Synthesis and Pharmacological Characterization of Nicotinic Acetylcholine Receptor Properties of (+)- and (−)-Pyrido-[3,4-*b*]homotropanes

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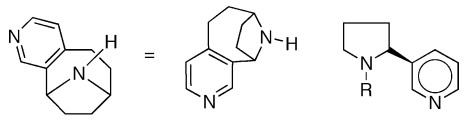
(±)-Pyrido[3,4-*b*]homotropane [(±)-**1**] is a conformationally rigid analogue of nicotine (**2**) or nornicotine (**3**) that showed high affinity for nicotinic acetylcholine receptors. Even though the synthesis and potent activity of this highly interesting compound was originally reported in 1986 (Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. C.; Abood, L. G. Synthesis of the first highly potent bridged nicotinoid. 9-Azabicylo[4.2.l]nona[2,3-*c*]pyridine (pyrido[3,4-*b*]homotropane). *J. Am. Chem. Soc.* **1986**, *108*, 7864−7865), the individual optical isomers have not been prepared and studied. In this study, we report the synthesis of (+)- and (−)-**1** and show that (+)-**1** has $K_i = 1.29$ nM at the α4β2* nAChR and has over 260 times higher affinity than (−)-**1**. Single-crystal X-ray analysis of an intermediate used to prepare the isomers established the absolute stereochemistry as (1*S*,6*S*)-(+)-**1** and (1*R*,6*R*)-(−)-**1**. Surprisingly, both isomers failed to produce antinociception in the mouse tail-flick and hot-plate assays, engender nicotine-like responding in rat drug discrimination, or alter current amplitude in α4β2- and α3β4-containing cells. However, (−)-**1** antagonized nicotine-induced antinociception with an ED_{50} of 0.07 μg/kg in the tail-flick assay. The reason for this unusual pharmacology is unknown, but it is possible that (−)-**1** is acting at a non-epibatidine-sensitive receptor subtype to antagonize nicotine's effects in the tail-flick assay.

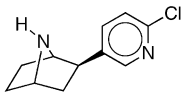
There is a continuing interest concerning the pharmacophores for the α4β2 and α7 nicotinic acetylcholine receptors (nAChRs), the two major subtypes present in the brain. Compounds that interact with these receptors are of interest because of their potential therapeutic utility in the treatment of central nervous system (CNS) disorders including Parkinson's disease, Alzheimer's disease, schizophrenia, attention-deficit hyperactivity disorder (ADHD), Tourette's syndrome, smoking cessation, epilepsy, and depression.[1,2] In the late 1980s, Kanne and Abood reported that racemic pyrido-[3,4-*b*]homotropane (**1**, PHT), a conformationally rigid analogue of nicotine (**2**), or nornicotine (**3**) possessed high nAChR activity.[3,4] Since this initial report the nAChR activity of a number of conformationally restricted analogues of nicotine (**2**) or nornicotine (**3**) have been reported. With the exception of natural product epibatidine (**4**) and some of its analogues, none of these compounds has provided highly useful information about the active pharmacophore of **1**. In this study we report the synthesis and pharmacological properties of (+)- and (−)-**1**. The (+)-**1** isomer shows 260 times higher affinity than the (−)-**1** in binding to the α4β2 nAChR. Surprisingly, both isomers failed to produce antinociception in the mouse tail-flick and hot-plate assays, engender nicotine-like responding in rat drug discrimination, or alter current amplitude in α4β2- and α3β4-containing cells. However, (−)-1 antagonized nicotine-induced antinociception with particularly high potency in the tail-flick test. It failed to antagonize the other pharmacological effects of nicotine.

The synthesis of (+)- and (−)-**1** was carried out using a procedure similar to that reported by Kanne and Abood.[3]



