# A New and Efficient Approach to the Synthesis of Nicotine and Anabasine Analogues



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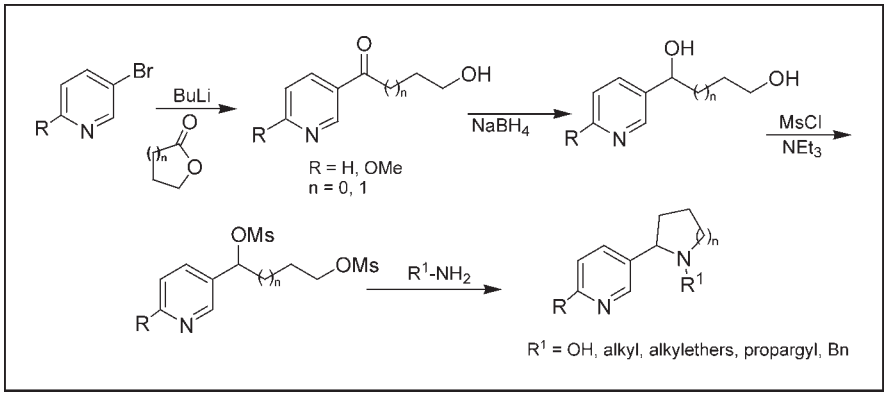


A straightforward and practical approach was established for the synthesis of nicotine and anabasine analogues by the cyclization of mesylated 1-(3-pyridinyl)-1,4, and 1,5-diol derivatives to form the pyrrolidino or piperidino fragments. Nicotine analogue (*S*)-**15** was prepared with good enantioselectivity using the developed azacyclization procedure of nonracemic (*R*)-1-pyridin-3-yl-butane-1,4-diol, which was obtained by the borane-mediated reduction of ketone **12** in the presence of the spiroborate ester derived from diphenyl prolinol and ethylene glycol.

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## INTRODUCTION

As a group of ligand-gated ion channels, neuronal nicotinic acetylcholine receptors (nAChRs) hold significant promise as therapeutic targets for the treatment of the central nervous system (CNS) and peripheral nervous disorders [1]. Recent studies have shown that nicotine **1** (Fig. 1) displays beneficial effects on patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, ulcerative colitis, and other CNS disorders [2]. Furthermore, nicotine has been used on a large scale as an insecticide [3].

In the past decade, much attention has been concentrated on the discovery of novel nicotine analogues (Fig. 1) that would display higher selectivity to particular AChRs subtypes, targeting the beneficial actions of nicotine whereas reducing the toxicity effects [2–8]. SIB-1508Y (**2**) was designed as a memory enhancer and anti-Parkinson's agent [4]. The nAChR agonist ABT-418 (**3**), containing an isoxazole bioisostere of pyridine, was promising for the treatment of Alzheimer's patients because this analogue not only have binding potencies comparable with nicotine but also produce enhanced cognitive activity with less adverse effects [5]. The four-member ring analogue, *N*-methyl-(3-pyridyl)azetidine (**4**), produced a 10-fold increase in binding affinity compared with nicotine [6]. Wang et al. demonstrated that 6-methylnicotine (**5**) possess higher affinity in competition studies for [3H]nicotine in rat brain membranes [7]. Anabasine **6** has been established to be a selective α7-nAChR agonist in an animal model and with low toxicity for the potential treatment of schizophrenia [1e]. Recently, Bhatti et al. [8] evaluated the activity of bicyclic analogue **7**, which displayed high affinity for the α4β2 receptor.

Consequently, considerable efforts had been focused on the development of new syntheses of nicotine and anabasine analogues, which have been recently reviewed [9a]. Although various methods have been reported, including asymmetric induction using chiral auxiliaries [9b,c] and enantioselective stoichiometric allylboration of the 3-pyridyl carboxaldehyde [9d], surprisingly, there is a lack of a suitable direct synthetic routes for the pyrrolidine and piperidine ring construction of nicotine and anabasine analogues, respectively. Furthermore, our research program for the synthesis of potential biological active amino derivatives as nicotinic receptor

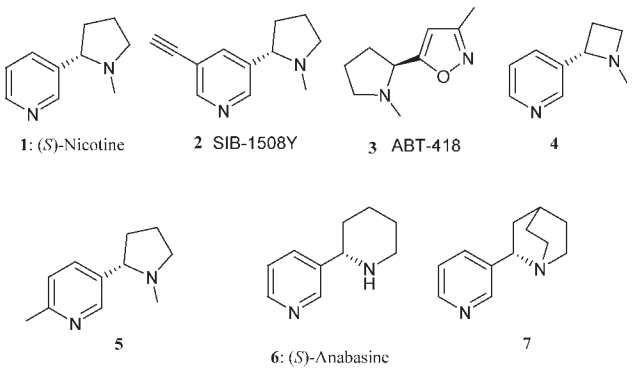



**Figure 1.** Nicotinic acetylcholine receptor agonists.

agonists, a practical synthesis of racemic and nonracemic nicotine and anabasine analogues was required. Herein, we report a new and efficient approach to prepare these compounds in racemic form from inexpensive commercial sources in good to excellent yields. In addition, an asymmetric synthesis of a representative nicotine derivative using our recently developed chiral spiroborate ester, as an environmentally friendly catalyst, is also described.

