JOC Article
pubs.acs.org/joc

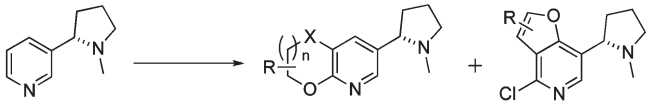
Synthesis of Fused-Ring Nicotine Derivatives from (*S*)-Nicotine

Pauline W. Ondachi and Daniel L. Comins*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

daniel_comins@ncsu.edu

Received December 21, 2009



The synthesis of novel fused-ring bicyclic (**4**−**6**) and tricyclic (**7**−**10**) nicotine derivatives from natural (*S*)-nicotine are described. Enantiopure bicyclic dioxino, dihydrofuro, and dihydropyranol nicotine derivatives as well as tricylic benzofuro and benzopyran derivatives were synthesized from simple alkoxy or halonicotine intermediates. Attempts to synthesize furonicotines (**11**, **12**) resulted in formation of the furonicotine dimers **42** and **49**.

Introduction

Recently, (*S*)-nicotine (**1**, Figure 1), the most abundant alkaloid isolated from dried leaves of the tobacco plants *Nicotiana tabacum* and *N. rustica*,[1,2] and nicotine derivatives have drawn a lot of interest from both medicinal and synthetic chemists due to their potential pharmacological role in the treatment of Parkinson's disease, Alzheimer's disease, depression, and other central nervous system related disorders.[3] Despite the beneficial pharmacological properties of nicotine, its clinical utility is limited by its cardiovascular, gastrointestinal, and neuromuscular side effects and its addictive liability. Consequently, there is a need to develop nicotine analogues that exhibit the beneficial properties of **1** but are devoid of its undesirable effects.

Current synthetic efforts are directed toward the development of analogues that are more selective to specific subtypes of nicotinic acetylcholine receptors (nAChRs).[4] Reported in the literature is the synthesis of a plethora of nicotine analogues of diverse variations (see examples, **3a**−**j**, Figure 2). Of these analogues, some have substitutions on either the pyrrolidine or pyridine rings,[5,6] modifications such as a linker between the two heterocyclic rings,[7] or pyrrolidine ring opening or replacement,[8] and in some cases the pyridine has been replaced with a surrogate ring.[9] Reports reveal that among the most active nicotine analogues, those with fused rings, bridged or constrained conformations have surfaced as the most attractive candidates for selective nAChRs-targeting ligands.[8,10,11]

(1) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th ed.; O'Neil, M. J., Heckelman, P. E., Koch, C. B., Roman, K. J., Eds.; Merck & Co., Inc.: Whitehouse Station, NJ, 2006.

(2) (a) Porgocki, D.; Ruman, T.; Danilczuk, M.; Danilczuk, M.; Celuch, M.; Waljtys-Rode, E. *Eur. J. Pharmacol.* **2007**, *563*, 18–39. (b) Amstrong, D. W.; Wang, X.; Ercal, N. *Chirality* **1998**, *10*, 587–591. (c) Amstrong, D. W.; Wang, X.; Jauh-Tzou, L.; Yan-Song, L. *Chirality* **1999**, *11*, 82–84.

(3) (a) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169–4190. (b) Kim, K. H.; Lin, N.; Anderson, D. J. *Bioorg. Med. Chem.* **1996**, *4*, 2211–2217. (c) Gotti, C.; Zoli, M.; Clementi, F. *Trends Pharm. Sci.* **2006**, *27*, 482–491. (d) Lee, C. *Pharmacol. Ther.* **2003**, *98*, 143–169.

(4) (a) Bunnelle, W. L.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299–334. (b) Glennon, R. A. Medicinal Chemistry of α4β2 Nicotine Chlinergic Receptor Ligands. In *Progress in Medicinal Chemistry*; King, F. D., Lawton, G., Oxford, A. W., Eds.; Elsevier: Amsterdam, 2004; Vol. 42, pp 55−123. For reviews on nicotine related synthesis, see: (c) Seeman, J. I. *Heterocycles* **1984**, *22*, 165–193. (d) Breining, S. P. *Curr. Top. Med. Chem.* **2004**, *4*, 609–629. (e) Kovganko, N. V.; Kashkan, Zh. N. *Russ. J. Org. Chem.* **2004**, *40*, 1709–1726. (f) Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353–2383. (g) Wagner, F. F.; Comins, D. L. *Tetrahedron* **2007**, *63*, 8065–8082.

(5) Lin, N.-H.; Carrera, G. M.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542–3553.

(6) (a) Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121–1124. (b) Dallacker, F.; Jouck, W. *Org. Chem.* **1984**, *39B* (11), 1598–1606.

(7) (a) Holladay, M. W.; Wasicak, J. T.; Lin, N.-H.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. J. B.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D. L.; Piarroni-Kaplan, M.; Briggs, C. A.; Williams, M.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407–412. (b) Garvey, D. S.; Wasicak, J. T.; Decker, M. W.; Brioni, J. D.; Buckley, M. J.; Sullivan, J. P.; Carrera, G. M.; Holladay, M. W.; Arneric, S. P.; Williams, M. *J. Med. Chem.* **1994**, *37*, 1055–1059.

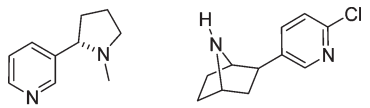
(8) Jensen, A. A.; Frølund, B.; Liljeefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705–4745.

(9) Efange, S. M. N.; Tu, Z.; von Hohenberg, K.; Francesconi, L.; Howell, R. C.; Rampersad, M. V.; Todaro, J. L.; Papke, R. L.; Kung, M.-P. *J. Med. Chem.* **2001**, *44*, 4704–4715.

(10) Dukat, M.; Fiedler, W.; Duma, D.; Damaj, I.; Martin, B. R.; Rosecrans, J. A.; James, J. R.; Glennon, R. A. *Eur. J. Med. Chem.* **1996**, *31*, 875–888.

(11) (a) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41–50. (b) Yang, X.; Luo, S.; Fang, F.; Liu, P.; Lu, Y.; He, M.; Zhai, H. *Tetrahedron* **2006**, *62*, 2240–2246. and the references therein.

Published on Web 02/09/2010 DOI: 10.1021/jo9026929



1 2

FIGURE 1. Natural agonists for nAChRs, (*S*)-nicotine (**1**) and epibatidine (**2**).

This trend is partially attributed to the discovery of epibatidine (**2**, Figure 1), an alkaloid containing a bridged structure that displays strong activity despite its toxicity.[12] Several bridged or conformationally restricted nicotine analogues have exhibited much higher affinity and better selectivity than nicotine for nAChRs.[13,14]

Our group has been engaged in the enantioselective synthesis of nicotine derivatives by starting with commercially available natural nicotine.[15] Although the use of (*S*)-nicotine as a starting material is attractive because it avoids a resolution step to obtain enantiopure analogues, it was necessary to develop appropriate methodologies to introduce functionalities around the pyridine ring. From this effort, regioselective substitutions at all positions of nicotine's pyridine ring, C-6,[15a,c] C-5,[15a,d,f] C-4,[15a,b] and C-2,[15c,f] have effectively been accomplished. In addition, utilizing the methodologies developed, two syntheses of SIB-1508Y[15g,h] (**3a**) in five and six steps from (*S*)-nicotine and a six-step synthesis of the nicotine-related natural product (*S*)-brevicolline[15e] have been reported. As part of this program, we were interested in synthesizing cyclic ether and benzofuro fused-ring derivatives of nicotine as potential nAChRs agonists. Heterocycle-containing analogues[16] and in particular benzofuran derivatives[17] are of considerable interest because they are common structural motifs in biologically active compounds and drug candidates.[18] We report herein the enantioselective synthesis of fused bicyclic and tricyclic nicotine derivatives from commercially available (*S*)-nicotine.

Results and Discussion

Bicyclic dioxino (**4**), hydropyranol (**5**), and dihydrofuro (**6**) nicotine derivatives, as well as tricylic benzofused-ring derivatives (**7**−**10**), were targeted and synthesized (Figure 3). Attempts to prepare furo-fused nicotine derivatives **11** and **12** were unsuccessful and resulted in the formation of unexpected dimers.

I. Synthesis of Dioxino Nicotine Derivative 4. Initial attempts to prepare the known[6b] **4** via a one-pot process through a copper(I)-catalyzed reaction of (*S*)-6-chloro-5-iodonicotine (**13**) with ethylene glycol in the presence of a 1,10-phenanthroline as ligand resulted in only a 4% yield of the desired product along with a mixture of the alcohols **14** and **15** (Scheme 1). A better synthesis of **4** was accomplished in two steps from the alkoxynicotine derivative **16** as shown in Scheme 2. The dihalo- and alkoxynicotines **13** and **16** were synthesized in two steps from (*S*)-nicotine as reported in our earlier work.[15] Lithiation of **16** at the C-5 position was accomplished via a directed *ortho* metalation[19] using 3.0 equiv of mesityllithium as base in THF at 0 °C. The lithio anion was quenched with iodine to provide the intermediate **15** in a 43% yield. Attempts to cyclize **15** via copper-mediated reactions were unfruitful, but use of Buchwald's conditions[20] for palladium-catalyzed intramolecular C−O bond formation gave the cyclized product **4** in a 64% yield.

II. Synthesis of Dihydropyranol Nicotine Derivative 5. Our initial strategy for the synthesis of the dihydropyranol derivative **5** was as outlined in Scheme 3. Derivative **5** was envisioned to come from the cyclization of **18** through an intramolecular C−O bond formation (Scheme 3). Furthermore, it appeared that **18** could be derived from a hydroboration reaction[21] of the allylic moiety in intermediate **19**, which would come from **13** via a Stille reaction.

A Stille cross-coupling of dihalonicotine **13** with allyltributylstannne under standard conditions provided the nicotine intermediate **19** in 94% yield. With **19** in hand, the hydroboration reaction was investigated. Use of less than 3.0 equiv of 9-BBN resulted mainly in recovery of starting material (entry 1, Table 1). This was mainly attributed to a competing complexation of the borane with the two basic nitrogens in nicotine.[22] The use of 3.0 equiv of 9-BBN provided the desired product **18** upon oxidation with alkaline hydrogen peroxide (entry 2); however, the excess borane used in the reaction resulted in what was concluded to be a complexed boron impurity in the product observed in the ^{1}H and ^{13}C NMR spectra. All efforts to purify **18** by chromatography or to remove the impurity by refluxing in MeOH were unfruitful. Attempts at using a more reactive borane, BH_3 in THF, or 1.0 equiv of 9-BBN in the presence of $BF_3 \cdot OEt_2$, which can complex with the basic nitrogens as reported by Brown and co-workers,[22] were unsuccessful (entries 3−5).

(12) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannel, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478.

(13) (a) Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177–179. and the references therein. (b) Cakta, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125–2127. (c) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381–3385.

(14) (a) Sarkar, T.; Basak, S.; Slanina, Z.; Chow, T. J. *J. Org. Chem.* **2003**, *68*, 4206–4214. (b) Vernier, J.-M.; Holsenback, H.; Cosford, N. D. P.; Whitten, J. P.; Menzaghai, F.; Reid, R.; Rao, T. S.; Sacaan, A. I.; Lloyd, G. K.; Suto, C. M.; Chavez-Noriega, L. E.; Washburn, M. S.; Urrutia, A.; McDonald, I. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2173–2178.

