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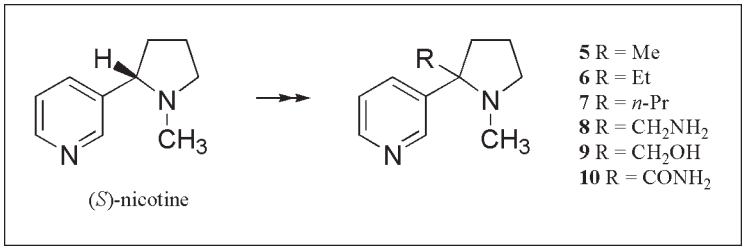

The chemical and pharmacological properties of 2′-substituted nicotines are poorly understood relative to other substituted nicotines. We developed a practical synthesis of the key intermediate (±)-2′-cyanonicotine using the Polonovski reaction. Alkylation of (±)-2′-cyanonicotine with Grignard reagents led to several 2′-alkylnicotines; (±)-2′-aminomethylnicotine, (±)-2′-hydroxymethylnicotine, and (±)-2′-carbamoylnicotine were also synthesized.

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INTRODUCTION

Deficits in brain nicotinic acetylcholine receptor (nAChR) expression have been reported in neurodegenerative and mental diseases [1,2]. Therefore, nicotinic acetylcholine agonists are being developed to alleviate these deficits [3,4]. Nicotine addiction is also being treated with nAChR agonists, including nicotine [5,6]. A variety of nicotine analogs have been synthesized and tested pharmacologically, largely by equilibrium radioligand binding assays. Synthetic methods for preparing racemic 1′, 3′-, 4′-, and 5′- substituted nicotine analogs have been reported. Also, 2′-methyl- and 2′-ethyl-nicotine were reported to displace the binding of radiolabeled methylcarbamylcholine to rat brain nAChRs that bind nicotine with high affinity [7]. However, their method of synthesis was not reported.

Methods for the synthesis of the 3′-, 4′-, and 5′-substituted nicotine derivatives are listed in Scheme 1. 4′-Methylnicotine and 5′-methylnicotine, 4′-cyanonicotine and 5′-cyanonicotine, 4′-carbamoylnicotine and 5′-carbamoylnicotine, and 4′-hydroxymethylnicotine were obtained by multistep transformations of (*S*)-cotinine; 5′-cyanonicotine was also prepared from (*S*)-nicotine [8–10]. *N*-3-Pyridylidenemethylamine with succinic anhydride gave 3′-methylnicotine and 3′-carboxynicotine [11]. The 3′-, 4′-, and 5′-carboxynicotines were transformed into the corresponding amides, aminomethylnicotines, and hydroxymethylnicotines [12–15]. Most of the reactions were nonstereospecific and generated mixture of diastereoisomers; however, some procedures were stereospecific and gave specific enantiomers.

In this work, we report new synthetic methods for obtaining the following 2′-nicotine derivatives: (±)-2′-cyanonicotine **3**, (±)-2′-methylnicotine **5**, (±)-2′-ethylnicotine **6**, (±)-2′-*n*-propylnicotine **7**, (±)-2′-aminomethylnicotine **8**, (±)-2′-hydroxymethylnicotine **9**, and (±)-2′-carbamoylnicotine **10**. The pharmacological properties of these racemic nicotines and their enantiomers, separated by chiral HPLC, will be reported elsewhere.