## RESULTS AND DISCUSSION

As shown in Scheme 1, lithiation of 3-bromopyridine with *n*-butyl lithium at −78°C, followed by treatment with γ-butyrolactone at the same temperature, furnished ketone [8] in good yield (81%) [10]. Diol **9** was readily available from **8** by reduction with $NaBH_4$ in excellent yield (96%). Treatment of **9** with methanesulfonyl chloride in the presence of $Et_3N$ afforded dimesylate **10**. Attempts to purify this product by column chromatography on silica gel failed because it decomposed during the process. Accordingly, after a simple work-up and solvents removal under reduced pressure, compound **10** was used directly for the next step. After stirring overnight the crude dimesylated diol with neat benzylamine, the benzyl substituted nornicotine (**11**) was obtained. Purification of this compound by flash column chromatography provided the desired pure product in 83% overall yield from **9**. This facile and effective azacyclization reaction opens a new way for the direct access to *N*-substituted nornicotine derivatives.

With an interest in developing compounds with potential biological activity and to demonstrate the synthetic potential of our new methodology, we prepared nicotine and a variety of analogues with N-substitution on the pyrrolidine ring (Table 1). The corresponding primary amines were allowed to react with dimesylate **10** under the previous established reaction conditions. By TLC and GC-MS analysis of the reaction mixture, only the azacyclization product was observed. As a result, the desired nicotine and its derivatives were easily purified and obtained in high yield (entries 1–7).

To further develop our methodology, the aza-annulation of the 1,5- and 1,6-dimesylated 1-(6-methoxypyridyl)diol to form six and seven member rings were investigated (Scheme 2). In general, the 1,5-dimesylated diol was readily annulated to yield the desired anabasine derivatives in moderate to good yield (Table 1, entries 8–11). On the other hand, as observed by GC-MS analysis, the 1,6-dimesylate was found to be unsuitable for the formation of azepanes under the previous conditions due to the less favored seven membered ring closure.

Enantiomers of a given racemate often display difference on the basis of potency, selectivity, or efficacy at biologic targets. (*S*)-Nicotine is more bioactive than the (*R*)-enantiomer, as it is also observed for related analogues [11]. The high yield and excellent enantionselectivity achieved in the borane reduction of heterocyclic ketones catalyzed by our spiroborate ester **13** derived from diphenyl prolinol (Scheme 3) [12a], prompted us to investigate the asymmetric synthesis of the nicotine derivative (*S*)-**15**.

Considering that borane can react with the hydroxyl group of ketone **8**, and that an intramolecular uncatalyzed reaction can take place, the hydroxyl group was initially protected with an acetyl group. The acetylated ketone was then reduced with borane employing 10% and 30% mol of catalyst **13** obtaining 81% ee and 85.5% ee of the diacetylated product, respectively. When the temperature was decreased at −10°C using 30% of catalyst, the enantioselectivity decreased to 78% ee. Therefore, the hydroxyl group was protected with TIPSCl affording **12** in 95% yield. High yield and excellent enantioselectivity (94% ee) was then achieved by the borane-mediated reduction of **12** employing 50% of catalyst **13**. The absolute *R* configuration of the product was assigned according to the catalyst **13** predicted stereoselectivity. After deprotection of silylated ether (***R***)-**14** with $Bu_4F$ to yield the diol (***R***)-**9**, followed by dimesylation according to our previous procedure, the