(15) For our previous work, see: (a) Ondachi, P. W.; Comins, D. L. *Tetrahedron Lett.* **2008**, *49*, 569–572. (b) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. *Org. Lett.* **2005**, *7*, 5059–5062. (c) Février, F. C.; Smith, E. D.; Comins, D. L. *Org. Lett.* **2005**, *7*, 5457–5460. (d) Smith, E. D.; Février, F. C.; Comins, D. L. *Org. Lett.* **2006**, *8*, 179–182. (e) Wagner, F. F.; Comins, D. L. *Org. Lett.* **2006**, *8*, 3549–3552. (f) Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, 3562–3565. (g) Comins, D. L.; Smith, E. D. *Tetrahedron Lett.* **2006**, *47*, 1449–1451. (h) Wagner, F. F.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 8673–8675.

(16) (a) *Comprehensive Heterocylic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, NY, 1996. (b) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722.

(17) (a) Liu, J.; Fitzgerald, A. E.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2951–2954. and references therein. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820.

(18) (a) Oliveira, A. M. A. G.; Raposo, M. M. M.; Oliveira-Campos, A. M. F.; Machado, A. E. H.; Puapairoj, P.; Pedro, M.; Nascimento, M. S. J.; Portela, C.; Afonso, C.; Pinto, M. *Eur. J. Med. Chem.* **2006**, *41*, 367–372. (b) Voigt, B.; Meijer, L.; Lozach, O.; Schächetele, C.; Totzke, F.; Hilgeroth, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 823–825.

(19) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Gros, P.; Choppin, S.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2243–2247. (c) Marsais, F.; Quéguiner, G.; Snieckus, V.; Epsztanjn, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1991; Vol. 52, pp 187−304.

(20) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.

(21) (a) Brown, H. C. *Hydroboration*; Wiley Interscience: New York, 1962. (b) Belestskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957–5026.

(22) (a) Brown, H. C.; Vara-Prasad, J. V. N.; Zee, S.-H. *J. Org. Chem.* **1986**, *51*, 439–445. (b) Beierle, J. M.; Osimbone, E. B.; Metallinos, C.; Zhao, Y.; Kelly, R. T. *J. Org. Chem.* **2003**, *68*, 4970–4972.

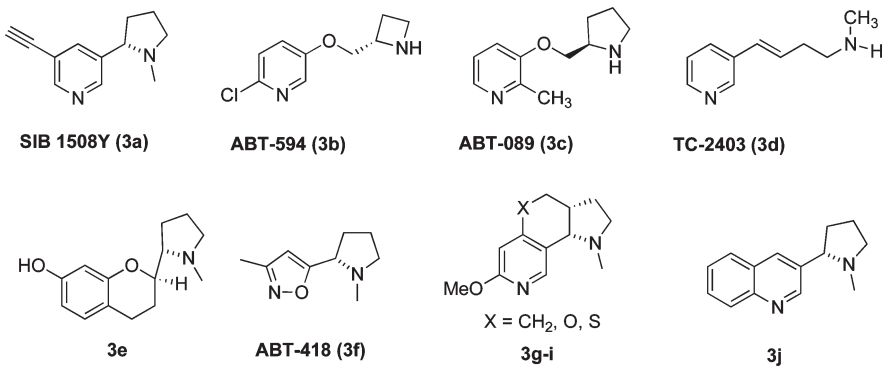


FIGURE 2. Examples of some reported synthetic analogues of (*S*)-nicotine.

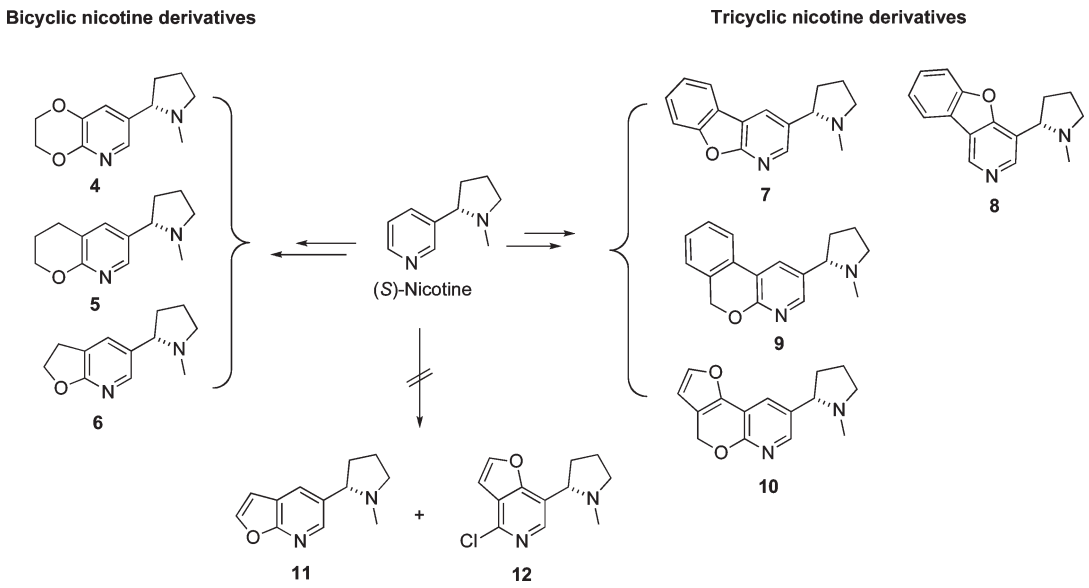
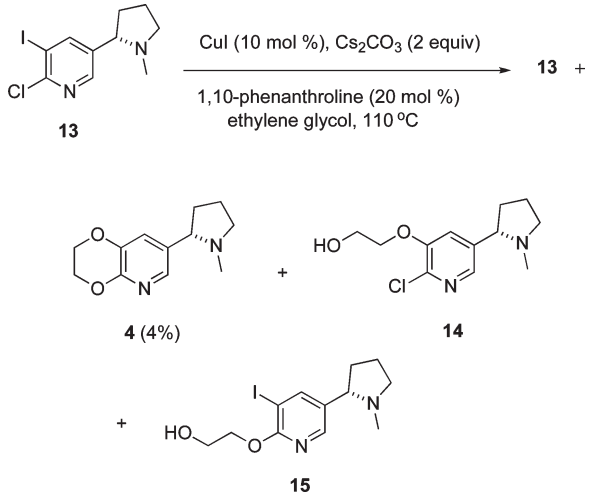
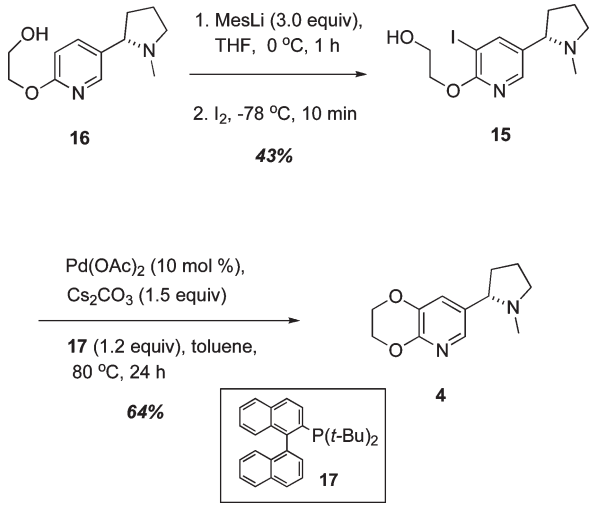


FIGURE 3. Fused-ring nicotine analogues targeted for synthesis from natural (*S*)-nicotine.

SCHEME 1. Synthesis of 4 from 13 via a Copper-Mediated Reaction



SCHEME 2. Improved Synthesis of Dioxino Nicotine Derivative 4



With unsatisfactory results obtained, another route to the synthesis of the intermediate **18** was developed after a series of investigations. A Sonogashira cross-coupling of **13** with propargyl alcohol furnished the alkynylnicotine derivative **20** in 82% yield (Scheme 4). Catalytic hydrogenation of **20** at room temperature under balloon pressure with Pd/C in ethyl acetate or Pt/C in methanol provided intermediate **18** in high

SCHEME 3. Retrosynthetic Route to Nicotine Derivative 5

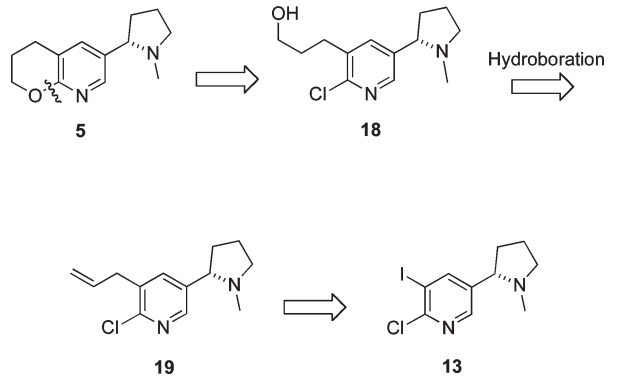
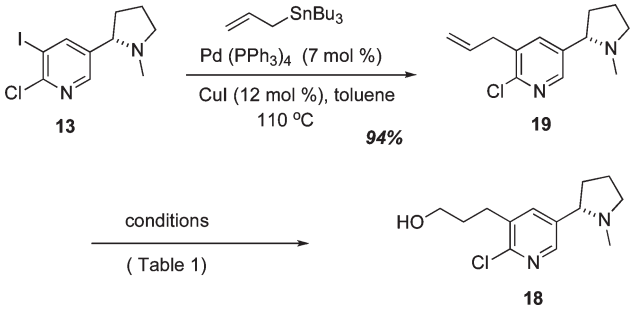


TABLE 1. Synthesis of Intermediate 18 via a Hydroboration Route



entry	conditions	results
1	1. 9-BBN (1.2−2.0 equiv), THF, rt, 24 h → 3 d 2. $NaOH/H_2O_2$	sm
2	1. 9-BBN (3.0 equiv), THF, rt, 10 h or reflux 2. $NaOH/H_2O_2$	**18**[a]
3	1. $BF_3 \cdot OEt_2$ (2.2 equiv), 0 °C → rt 2. $NaOH/H_2O_2$	[b]
4	1. $BF_3 \cdot OEt_2$, (2.0 equiv), rt 2. 9-BBN, 0 °C (1.2 equiv), overnight 3. TMEDA (0.5 equiv) 4. $NaOH/H_2O_2$	sm
5	1. $BF_3 \cdot OEt_2$, (4.0 equiv), rt 2. 9-BBN, 0 °C (1.2 equiv), overnight 3. TMEDA (1.0 equiv) 4. $NaOH/H_2O_2$	sm

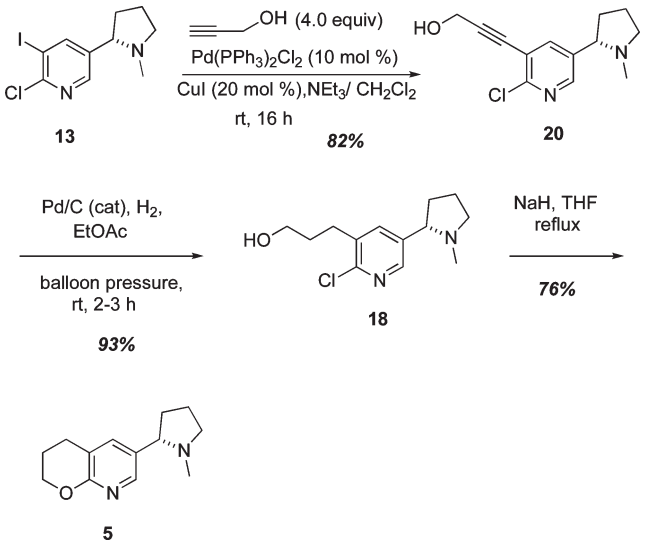
[a]Purification of product not achieved. ^{1}H NMR showed signals in the alkyl region most likely due to borane-pyrrolidine complexation. [b]Conditions decomposed **19**.

yield. Subsequently, the cyclization step to complete the synthesis of dihydropyranol nicotine **5** was accomplished in 76% yield by refluxing **18** in THF in the presence of NaH.