RESULTS AND DISCUSSION

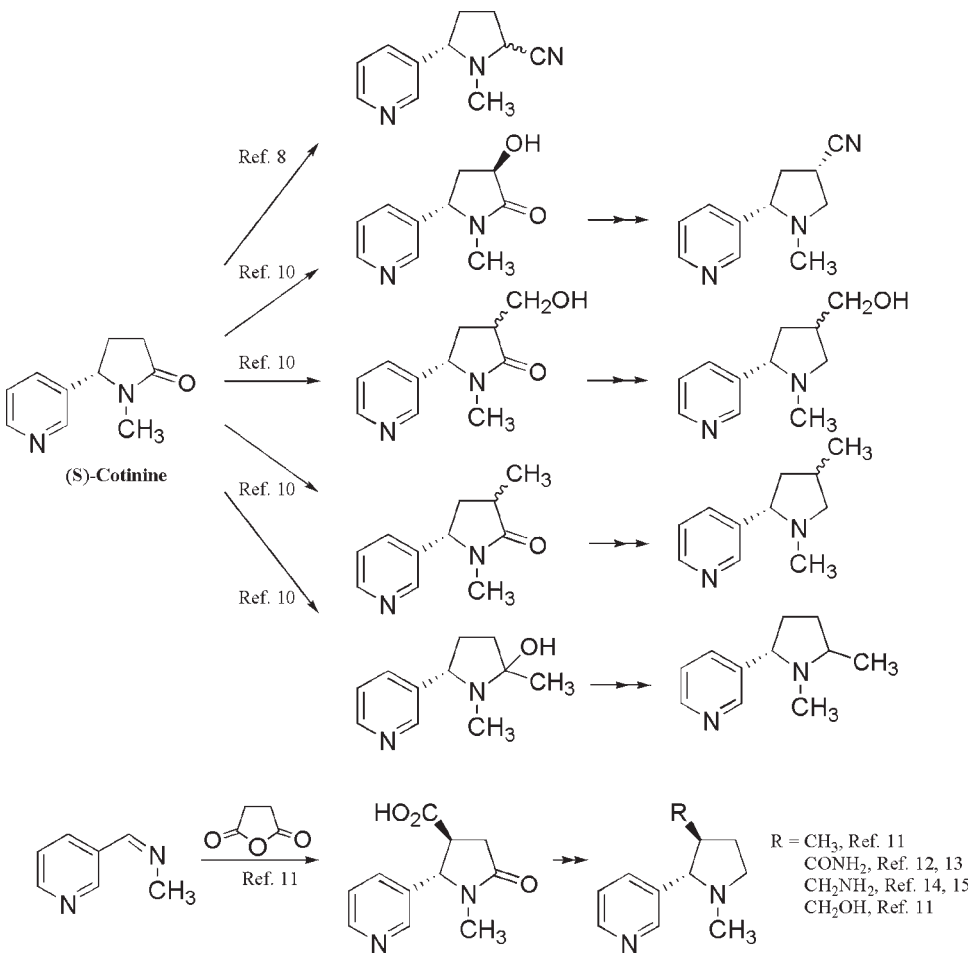
Initially, we examined the preparation of (±)-2′-methylnicotine by reacting 2-methyl-1-pyrroline with 3-pyridylmagnesium bromide (Scheme 2).

Reaction of an organometallic reagent with a cyclic imine group has been described in the literature. Methyllithium has been added to a 1-alkyl-3,4-dihydroisoquinoline to generate 1-alkyl-1-methyl-1,2,3,4-tetrahydroisoquinoline [16]. Allylmagnesium bromide has been reacted with 2-methyl-1-pyrroline, giving a 2-allyl-2-methyl-pyrrolidine [17].

In this work, 3-pyridylmagnesium bromide [18], 3-pyridylmagnesium chloride [19], and 3-pyridyllithium [18] were prepared from 3-bromopyridine. The addition of each of these organometallics to 2-methyl-1-pyrroline was attempted at −50°C or −78°C. In the case of the addition of pyridylmagnesium bromide or chloride, boron trifluoride-diethyl etherate was added before the addition of the Grignard reagent. However, 2′-methyl-2′-(pyridyl-3)-pyrrolidine was not obtained.