(±)-**1**
(+)-**1**
(−)-**1**

2, R = CH_3
3, R = H



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Importantly, (*R*)-(+)-methylbenzylamine was used in place of benzylamine to generate diastereoisomers that could be separated and then converted to (+)- and (−)-**1** (Scheme 1). Heating a solution of 9-oxabicyclo[6.1.0]non-4-ene (**5**) and (*R*)-(+)-methylbenzylamine in methanol at 120 °C for 24 h in a sealed tube gave *trans*-8-[(*R*)-phenylethylamino]cyclooct-4-enol as a diastereoisomeric mixture of **6** and **7**, which were separated by chromatography. Compounds **6** and **7** had optical rotation of $[\alpha]^{25}_D$ +105 and −20, respectively. A single-crystal X-ray analysis of **6** showed that it was (1*S*,8*S*)-*trans*-8-[(*R*)-phenylethylamine]cyclooct-4-enol (Figure 1). Aminomercuration of **6** and **7** with 1 equiv of mercuric acetate in aqueous tetrahydrofuran at 0 °C followed by demercuration with sodium borohydride yielded (1*S*,2*S*,6*S*)- and (1*R*,2*R*,6*R*)-9-[(*R*)-phenylethyl]-9-azabicyclo[4.2.1]nonan-2-ol (**8a** and **8b**, respectively) in 61% and 60% yield, respectively, along with small amounts of **9a** or **9b**. Swern (Moffott−Swern) oxidation of **8a** or **8b** using oxalyl chloride and dimethyl sulfoxide in methylene chloride gave (1*S*,6*S*)- and (1*R*,6*R*)-[(*R*)-phenylethyl]ketones (**10a** and **10b**, respectively) in 85% yield each. Allylation of **10a** or **10b** with allyl bromide via the boron enolate formed with potassium bis(trimethylsilyl)amide and triethylboron in tetrahydrofuran

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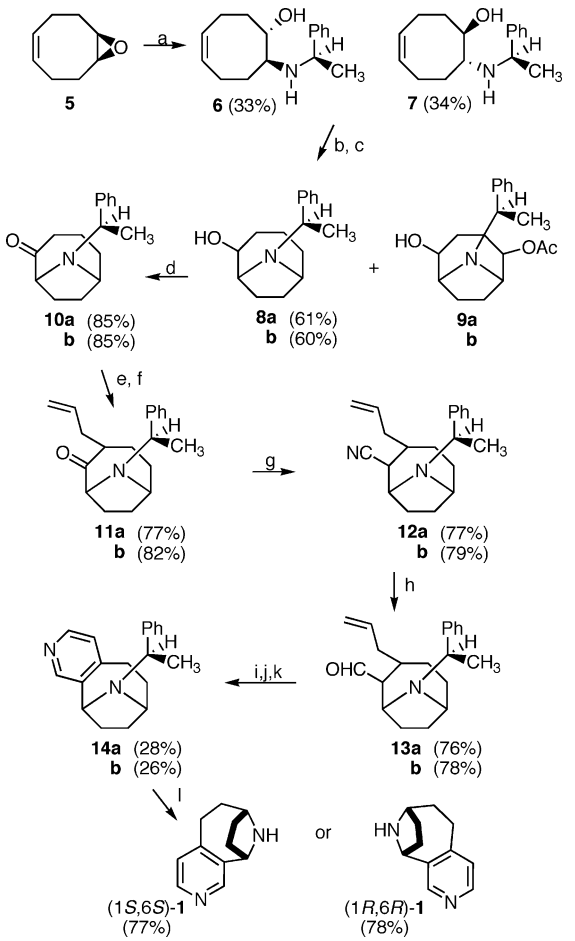
Scheme 1[a]



[a] Reagents: (a) (*R*)-$C_6H_5CH(CH_3)NH_2$, CH_3OH, sealed tube 120 °C; (b) $Hg(OAc)_2$, THF/H_2O, 0 °C, 5 h; (c) $NaBH_4$, 3 M NaOH; (d) $(COCl)_2$, $(CH_3)_2SO$, CH_2Cl_2, −78 to 25 °C; (e) $KN[Si(CH_3)_3]_2$, Et_3B, THF, −78 °C; (f) $CH_2{=}CHCH_2Br$, −78 to 25 °C, 24 h; (g) TosMic, *t*-BuOK, DME/CH_3OH; (h) DIBAl-H, CH_2Cl2, 0−25 °C; (i) O_3, CH_2Cl_2, CF_3CO_2H (1 equiv), −78 °C; (j) $(CH_3)_2S$, −78 to 25 °C; (k) $H_2NOH{\cdot}HCl$, AcOH, 105 °C, 40 min; (l) HCO_2NH_4, CH_3OH, 10% Pd/C.