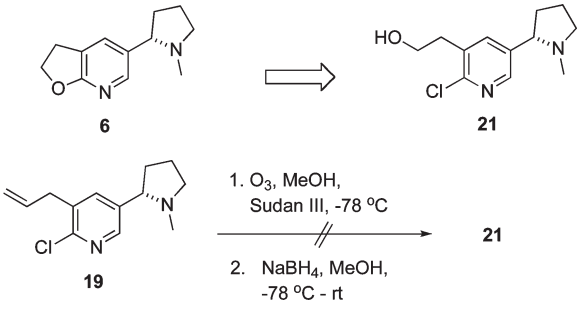
III. Synthesis of Dihydrofuro Nicotine Derivative 6. Dihydrofuro derivative **6** was envisioned to arise from cyclization of **21** in an approach similar to that used for the synthesis of **5** (Scheme 5). However, preparation of **21** proved to be more challenging than expected, and several routes had to be examined. Initially, the potential of preparing **21** via a one-pot reaction through cleavage of the olefin bond in **19** via ozonolysis and a reductive workup with $NaBH_4$ was explored. Unfortunately, bubbling ozone into a solution of **19** in MeOH at −78 °C for 5 min, followed by addition of $NaBH_4$ at −78 °C (warmed to rt), led only to decomposition.

A second route aimed at obtaining a β-aldehyde via a one-carbon homologation of (*S*)-6-chloro-5-formylnicotine[15f] (**22**) also proved problematic. Wittig olefination of **22** with

SCHEME 4. Synthesis of Dihydropyranol Derivative 5



SCHEME 5. Attempted Ozonolysis of 20 To Prepare 22



the Levine reagent[23] (**23**) gave the methyl vinyl ether **24** in 63% yield as a mixture of inseparable diastereomers (Table 2). Hydrolysis of the vinyl ether was limited to mild acidic conditions due to the presence of the basic pyrrolidine ring that is prone to ring opening. Unfortunately, hydrolysis of the vinyl ether under all conditions examined failed, presumably due to the unusual stability of the methyl vinyl ether. Notably, further attempts to reduce the vinyl ether by catalytic hydrogenation followed by demethylation of the resulting alkyl methyl ether to provide **21** failed at the demethylation step. Other unsuccessful attempts to obtain **21** included efforts to carry out hydrosilylation[24] on (*S*)-6-chloro-5-vinylnicotine followed by a Fleming−Tamao−Kumada[25] oxidation, a method that allows silyl groups to be used as masked hydroxyl groups, and preparation of an

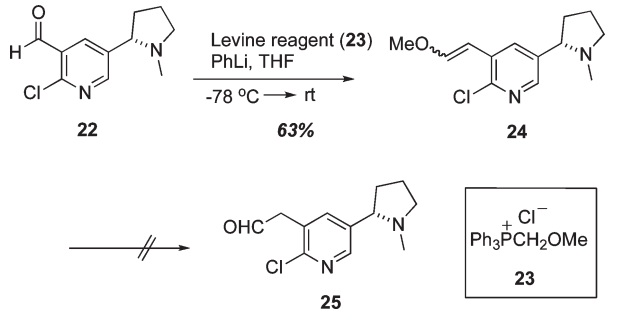
(23) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151.

(24) (a) Ojima, I. The Hydrosilylation Reaction. In *The Chemistry of Organic Silicon Compounds*; Patai S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1989; Vol. 1, Chapter 25, pp 1479−1526. (b) Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin, B. *Angew Chem., Int. Ed.* **2007**, *46*, 7417–7419.

(25) For reviews on Fleming−Tamao−Kumada oxidations, see: (a) Angelaud, R.; Landais, Y. *Tetrahedron* **2000**, *56*, 2025–2036. (b) Jones, G.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662. (c) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans.1* **1995**, 317–337. (d) Tamao, K.; Ishinda, N.; Tanaka, K.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696. (e) Tamao, K.; Ishinda, N. *Tetrahedron Lett.* **1984**, *25*, 4245–4248.

(26) (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–800. (b) Kondo, Y.; Inamoto, K.; Uchiyama, M.; Sakamoto, T. *Chem. Commun.* **2001**, 2704–2705.

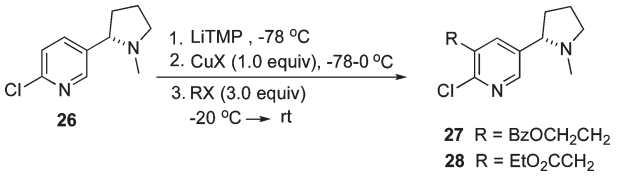
TABLE 2. Attempts To Prepare the Aldehyde Intermediate 25



entry	conditions	result
1	oxalic acid (3.0 equiv), THF/H_2O (4:1), 65 °C, 20 h	**24**
2	oxalic acid (5.0 equiv), MeOH, reflux	*a*
3	formic acid, Et_2O, H_2O, rt, overnight	**24**
4	TMSCl, NaI (3.0 equiv), MeCN, rt	**25**^{b}
5	BBr_3 (3.2 equiv), CH_2Cl_2, −78 °C → rt	*c*
6	1. PPTS (1.0 equiv), acetone, rt 2. $NaBH_4$, MeOH, CH_2Cl_2	**24**
7	*p*TsOH (2.0 equiv), H_2O (10 equiv), MeCN, 40 °C, 24 h	**24**

[a]Pyrrolidine ring opened. [b]Only one diastereomer was hydrolyzed. Product was formed in ~20% yield. [c]Trace amount of product with a lot of decomposition.

TABLE 3. Synthesis of 27 and 28



entry	CuX	RX	product	yield (%)[a]
1[b]	CuCN·2LiCl/ $P(OMe)_3$	$BzOCH_2CH_2I$	**27**	43
2	PhSCu	$BzOCH_2CH_2I$	**27**	61
3	CuCN·2LiCl	EtO_2CCH_2Br	**28**	27
4	PhSCu	EtO_2CCH_2Br	**28**	44

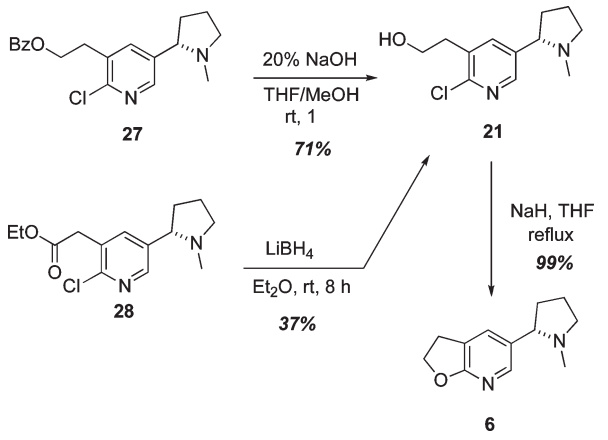
[a]Isolated yields after radial PLC. [b]$P(OMe)_3$ (1.9 equiv) was added, and the reaction was warmed to rt.

α-aryl ester via Buchwald's conditions[26] via palladium-catalyzed cross-coupling of **13** with *tert*-butyl acetate.

After extensive experimentation, an efficient synthesis of intermediate **21** was accomplished through hydrolysis of the benzoate ester in nicotine derivative **27** or by reduction of the ester in the *β*-ester derivative **28** (Table 3). Both **27** and **28** were obtained from a copper(I)-catalyzed cross-coupling reaction of C-5 metalated (*S*)-6-chloronicotine (**26**) with 2-iodoethyl benzoate and α-bromoacetate, respectively. Knochel and co-workers[27] reported a protocol where aryl Grignards undergo a transmetalation with CuCN·2LiCl, with or without trimethyl phosphite as an additive, to provide a stable arylcopper compound that undergoes a cross-coupling reaction with functionalized alkyl iodides. Adopting this protocol, **26** was lithiated at the C-5 position

(27) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320. (b) Dohle, W.; Lindsey, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871–2873. (c) Knochel, P.; Yeh, C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390–2392.

SCHEME 6. Completion of the Synthesis of 6



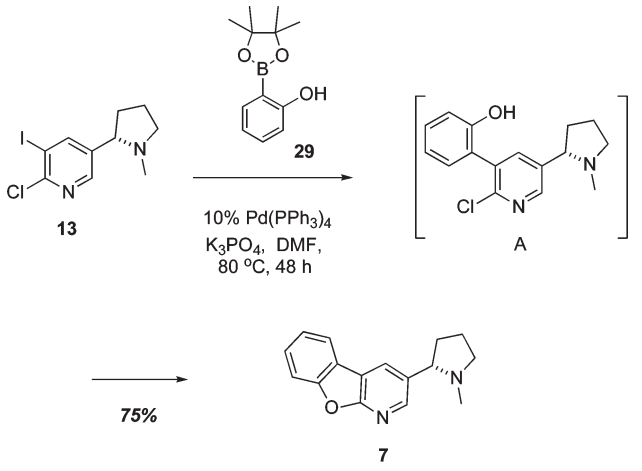
using LiTMP at −78 °C in THF. The aryllithium was transmetalated with Cu by addition of a solution of CuCN·2LiCl in THF, or PhSCu, at −78 °C. The reaction was warmed up to 0 °C when no additive was added, or to room temperature in the presence of $P(OMe)_3$. The cross-coupling halide partners, 2-iodoethyl benzoate (entries 1 and 2, Table 3) and ethyl 2-bromoacetate (entries 3 and 4), were added at −20 °C and stirred at room temperature for several hours to provide the derivatives **27** and **28**, respectively, in modest yields. Hydrolysis of **27** using aqueous NaOH provided **21** in 71% yield. Similarly, reduction of the ester **28** using $LiBH_4$ in ether provided **21** in a lower yield of 37%. Completion of the synthesis of the dihydrofuro derivative **6** was accomplished by refluxing **21** with NaH in THF to afford the cyclized product in near quantitative yield (Scheme 6).