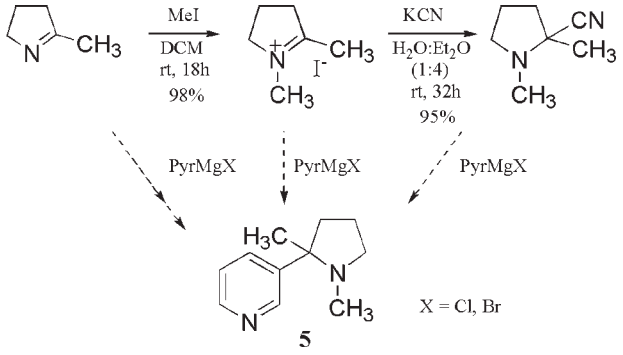
The imine bond can be activated by quaternization to allow the nucleophilic addition of a Grignard reagent.

Scheme 1



For instance, methyl iodide was added to 1-methyl-3,4-dihydroisoquinoline, generating the iminium salt 1,2-dimethyl-3,4-dihydroisoquinolinium iodide [20]. This iminium salt is more reactive than the imine. Methylmagnesium chloride reacted with the iminium, generating 1,1,2-trimethyl-1,2,3,4-tetrahydroisoquinoline. Another example is the reaction of methylmagnesium chloride with the iminium salt *N*-isopropylidene-4-chloropiperidinium chloride giving 1-*tert*-butyl-4-chloropiperidine [21].

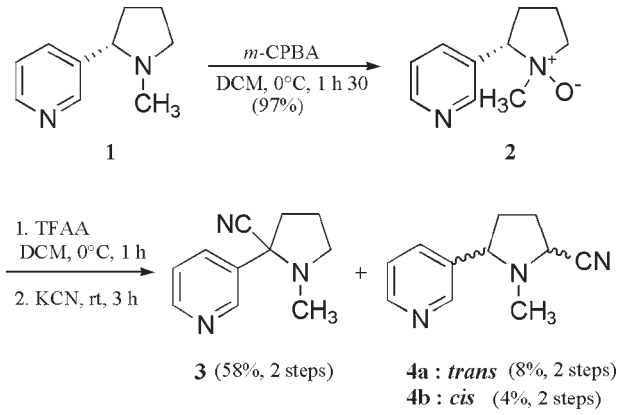
Scheme 2



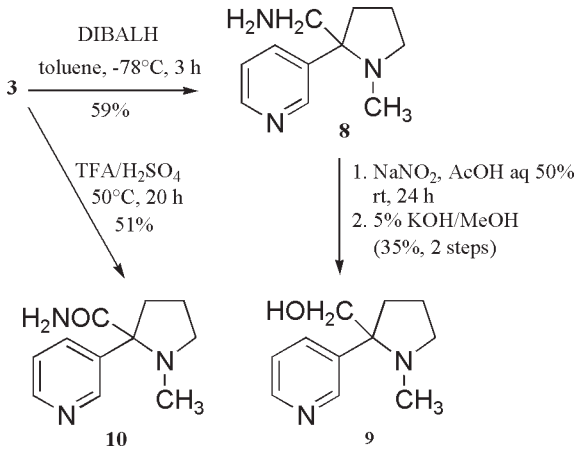
Expecting a higher reactivity for the iminium salt than for the imine, in this research 2-methyl-1-pyrroline was transformed with methyl iodide into the iminium 1,2-dimethyl-1-pyrrolinium iodide (Scheme 2). The condensation of this iminium with 2 or 5 equiv of 3-pyridylmagnesium bromide or chloride was attempted in THF or in the mixture of THF with diethyl ether, first at 0°C, then at room temperature and in some cases ending with heating to reflux. However, 2′-methylnicotine was never obtained.

In another approach, the iminium 1,2-dimethyl-1-pyrrolinium iodide in dichloromethane was reacted with an aqueous solution of potassium cyanide at rt (Scheme 2). The 1,2-dimethyl-2-cyanopyrrolidine was obtained in 95% yield. Its condensation with 5 equiv of 3-pyridylmagnesium bromide was attempted in THF at 0°C, followed by rt and in some cases by heating to reflux. However, the Bruylants reaction did not take place and 2′-methylnicotine was never obtained [22–24]. It only resulted in recovered starting material.

