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Expedient Five-Step Synthesis of SIB-1508Y from Natural Nicotine

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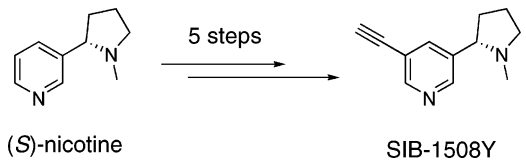

Altinicline (SIB-1508Y), an anti-Parkinson's agent, was prepared in five steps from natural nicotine in 32% overall yield via a regioselective substitution of the pyridine ring of (*S*)-nicotine.

SIB-1508Y (**1**), also known as Altinicline, was discovered and developed in the laboratories of SIBIA Neurosciences Inc.[1] Their investigations of the therapeutic properties of this novel agonist led to its selection for clinical development to treat Parkinson's disease. This remarkably simple nicotine derivative has undergone Phase II clinical trials.[2] In 1998, Bleicher and co-workers published the preparation of enantiomerically pure **1** in seven steps[3] (~16% yield) via a combination of enantioselective reduction of an imine and crystallization of enantiomerically enriched 5-bromonicotine as the dibenzoyl-L-tartaric acid salt. An asymmetric synthesis of **1** in 10 steps (18% overall) from 5-bromonicotinic acid was accomplished by Lebreton in 2001.[4] More recently, we reported a six-step synthesis (20% yield) involving a regioselective formylation at the C-5 position of the pyridine ring of a 1,4-dihydronicotine intermediate.[5] As part of a program directed at developing regioselective lithiation/substitution of (*S*)-nicotine, we devised and accomplished a second generation synthesis of **1** in five steps and 32% overall yield from natural nicotine.

Two routes were designed around our recently developed regioselective C-5 halogenation of 6-chloronicotine (Scheme 1).[6] Route 1 involves the reduction of the C-6 chlorine of **4**. The resulting C-5 halogenated nicotine **5** would then be submitted to a Sonogashira cross-coupling, which has been previously reported in the literature.[3] In route 2, the cross-coupling reaction would be carried out first, followed by dehalogenation and deprotection of the acetylene nicotine derivative **6**.

Our group recently reported the selective C-6 dehalogenation of (*S*)-5,6-dichloronicotine.[6] Unfortunately, (*S*)-5-chloronicotine (**5c**) is not the best intermediate for a cross-coupling reaction. A chlorine is less prone to oxidative addition than a bromine or an iodine, and the C-5 position of the pyridine is deactivated compared to C-2, C-4, or C-6. Attempts to reduce the C-6 chlorine of (*S*)-5-bromo-6-chloronicotine (**4b**) using our conditions for dechlorination of the corresponding dichloro derivative failed as an inseparable mixture of (*S*)-5-bromonicotine (**5b**) and (*S*)-6-chloronicotine (**3**) was isolated (Table 1). A regioselective reduction using sodium bis(2-methoxyethoxy)aluminum hydride (RedAl) was also attempted on (*S*)-6-chloro-5-iodonicotine (**4a**) but afforded **3** as the sole product.

Route 2 was investigated (Scheme 2) starting with a Sonogashira cross-coupling reaction on 6-chloro-5-iodonicotine (**4a**) with trimethylsilylacetylene using $Pd(PPh_3)_2Cl_2$ as the catalyst, copper iodide as a co-catalyst, and triethylamine as a solvent (72% yield). Addition of **6** to a Zn/AcOH mixture and heating at 70 °C afforded desilylated acetylene **7** in a 1:1 ratio with starting material **6**. Resubmission of **7** to a mixture and Zn/AcOH at 75 °C afforded the known vinylnicotine **8**[7] in 50% yield.