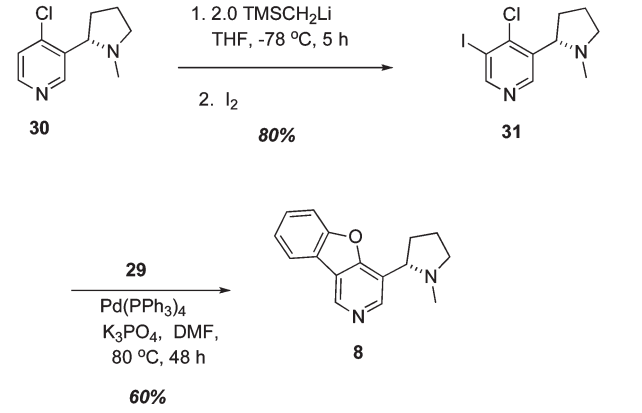
IV. Synthesis of Tricyclic Benzofuronicotine Derivatives 7 and 8. The synthesis of the benzofuro derivatives was expected to proceed via a two-step procedure from the appropriate dihalonicotines. In the case of derivative **7**, a Suzuki cross-coupling of **13** with the commercially available 2-hydroxyphenylboronic ester **29** was anticipated to provide an intermediate that could then be cyclized after isolation. Unexpectedly, when **13** was heated at 80 °C for 48 h in the presence of 1.2 equiv of **29**, $Pd(PPh_3)_4$ as catalyst, K_3PO_4 as base, and DMF as solvent, the cyclized product **7** was obtained directly in 75% yield (Scheme 7). The basic reaction conditions must have provided an alkoxide of intermediate **A** that readily undergoes an intramolecular cyclization to form the five-membered ring. Similarly, the C4−C5 benzofuran-2-ly derivative **8** was synthesized in a 60% yield from the cross-coupling of **29** with chloroiodonicotine **31**. (*S*)-4-Chloronicotine (**30**) was prepared from nicotine using $TMSCH_2Li$ as base in toluene at room temperature as reported by Gros and co-workers.[28] Lithiation of **30** at the C-5 position was also done using $TMSCH_2Li$ in THF at −78 °C for 5 h, followed by addition of iodine, to afford **31** in 80% yield.

V. Synthesis of Tricyclic Nicotine Derivatives 9 and 10. In the same vein, the benzopyran nicotine derivative **9** was prepared in two steps from (*S*)-6-chloro-5-(tributylstannane)-nicotine (**32**). A Stille cross-coupling reaction of **32** with

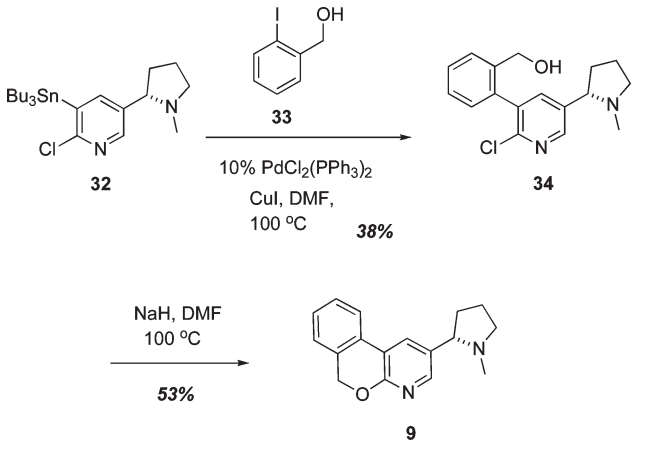
(28) Gros, P. C.; Doudouh, A.; Woltermann, C. *Org. Biomol. Chem.* **2006**, *4*, 4331–4335.

SCHEME 7. Synthesis of Tricyclic Benzofuro Derivatives 7 and 8

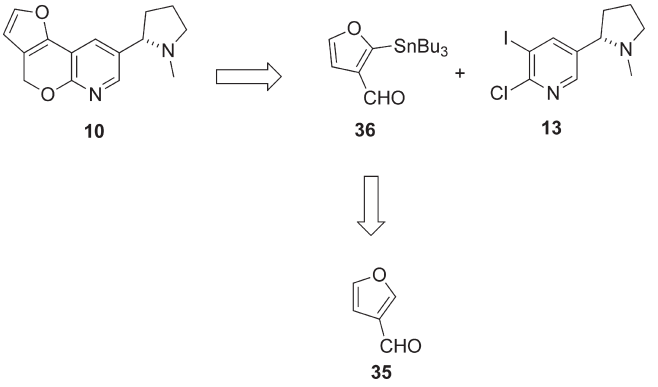




SCHEME 8. Two-Step Synthesis of Benzopyran Derivative 9 from 32



SCHEME 9. Retrosynthetic Route to Tricyclic Derivative 10



commercially available 2-iodobenzyl alcohol (**33**) provided 38% yield of the coupled product **34**. Cyclization of **34** in DMF at 100 °C in the presence of NaH provided the benzopyran **9** in 53% yield (Scheme 8).

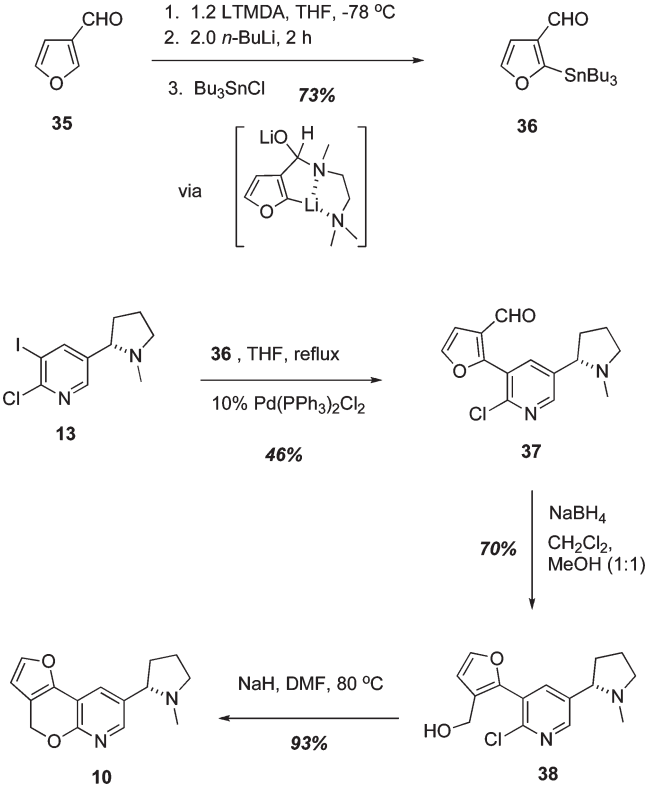
As shown in Scheme 9, the fused furo derivative **10** would be obtained by a cross-coupling of **13** with 2-(tributylstannane)-furan-3-carbaldehyde (**36**), which could be derived from commercially available 3-furaldehyde (**35**) via an α-amino alkoxide directed lithiation.[29] Following this protocol, **36** was prepared by treatment of 3-furaldehyde with 1.2 equiv of LTMDA (lithium salt of *N*,*N*,*N*′-trimethylethylenediamine) at −78 °C, to form the α-amino alkoxide *in situ*, followed by addition of 2.0 equiv of *n*-BuLi to effect C-2 deprotonation. Quenching of the anion with Bu_3SnCl followed by hydrolysis of the amino alkoxide upon aqueous workup provided **36** in 73% yield (Scheme 10). A Stille cross-coupling of **36** with **13** using $Pd(PPh_3)_2Cl_2$ as catalyst and refluxing in THF provided the cross-coupled aldehyde **37**. Reduction of the aldehyde with $NaBH_4$ gave the alcohol **38** (70%), which upon heating in DMF in the presence of NaH furnished the furo derivative **10** in high yield.

VI. Attempted Synthesis of Furofused Nicotines 11 and 12. As outlined in Schemes 11 and 12, the synthesis of nicotine analogues **42** and **49** commenced from halonicotine intermediates **39** and **46**. Preparation of **39** via *ortho*-lithiation of (*S*)-6-methoxynicotine with MesLi has previously been reported from our laboratories.[15a] The intermediate **46** was prepared in two steps from (*S*)-6-chloro-4-iodonicotine (**43**). Heating **43** in a sealed tube in the presence of CuI/1,10-phenathroline catalyst, MeOH, and Cs_2CO_3 provided **44** in modest yield. Lithiation of **44** with *n*-BuLi in THF and quenching with iodine afforded **46** in 67% yield. The demethylation of intermediates **39** and **46** was troublesome, resulting in a lot of decomposition or recovery of the starting materials. However, use of 3.0 equiv of BBr_3 in CH_2Cl_2 at −78 → 0 °C provided the demethylated products **40** (21%) and **47** (19%) albeit in low yields. A Sonogashira cross-coupling of **40** and **47** with trimethylsilylacetylene at room temperature provided the products **41** and **48** in 65% and 41% yield, respectively. With the *o*-hydroxylacetylene derivatives in hand, ring cyclization was attempted by heating each of the acetylenes **41** and **48** at 75 °C in the presence of CuI in EtOH/Et_3N (1:1) as solvent overnight, followed by addition of K_2CO_3 at room temperature, a protocol that has been reported in the literature.[30] Surprisingly, both reactions resulted in the formation of the dimers **42** and **49** instead of the expected furonicotines

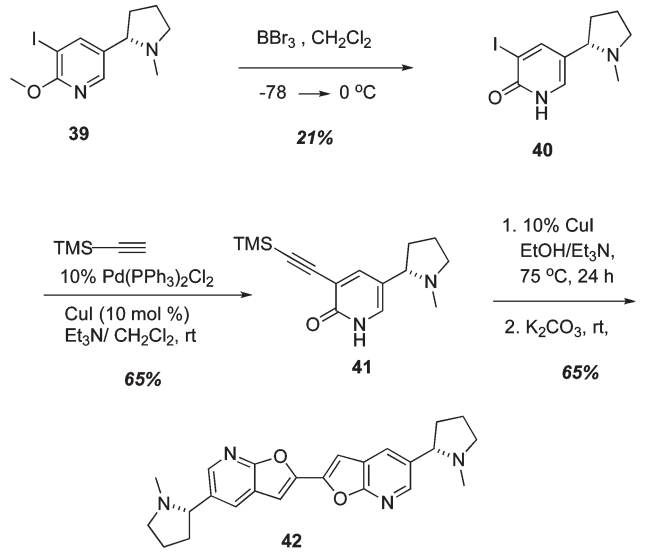
(29) (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104–109. (b) For a review of α-amino alkoxide directed lithiations, see: Comins, D. L. *Synlett* **1992**, 615–625.

(30) (a) Houpis, I. N.; Choi, W. B.; Reider, P. J.; Molina, A.; Churchill, H.; Lynch, J.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9344–9358. (b) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851–7859.