Scheme 3



Scheme 5



The probable reason that the condensations of 3-pyridylmagnesium chloride or bromide with 2-methyl-1-pyrroline, 1,2-dimethyl-1-pyrrolinium iodide or 1,2-dimethyl-2-cyano-pyrrolidine did not succeed is steric hindrance due both to the reagents and to the desired product, 2′-methylnicotine. Also, deprotonation of the methyl group of the 2-methyl-1-pyrroline and the iminium salt was probably competing with the desired addition, which would explain the recovery of the starting imine or iminium.

To circumvent these problems, we developed a practical synthesis of the key intermediate (±)-2′-cyanonicotine **3** using the Polonovski reaction [25,26]. The *N*-oxides **2** of nicotine were reacted with trifluoroacetic anhydride; the iminium intermediate then reacted with the cyano ion (Scheme 3). In practice, (*S*)-nicotine **1** was transformed by *m*-CPBA into the diastereomeric mixture of *N*-oxides **2** with a yield of 97%. Trifluoroacetic anhydride transformed in dichloromethane at 0°C the *N*-oxides **2** to $\Delta^{1',2'}$ iminium trifluoroacetate. Thereafter, addition of solid potassium cyanide to the reaction mixture yielded (±)-2′-cyanonicotine **3** (58% from **2**). Small amounts of the 5′-cyanonicotine diastereomers **4** (12%) were also formed; these were separated by normal phase (silica gel) HPLC into the trans and cis isomers.

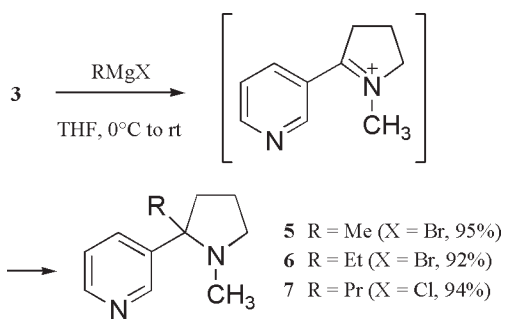
The cyano group in amino nitrile **3** is in an α-position relative to the tertiary amine. Replacement of this cyano group with an alkyl substituent was accomplished by a Bruylants reaction with an organomagnesium compound [22–24]. Displacement of the cyano group leads to an intermediate, stabilized iminium carbocation, which reacts further with the nucleophile alkyl organomagnesium (Scheme 4). The reaction of 5 equivalents of methyl-, ethyl-magnesium bromide, or *n*-propylmagnesium chloride with amino nitrile **3** in THF at −10°C generated (±)-2′-methyl- (**5**), (±)-2′-ethyl- (**6**), and (±)-2′-*n*-propylnicotine (**7**) with yields of 95%, 92%, and 94%, respectively.

Transformations of the cyano group of the amino nitrile **3** gave several (±)-2′-derivatives of nicotine (Scheme 5). DIBALH in toluene at −78°C reduced the amino nitrile **3**, providing (±)-2′-aminomethylnicotine **8** in 59% yield.

To obtain (±)-2′-hydroxymethylnicotine **9**, (±)-2′-aminomethylnicotine **8** was first treated with sodium nitrite in aqueous acetic acid; then, the reaction mixture was made alkaline and extracted with dichloromethane. After rotary evaporation, the resulting organic extract was treated with potassium hydroxide in methanol, giving **9** in 35% yield.

Hydrolysis of (±)-2′-cyanonicotine **3** in a mixture of trifluoroacetic acid and sulfuric acid (4:1) gave (±)-2′-carbamoylnicotine **10** in 51% yield.