The need for a more resistant protecting group for the acetylene prompted us to use the bulkier triisopropylsilyl derivative. The same Sonogashira cross-coupling conditions used previously afforded compound **9** in near quantitative yield (Scheme 3). The reaction of **9** with a hot mixture of Zn/AcOH afforded the desired dehalogenated product **10** in 52% yield. Desilylation of the acetylene moiety using tetrabutylammonium fluoride (TBAF) (98%) completed the synthesis of SIB-1508Y (**1**). The spectral properties[1,3] and optical rotation of our (−)-**1** are in agreement with reported data ($[\alpha]^{30}_D$ −162° (*c* 0.77, EtOH); lit.[3] $[\alpha]_D$ −164° (*c* 5, EtOH)). To determine if this route could be used to prepare analogues of **1** and to see if an alkylacetylene at C-5 would survive the dissolving metal reduction step, dihalonicotine **4a** was converted to **11** in 66% yield, as shown in Scheme 4. Dehalogenation was achieved as before with Zn/AcOH in 45% yield to afford nicotine derivative **12**.

In conclusion, enantiopure SIB-1508Y (**1**) was prepared via a five-step sequence from (*S*)-nicotine in 32% overall yield. This practical synthesis was carried out with retention of configu-

(1) Cosford, N. D. P.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. *J. Med. Chem.* **1996**, *39*, 3235−3237.

(2) (a) Wang, D. X.; Booth, H.; Lerner-Marmarosh, N.; Osdene, T. S.; Abood, L. G. *Drug Dev. Res.* **1998**, *45*, 10. (b) Cosford, N. D. P.; Bleicher, L. S.; Vernier, J.-M.; Chavez-Noriega, L.; Rao, T. S.; Siegel, R. S.; Suto, C.; Washburn, M.; Llyod, G. K.; McDonald, I. A. *Pharm. Acta Helv.* **2000**, *74*, 125.

(3) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118.

(4) (a) Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121. (b) Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381.

(5) (a) Comins, D. L.; Smith, E. D. *Tetrahedron Lett.* **2006**, *47*, 1449−1451. (b) Smith, E. D.; Février, F. C.; Comins, D. L. *Org. Lett.* **2006**, *8*, 179−182. (c) Comins, D. L.; Despagnet, E. U.S. Patent Application No. 10/925, 516.

(6) (a) Février, F. C.; Smith, E. D.; Comins, D. L. *Org. Lett.* **2005**, *7*, 5457. (b) Comins, D. L.; Février, F. C.; Smith, E. D. U.S. Patent No. 7,-067,672. (c) Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, 3562. (d) Comins, D. L.; Février, F. C.; Ondachi, P. W. U.S. Provisional Application No. 60/787,116.

(7) Cosford, N. D. P.; Bleicher, L.; Vernier, J.-M.; Chavez-Noriega, L.; Rao, T. S.; Siegel, R. S.; Suto, C.; Washburn, M.; Lloyd, G. K.; McDonald, I. A. *Pharm. Acta Helv.* **2000**, *74*, 125.

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SCHEME 1. Retrosynthetic Plans for the Synthesis of SIB-1508Y

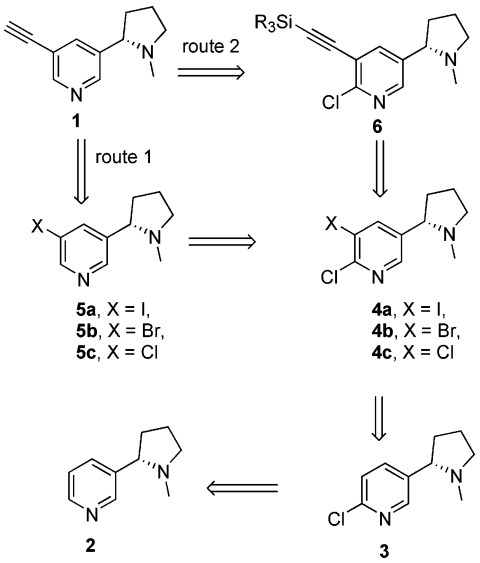
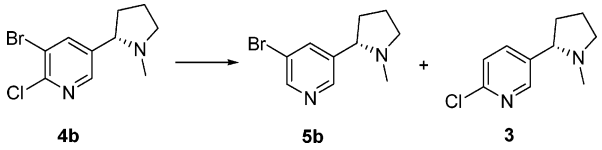
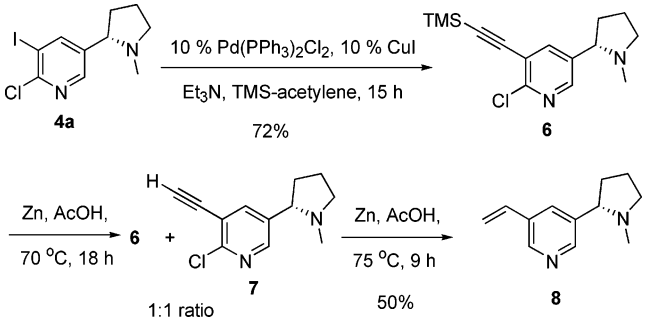