SCHEME 10. Synthesis of Furo Derivative 10

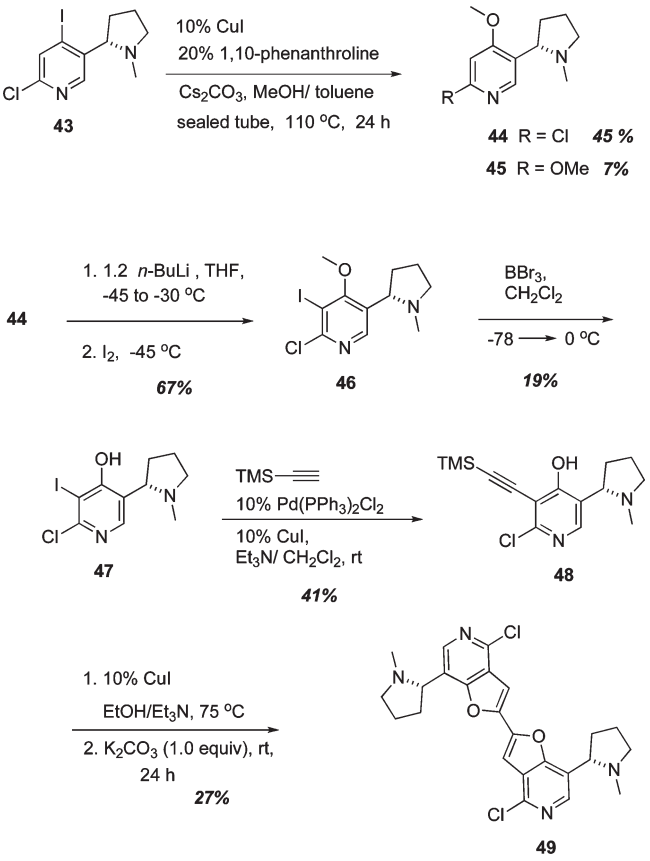


SCHEME 11. Synthesis of Heteroannulated Nicotine Dimer 42



11 and **12**. This was established from analysis of ^{1}H and ^{13}C NMR data and confirmed by high resolution mass spectrometry (HRMS). We suggest that the unexpected products resulted from hydrolysis of the TMS group under the reaction conditions. The unprotected acetylene then undergoes cross-coupling in the presence of copper iodide leading to the formation of bis-acetylene nicotines which upon cyclization form the dimer as illustrated in Scheme 13. Exploring other routes for achieving the synthesis of the furonicotines **11** and **12** is part of the ongoing work in our laboratories.

SCHEME 12. Synthesis of Heteroannulated Nicotine Dimer 49



Conclusion

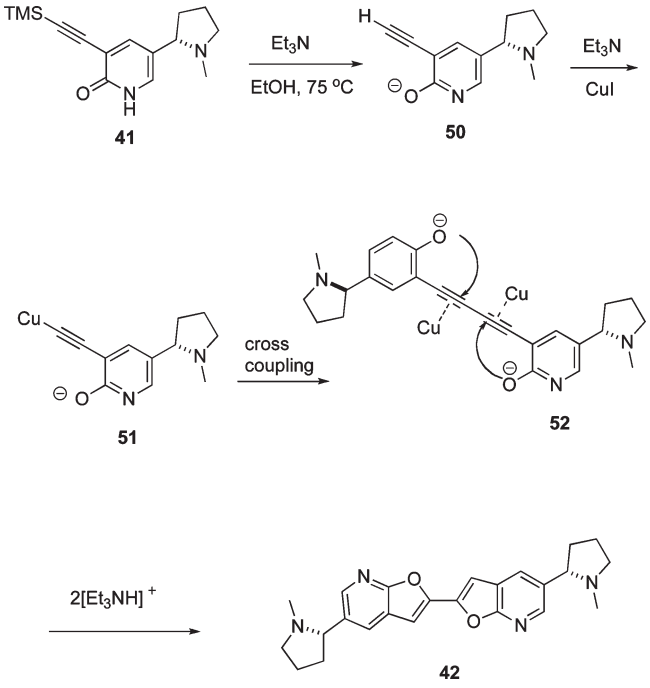
In summary, we have accomplished the synthesis of enantiopure dioxino (**4**), dihydropyranol (**5**), dihydrofuro (**6**), and benzofuro and benzopyrano (**7**−**10**) nicotine derivatives in good yields from readily available natural (*S*)-nicotine. Appropriate methodologies to prepare the key intermediates via directed *ortho* lithiations and Pd- or Cu-catalyzed reactions were developed. Attempts to synthesize furonicotines resulted in formation of the furonicotine dimers. This work is part of an ongoing program to develop appropriate methodologies for the synthesis of nicotine derivatives as potential pharmaceuticals, insecticides, synthetic intermediates, and novel ligands for catalytic asymmetric synthesis.

Experimental Section

For general information see Supporting Information.

(*S*)-6-(2-Hydroxy)ethoxy-5-iodonicotine (15). To a solution of *t*-BuLi (422 μL, 1.7 M in pentane, 0.54 mmol, 6.0 equiv) in freshly distilled THF (1 mL) at −78 °C was added dropwise bromomesitylene (40 μL, 0.27 mmol, 3.0 equiv). After the mixture stirred at −78 °C for 1 h, a solution of **16** (20 mg, 0.09 mmol, 1.0 equiv) in THF (1 mL) was added dropwise, and then the mixture was warmed to 0 °C. After 2 h at 0 °C, the temperature was lowered to −78 °C, and a solution of iodine (27 mg, 0.11 mmol, 1.2 equiv) in THF (stored over 4 Å sieves) was added to the mixture. The reaction was stirred for an additional 5 min and then quenched with a 2-mL aqueous solution of saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered through Celite, and

SCHEME 13. Proposed Mechanism for Dimer Formation



concentrated under reduced pressure. The crude product was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) to afford 13.3 mg (43%) of **15** as a colorless oil. $[\alpha]^{33}_D$ −85 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 4.48 (dt, J = 8.8, 2 Hz, 2H), 3.95 (dt, J = 8.8, 2 Hz, 2H), 3.40 (s, 1H), 3.20 (dt, J = 8.8, 2.4 Hz, 1H), 2.97 (t, J = 8.8 Hz, 1H), 2.26 (q, J = 8.8 Hz, 1H), 2.14 (s, 3H), 2.09−2.19 (m, 1H), 1.88−1.99 (m, 1H), 1.61−1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.2, 40.5, 57.1, 62.4, 67.7, 70.1, 80.8, 134.3, 145.5, 147.8, 161.2; IR (neat) 3434, 2963, 1642, 1447, 1306, 1248, 1048 cm^{-1}; HRMS calcd for $C_{12}H_{17}IN_2O_2$ $(M + H)^+$ 349.0413, found 349.0406.

(*S*)-2,3-Dihydro[1,4]dioxino[5,6-*b*]nicotine (4). A solution of **15** (44 mg, 0.13 mmol, 1.0 equiv) in toluene (1 mL) was added to a mixture of $Pd(OAc)_2$ (4.0 mg, 0.016 mmol, 0.1 equiv), Cs_2CO_3 (77.2 mg, 0.24 mmol, 1.5 equiv), and racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl (75.5 mg, 0.19 mmol, 1.2 equiv) in 3 mL of toluene. The mixture was purged with argon for 20 min and then heated to 80 °C. After 24 h, the reaction mixture was cooled to rt, diluted with EtOAc (2 mL), filtered through a pad of Celite, and concentrated *in vacuo*. Purification by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) afforded 18 mg (64%) of **4** as a colorless oil. $[\alpha]^{30}_D$ −79 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 1.6 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 4.4 (dt, J = 4.4, 3.2 Hz, 2H), 4.23 (dt, J = 4.0, 2.4 Hz, 2H), 3.2 (dt, J = 8.8, 2.0 Hz, 1H), 2.99 (t, J = 8.6 Hz, 1H), 2.25 (q, J = 8.8 Hz, 2.15 (s, 3H), 2.16- 2.09 (m, 1H), 1.98−1.84 (m, 1H), 1.82- 1.76 (m, 1H), 1.72−1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 35.1, 40.5, 57.1, 64.1, 65.1, 68.3, 123.7, 134.2, 139.2, 139.7, 150.6; IR (neat) 2967, 2943, 1581, 1481, 1429, 1357, 1282 cm^{-1}; HRMS calcd for $C_{12}H_{16}N_2O_2$ $(M + H)^+$ 221.1290, found 221.1286.

(*S*)-5-Ally-6-chloronicotine (19). A mixture of **13** (500 mg, 1.6 mmol, 1.0 equiv), allyltributylstannane (580 μL, 1.9 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (125 mg, 0.11 mmol, 7 mol %), and CuI (35 mg, 0.19 mmol, 12 mol %) in toluene (3 mL) was placed in a pressure vessel and degassed for 20 min with argon. The vessel was sealed, and the reaction mixture was stirred at 100 °C for 2 d. The mixture was allowed to cool to rt, and a 2-mL solution of a 1:1 mixture of ammonium hydroxide and ammonium chloride was added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/ hexanes) to afford 344 mg (94%) of **19** as a bright yellow oil. $[\alpha]^{33}_D$ −123 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 5.89−5.98 (m, 1H), 5.12 (dd, J = 12, 1.6 Hz, 2H), 3.47 (d, J = 6.8 Hz, 1H), 3.22 (dt, J = 8.8, 2 Hz, 1H), 3.05 (t, J = 8.8 Hz, 1H), 2.28 (q, J = 9.2 Hz, 1H), 2.22−2.12 (m, 1H), 2.14 (s, 3H), 1.88−1.98 (m, 1H), 1.75−1.85 (m, 1H), 1.61−1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.5, 37.4, 40.6, 57.2, 68.3, 117.6, 134.3, 138.0, 138.5, 147.1, 150.1; IR (neat) 2965, 2780, 1407, 1349, 1162, 1065, 914 cm^{-1}; HRMS calcd for $C_{13}H_{17}ClN_2$ $(M + H)^+$ 237.1159, found 237.1153.

(*S*)-3-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridine-3-yl)prop-2-yn-1-ol (20). A solution of **13** (150 mg, 0.465 mmol, 1.0 equiv) in triethylamine (2 mL) was added to a mixture of $Pd(Ph_3)_2Cl_2$ (32.6 mg, 0.047 mmol, 0.10 equiv) and copper(I) iodide (17.7 mg, 0.093 mmol, 0.20 equiv) in a flame-dried flask. Methylene chloride (2 mL) was added, and then the mixture was degassed with argon for 15 min. Propargyl alcohol (110 μL, 1.860 mmol, 4.0 equiv) was added, and the mixture was stirred at rt overnight. Water (2 mL) was added, and then the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered through Celite, and concentrated *in vacuo*. Purification by radial PLC (SiO_2, 5% MeOH/CH_2Cl_2) afforded 95.8 mg (82%) of **20** as a white solid, mp 103−110 °C. $[\alpha]^{23}_D$ −98 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 4.55 (s, 2H), 3.23 (dt, J = 8.8, 2.4 Hz, 1H), 3.09 (t, J = 8.0 Hz, 1H), 2.62−2.40 (broad OH signal), 2.32 (q, J = 9.2 Hz, 1H), 2.26−2.18 (m, 1H), 2.16 (s, 3H), 2.02−1.88 (m, 1H), 1.88−1.76 (m, 1H), 1.72−1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.2, 40.5, 51.4, 57.1, 68.0, 80.4, 95.4, 120, 137.7, 141.2, 148.2, 151; IR (neat) 3640, 3350, 2942, 2790, 1401, 1359, 1198, 1092 cm^{-1}; HRMS calcd for $C_{13}H_{15}ClN_2O$ $(M + H)^+$ 251.0951, found 251.0950.