Scheme 4



EXPERIMENTAL

General. ESI-HRMS were performed on a Agilent 6210 TOF mass spectrometer. GC/CI analyses were performed on a Thermo Trace GC DSQ—Single Quadrupole. The ^{1}H-NMR

spectra were recorded in $CDCl_3$ at 300 MHz with a Varian Mercury 300 and are reported in ppm from internal TMS on the δ scale. The ^{13}C-NMR spectra were recorded in $CDCl_3$ at 75.4 MHz with a Varian Mercury 300 instrument. Flash chromatographies were performed on silica gel (Fisher, Silica Gel Sorbent, 230–400 Mesh) or on alumina (Aluminoxid 90, Activity II-III, EMD) columns.

Nicotine-*N*-oxides (2). To a solution of (*S*)-nicotine (4 mL, 25.04 mmol) in CH_2Cl_2 (120 mL) at 0°C was added a 70% aqueous *m*-CPBA (6.172 g, 25.04 mmol). After stirring 1 h 30 at 0°C under argon, the reaction mixture was concentrated *in vacuo* to a volume of 10 mL and then poured over alumina and chromatographed using CH_2Cl_2/CH_3OH (98:2 to 95:5) as eluent to afford a diasteromeric mixture of *trans*- and *cis*-nicotine-*N*-oxide **2** (4.354 g, 24.4 mmol, 97%).

(±)-2′-Cyanonicotine (3). Trifluoroacetic anhydride (3.42 mL, 24.4 mmol) was slowly added under argon atmosphere to a solution of *N*-oxides **2** (2.177 g, 12.2 mmol) in dry methylene chloride (30 mL) cooled to 0°C. The resulting mixture was stirred at 0°C for 1 h and at room temperature for 15 min. Following this period, excess solid potassium cyanide (1.586 g, 24.4 mmol) was added to the reaction mixture and vigorous stirring was continued for 3 h. The reaction mixture was then basified with saturated aqueous sodium carbonate and extracted with methylene chloride (3× 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. After column chromatography of the crude product on silica gel ($CH_2Cl_2/CH_3OH/NH_4OH$ concentrated 95:5:0.1), pure (±)-2′-cyanonicotine **3** was obtained as a colorless oil (1.325 g, 7.08 mmol, 58%) as well as *cis*- and *trans*-5′-cyanonicotine **4** (0.274 g, 1.46 mmol, 12%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) **3**: δ 8.86 (d, 1 H, J = 2.4 Hz, ArH), 8.61 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 7.90 (dt, 1 H, J = 8.1, 2.4 Hz, ArH), 7.34 (ddd, 1 H, J = 8.1, 5.1, 0.9 Hz, ArH), 3.37 (m, 1 H), 2.71 (m, 1 H), 2.57 (m, 1 H), 2.25 (s, 3 H, NCH_3), 2.16–2.02 (m, 3 H). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 150.0 (CH), 148.0 (CH), 134.1 (CH), 133.9 (C), 123.5 (CH), 116.8 (CN), 69.7 (C), 53.8 (CH_2), 43.1 (CH_2), 36.2 (CH_3), 21.1 (CH_2). ESI-HRMS: m/z = 188.1175 (calculated for $[M + H]^+$: 188.1182).

Subsequently, the mixture of *cis*- and *trans*-5′-cyanonicotine **4** was separated by HPLC with a Beckman Coulter Ultrasphere silica column (10× 250 mm), using a 2% B to 20% B 25 min gradient (solvent A: Hexane-DEA [99.5, 0.5 v/v]; solvent B: EtOH-DEA [99.5, 0.5]), preceded by 10 min elution at 2% B. The flow rate was 2.7 mL/min and column temperature was 24°C. The eluate was monitored at 260 nm. In this way, *trans*-5′-cyanonicotine (**4a**, 182 mg, 8%) eluting at 17.8 min and *cis*-5′-cyanonicotine (**4b**, 91 mg, 4%) eluting at 25.7 min were isolated.