**Scheme 1.** Synthesis of *N*-1′-benzyl nornicotine as a model method for the preparation of nicotine analogues.

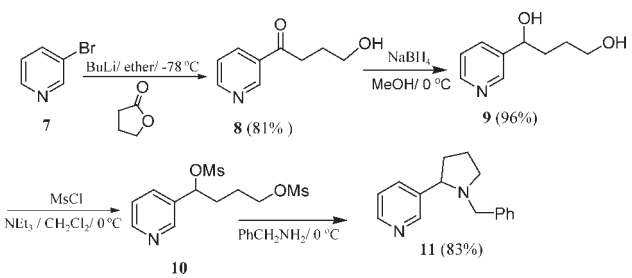
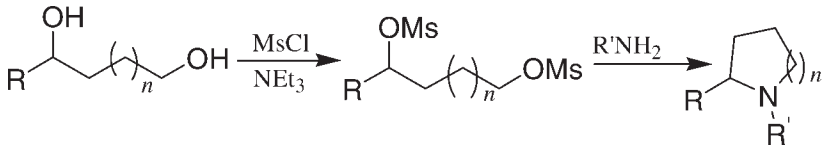
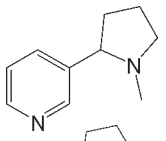
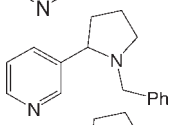
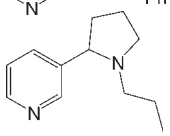
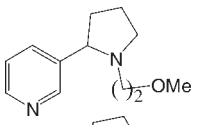
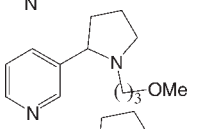
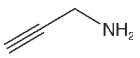
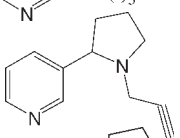
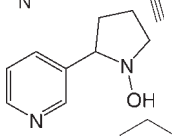
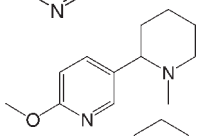
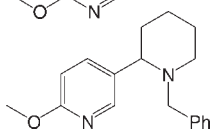
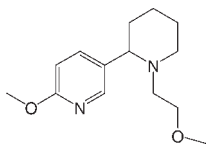
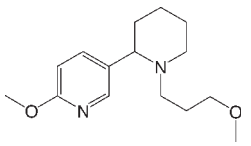


**Table 1**

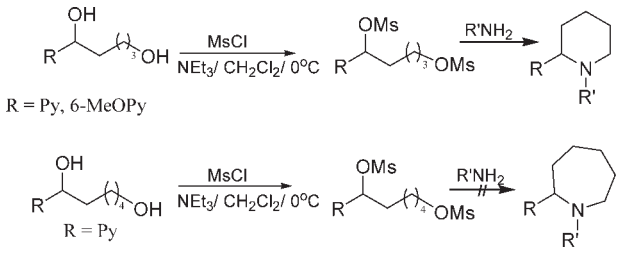
Aza-cyclization of dimesylated diols with representative primary amine.




| Entry | *n* | *R* | *R′* | Product[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1 | Py | $CH_3NH_2$[c] |  | 86 |
| 2 | 1 | Py | $PhCH_2NH_2$ |  | 83 |
| 3 | 1 | Py | $CH_3(CH_2)_2NH_2$ |  | 88 |
| 4 | 1 | Py | $CH_3O(CH_2)_2NH_2$ |  | 81 |
| 5 | 1 | Py | $CH_3O(CH_2)_3NH_2$ |  | 83 |
| 6 | 1 | Py |  |  | 82 |
| 7 | 1 | Py | $NH_2OH{\cdot}HCl$[d] |  | 82 |
| 8 | 2 | 6-MeOPy | $CH_3NH_2$[c] |  | 78 |
| 9 | 2 | 6-MeOPy | $PhCH_2NH_2$ |  | 76 |
| 10 | 2 | 6-MeOPy | $CH_3O(CH_2)_2NH_2$ |  | 78 |
| 11 | 2 | 6-MeOPy | $CH_3O(CH_2)_3NH_2$ |  | 81 |

[a] The mixture of the corresponding dimesylate diol and the neat primary amine was stirred at 0°C overnight.
[b] Purified by flash column chromatography.
[c] Methylamine solution (33 wt %) in absolute ethanol was employed and the reaction was conducted at room temperature.
[d] $NH_2OH.HCl$ and $Et_3N$ was used in ethanol and dichloromethane at room temperature.

**Scheme 2.** Pyperidine and azepane rings formation of pyridyl analogues.




azacyclization of (***R***)-**10** was successfully achieved, providing the desired nicotine derivative (***S***)-**15**.

Although some racemization took place at the benzylic position during the cyclization step, even at −10°C, the desired nicotine derivative (*S*)-15 was obtained in good enantiomeric excess (82% ee) and in good overall yield (76%).

## CONCLUSION

In summary, a direct, mild, and efficient methodology for the synthesis of a variety of nicotine and anabasine analogues from commercially available sources has been described. Moreover, a catalytic asymmetric synthesis of the nicotine derivative (***S***)-**15** in good enantiomeric purity was established by the enantioselective reduction of the TIPS protected ketone **12**. Considering the readily available starting materials, facile synthetic procedures, easy purification and high yields, the present work constitutes an excellent methodology for the rapid access to important nicotinic receptor agonists, and will find applications in academic research and in the pharmaceutical industry.

