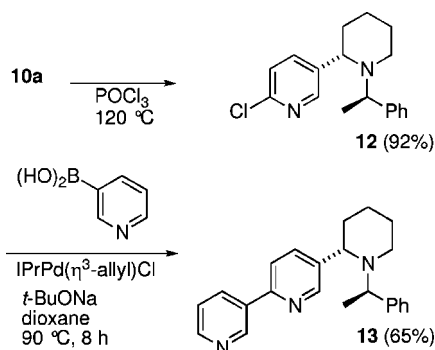
Suzuki−Miyaura coupling of **12** with 3-pyridineboronic acid could be achieved using several different types of palladium/ligand systems.[12] Initially we employed the catalytic system reported by Nolan and co-workers for the coupling sequence.[13] This furnished the tricyclic compound **13** in 65% isolated yield. Unfortunately, despite numerous attempts and various conditions to remove the *N*-phenylethyl auxiliary group, none were successful. The increased basicity of the molecule and the additional steric hindrance around the nitrogen atom completely shut down the hydrogenolysis of the *N*-1-phenylethyl group. High pressure, high temperature, and extended reaction times either resulted in recovery of unreacted starting material or decomposition and formation of intractable mixtures.

To avoid the problematic hydrogenolysis of **13**, an alternative sequence of reactions was devised to prepare **1** (Scheme 5). The methoxy derivative **10a** was subjected to hydrogenolysis conditions to furnish **14** and concomitant treatment with POCl$_3$ provided the chloro analogue **15** in 56% yield over the two-step procedure. This sequence was also applied to **11a** and furnished the corresponding **17** in 60% yield.

Scheme 5. Synthesis of Noranabasamine
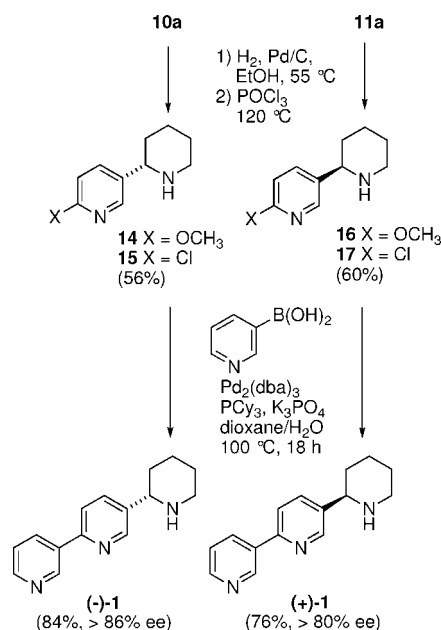
For the final step, the Suzuki−Miyaura coupling conditions developed by Fu and co-workers were utilized.[14] These conditions for the coupling of 3-pyridineboronic acid with **15** were found to be superior to other methods because of the ease of the workup and purification steps. This afforded the (*S*)-noranabasamine (−)-**1** in 84% yield, $[\alpha]^{25}_D = -32.9$ (*c* 0.33, CH$_3$OH). The NMR data of (−)-**1** was identical to the reported data of the isolated material, and the optical rotation was also levorotatory.[15] The synthesis of the (*R*)-noranabasamine (+)-**1** {$[\alpha]^{25}_D$ +34.6 (*c* 0.5, CH$_3$OH) from **17** provided additional support of a 2*S*-configuration of the natural antipode of noranabasamine.

At this point we sought to establish the enantiopurity of the piperidine ring systems. As expected use of the chiral

(8) (a) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244. (b) Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261. (c) Castro, A.; Ramírez, J.; Juárez, J.; Terán, J. L.; Orea, L.; Galindo, A.; Gnecco, D. *Heterocycles* **2007**, *71*, 2699. (d) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Peréz, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872. (e) Ayers, J. T.; Xu, Rui; Dwoskin, L. P.; Crooks, P. A. *AAPS J.* **2005**, *7*, E752. (f) Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Commun.* **2002**, *5*, 526. (g) Felpin, F.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. (h) Felpin, F.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *Synlett* **2000**, *11*, 1646. (i) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749–1760. (j) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 1041. (k) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. (l) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.

(9) Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525.

(10) Commercially available from Alfa Aesar Chemical Co. with enantiopurity of 99% ee. The (*S*)-enantiomer was available in 99.5% ee.

(11) Ravard, A.; Crooks, P. A. *Chirality* **1996**, *8*, 295.

(12) For a review, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000; pp 191−197.

(13) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.

(14) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

(15) The specific rotation for the natural material was reported as $[\alpha]_D$ −14.4 (CH$_3$OH). See ref 2.

shift reagent BNPPA afforded baseline resolution of the proton signals for H2, H6, and H2″ of both enantiomers of **1**.[16] From the NMR study it was quite clear that the enantiopurity of (−)-**1** was greater than 86% ee, and that of (+)-**1** was greater than 80% ee. From these results it can be inferred that the diastereoselective *N*-heterocyclization reactions that furnished **10a** and **11a** (Scheme 3) are highly enantioselective (>80% ee) and consistent with previous studies.[9]

In summary, we have shown that the iridium-catalyzed *N*-heterocyclization reaction is a facile method for the efficient and enantioselective construction of 2-(pyridin-3-yl)-piperidine alkaloids. This reaction was a key step in the first total synthesis of both enantiomers of the amphibian alkaloid noranabasamine (**1**) in greater than 30% overall yield and has allowed us to establish the absolute configuration of the natural product as levorotatory. Additional studies with

regard to the scope and limitations of this reaction system are ongoing and will be reported in due course. The biological evaluation of both enantiomeric forms of noranabasamine is currently under investigation and will be reported elsewhere.

Supporting Information Available: Full experimental details and characterization data of all synthetic products. The material is available free of charge via the Internet at http://pubs.acs.org.

(16) See Supporting Information for details and spectra.

OL9002288