***trans*-5′-Cyanonicotine (4a).** ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.57 (d, 1 H, J = 2.1 Hz, ArH), 8.54 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 7.65 (dt, 1 H, J = 8.1, 1.8 Hz, ArH), 7.29 (ddd, 1 H, J = 8.1, 5.1, 0.9 Hz, ArH), 4.16 (d, 1 H, J = 8.1 Hz), 3.59 (t, 1 H, J = 7.2 Hz), 2.45 (m, 2 H), 2.30 (s, 3 H, NCH_3), 2.19 (m, 1 H), 1.80 (m, 1 H). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 149.6 (CH), 149.5 (CH), 135.0 (CH), 134.1 (C), 123.9 (CH), 117.5 (CN), 65.4 (CH), 56.9 (CH), 36.8 (CH_3), 33.4 (CH_2), 28.7 (CH_2). ESI-HRMS: m/z = 188.1176 (calculated for $[M + H]^+$: 188.1182).

***cis*-5′-Cyanonicotine (4b).** ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.55 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 8.53 (d, 1 H, J = 2.1 Hz, ArH), 7.74 (dt, 1 H, J = 7.8, 2.1 Hz, ArH), 7.30 (ddd, 1 H, J = 8.1, 5.1, 0.9 Hz, ArH), 3.39 (t, 2 H, J = 7.1 Hz), 2.33 (s, 3 H, NCH_3), 2.29 (m, 3 H), 1.88 (m, 1 H). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 149.6 (CH), 149.5 (CH), 138.5 (C), 134.9 (CH), 124.1 (CH), 117.0 (CN), 68.1 (CH), 55.9 (CH), 39.0 (CH_3), 34.2 (CH_2), 28.7 (CH_2). ESI-HRMS: m/z = 188.1176 (calculated for $[M + H]^+$: 188.1182).

(±)-2′-Methylnicotine (5). A solution of methylmagnesium bromide (3*M* solution in ether, 445 μL, 1.335 mmol) was added dropwise to a solution of 2′-cyanonicotine **3** (50 mg, 0.27 mmol) in THF (2 mL) cooled to −10°C. The mixture was stirred at −10°C for 1 h followed by 1 h at room temperature and then hydrolyzed by a saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted with methylene chloride. The organic extracts were dried and evaporated to give an oil, which was purified by flash chromatography on silica gel ($CH_2Cl_2/CH_3OH/NH_4OH$ concentrated 95:5:0.1) to give (±)-2′-methylnicotine **5** as a clear oil (45.2 mg, 0.26 mmol, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 1 H, J = 1.5 Hz, ArH), 8.45 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 7.81 (dt, 1 H, J = 8.1, 1.8 Hz, ArH), 7.23 (ddd, 1 H, J = 8.1, 5.1, 0.6 Hz, ArH), 3.11 (m, 1 H), 2.70 (m, 1 H), 2.12 (s, 3H, NCH_3), 1.90 (m, 4H) 1.34 (s, 3H, CH_3). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 148.6 (CH), 147.7 (CH), 143.0 (C), 134.2 (CH), 123.1 (CH), 64.1 (C), 53.4 (CH_2), 43.3 (CH_2), 34.9 (CH_3), 22.0 (CH_2), 16.9 (CH_3). ESI-HRMS: m/z = 177.1381 (calculated for $[M + H]^+$: 177.1386); 353.2686 (calculated for $[2M + H]^+$: 353.2700).