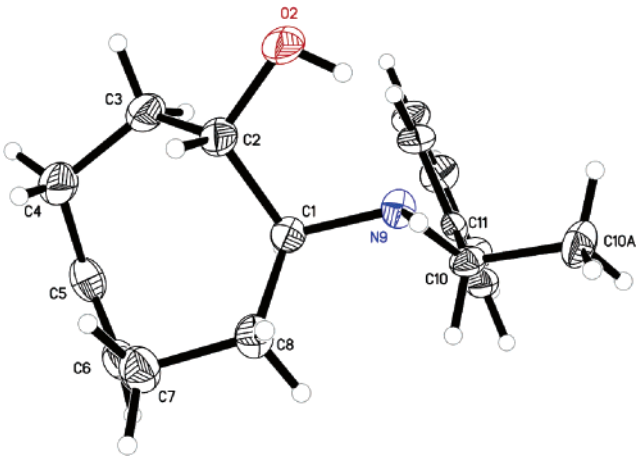


Figure 1. Structure of compound **6** showing labeling of the non-hydrogen atoms. Displacement ellipsoids are at the 50% probability level.

afforded (1*S*,6*S*)- or (1*R*,6*R*)-3-allyl-[(*R*)-phenyethyl]ketones (**11a** or **11b**, respectively) in 77% and 82% yield, respectively. Conversion of **11a** and **11b** to the nitriles **12a** or **12b** in 77% and 79% yield, respectively, was accomplished using tosylmethyl isocyanide (TosMic) and potassium *tert*-butoxide in a mixture of ethylene glycol dimethyl ether and methanol. Diisobutylaluminum hydride reduction of **12a** or **12b** in methylene chloride afforded the (1*S*,6*S*)- and (1*R*,6*R*)-aldehydes **13a** and **13b** in 76% and 78% yield, respectively. Ozonolysis of **13a** or **13b** in methylene chloride containing 1 equiv of trifluoroacetic acid followed by a dimethyl sulfide workup furnished a dialdehyde that was not isolated but treated with hydroxylamine hydrochloride in acetic acid at 105 °C to yield (1*S*,6*S*)- and (1*R*,6*R*)-9-[(*R*)-phenylethyl]pyrido[3,4-*b*]homotropanes **14a** and **14b** in 28% and 26% overall yield, respectively. Subjection of **14a** and **14b** to transfer hydrogenation using ammonium formate and 10% palladium on carbon catalyst in methanol yielded the desired (1*S*,6*S*)-**1** and (1*R*,6*R*)-**1** in 77% and 78% yield, respectively. The hydrochloride salts of (−)-**1** and (+)-**1** possessed optical rotations of −48.3° and +48.5°, respectively.

A racemic sample of pyrido[3,4-*b*]homotropane was synthesized using a procedure similar to that reported by Kanne and Abood.[3] The proton and carbon-13 NMR spectra of (±)-, (+)-, and (−)-**1** as well as those of their hydrochloride salts were identical.

Biology

The K_i values for the inhibition of [^{3}H]epibatidine (**4**) binding at the α4β2* nAChR in male rat cerebral cortex for the (+)- and (−)-pyrido-[3,4-*b*]homotropanes (+)- and (−)-**1**, for nicotine (**2**), and (+)- and (−)-epibatidine are listed in Table 1. The binding assays were conducted and the K_i values calculated as previously described.[5] Compounds (+)- and (−)-**1** were also evaluated for percent inhibition at 10 μM of binding to α7 nAChR using [^{125}I] iodoMLA and methods previously reported.[5] Both compounds showed less than 50% inhibition at 10 μM.

The above compounds were evaluated in two acute pain models, the tail-flick and the hot-plate tests, and the results are listed in the Table 1.[6] In the tail-flick method of D'Amour and Smith,[7] the tail is exposed to a heat lamp and the amount of time taken for the animal to move (flick) its tail away from the heat is recorded. A control response (2−4 s) was determined for each mouse before treatment, and a test latency was determined after drug administration. The method used for the hot-plate test is a modification of those described by Eddy and Leimbach[8] and Atwell and Jacobson.[9] Mice were placed into a 10-cm wide glass cylinder on a hot plate (Thermojust apparatus) maintained at 55.0 °C. Two control latencies at least 10 min apart were determined for each mouse. The normal latency (reaction time) was 8−12 s. The reaction time was scored when the animal jumped or licked its paws. The mice were tested 5 min after sc injections of nicotinic ligands for the dose−response evaluation. Antinociceptive response was calculated as percentage of maximum possible effect (% MPE, where %MPE = [(test − control)/(maximum latency − control) × 100]).