(*S*)-3-(2-Chloro-5-(1-methylpyrrolidin-3-yl)propan-1-ol (18). To a solution of **20** (300 mg, 1.2 mmol, 1.0 equiv) in EtOAc (10 mL) was added a catalytic amount of Pd/C. The mixture was flushed with hydrogen gas and then was stirred under a balloon pressure of hydrogen at rt for 2 h. Filtration through Celite and concentration *in vacuo* afforded 300 mg (98%) of **18** that was used in the next reaction without further purification. $[\alpha]^{25}_D$ −100 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 3.68−3.64 (m, 2H), 3.21 (dt, J = 7.6, 2.0 Hz, 1H), 3.04 (t, J = 8.4 Hz, 1H), 2.81 (t, J = 8.0 Hz, 1H), 2.51 (s, OH signal), 2.27 (q, J = 8.4 Hz, 1H), 2.17−2.14 (m, 1H), 2.13 (s, 3H), 1.98−1.85 (m, 3H), 1.85−1.75 (m, 1H), 1.72−1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 29.6, 32.1, 35.3, 40.5, 57.1, 61.7, 68.2, 136.0, 138.1, 138.2, 146.9, 150.1; IR (neat) 3368, 3046, 2943, 1665, 1565, 1409, 1359, 1153 cm^{-1}; HRMS calcd for $C_{13}H_{19}ClN_2O$ $(M + H)^+$ 255.1264, found 255.1253.

(*S*)-6-(1-Methylpyrrolidin-2-yl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]-pyridine (5). Solid NaH (93 mg, 3.88 mmol, 3.0 equiv) was weighed under a nitrogen atmosphere and placed in a flame-dried flask followed by THF (2 mL). To this was added a solution of **18** (330 mg, 1.29 mmol, 1.0 equiv) in THF (2 mL), and the reaction mixture was refluxed for 24 h. The reaction was allowed to cool to rt, 1 mL of water was added, and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered through a plug of Celite, and concentrated *in vacuo*. Purification by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) afforded 213.5 mg (76%) of **5** as a pale yellow oil. $[\alpha]^{30}_D$ −126 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.92 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 4.32 (dd, J = 5.2, 4.8 Hz, 2H), 3.22 (dt, J = 8.8, 1.6 Hz, 1H), 2.96 (t, J = 8.0 Hz, 1H), 2.79 (t, J = 6.4 Hz, 2H), 2.26 (q, J = 8.8 Hz, 1H), 2.14 (s, 3H), 2.16−2.10 (m, 1H), 2.0−1.85 (m, 1H), 2.01−1.98 (dd, J = 4.0, 1.6 Hz, 2H), 1.84−1.78 (m, 1H), 1.76−1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.4, 24.9, 34.8, 40.3, 57.0, 67.2, 68.3, 117.3, 131.6, 137.4, 145.8, 160.9; IR (neat) 2963, 2944, 1578, 1477, 1459, 1275, 1260 cm^{-1}; HRMS calcd for $C_{13}H_{19}N_2O$ $(M + H)^+$ 219.1491, found 219.1494.

(*S*)-6-Chloro-5-(2-methoxyvinyl)nicotine (24). A solution of potassium *tert*-butoxide (5.56 mL, 1 M solution in THF, 5.56 mmol, 3.0 equiv) was added to a solution of the Levine reagent (1.91 g, 5.56 mmol, 3.0 equiv) in THF (15 mL) at 0 °C under argon. The resulting dark red suspension was stirred for 0.5 h at 0 °C. To this mixture was added a solution of **22** (417 mg, 1.85 mmol, 1.0 equiv) in THF (2 mL over 4 Å molecular sieves), and the ensuing mixture was allowed to warm to rt and stirred overnight. The mixture was poured into an aqueous saturated solution of NH_4Cl (6 mL) and then extracted with Et_2O (3 × 10 mL). The combined organic layers were washed sequentially with water (8 mL) and brine (8 mL), dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 1% TEA/2% EtOAc/hexanes) to afford 294 mg (63%) of **24** as a pale yellow oil containing a mixture inseparable diastereomers in the ratio of 2:1 (*cis*:*trans*). $[\alpha]^{29}_D$ −95 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *cis* diastereomer: δ 8.27 (d, J = 2.8 Hz 1H), 8.10 (d, J = 2.8 Hz 1H), 6.32 (d, J = 9.2 Hz, 1H), 5.55 (d, J = 9.2 Hz, 1H), 3.81 (s, 3H), 2.17 (s, 3Hs); *trans* diastereomer: δ 8.07 (d, J = 2.8 Hz 1H), 7.65 (d, J = 2.8 Hz 1H), 7.07 (d, J = 17.2 Hz 1H), 6.00 (d, J = 17.2 Hz 1H), 3.74 (s, 3H), 2.16 (s, 3Hs); overlapped signals: δ 3.22 (t, J = 11.2 Hz, 2 Hs), 3.04 (t, J = 11.2 Hz, 2 Hs), 2.34−2.24 (m, 2H), 2.23−2.12 (m, 2Hs), 2.02−1.88 (m, 2Hs), 1.87−1.62 (m, 4Hs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.3, 35.5, 40.6, 57.0, 57.1, 61.4, 67.9, 68.4, 68.6, 99.9, 110.5, 130.1, 132.2, 137.6, 138.8, 145.7, 146.2, 147.5, 151.1, 152.0; IR (neat) 2980, 2936, 2904, 1718, 1587, 1476, 1393, 1271, 1104, 1010 cm^{-1}; HRMS calcd for $C_{13}H_{17}ClN_2O$ $(M + H)^+$ 253.1106, found 253.1102.

(*S*)-2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-3-yl)ethyl Benzoate (27). A solution of 2,2,6,6-tetramethylpiperidine (630 μL, 3.69 mmol, 1.1 equiv) in dry THF (5 mL) at −78 °C was treated with *n*-BuLi (1.69 mL, 2.5 M in hexanes, 3.69 mmol, 1.1 equiv), and the mixture was stirred for 1 h. A solution of **26** (659 mg, 3.35 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. After an additional 1 h at −78 °C, copper(I) thiophenolate (694 mg, 4.02 mmol, 1.2 equiv) was added directly into the reaction mixture by removing the septum briefly. The temperature of the reaction was slowly allowed to warm up to 0 °C. The reaction mixture was cooled to −20 °C, 2-iodoethyl benzoate (2.78 g, 10.1 mmol, 3.0 equiv) was added, and stirring was continued at rt for 6 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl (3 mL) and then the mixture was filtered through Celite. The filtrate was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with aqueous 10% NH_4OH, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated *in vacuo*. Purification of the residue by radial PLC (silica gel, 1% TEA/2% EtOAc/ hexanes) afforded 698 mg (61%) of **27** as a clear oil. $[\alpha]^{30}_D$ −86 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.4, 1.2 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.49 (dt, J = 8.0, 1.2 Hz, 1H), 7.36 d, J = 8.0, 1.2 Hz, 2H), 4.56 (t, J = 6.4 Hz, 2H), 3.16 (dt, J = 6.4, 0.8 Hz, 2H), 3.15 (dt, J = 7.6, 2.0 Hz, 1H) 3.01 (t, J = 8.0 Hz, 1H), 2.23 (q, J = 8.8 Hz, 1H), 2.14−2.04 (m, 1H), 2.05 (s, 3H), 1.92−1.80 (m, 1H), 1.80−1.68 (m, 1H), 1.62−1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 32.7, 35.4, 40.4, 57.0, 63.1, 67.9, 128.4, 128.5, 129.6, 130.0, 132.2, 133.1, 138.6, 138.9, 147.5, 150.0, 166.3; IR(neat) 2968, 2943, 2840, 2781, 1719, 1584, 1452, 1274, 1113 cm^{-1}; HRMS calcd for $C_{19}H_{21}ClN_2O_2$ $(M + H)^+$ 345.1360, found 345.1364.

(*S*)-2-(2-Chloro-5-(1-methylpyrrolidin-3-yl)ethanol (21). A solution of **27** (58 mg, 0.168 mmol, 1.0 equiv) in a 1:1 methanol/ THF (2 mL) was treated with 0.5 mL of aqueous 20% NaOH solution. The mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 1% TEA/50% EtOAc/hexanes) to afford 29 mg (71%) of **21** as clear oil. $[\alpha]^{25}_D$ −126 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 3.90 (dt, J = 6.8, 1.6 Hz, 2H), 3.22 (dt, J = 8.4, 2.0 Hz, 1H), 3.07 (t, J = 8.8 Hz, 1H), 3.07 (t, J = 8.4 Hz, 1H), 2.98 (dt, J = 6.8, 1.6 Hz, 2H), 2.37(s, OH signal), 2.2 (q, J = 9.2 Hz, 1H), 2.24−2.16 (m, 1H), 2.14 (s, 3H), 2.01−1.88 (m, 1H), 1.87−1.76 (m, 1H), 1.74−1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.1, 36.5, 40.5, 57.1, 61.0, 68.1, 133.3, 137.9, 138.9, 147.2, 150.3; IR (neat) 3369, 2947, 2878, 2783, 1765, 1411, 1357, 1074 cm^{-1}; HRMS calcd for $C_{12}H_{17}ClN_2O$ $(M + H)^+$ 240.1100, found 240.1102.

(*S*)-5-(1-Methylpyrrolidin-2-yl)-2,3-dihydrofuro[2,3-*b*]pyridine (6). A solution of **21** (243 mg, 1.0 mmol, 1.0 equiv) in THF (2 mL) was added to NaH (48.5 mg, 2.0 mmol, 2.0 equiv) in THF (1 mL) at rt, and the mixture was refluxed overnight. After cooling to rt, water (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and then filtered through a plug of Celite and silica gel. The solvent was removed *in vacuo* to afford 205 mg (99%) of **6** as a white solid, mp 62−64 °C. $[\alpha]^{31}_D$ −145 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 4.46 (dt, J = 5.6, 2.8 Hz, 2H), 3.09 (dt, J = 5.6, 2.8 Hz, 2H), 3.08−3.07 (m, 1H), 2.89−2.83 (m, 1H), 2.14 (q, J = 8.4 Hz, 1H), 2.01 (s, 3H), 2.05−1.95 (m, 1H), 1.86−1.76 (m, 1H), 1.70−1.62 (m, 1H), 161−1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 27.9, 34.6, 10.1, 56.8, 68.3, 69.1, 120.0, 131.0, 132.5, 145.8, 168.3; IR (neat) 2967, 2944, 2776, 1613, 1595, 1464, 1410, 1351, 1224 cm^{-1}; HRMS calcd for $C_{14}H_{16}N_2O$ $(M + H)^+$ 205.1335, found 205.1334.