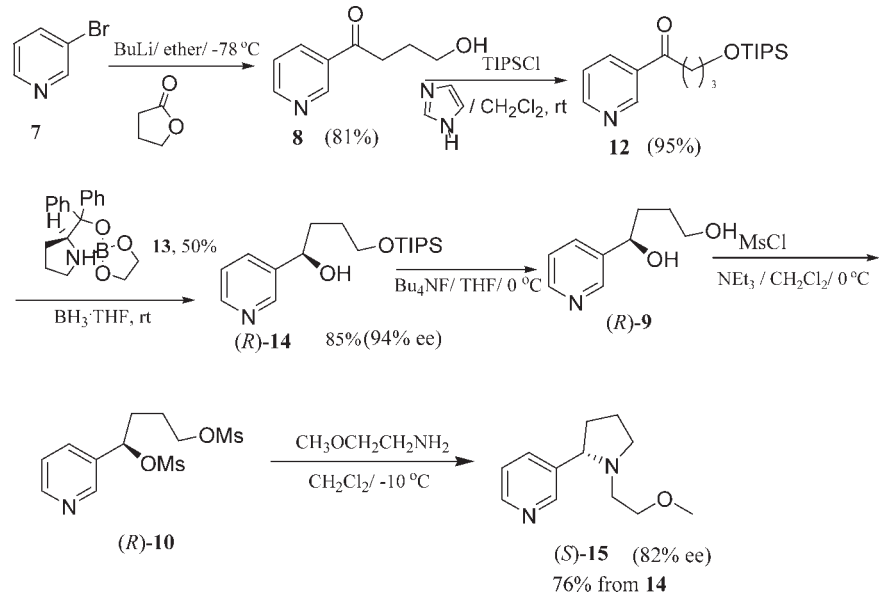
## EXPERIMENTAL

Air- and moisture-sensitive reactions were performed under $N_2$ atmosphere in flame-dried glassware. Common solvents were dried and distilled by standard procedures. All reagents were obtained commercially unless otherwise noted. Chromatographic purification of products was accomplished using flash chromatography on a Merck silica gel® Si 60 Å (70–230 mesh). $^1$H and $^{13}$C spectra were recorded on a Bruker Avance 400 MHz spectrometer with standard pulse sequences operating at 400.152 MHz and 100.627 MHz for $^1$H and $^{13}$C, respectively. Chiral GC analysis was processed with a Crompack Chirasil-Dex-CB column (30 m × 0.25 mm × 0.25 μm). High-resolution mass spectral analyses (HRMS) were performed at the University of Florida.

**General procedure for the synthesis of hydroxy ketones [10].** To a stirred solution of 3-bromopyridine (10 g, 63.3 mmol) in anhydrous ether (100 mL) was added *n*-BuLi (40 mL, 1.6 *M* in hexane, 64 mmol) dropwise at −78°C. The mixture was stirred for 15 min and a solution of γ-butyrolactone, δ-valerolactone, or ε-caprolactone (63.6 mmol) in ether (20 mL) was added dropwise. The solution was stirred 1 h and then it was left overnight at room temperature. The mixture was diluted with brine (100 mL). The product was extracted with *n*-BuOH (3 × 150 mL) and the combined extracts were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography, eluted by $CH_2Cl_2$/MeOH (10/1).

**4-Hydroxy-1-(pyridin-3-yl)butan-1-one.** Yellow oil, Lit [10] mp 36–37°C; yield 81% (6.45 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 2.06 (m, 2H, $CH_2$), 2.22 (br s, 1H, OH), 3.19 (m, 2H, $CH_2$), 3.80 (m, 2H, $CH_2$), 7.46 (m, 1H, Py), 8.28 (m, 1H,

**Scheme 3.** Asymmetric synthesis of nicotine analogue (*S*)-**15**.



Py), 8.81 (m, 1H, Py), 9.22 (m, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.6, 35.5, 61.9, 123.7, 132.2, 135.4, 149.6, 153.5, 199.2.

**5-Hydroxy-1-(6-methoxypyridin-3-yl)pentan-1-one.** Colorless oil, yield 85% (5.68 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.66 (m, 2H, $CH_2$), 1.87 (m, 2H, $CH_2$), 2.05 (br s, 1H, OH), 2.99 (t, $J$ = 7.0 Hz, 2H, $CH_2$), 3.70 (t, $J$ = 6.2 Hz 2H, $CH_2$), 4.03 (s, 3H, $OCH_3$), 6.80, d, $J$ = 9 Hz, 1H, Py), 8.18 (dd, $J_1$ = 2,4 Hz, $J_2$ = 8.7 Hz, 1H, Py), 8.83 (d, $J$ = 2.0 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 203, 32.2, 38.0, 54.1, 62.3, 111.2, 126.7, 138.2, 149.0, 166.8, 198.1. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{16}NO_3$: 210.1125; found 210.1124.

**6-Hydroxy-1-(pyridin-3-yl)hexan-1-one [10].** Light yellow crystals, mp 27–29°C; yield 68% (8.26 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.47 (m, 2H, $CH_2$), 1.67 (m, 2H, $CH_2$), 1.85 (m, 2H, $CH_2$), 2.18 (br s, 1H, OH), 3.03 (m, 2H, $CH_2$), 3.70 (m, 2H, $CH_2$), 7.44 (m, 1H, Py), 8.26 (m, 1H, Py), 8.78 (m, 1H, Py), 9.22 (m, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 23.6, 25.5, 32.5, 38.8, 62.5, 123.7, 132.2, 135.4, 149.6, 153.3, 199.1.