TABLE 1. Dechlorination of (*S*)-5-Bromo-6-chloronicotine (4b)



entry	conditions	results
1	4.0 equiv of Zn, 1.0 M HCl in AcOH, 60 °C, 2 h	2:1 ratio of **5b**:**3**
2	4.0 equiv of Zn, AcOH, room temperature, 10 h	1:1 ratio of **5b**:**3**

SCHEME 2. Attempts at C-2 Dechlorination of 6



ration on the pyrrolidine ring and constitutes the shortest and highest yielding synthesis of this potential anti-Parkinson's drug to date. Our strategy is amenable to the synthesis of various enantiopure C-5-substituted nicotine analogues that are currently being tested for potential pharmaceutical value.

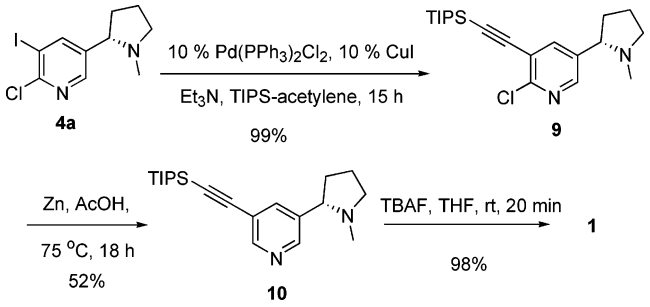
Experimental Section

(*S*)-6-Chloro-5-[(trimethylsilanyl)ethynyl]nicotine (6): A solution of 6-chloro-5-iodonicotine (**4a**) (188 mg, 0.58 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (42 mg, 0.06 mmol, 0.1 equiv), and copper iodide (15 mg, 0.06 mmol, 0.1 equiv) in triethylamine (5 mL) was degassed with argon for 20 min then treated dropwise with (trimethylsilyl)acetylene (95 μL, 0.64 mmol, 1.1 equiv). The mixture was stirred at room temperature for 18 h. The mixture was then diluted in ethyl ether and filtered through a pad of Celite. The filtrate was washed with a 10% solution of ammonium hydroxide until the persistent blue color disappeared. The organic layer was washed once with deionized water, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/hexanes) to afford 122 mg (72%) of **6** as a yellow oil: $[\alpha]^{22}_{D}$ −142 (*c* 0.8, CH_2Cl_2); IR (neat) 2964, 2780, 1396, 1354, 1249, 1077, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 2.8 Hz, 1H), 7.82 (d, J = 2.8 Hz, 1H), 3.21 (dt, J = 7.6, 2.4 Hz, 1H), 3.06 (t, J = 8.4 Hz, 1H), 2.31 (q, J = 8.4 Hz, 1H), 2.22−2.16 (m, 1H), 2.15 (s, 3H), 2.00−1.87 (m, 1H), 1.85−1.75 (m, 1H), 1.70−1.60 (m, 1H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.1, 141.0, 138.1, 120.3, 103.0, 99.7, 67.9, 57.2, 40.6, 35.5, 22.9, −0.08; HRMS calcd for $C_{15}H_{21}ClN_2Si$ ($[M + H]^+$) 293.1241, found 293.1255.