(*S*)-3-(1-Methylpyrrolidin-2-yl)benzofuro[2,3-*b*]pyridine (7). A solution of **13** (158 mg, 0.49 mmol, 1.0 equiv), K_3PO_4 (416 mg, 1.96 mmol, 4.0 equiv), $Pd(Ph_3)_4$ (57 mg, 0.05 mmol, 10 mol %), and **29** (140 mg, 0.637 mmol, 1.3 equiv) in DMF (3 mL) was degassed with argon for 20 min. The mixture was heated at 80 °C for 48 h. The DMF was removed under reduced pressure, and the residue was dissolved in Et_2O, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) to afford 93 mg (75%) of **7** as a white solid, mp 94−97 °C. $[\alpha]^{25}_D$ −131 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.92 (dt, J = 7.6, 0.8 Hz, 1H), 7.60 (dt, J = 8.4, 0.8 Hz, 1H), 7.48 (dt, J = 8.4, 0.8 Hz, 1H), 7.35 (dt, J = 7.2, 0.8 Hz, 1H), 3.29 (dt, J = 7.6, 0.8 Hz, 1H), 3.24 (t, J = 8.0 Hz, 1H), 2.36 (q, J = 9.2 Hz, 1H), 2.30−2.22 (m, 1H), 2.19 (s, 3H), 2.19−1.96 (m, 1H), 1.91−1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.9, 40.6, 57.2, 69.0, 112.3, 117.3, 121.6, 122.7, 123.4, 128.4, 128.6, 134.6, 146.4, 155.1, 163.1; IR (neat) 3030, 2968, 2944, 2844, 2779, 1558, 1476, 1471 cm^{-1}; HRMS calcd for $C_{16}H_{16}N_2O$ $(M + H)^+$ 253.1335, found 253.1338.

(*S*)-4-Chloro-5-iodonicotine (31). To a solution of **30** (125 mg, 0.635 mmol, 1.0 equiv) in THF (2 mL) at −78 °C was added $TMSCH_2Li$ (1.3 mL, 1.0 M in hexanes, 1.27 mmol, 2.0 equiv), and the mixture was stirred for 3 h at −78 °C. Iodine (355 mg, 1.4 mmol, 2.2 equiv) in 1 mL of THF (over 4 Å sieves) was added, stirring was continued for an additional 10 min, and then the reaction was quenched with water (2 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic

layers were washed with 2 mL of saturated aqueous sodium thiosulfate. The organic portion was dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was purified on radial PLC (SiO_2, 1% TEA/ 20% EtOAc/hexanes to afford 163 mg (80%) of **31** as a white solid, mp 65−68 °C. $[\alpha]^{23}_D$ −172 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.69 (s, 1H), 3.62 (t, J = 8.0 Hz, 1H), 3.24 (dt, J = 8.0, 2.0 Hz, 1H), 2.44−2.32 (m, 2H), 2.24 (s, 3H), 1.96−1.76 (m, 2H), 1.58−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 33.5, 57.0, 66.8, 98.8, 139.4, 146.7, 149.1, 156.2; IR (neat) 2963, 2945, 2845, 2787, 1553, 1527, 1452, 1411, 1349, 1332, 1209, 1135, 1070 cm^{-1}; HRMS calcd for $C_{10}H_{12}ClIN_2$ $(M + H)^+$ 322.9806, found 322.9806.

(*S*)-4-(1-Methylpyrrolidin-2-yl)benzofuro[3,2-*c*]pyridine (8). Prepared from **31** and **29** using a similar procedure as outlined for derivative **7**. $[\alpha]^{25}_D$ −138 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.68 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 7.4 Hz, 1H), 3.69 (t, J = 8.0 Hz, 1H), 3.33 (t, J = 8.4 Hz, 1H), 2.46−2.32 (m, 2H), 2.28 (s, 3H), 2.38−2.00 (m, 2H), 1.98−1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 33.2, 41.0, 57.3, 64.4, 112.4, 121.2, 121.3, 122.0, 123.2, 123.9, 128.3, 142.2, 146.6, 156.1, 159.8; IR (neat) 3046, 2945, 2831, 2779, 1576, 1466, 1429, 1340, 1281, 1193, 1128, 1042 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2O_2$ $(M + H)^+$ 252.1263, found 252.1267.

(*S*)-{2-[2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridn-3-yl]-phenyl}-methanol (34). A solution of **32** (57.8 mg, 0.119 mmol, 1.0 equiv) in DMF (1 mL) was added to a mixture of $Pd(PPh_3)_2Cl_2$ (8.4 mg, 0.12 mmol, 10 mol %), **33** (41.8 mg, 0.179 mmol, 1.5 equiv), and CuI (4.5 mg, 0.021 mmol, 20 mol %) in DMF (3 mL). The mixture was degassed for 15 min and then heated at 100 °C overnight. The reaction mixture was allowed to cool to rt, and the DMF was removed *in vacuo*. The product was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) to afford 13.8 mg (38%) of **34** as a clear oil. $[\alpha]^{30}_D$ −108 (*c* 0.96, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.65−7.33 (m, 5H), 7.18 (d, J = 8.0 Hz, 1H), 4.53 (m, 1H), 4.41 (m, 1H), 3.23−3.12 (m, 2H), 2.32 (q, J = 8.8 Hz, 1H), 2.18 (s, 3H), 2.26−2.12 (m, 1H), 1.98−1.84 (m, 1H), 1.84−1.76 (m, 1H), 1.76−1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 35.6, 40.6, 57.2, 63.1, 68.1, 127.7, 127.8, 128.1, 128.3, 129.1, 129.9, 130.0, 132.3, 139.2, 139.3, 148.5; IR (neat) 3413, 2969, 2875, 2780, 1645, 1401, 1211 cm^{-1}; HRMS calcd for $C_{17}H_{19}ClN_2O$ $(M + H)^+$ 303.1259, found 303.1263.

(*S*)-2-(1-Methylpyrrolidin-2-yl)-6*H*-isochromeno(3,4-*b*)pyridine (9). A solution of **34** (64.3 mg, 0.212 mmol, 1.0 equiv) in DMF (3 mL) was added to NaH (10.1 mg, 0.427 mmol, 2.0 equiv) in DMF (1 mL). The mixture was heated overnight at 105 °C, and then the DMF was removed *in* vacuo. The residue was redissolved in EtOAc, filtered through Celite, and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 1% TEA/50% EtOAc/hexanes) to afford 30 mg (53%) of **9** as a clear oil. $[\alpha]^{23}_D$ −91 (*c* 1.5, CH_2Cl_2)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.05 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 5.32 (s, 2H), 3.25 (t, J = 9.2 Hz, 1H), 3.06 (t, J = 8.8 Hz, 1H), 2.30 (q, J = 8.8 Hz, 1H), 2.24−2.14 (m, 1H), 2.18 (s, 3H), 2.04−1.92 (m, 1H), 188−1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 35.3, 40.5, 57.1, 68.6, 69.1, 117.3, 122.7, 124.8, 128.6, 128.7, 129.2, 130.9, 131.0, 133.7, 147.6, 160.8; IR (neat) 3049, 2964, 2836, 2781, 1601, 1566, 1415, 1259, 1207, 1029 cm^{-1}; HRMS calcd for $C_{17}H_{18}N_2O$ $(M + H)^+$ 267.1492, found 267.1496.

(*S*)-2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridine-3-yl)furan-3-carbaldehyde (37). To a solution of **13** (135 mg, 0.417 mmol, 1.0 equiv) and **36** (241 mg, 0.625 mmol, 1.5 equiv) in THF (2 mL) was added solid $Pd(PPh_3)_2Cl_2$ (29 mg, 0.042 mmol, 0.1 equiv). The mixture was degassed with argon for 15 min then heated to reflux overnight. The reaction was cooled to rt and concentrated *in vacuo*. The residue was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/ hexanes) to afford 56 mg (46%) of **37** as a clear oil. $[\alpha]^{25}_D$ −148 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.44 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.58 (s, 1H), 6.92 (s, 1H), 3.26−3.18 (2H's overlapped), 2.33 (q, J = 9.2 Hz, 1H), 2.20 (s, 3H), 2.29−2.22 (m, 1H), 2.04−1.91 (m, 1H), 1.90−1.80 (m, 1H), 1.79−1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 35.8, 40.6, 57.1, 67.7, 109.0, 124.8, 125.3, 139.0, 140.1, 144.4, 149.0, 150.6, 157.1, 185.1; IR (neat) 3126, 3042, 2966, 2784, 2668, 1685, 1608, 1574, 1513, 1440, 1407, 1148 cm^{-1}; HRMS calcd for $C_{15}H_{15}ClN_2O_2$ $(M + H)^+$ 291.0895, found 291.0897.

(*S*)-(2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)-pyridin-3-yl)furan-3-yl)methanol (38). A solution of **37** (80.0 mg, 0.280 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (3 mL) was treated with $NaBH_4$ (58.0 mg, 1.56 mmol, 5.0 equiv), and the mixture was stirred at rt for 20 min. The mixture was diluted with CH_2Cl_2 (10 mL), and then water (2 mL) was added. The organic layer was extracted CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered through a plug a Celite, and concentrated *in vacuo*. The residue was purified by radial PLC (SiO_2, 1% TEA/ 50% EtOAc/hexanes) to afford 56 mg (69%) of **38** as clear oil. $[\alpha]^{32}_D$ −80 (*c* 1.4, CH_2Cl_2)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.79 (s, 1H), 7.50 (s, 1H), 6.61 (s, 1H), 4.51 (s, 2H), 3.19−3.10 (2H's overlapped), 3.06−2.88 (broad OH signal), 2.30 (q, J = 9.2 Hz, 1H), 2.24−2.14 (m, 1H), 2.15 (s, 3H), 1.93−1.85 (m, 1H), 1.84−1.74 (m, 1H), 1.73- 1.62 (m, 1H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.4, 40.5, 56.8, 57.1, 68.0, 112.1, 124.4, 126.5, 138.1, 139.5, 143.4, 145.7, 148.9, 149.1; IR (neat) 3500−3200, 2944, 2785, 1586, 1557, 1505, 1402, 1349, 1153, 1116, 1084 cm^{-1}; HRMS calcd for $C_{15}H_{17}ClN_2O_2$ $(M + H)^+$ 293.1051, found 293.1049.

(*S*)-8-(-Methyl-pyrrolidin-2-nyl)-4*H*-1,5-dioxa-6-aza-cyclopenta-[*a*]naphthalene (10). To a mixture of NaH (8 mg, 0.322 mg, 2.0 equiv) in DMF (1 mL) was added a solution of **38** (47.1 mg, 0.161 mmol, 1.0 equiv) in DMF (1 mL), and then the mixture was heated overnight at 80 °C. The mixture was allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in ether, filtered through a plug of Celite and silica gel, and concentrated *in vacuo* to yield 38.2 mg (93%) of **10** as a white solid that needed no further purification. Mp 76−81 °C; $[\alpha]^{31}_D$ −145 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 6.29 (d, J = 1.2 Hz, 1 H), 5.58 (s, 2H), 3.23 (t, J = 8.8 Hz, 1H), 2.99 (t, J = 8.4 Hz, 1H), 2.28 (q, J = 9.2 Hz, 1H), 2.20−2.12 (m, 1H), 2.17 (s, 3H), 2.02−1.88 (m, 1H), 1.85−1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 35.0, 40.5, 57.2, 66.7, 68.5, 108.3, 112, 114.5, 126.5, 133.1, 141.5, 145.0, 145.7, 159.4; IR (neat) 3118, 2960, 2875, 2841, 2779, 1647, 1571, 1470, 1392, 1355, 1214, 1006 cm^{-1}; HRMS calcd for $C_{15}H_{16}N_2O_2$ $(M + H)^+$ 257.1284, found 257.1287.