**General procedure for the synthesis of diols.** To a flask was added the ketone (20 mmol) and MeOH (40 mL) at room temperature. Then, neat $NaBH_4$ (1.52 g, 40 mmol) was added portion-wise to the solution at 0°C. The resulting mixture was stirred for 1 h and the solvent was evaporated under reduced pressure. Distilled water was added (50 mL) and the mixture was extracted with $CH_2Cl_2$ (3 × 100 mL) and the combined organic phases were removed under reduced pressure. The residue was directly submitted to the next step or recrystallized.

**1-(Pyridin-3-yl)butane-1,4-diol (9) [13].** Light yellow oil; yield 96% (4.38 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.88 (m, 2H, $CH_2$), 1.93 (m, 2H, $CH_2$), 3.51 (br s, 1H, OH), 3.72 (m, 2H, $CH_2$), 4.63 (br s, 1H, OH), 4.80 (m, 1H, OCH), 7.30 (m, 1H, Py), 7.76 (m, 1H, Py), 8.46 (m, 1H, Py), 8.54 (m, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 29.0, 36.6, 62.5, 123.5, 133.9, 140.5, 147.5, 148.3.

**1-(6-Methoxypyridin-3-yl)pentane-1,5-diol.** Light yellow oil; yield 93% (1.88 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.38 (m, 1H, $CH_2$), 1.45 (m, 1H, $CH_2$), 1.62 (m, 2H, $CH_2$), 1.75 (m, 1H, $CH_2$), 1.85 (m, 1H, $CH_2$), 1.95 (br s, 1H, OH), 2.63 (br s, 1H, OH), 3.66 (t, $J$ = 6.3 Hz, 2H, $CH_2$), 3.96 (s, 3H, $CH_3$), 4.68 (t, $J$ = 6.6 Hz, 1H, OCH), 6.78 (d, $J$ = 8.6 Hz, 1H, Py), 7.63 (dd, $J_1$ = 2.4 Hz, $J_2$ = 8.6 Hz, 1H, Py), 8.01 (d, $J$ = 2.2 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.0, 32.3, 38.4, 53.5, 62.5, 71.8, 110.9, 132.8, 136.7, 144.6, 163.8. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{18}NO_3$: 212.1281; found 212.1288.

**1-(Pyridin-3-yl)hexane-1,6-diol.** Colorless oil; yield 96% (1.88 g); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.34–1.59 (m, 4H, $CH_2$), 1.55–1.62 (m, 2H, $CH_2$), 1.71–1.87 (m, 2H, $CH_2$), 2.39 (br s, 1H, OH), 3.66 (t $J$ = 6.4 Hz, over s, 3H, $CH_2$ and OH), 4.76 (m, 1H, OCH), 7.30 (t, $J$ = 3.8 Hz,, 1H, Py), 7.75 (dt, $J_1$ = 1.8 Hz, $J_2$ = 7.8 Hz, 1H, Py), 8.47 (dd, $J_1$ = 1.6 Hz, $J_2$ = 4.8 Hz, 1H, Py), 8.52 (d, $J_1$ = 2.0 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.6, 32.5, 39.0, 62.5, 71.9, 123.6, 133.8, 140.5, 147.6, 148.5. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{11}H_{18}NO_2$: 196.1332; found 196.1344.

**Typical procedure: Synthesis of *rac*-nicotine derivative 11 from diol 9.** To a two-neck round bottom flask was added a solution of diol **9** (1.67 mg, 10 mmol) in anhydrous $CH_2Cl_2$ (100 mL) and $Et_3N$ (7 mL, 50 mmol) under nitrogen. The mixture was cooled to 0°C and MsCl (2.3 mL, 30 mmol) was added dropwise for 1 h by a syringe pump. The resulting solution was stirred until TLC indicated that the starting material was consumed. Water (100 mL) was added to quench the reaction and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure at 25°C to obtain the crude dimesylate **10:** $^1$H NMR (400 MHz, $CDCl_3$): δ 1.90 (m, 2H), 2.10 (m, 1H), 2.19 (m, 1H), 2.96 (s, 3H, $CH_3SO_2$), 3.09 (s, 3H, $CH_3SO_2$), 4.35 (t, $J$ = 6.3 Hz 2H, $OCH_2$), 5.80 (m, 1H, OCH), 7.59 (m, 1H, Py), 8.01 (dt, $J_1$ = 1.8 Hz, $J_2$ = 7.9 Hz, 1H, Py), 8.74 (m, 1H, Py), 8.82 (m, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.1, 33.1, 37.5, 39.0, 52.6, 68.7, 124.9, 135.7, 136.9, 145.8, 148.0.