To measure the effect of analogues on spontaneous activity, mice were placed into individual Omnitech photocell activity cages (28 cm × 16.5 cm) 5 min after sc administration of either 0.9% saline or epibatidine analogues. Interruptions of the photocell beams (two banks of eight cells each) were then recorded for the next 10 min. Data were expressed as number of photocell interruptions. Rectal temperature was measured by a thermistor probe (inserted 24 mm) and digital thermometer (Yellow Springs Instrument Co., Yellow Springs, OH). Readings were taken just before and at different times after the sc injection of either saline or epibatidine analogues. The difference in rectal temperature before and after treatment was calculated for each mouse. The ambient temperature of the laboratory varied from 21 to 24 °C from day to day.

Finally, these compounds were evaluated in rat nicotine drug discrimination. Rats were trained and tested in standard operant

Table 1. Radioligand Binding and Pharmacological Data for (±)-, (+)-, and (−)-**1**, (+)- and (−)-Nicotine, and (+)- and (−)-Epibatidine

compd	X	α4β2* [^{3}H]epibatidine (K_i, nM)[a]	ED_{50} mg/kg tail-flick	ED_{50} mg/kg hot-plate	ED_{50} mg/kg hypothermia	ED_{50} mg/kg spontaneous activity	AD_{50} (μg/kg) tail-flick	AD_{50} (μg/kg) hot-plate	AD_{50} (μg/kg) body temp
(*S*)-(−)-nicotine (**2**)		1.50 ± 0.30	1.3 (0.5−1.8)	0.65 (0.25−0.85)	1 (0.6−2.1)	0.5 (0.15−0.78)			
(*R*)-(+)-nicotine (**2**)		35 ± 3	8.0 (4.1−8.7)	3.9 (3.1−4.5)	7.6 (4.3−8.5)	2.9 (2.1−5.4)			
(+)-epibatidine (**4**)		0.026 ± 0.002	0.0006	0.004	0.004	0.001			
(−)-epibatidine (**4**)		0.018 ± 0.001	0.006 (0.001−0.01)	0.004 (0.001−0.008)	0.004 (0.002−0.008)	0.001 (0.0005−0.005)			
(±)-**1**	H	6.1 ± 1.4	12% 10	2 at 10	1.6 (0.5−2.5)	2.6 (1.2−4.1)	5.0 (0.1−10)	1000 (600−2100)	
(+)-**1**	H	1.29 ± 0.18	8% at 1	8% at 1	2.9 (1.3−4.2)	2.0 (1.3−2.9)	0% at 1000	5% at 1000	0% at 1000
(−)-**1**	H	350 ± 160	2% at 1	2% at 1	−0.1 °C at 5*	10% at 5	0.07 (0.05−0.1)	0.8 (0.18−2.3)	0% at 1000

[a] The K_i's with mean and 95% CI are as follows: (*S*)-nicotine, 1.5 (0.6−3.4); (*R*)-(+)-nicotine, 35 (24−55); (+)-epibatidine, 0.026 (0.018−0.035); (−)-epibatidine, 0.18 (0.007−0.027); (±)-**1**, 6.1 (2.4−11.8); (+)-**1**, 1.29 (0.7−1.9); (−)-**1**, 346 (94−670).

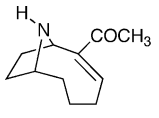
conditioning chambers (Lafayette Instruments Co., Lafayette, IN) as recently described.[10] Briefly, rats were trained to press one lever following administration of 0.4 mg/kg nicotine and to press another lever after injection with saline, each according to a fixed ratio 10 schedule of food reinforcement. Following successful acquisition of the discrimination, stimulus substitution tests with test compounds were conducted during 15-min test sessions. During test sessions, responses on either lever delivered reinforcement according to a fixed ratio 10 schedule. To be tested, rats must have completed the first FR and made at least 80% of all responses on the injection-appropriate lever on the preceding day's training session.