(±)-2′-Ethylnicotine (6). A solution of ethylmagnesium bromide (1*M* solution in THF, 1.23 mL, 1.23 mmol) was added dropwise to a solution of 2′-cyanonicotine **3** (46 mg, 0.25 mmol) in THF (1 mL) cooled to −10°C. The mixture was stirred at −10°C for 1 h then at room temperature for 16 h. After addition of a saturated aqueous solution of NH_4Cl (3 mL), the mixture was extracted with methylene chloride. The organic extracts were dried and evaporated to give an oil, which was purified by flash chromatography on silica gel ($CH_2Cl_2/CH_3OH/NH_4OH$ concentrated 95:5:0.1) to give (±)-2′-ethylnicotine **6** as a clear oil (44 mg, 0.23 mmol, 92%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1 H, J = 2.7 Hz, ArH), 8.47 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 7.59 (dt, 1 H, J = 8.1, 2.1 Hz, ArH), 7.27 (ddd, 1 H, J = 7.8, 5.1, 0.6 Hz, ArH), 2.92 (m, 1 H), 2.48 (m, 1 H), 2.27 (m, 2 H), 2.10 (s, 3 H, NCH_3), 1.93 (m, 4 H), 1.60 (m, 1 H), 0.83 (t, 3 H, J = 7.2 Hz). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 149.3 (CH), 147.8 (CH), 136.6 (C), 135.3 (CH), 122.9 (CH), 67.6 (C), 53.9 (CH_2), 36.7 (CH_2), 35.1 (CH_3), 29.1 (CH_2), 22.0 (CH_2), 10.0 (CH_3). ESI-HRMS: m/z = 191.1548 (calculated for $[M + H]^+$: 191.1543); 381.3008 (calculated for $[2M + H]^+$: 381.3013).

(±)-2′-*n*-Propylnicotine (7). A solution of *n*-propylmagnesium chloride (2*M* solution in ether, 334 μL, 0.67 mmol) was added dropwise to a solution of 2′-cyanonicotine **3** (25 mg, 0.13 mmol) in THF (1 mL) cooled to −10°C. The mixture was stirred at −10°C for 1 h then at room temperature for 16 h. After addition of a saturated aqueous solution of NH_4Cl (3 mL), the mixture was extracted with methylene chloride. The organic extracts were dried and evaporated to give an oil, which was purified by flash chromatography on silica gel ($CH_2Cl_2/CH_3OH/NH_4OH$ concentrated 95:5:0.1) to give (±)-

2′-*n*-propylnicotine **7** as a clear oil (25 mg, 0.12 mmol, 94%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.54 (d, 1 H, J = 2.1 Hz, ArH), 8.46 (dd, 1 H, J = 1.5, 4.8 Hz, ArH), 7.57 (dt, 1 H, J = 8.1, 1.8 Hz, ArH), 7.26 (ddd, 1 H, J = 8.1, 4.8, 0.6 Hz, ArH), 2.89 (m, 1 H), 2.47 (m, 1 H), 2.21 (m, 2 H), 2.10 (s, 3 H, NCH_3), 1.99 (m, 3 H), 1.52 (td, 1 H, J = 5.1, 12.0 Hz), 1.20 (m, 2 H), 0.93 (t, 3 H, J = 7.2 Hz). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 149.3 (CH), 147.8 (CH), 137.0 (C), 135.2 (CH), 122.9 (CH), 67.1 (C), 53.7 (CH_2), 39.1 (CH_2), 37.3 (CH_2), 35.2 (CH_3), 22.2 (CH_2), 19.0 (CH_2), 15.1 (CH_3). ESI-HRMS: m/z = 205.1695 (calculated for $[M + H]^+$: 205.1699).

(±)-2′-Aminomethylnicotine (8). A solution of 2′-cyanonicotine **3** (324 mg, 1.73 mmol) in toluene (12.4 mL) was treated at −78°C with DIBALH (8.65 mL of a 1.0*M* solution in hexane, 8.65 mmol). After the reaction mixture had been stirred for an additional 3 h at −78°C, it was quenched by slow addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH/NH_4OH concentrated 95:5:0.1) to give (±)-2′-aminomethylnicotine **8** as a clear oil (195.1 mg, 1.02 mmol, 59%) as well as nicotine (11 mg, 0.07 mmol, 4%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1 H, J = 2.7 Hz, ArH), 8.48 (dd, 1 H, J = 1.8, 4.8 Hz, ArH), 7.64 (dt, 1 H, J = 8.1, 1.8 Hz, ArH), 7.28 (ddd, 1 H, J = 8.1, 4.8, 0.9 Hz, ArH), 3.21 (d, 1 H, J = 12.9 Hz), 3.03 (d, 1 H, J = 12.9 Hz), 3.00 (m, 1 H), 2.74 (m, 1 H), 2.18 (m, 2 H), 2.17 (s, 3 H, NCH_3), 1.93 (m, 2 H), 1.32 (bs, 2 H, NH_2). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 149.1 (CH), 148.0 (CH), 138.3 (C), 135.0 (CH), 123.2 (CH), 68.0 (C), 54.8 (CH_2), 46.5 (CH_2), 36.5 (CH_2), 35.5 (CH_3), 22.5 (CH_2). ESI-HRMS: m/z = 192.1490 (calculated for $[M + H]^+$: 192.1495).