**3-(1-Benzylpyrrolidin-2-yl)pyridine (11) [9c].** To the crude dimesylate **10** (323 mg, 1 mmol), neat benzylamine (3 mL, 27 mmol) at 0°C was added. The resulting mixture was stirred overnight at the same temperature. The remaining benzylamine was removed in a Kugelrohr at 80°C under high vacuum and the residue was mixed with 10 mL water. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined organic phases were washed with brine (2 × 5 mL) solution and dried over $Na_2SO_4$. The pure product was obtained after flash column chromatography on silica gel eluted with hexane/EtOAc (1:1): Colorless oil, yield 83% (197 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.76–1.95 (m, 3H), 2.29 (m, 2H), 3.17 (m, 2H), 3.48 (m, 1H), 3.85 (m, 1H), 7.25–7.35 (m, 6H, Ar), 7.85 (m, 1H, Py), 8.54 (m, 1H, Py), 8.70 (m, 1H, Py; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.6, 35.3, 53.5, 58.1, 67.0, 123.6, 126.9, 128.2, 128.6, 135.0, 139.3, 139.5, 148.6, 149.7; GC-MS $m/z$ 238.1 ($M^+$).

**3-(1-Methylpyrrolidin-2-yl)pyridine (or 1-methyl-2-(3-pyridyl)pyrrolidine) (*rac*-nicotine) [9c].** Colorless oil, yield 86% (139 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.74–1.84 (m, 2H, $CH_2$), 1.96 (m, 1H, $CH_2$), 2.18 (m, 4H, $CH_2$), 2.34 (m, 1H, $CH_2$), 3.12 (t, $J$ = 8.5 Hz, 1H, CH), 3.28 (t, $J$ = 8.5 Hz, 1H, CH), 7.26 (m, 1H, Py), 7.70 (m, 1H, Py), 8.51 (s, 1H, Py), 8.55 (m, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.6, 35.2, 40.4, 57.0, 68.9, 123.6, 134.8, 138.8, 148.6, 149.6; GC-MS $m/z$ 162.0 ($M^+$).

**3-(1-Propylpyrrolidin-2-yl)pyridine [14].** Colorless oil, yield 88% (167 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.43–1.51 (m, 2H, $CH_2$), 1.72 (m, 1H, CH), 1.86 (m, 1H, CH), 1.98 (m, 1H, CH), 2.07 (m, 1H, CH), 2.21 (m, 2H, CH), 2.46 (m, 1H, CH), 3.36 (t, $J$ = 8.2 Hz, 1H, CH), 3.40 (td, $J_1$ = 2.4 Hz, $J_2$ = 8.5 Hz, 1H, CH), 7.26 (dd, $J_1$ = 4.8 Hz, $J_2$ = 7.8 Hz, 1H, Py), 7.75 (d, $J$ = 7.8 Hz, 1H, Py), 8.52 (dd, $J_1$ = 0.8 Hz, $J_2$ = 4.7 Hz, 1H, Py), 8.59 (d, $J$ = 1.9 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.9, 22.0, 22.7, 35.2, 53.6, 56.4, 67.6, 123.5, 134.9, 139.8, 148.4, 149.6; GC-MS $m/z$ 190.1 ($M^+$).

**3-[1-(2-Methoxyethyl)pyrrolidin-2-yl]pyridine [9c].** Colorless oil, yield 81% (167 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.73 (m, 1H, CH), 1.86 (m, 1H, CH), 2.01 (m, 1H, CH), 2.20 (m, 1H, CH), 2.36 (m, 2H, CH), 2.79 (m, 1H, CH), 3.29 (s, 3H, $OCH_3$), 3.34–3.47 (m, 4H, CH), 7.26 (dd, $J_1$ = 4.8 Hz, $J_2$ = 7.8 Hz, 1H, Py), 7.75 (d, $J$ = 7.8 Hz, 1H, Py), 8.52 (dd, $J_1$ = 1.5 Hz, $J_2$ = 4.7 Hz, 1H, Py), 8.59 (d, $J$ = 2.0 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.8, 35.0, 53.7, 54.5, 58.7, 67.8, 71.5, 123.5, 134.9, 139.4, 148.5, 149.6; GC-MS $m/z$ 206.0 ($M^+$).

**3-[1-(3-Methoxypropyl)pyrrolidin-2-yl]pyridine.** Colorless oil, yield 83% (183 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.68–1.74 (m, 3H, CH), 1.81–2.01 (m, 2H, CH), 2.17–2.27 (m, 3H, CH), 2.59 (m, 1H, CH), 3.28 (s, 3H, $OCH_3$), 3.29–3.43 (m, 4H, CH), 7.26 (dd, $J_1$ = 4.8 Hz, $J_2$ = 7.8 Hz, 1H, Py), 7.77 (dt, $J_1$ = 1.9 Hz, $J_2$ = 7.8 Hz, 1H, Py), 8.51 (dd, $J_1$ = 1.7 Hz, $J_2$ = 4.8 Hz, 1H, Py), 8.57 (d, $J$ = 2.0 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.7, 28.9, 35.3, 51.2, 53.6, 58.5, 67.6, 70.9, 123.4, 134.9, 139.7, 148.5, 149.5; GC-MS *m/z* 220.1 ($M^+$). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{14}H_{21}N_2O$: 221.1654; found 221.1626.