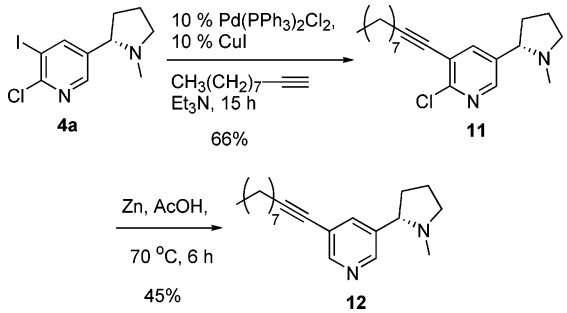
(*S*)-6-Chloro-5-ethynylnicotine (7): Zinc powder was added to a solution of (*S*)-6-chloro-5-[(trimethylsilyl)ethynyl]nicotine (**6**) (16 mg, 0.05 mmol) in acetic acid. After stirring at 70 °C for 18 h, the mixture was poured onto a saturated solution of sodium bicarbonate. Solid sodium carbonate was added to the mixture until basic pH was reached. The mixture was then extracted with ethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and the solvents removed by evaporation. The crude product was purified by radial PLC (silica gel, 1% TEA/hexanes) to afford 6 mg (50%) of **7** as a yellow oil: $[\alpha]^{22}_{D}$ −158 (*c* 1.75, CH_2Cl_2); IR (neat) 3294, 2968, 2780, 1397, 1351, 1164, 1072, 1043, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 3.45 (s, 1H), 3.22 (dt, J = 2.8, 8.5 Hz, 1H), 3.08 (t, J = 8.4 Hz, 1H), 2.30 (q, J = 9.0 Hz, 1H), 2.20 (m, 1H), 2.15 (s, 3H), 2.00−1.88 (m, 1H), 1.86−1.76 (m, 1H), 1.70−1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.7, 141.5, 138.3, 119.4, 84.7, 78.8, 67.9, 57.1, 40.6, 35.6, 22.9; HRMS calcd for $C_{12}H_{13}ClN_2$ ($[M + H]^+$) 221.0846, found 221.0838.

(*S*)-5-Vinylnicotine[7] (8): Zinc powder (15 mg) was added to a solution of (*S*)-6-chloro-5-(ethynyl)nicotine (**7**) (7.0 mg, 0.032 mmol) in acetic acid (2 mL). The mixture was stirred at 75 °C for 9 h. The mixture was poured into a saturated aqueous solution of sodium bicarbonate and then treated with solid sodium carbonate until a basic pH was reached. The aqueous layer was extracted with methylene chloride. The organic layers were combined, dried

SCHEME 3. Completion of the Synthesis



SCHEME 4. Synthesis of Nicotine Derivative 12



over potassium carbonate, filtered, and concentrated. The product was purified by radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 3 mg (50%) of **8** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 1.8 Hz, 1H), 7.74 (s, 1H), 6.75−6.62 (m, 1H), 5.82 (dd, J = 17.7, 0.5 Hz, 1H), 5.38 (dd, J = 11.0, 0.5 Hz, 1H), 3.23 (dt, J = 1.8, 8.7 Hz, 1H), 3.08 (t, J = 8.1 Hz, 1H), 2.31 (q, J = 8.0 Hz, 1H), 2.20 (s, 3H), 2.10−1.65 (m, 3H); HRMS calcd for $C_{12}H_{16}N_2$ ([M + H]$^+$) 189.1392, found 189.1396.