(*S*)-6-Chloro-4-methoxynicotine (44). A mixture of **43** (960 mg, 2.98 mmol, 1.0 equiv), CuI (56.7 mg, 0.298 mmol, 10 mol %), 1, 10-phenanthroline (108 mg, 0.595 mmol, 20 mol %), and Cs_2CO_3 (1.94 mg, 5.95 mmol, 2.0 equiv) in 1:1 MeOH/toluene (6 mL) was heated at 110 °C in a 15-mL pressure vessel for 24 h. After cooling to rt, the solvent was removed *in vacuo*, and EtOAc was added to the residue. The mixture was filtered through Celite and concentrated *in vacuo*, and the residue was purified by radial PLC (SiO_2, 1% TEA/2% EtOAc/hexanes) to afford 301 mg (45%) of **44** and 50 mg (7.4%) of **45** as white solids. **44**: white solid, mp 86−88 °C; $[\alpha]^{25}_D$ −189 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s 1H), 6.72 (s, 1H), 3.82 (s, 3H), 3.36 (t, J = 8.0 Hz, 1H), 3.16 (t, J = 8.8 Hz, 1H) 2.25 (q, J = 8.0 Hz, 1H), 2.28−2.12 (m, 1H), 2.17 (s, 3H), 1.90−1.68 (m, 2H), 1.56−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 33.3, 40.9, 55.8, 57.0, 62.5, 105.9, 126.9, 148.3, 150.9, 165.3; IR (neat) 2968, 2943, 2875, 2840, 2779, 2669, 1581, 1477, 1437, 1371, 1290 cm^{-1}; HRMS calcd for $C_{11}H_{15}ClN_2O$ $(M)^+$ 226.0873, found 226.0872.

(*S*)-4,6-Dimethoxynicotine (45). White solid, mp 48−50 °C; $[\alpha]^{25}_D$ −165 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.13 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.23 (t, J = 8.4 Hz, 1H), 3.16 (t, J = 8.4 Hz, 1H) 2.19 (q, J = 9.2 Hz, 1H), 2.18−2.10 (m, 1H), 2.17 (s, 3H), 1.90−1.80 (m, 1H), 1.78−1.68 (m, 1H), 1.66−1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 33.1, 40.9, 53.5, 55.4, 57.2, 63.1, 91.9, 121.3, 145.5, 165.0, 166.1; IR (neat) 3073, 2993, 2945, 2839, 2667, 1606, 1575, 1493, 1383, 1250 cm^{-1}; HRMS calcd for $C_{12}H_{18}N_2O$ $(M)^+$ 222.1368, found 222.1366.

(*S*)-6-Chloro-5-iodo-4-methoxynicotine (46). To a solution of **44** (290 mg, 1.28 mmol, 1.0 equiv) in THF at −45 °C was added dropwise *n*-BuLi (680 μL, 2.5 M in hexanes, 1.54 mmol, 1.2 equiv). After 1 h, a solution of iodine (520 mg, 2.05 mmol, 2.0 equiv) in 1 mL THF (over 4 Å sieves) was added, and stirring was continued for an additional 40 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium thiosulfate, dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was purified by radial PLC (SiO_2, 1% TEA/20% EtOAc/hexanes) to afford 300 mg (67%) of **46** as a white solid, mp 56−58 °C. $[\alpha]^{25}_D$ −126.5 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 3.85 (s, 3H), 3.40 (t, J = 8.4 Hz, 1H), 3.21 (dt, J = 8.4, 2.0 Hz, 1H) 2.25 (q, J = 9.2 Hz, 1H), 2.26−2.18 (m, 1H), 2.16 (s, 3H), 1.98−1.86 (m, 1H), 1.86−1.74 (m, 1H), 1.68−1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 35.0, 40.8, 57.0, 62.0, 63.3, 93.4, 133.2, 150.4, 154.6, 167.7; IR (neat) 2966, 2941, 2871, 2838, 2783, 2667, 1556, 1533, 1452, 1358 cm^{-1}; HRMS calcd for $C_{11}H_{14}ClIN_2O$ $(M)^+$ 351.9839, found 351.9842.

General Demethylation Procedure for Synthesis of 40 and 47. To a solution of the methoxynicotine (1.0 equiv) in dry CH_2Cl_2 at −78 °C was added dropwise BBr_3 (1.0 M in CH_2Cl_2, 3.0 equiv). The mixture was allowed to warm up to −10 °C and then quenched with MeOH (5 mL). The pH of the solution was lowered to 8−9 by addition a few drops of NaOH. Brine was added, and then the mixture was extracted with 10% MeOH/CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered through Celite, and concentrated *in vacuo*. The residue was purified by radial PLC (SiO_2, 2% TEA/70% EtOAc/hexanes) to afford the demethylated product.

(*S*)-3-Iodo-5-(1-methylpyrrolidin-2-yl)pyridin-2(1*H*)-one (40). White solid, mp 196−198 °C; $[\alpha]^{25}_D$ −117 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 3.15 (t, J = 8.4 Hz, 1H), 2.80 (t, J = 8.4 Hz, 1H) 2.23 (q, J = 8.8 Hz, 1H), 2.12 (s, 3H), 2.12−2.02 (m, 1H), 1.95−1.82 (m, 1H), 1.81−1.70 (m, 1H), 1.68−1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 34.3, 40.3, 56.71, 67.1, 92.0, 123.8, 133.6, 150.5, 162.8; IR (neat) 3464, 3116, 2943, 2843, 2783, 1857, 1729, 1647, 1619, 1533, 1454, 1292, 1226 cm^{-1}; HRMS calcd for $C_{10}H_{13}IN_2O$ $(M)^+$ 304.0073, found 304.0073.

(*S*)-2-Chloro-3-iodo-5-(1-methylpyrrolidin-2-yl)pyridin-4-ol (47). White solid, mp 196−198 °C; $[\alpha]^{25}_D$ −78 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 3.66 (t, J = 8.4 Hz, 1H), 3.5−3.44 (m, 1H), 2.66 (q, J = 8.4 Hz, 1H), 2.45 (s, 3H), 2.36−2.28 (m, 1H), 2.12−1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 33.3, 39.9, 55.1, 69.2, 88.2, 117.6, 146.9, 155.1, 169.2; IR (neat) 3392, 3047, 29245, 2854, 1722, 1648, 1575, 1502, 1465, 1373, 1286 cm^{-1}; HRMS calcd for $C_{10}H_{12}ClIN_2O$ $(M)^+$ 337.9683, found 337.9677.

Procedure for synthesis of **41** and **48** via a Sonogashira cross-coupling was as outlined in the case of derivative **20**.

(*S*)-5-(1-Methylpyrrolidin-2-yl)-3-((trimethylsilyl)ethynyl)pyridin-2(1*H*)-one (41). White solid, mp 97−102 °C; $[\alpha]^{25}_D$ −115 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 3.18 (t, J = 8.0 Hz, 1H), 2.82 (t, J = 8.2 Hz, 1H), 2.24 (q, J = 8.8 Hz, 1H), 2.14 (s, 3H), 2.12−2.04 (m, 1H), 1.96−184 (m, 1H), 1.93−1.74 (m, 1H), 1.72−1.62 (m, 1H) 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.21, 22.6, 34.2, 40.3, 56.8, 67.6, 100.2, 100.5, 115.7, 122.1, 133.8, 145.7, 164.7; IR (neat) 3261, 3145, 2962, 2906, 2780, 2154, 1651, 1620, 1549, 1294, 1248 cm^{-1}; HRMS calcd for $C_{15}H_{22}N_2OSi$ $(M)^+$ 274.1501, found 274.1500.

(*S*)-2-Chloro-5-(1-methylpyrrolidin-2-yl)-3-((trimethylsilyl)-ethynyl)pyridin-4-ol (48). White solid, mp 135−137 °C; $[\alpha]^{25}_D$ −113 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 3.61 (t, J = 8.8 Hz, 1H), 3.42- 3.36 (m, 1H) 2.55 (q, J = 8.4 Hz, 1H), 2.42 (s, 3H), 2.32−2.24 (m, 1H), 2.06−1.88 (m, 4H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.17, 23.2, 33.6, 40.2, 55.5, 68.9, 96.7, 105.6, 108.9, 119.0, 146.3, 153.7, 169.1; IR (neat) 3354, 2945, 2876, 2782, 1769, 1607, 1490, 1384, 1283, 1248 cm^{-1}; HRMS calcd for $C_{15}H_{21}ClN_2OSi$ $(M)^+$ 308.1112, found 308.1110.

General Procedure for Formation of the Dimers 42 and 49. A solution of **41** or **48** (1.0 equiv) in 1:1 EtOH/Et_3N was added to solid CuI (5 mol %) in a flame-dried flask, and the mixture was heated at 70 °C for 24 h. Solid K_2CO_3 (1.0 equiv) was added, and then stirring was continued for an additional 24 h at rt. The mixture was quenched with an aqueous solution of EDTA and was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was purified by radial PLC (SiO_2, 1% TEA/50% EtOAc/hexanes to afford **42** or **49**, respectively.

5,5′-Bis(1-methyl-pyrrolidin-2-yl)-[2,2′-bi[furo[2,3-*b*]pyridinyl] (42). White solid, mp 200−204 °C; $[\alpha]^{25}_D$ −204 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 1.6 Hz, 1H), 3.28 (dt, J = 8.4, 1.6 Hz, 1H), 2.34 (q, J = 8.4 Hz, 1H), 2.30−2.22 (m, 1H), 2.19 (s, 3H), 2.06−1.94 (m, 1H), 1.90−1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 35.9, 40.6, 57.2, 69.1, 103.8, 120.9, 129.5, 135.8, 145.2, 147.1, 162.0; IR (neat) 3450, 3272, 3116, 2951, 2873, 2840, 2779, 2665, 1631, 1537, 1466, 1242 cm^{-1}; HRMS calcd for $C_{24}H_{26}N_4O_2$ $(M)^+$ 402.2056, found 402.2051.

4,4′-Dichloro-7,7′-bis((*S*)-1-methylyrrodin-2-yl)-2,2′-bifuro-[3,2-*c*]pyridine (49). White solid, mp 295−300 °C; $[\alpha]^{26}_D$ −130 (*c* 0.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.30 (s, 1H), 3.70 (t, J = 8.0 Hz, 1H), 3.33 (t, J = 7.6 Hz, 1H) 2.42−2.39 (m, 2H), 2.30 (s, 3H), 2.14−2.05 (m, 1H), 2.02−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 33.6, 41.0, 57.3, 63.5, 103.4, 123.3, 124.5, 143.1, 144.0, 147.6, 159.3; IR (neat) 3354, 2945, 2876, 2782, 1769, 1607, 1490, 1384, 1283, 1248 cm^{-1}; HRMS calcd for $C_{24}H_{24}Cl_2N_4O_2$ $(M)^+$ 470.1276, found 470.1269.

Acknowledgment. NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from North Carolina Biotechnology Center and National Science Foundation (Grant No. CHE-0078253). The authors acknowledge Targacept Inc. for financial support. P.W.O also thanks Targacept Inc. for funding of a Research Assistantship.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **4**−**10**, **15**, **18**−**21**, **24**, **27**, **31**, **34**, **37**−**38**, **40**−**42**, and **44**−**49**. This material is available free of charge via the Internet at http://pubs.acs.org.