**3-[1-(Prop-2-ynyl)pyrrolidin-2-yl]pyridine [14].** Colorless oil, yield 82% (152 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ δ1.77 (m, 1H, CH), 1.85 (m, 1H, CH), 2.03 (m, 1H, CH), 2.24 (m, 2H, CH), 2.78 (q, $J$ = 8.8 Hz, 1H, CH), 3.22 (m, 2H, CH), 3.47 (m, 1H, CH), 3.61 (t, $J$ = 8.2 Hz, 1H, CH), 7.26 (dd, $J_1$ = 4.8 Hz, $J_2$ = 7.7 Hz, 1H, Py), 7.71 (d, $J$ = 7.8 Hz, 1H, Py), 8.52 (d, $J$ = 3.5 Hz, 1H, Py), 8.59 (d, $J$ = 1.4 Hz, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.6, 34.9, 40.1, 52.2, 63.7, 72.9, 78.5, 123.6, 135.0, 138.2, 148.8, 149.7; GC-MS *m/z* 186.1 ($M^+$).

**2-(Pyridin-3-yl)pyrrolidin-1-ol [15].** Colorless oil, yield 82% (134 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.76 (m, 1H, CH), 1.92 (m, 2H, CH), 2.26 (m, 1H, CH), 2.87 (q, $J$ = 9.5 Hz, 1H, CH), 3.38 (m, 1H, CH), 3.76 (m, 1H, CH), 7.18 (dd, $J_1$ = 4.8 Hz, $J_2$ = 7.8 Hz, 1H, Py), 7.65 (dt, $J_1$ = 1.6 Hz, $J_2$ = 7.8 Hz 1H, Py), 8.35 (dd, $J_1$ = 1.4 Hz, $J_2$ = 4.8 Hz, 1H, Py), 8.54 (d, $J$ = 1.8 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 19.9, 30.3, 57.5, 70.2, 123.2, 135.6, 137.5, 148.1, 149.3.

**6-Methoxy-3-(1-methylpiperidin-2-yl)pyridine.** Colorless oil, yield 78% (161 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 1H, CH), 1.48 (m, 1H, CH), 1.61 (m, 3H, OH), 1.73 (m, 1H, CH), 1.90 (s, 3H, $CH_3$), 2.02 (m, 1H, CH), 2.65 (dd, $J_1$ = 2.9 Hz, $J_2$ = 11 Hz, 1H, CH), 2.95 (m, 1H, CH), 3.85 (s, 3H, $OCH_3$), 6.63 (d, $J$ = 8.6 Hz, 1H, Py), 7.50 (dd, $J_1$ = 2.4 Hz, $J_2$ = 8.5 Hz, 1H, Py), 7.93 (d, $J$ = 2.3 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.1, 35.8, 44.5, 53.4, 57.5, 67.5, 110.9, 132.9, 137.7, 145.7, 163.6; GC-MS *m/z* 206.1 ($M^+$). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{12}H_{19}N_2O$: 207.1492; found 207.1500.

**6-Methoxy-3-(1-benzylpiperidin-2-yl)pyridine.** Colorless oil, yield 76% (214 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 1H, CH), 1.63 (m, 3H, CH), 1.82 (m, 2H, CH), 1.99 (td, $J_1$ = 3.5 Hz, $J_2$ = 11.5 Hz, 1H, CH), 2.86 (d, $J$ = 13.6 Hz, 1H, CH), 3.00 (m, 1H, CH), 3.17 (dd, $J_1$ = 2.8 Hz, $J_2$ = 11 Hz 1H, CH), 3.80 (d, $J$ = 13.5 Hz, 1H, CH), 3.98 (s, 3H, $OCH_3$), 6.78 (d, $J$ = 8.5 Hz, 1H, Py), 7.24–7.33 (m, 5H, Ph), 7.78 (dd, $J_1$ = 2.3 Hz, $J_2$ = 8.5 Hz, 1H, Py), 8.19 (d, $J$ = 2.2 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.1, 26.0, 36.9, 53.37, 53.4, 59.6, 65.7, 111.1, 126.6, 128.1, 128.6, 133.7, 137.8, 139.6, 145.8, 163.5; GC-MS *m/z* 282.1 ($M^+$). EIS TOF HRMS calcd. for $[M + H]^+$ $C_{18}H_{23}N_2O$: 283.1805; found 283.1817.