(*S*)-6-Chloro-5-[(triisopropylsilyl)ethynyl]nicotine (9): A solution of 6-chloro-5-iodonicotine (**4a**) (47.5 mg, 0.15 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (11 mg, 0.015 mmol, 0.1 equiv), and copper iodide (3 mg, 0.015 mmol, 0.1 equiv) in freshly distilled triethylamine (3 mL) was degassed with argon for 20 min, then treated dropwise with (triisopropylsilyl)acetylene (37 μL, 0.165 mmol, 1.1 equiv). The mixture was stirred at room temperature for 15 h. The mixture was diluted in ethyl ether and filtered through a pad of Celite. The filtrate was washed with a 10% solution of ammonium hydroxide until the persistent blue color disappeared. The organic layer was washed once with deionized water, dried over sodium sulfate, filtered, and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 135 mg (99%) of **9** as a yellow oil: $[\alpha]^{31}_D$ −109 (*c* 0.35, CH_2Cl_2); IR (neat) 2944, 2866, 2781, 1462, 1397, 1077, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 3.24 (dt, J = 2.4, 8.4 Hz, 1H), 3.08 (t, J = 8.1 Hz, 1H), 2.32 (q, J = 9.0 Hz, 1H), 2.25 (m, 1H), 2.18 (s, 3H), 2.02−1.90 (m, 1H), 1.90−1.76 (m, 1H), 1.76−1.62 (m, 1H), 1.15−1.13 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 148.0, 140.7, 137.9, 120.6, 101.4, 99.9, 68.1, 57.2, 40.7, 35.5, 22.9, 18.9, 11.5; HRMS calcd for $C_{21}H_{33}ClN_2Si$ ([M + H]$^+$) 377.2180, found 377.2198.

(*S*)- 5-[(Triisopropylsilyl)ethynyl]nicotine (10): Zinc powder (100 mg) was added to a solution of (*S*)-6-chloro-5-[(triisopropylsilyl)ethynyl]nicotine (**9**) (40 mg, 0.10 mmol) in acetic acid (3 mL). The mixture was stirred at 75 °C for 16 h. Since starting material was present by TLC, an extra 140 mg of zinc powder was added to the reaction mixture. The starting material spot was gone after 5 h. The mixture was poured into a saturated aqueous solution of sodium bicarbonate and then treated with solid sodium carbonate until a basic pH was reached. The aqueous layer was extracted with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 19 mg (52%) of **10** as a yellow oil: $[\alpha]^{29}_D$ −130 (*c* 0.5, CH_2Cl_2); IR (neat) 2944, 2865, 1780, 2158, 1500, 1414, 1153, 996, 883 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.75 (t, J = 1.8 Hz, 1H), 3.25 (dt, J = 1.5, 8.7 Hz, 1H), 3.07 (t, J = 8.1 Hz, 1H), 2.31 (q, J = 8.1 Hz, 1H), 2.24−2.14 (m, 1H), 2.17 (s, 3H), 2.04−1.68 (m, 3H), 1.15−1.11 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 148.7, 138.5, 137.8, 120.7, 103.8, 94.6, 68.8, 57.3, 40.7, 35.4, 22.9, 18.9, 11.5; HRMS calcd for $C_{21}H_{34}N_2Si$ ([M + H]$^+$) 343.2570, found 343.2560.

(*S*)-SIB-1508Y[1,3] (1): A solution of (*S*)-5-[(triisopropylsilyl)-ethynyl]nicotine (**10**) (32 mg, 0.093 mmol, 1.0 equiv) in THF (2 mL) was treated at room temperature with a 1.0 M solution of TBAF (112 μL, 0.112 mmol, 1.2 equiv). The mixture was stirred at room temperature for 20 min. The solvent was then removed under pressure and the crude residue purified by radial PLC (silica gel, 1% TEA/50% EtOAc/hexanes) to afford 17 mg (98%) of SIB-1508Y as a brown oil: $[\alpha]^{30}_D$ −162 (*c* 0.77, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 2.4 Hz, 1H), 7.80 (t, J = 2.4 Hz, 1H), 3.25 (t, J = 8.4 Hz, 1H), 3.20 (s, 1H), 3.09 (t, J = 8.4 Hz, 1H), 2.36−2.26 (m, 1H), 2.26−2.15 (m, 1H), 2.17 (s, 3H), 2.02−1.90 (m, 1H), 1.88−1.76 (m, 1H), 1.75−1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.2, 138.9, 138.2, 119.3, 80.8, 80.5, 68.6, 57.2, 40.6, 35.5, 22.9.