(±)-2′-Hydroxymethylnicotine (9). A solution of **8** (51 mg, 0.27 mmol) in 50% aqueous acetic acid (2 mL) was treated with $NaNO_2$ (37 mg, 0.54 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then basified with 40% aqueous NaOH and extracted with methylene chloride. The organic extract was treated with a solution of 5% KOH/MeOH (5 mL) for 4 h. The reaction mixture was washed with water, and the organic layer was concentrated *in vacuo*. Chromatographic purification (SiO_2, elution with CH_2Cl_2/CH_3OH/NH_4OH concentrated 95:5:0.1) of the residue afforded (±)-2′-hydroxymethylnicotine **9** (18 mg, 0.095 mmol, 35%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1 H, J = 2.4 Hz, ArH), 8.49 (dd, 1 H, J = 1.5, 4.5 Hz, ArH), 7.59 (dt, 1 H, J = 8.4, 1.8 Hz, ArH), 7.28 (ddd, 1 H, J = 8.1, 4.8, 0.9 Hz, ArH), 3.97 (d, 1 H, J = 10.5 Hz), 3.79 (d, 1 H, J = 10.5 Hz), 3.16 (m, 1 H), 2.88 (m, 1 H), 2.39 (m, 1 H), 2.14 (s, 3 H, NCH_3), 1.95 (m, 3 H). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 148.7 (CH), 148.3 (CH), 138.4 (C), 134.7 (CH), 123.3 (CH), 67.6 (C), 63.0 (CH_2), 55.3 (CH_2), 36.7 (CH_2), 35.2 (CH_3), 22.7 (CH_2). ESI-HRMS: m/z = 193.1330 (calculated for $[M + H]^+$: 193.1335); 385.2585 (calculated for $[2M + H]^+$: 385.2598).

(±)-2′-Carbamoylnicotine (10). A solution of 2′-cyanonicotine **3** (89 mg, 0.48 mmol) in 4 mL of a solution TFA/concentrated H_2SO_4 (4:1) was stirred at 50°C for 20 h. After cooled at 0°C, the mixture was basified by addition of NH_4OH concentrated and extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH/NH_4OH concentrated 95:5:0.1) to give (±)-2′-carbamoylnicotine **10** as a yellow solid (50 mg, 0.24 mmol, 51%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.54 (d, 1 H, J = 2.1 Hz, ArH), 8.51 (dd, 1 H, J = 1.2, 4.8 Hz, ArH), 7.59 (dt, 1 H, J = 7.8, 2.1 Hz, ArH), 7.48 (bs, 1H), 7.29 (ddd, 1 H, J = 8.1, 4.8, 0.9 Hz, ArH), 6.58 (bs, 1H), 3.11 (m, 1 H), 2.56 (m, 3 H), 2.03 (m, 2 H), 1.99 (s, 3 H, NCH_3). ^{13}C-NMR (75.3 MHz, $CDCl_3$): δ 177.8 (C), 149.8 (CH), 148.6 (CH), 136.4 (CH), 133.7 (C), 122.8 (CH), 73.7 (C), 54.9 (CH_2), 38.7 (CH_2), 37.4 (CH_3), 23.0 (CH_2). ESI-HRMS: m/z = 206.1283 (calculated for $[M + H]^+$: 206.1288); 411.2495 (calculated for $[2M + H]^+$: 411.2503).

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