**6-Methoxy-3-[1-(2-methoxyethyl)piperidin-2-yl]pyridine.** Colorless oil, yield 78% (195 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 1H, CH), 1.48 (m, 1H, CH), 1.58 (m, 3H, CH), 1.70 (m, 1H, CH), 2.01 (m, 2H, CH), 2.60 (m, 1H, CH), 2.97 (dd, $J_1$ = 2.7 Hz, $J_2$ = 11 Hz, 1H, CH), 3.11 (s, 3H, $OCH_3$), 3.30 (m, 2H, CH), 3.85 (s, 3H, $CH_3$), 6.62 (d, $J$ = 8.5 Hz, 1H, Py), 7.52 (dd, $J_1$ = 2.2 Hz, $J_2$ = 8.5 Hz, 1H, Py), 7.94 (d, $J$ = 2.3 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.0, 36.6, 53.4, 54.3, 54.4, 58.7, 65.7, 70.6, 110.9, 133.2, 137.9, 145.8, 163.5. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{14}H_{23}N_2O_2$: 251.1754; found 251.1762.

**6′-Methoxy-1-(3-methoxypropyl)-1,2,3,4,5,6-hexahydro-[2,3′]bipyridinyl.** Colorless oil, yield 81% (206 mg); $^1$H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 1H, CH), 1.43 (m, 1H, CH), 1.52–1.71 (m, 6H, CH), 1.86 (m, 1H, CH), 1.94 (m, 1H, CH), 2.39 (m, 1H, CH), 2.91 (dd, $J_1$ = 2.7 Hz, $J_2$ = 11 Hz, 1H, CH), 3.05–3.21 (m, 6H, CH), 3.85 (s, 3H, $OCH_3$), 3.34–3.47 (m, 4H, CH), 6.62 (d, $J$ = 8.5 Hz, 1H, Py), 7.50 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, Py), 7.93 (d, $J$ = 2.3 Hz, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.1, 26.4, 36.7, 51.8, 53.2, 53.3, 58.4, 65.6, 71.1, 110.8, 133.4, 137.9, 145.7, 163.4. EIS TOF HRMS calcd. for $[M + H]^+$ $C_{15}H_{25}N_2O_2$: 265.1911; found 265.1929.

**Asymmetric synthesis of (*S*)-3-[1-(2-methoxyethyl)pyrrolidin-2-yl]pyridine (*S*)-15 [9c]**

***Borane reduction of ketone 12.*** To a 25 mL round flask, equipped with a septa and nitrogen flow, was added catalyst **13** (244 mg, 0.75 mmol). Then, dry THF (4 mL) and $BH_3$.THF (2.6 mL, 1 *M*, 2.6 mmol) were added to the flask and the resulting mixture was stirred about 1 h at room temperature. A solution of ketone **12** (482 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise by a syringe pump for 1 h. After addition, the mixture was stirred for 1 h and then cooled by an ice bath. MeOH (5 mL) was added slowly to quench the excess of borane and the mixture was refluxed overnight. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluted with $CH_2Cl_2$/MeOH (20/1).

**(*R*)-1-(Pyridin-3-yl)-4-triisopropylsilyloxybutan-1-ol (*R*)-14.** This was obtained as a colorless oil; yield 85% (411 mg); 94% ee. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.08–1.19 (m, 21H, TIPS), 1.60–1.70 (m, 2H, $CH_2$), 1.77 (m, 2H, $CH_2$), 3.84 (m, 2H, $CH_2$), 3.98 (br s, 1H, OH), 4.84 (m, 1H, CH), 7.32 (m, 1H, Py), 7.79 (m, 1H, Py), 8.53 (m, 1H, Py), 8.63 (s, 1H, Py); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.9, 18.0, 29.4, 37.3, 63.7, 71.9, 123.4, 133.5, 140.4, 147.9, 148.6. Chiral-GC analysis of acetyl derivate gave $t_R$ = 121.479 min for major enantiomer, $t_R$ = 124.10 min for minor enantiomer under the following gradient conditions: 80°C, 1°C/min up to 120°C, maintained for 40 min; then, 2°C/min up to 150°C, maintained for 30 min; 2°C/min up to 160°C and maintained for 15 min.

**Azacyclization of (*R*)-14.** To a solution of (*R*)-**14** (323 mg, 1 mmol) in 15 mL THF was added $Bu_4NF$ (1.5 mL, 1.0 *M* in THF) dropwise at 0°C. The mixture was stirred until TLC indicated that the starting material was consumed (about 1 h). The solvents were removed under reduced pressure and the residue was directly submitted to the cyclization at −10°C following the general procedure given above. Compound (*S*)-**15** was obtained as a colorless oil after purification by column chromatography on silica gel, eluted with $CH_2Cl_2$/MeOH (30:1); yield 76% (156 mg, three steps); 82% ee; $[\alpha]_D^{20} = -82$ (*c* 1.7, $CHCl_3$); Chiral-GC analysis gave $t_R$ = 110.67 min for major enantiomer, $t_R$ = 118.38 min for minor enantiomer under the following gradient condition: 80°C, 1°C/min up to 110°C, and maintained for 20 min; then 1°C/min up to 120°C, then, maintained for 50 min; then, 1°C/min up to 130°C, and maintained for 30 min.

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