(*S*)-6-Chloro-5-(1-decynyl)nicotine (11): A solution of 6-chloro-5-iodonicotine (**4a**) (72 mg, 0.22 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (15 mg, 0.022 mmol, 0.1 equiv), and copper iodide (4 mg, 0.022 mmol, 0.1 equiv) in freshly distilled triethylamine (3 mL) was degassed with argon for 20 min, then treated dropwise with 1-decyne (45 μL, 0.24 mmol, 1.1 equiv) for 42 h. One milliliter of a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with methylene chloride (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/20% ethyl acetate/hexanes) to afford 48 mg (66%) of **11** as a colorless oil: $[\alpha]^{30}_D$ −108 (*c* 1.4, CH_2Cl_2); IR (neat) 2927, 2855, 2783, 1399, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 3.21 (dt, J = 1.8, 8.4 Hz, 1H), 3.05 (t, J = 8.4 Hz, 1H), 2.46 (t, J = 6.9 Hz, 2H), 2.29 (q, J = 8.4 Hz, 1H), 2.22−2.18 (m, 2H), 2.15 (s, 3H), 2.10−1.88 (m, 1H), 1.88−1.78 (m, 1H), 1.70−1.60 (m, 2H), 1.52−1.42 (m, 2H), 1.36−1.24 (m, 8H), 0.90−0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 147.3, 140.6, 138.0, 98.7, 94.5, 76.2, 68.0, 57.2, 40.6, 35.5, 32.1, 29.4, 29.3, 29.1, 28.6, 22.90, 22.88, 19.9, 14.4; HRMS calcd for $C_{20}H_{29}ClN_2$ ([M + H]$^+$) 333.2098, found 333.2108.

(*S*)-5-(1-Decynyl)nicotine (12): Zinc powder (120 mg) was added to a solution of (*S*)-6-chloro-5-(1-decynyl)nicotine (**11**) (28 mg, 0.075 mmol) in acetic acid (3 mL). The mixture was stirred at 70 °C for 10 h. The solvent was removed by evaporation, and the residue was dissolved in methylene chloride and filtered through a pad of Celite. The crude residue was purified by radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 10 mg (46%) of **12** as a colorless oil: $[\alpha]^{29}_D$ −83 (*c* 0.5, CH_2Cl_2); IR (neat) 2928, 2856, 2780, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 1.8 Hz, 1H), 7.70 (t, J = 1.8 Hz, 1H), 3.23 (dt, J = 1.8, 8.7 Hz, 1H), 3.05 (t, J = 8.1 Hz, 1H), 2.40 (t, J = 7.2 Hz, 2H), 2.28 (q, J = 9.6 Hz, 1H), 2.22−2.17 (m, 1H), 2.16 (s, 3H), 2.00−1.90 (m, 1H), 1.88−1.78 (m, 1H), 1.78−1.64 (m, 1H), 1.64−1.54 (m, 2H), 1.48−1.36 (m, 2H), 1.36−1.20 (m, 8H), 0.90−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 148.0, 138.5, 137.6, 121.2, 100.1, 94.1, 77.5, 68.8, 57.2, 40.7, 35.4, 32.1, 29.4, 29.3, 29.2, 28.8, 22.9, 19.7, 14.4; HRMS calcd for $C_{20}H_{30}N_2$ ([M + H]$^+$) 299.2487, found 299.2487.

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Supporting Information Available: General experimental methods and NMR spectra for **6**−**11**, **1**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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