ED_{50} values with 95% confidence limits for behavioral data were calculated by unweighted least-squares linear regression as described by Tallarida and Murray.[11]

The effects of (+)- and (−)-**1** on the function of nicotinic receptors were evaluated using patch−clamp technique in the whole-cell configuration in recombinant α3β4 and α4β2 neuronal nAChRs. Cell lines were generously provided Dr. R. Lukas from Barrow Neurological Institute (human α4β2 in SH-EP1 cells) and Dr. K. Kellar from Georgetown University (rat α3β4 in HEK 293 cells).

Results and Discussion

Kanne, Abood, and co-workers[3,4] synthesized (±)-pyrido[3,4-*b*]homotropane [(±)-**1**] as a rigid analogue of anatoxin-a (**15**) and nornicotine (**3**). Compound (±)-**1** had an IC_{50} value of 5 nM compared to 7 nM for (±)-nicotine and 80 nM for (±)-nornicotine using [^{3}H]nicotine-labeled α4β2 nAChRs in rat brain. These workers also reported that (+)-nicotine, which can be viewed as resulting from N-methylation of (+)-nornicotine, was over 10 times more potent than (+)-nornicotine. However, they found that N-methyl analogue **16** was 200 times less potent than (±)-**1**.



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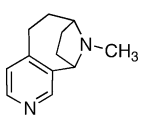

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Even though this highly interesting conformationally rigid analogue of nornicotine and nicotine was originally reported in 1986,[3,4] the individual isomers had not been reported and studied. By replacing benzylamine with (*R*)-(+)-methylbenzylamine in the first step of the originally reported Kanne and Abood[3,4] synthesis, we were able to obtain a separable mixture of **6** and **7** (see Scheme 1). Subjection of **6** and **7** to a sequence of improved steps similar to that of Kanne and Abood led to overall good yield of the final described individual isomers (1*S*,6*S*)-(+)-**1** and (1*R*,6*R*)-(−)-**1**.

Table 2. In Vitro Agonist/Antagonist Activity of Test Compounds at the Expressed α4β2 and α3β4 nAChRs

compd (10 μM)	effect at α4β2 nAChR: % of ACh response[a]	effect at α4β2 nAChR: % remaining ACh response[b]	effect at α3β4 nAChR: % of ACh response[a]	effect at α3β4 nAChR: % remaining ACh response[b]
(+)-**1**	28 ± 5	117 ± 3	13 ± 2	101 ± 5
(−)-**1**	0	89 ± 3	0.9 ± 0.2	93 ± 3

[a] Percent agonist activity of 10 μM test compound relative to that of ACh at its EC_{50} concentration (20 μM ACh for α4β2 nAChR and 100 μM ACh for α3β4 nAChR). [b] Percent antagonist activity of 10 μM test compound against the ACh EC_{50} concentration. Results are presented as means ± SEM (n = 3−4). Whole-cell currents were recorded at a holding potential of −80 mV.

In this study, using [^{3}H]epibatidine (**4**) to label α4β2* nAChRs in rat brain we found that (±)-, (+)-, and (−)-**1** possessed K_i's of 6.1, 1.3, and 346 nM, respectively. Thus, (1*R*,2*R*)-(+)-**1** has a 266 times higher affinity than (1*S*,2*S*)-(−)-**1**. This contrasts sharply with natural (*S*)-(−)-nicotine (**2**), which is only 23 times more potent than (*R*)-(+)-nicotine (**2**), and (+)-epibatidine (**4**), which is 0.7 times less potent than (−)-epibatidine (**4**). Both (+)-**1** and (−)-**1** inhibited binding of the selective α7 nAChR ligand [^{125}I] iodoMLA by less than 50% at 10 μM, and they had very low affinity for the subtype.

To assess in vitro function (+)-**1** and (−)-**1** were tested for both agonist and antagonist activity in α4β2 or α3β4 nAChRs. Prior to examination of the test compound activity, whole-cell currents were elicited by pulse application (200 ms) of ACh, at the concentration close to its EC_{50} value for each nAChR subtype.[12,13] When (+)- and (−)-**1** were tested alone at 10 μM, (−)-**1** did not activate currents in α4β2 or α3β4 nAChR-expressing cells (Table 2), while some low agonist activity was induced by (+)-**1** in both nAChR subtypes being more pronounced in α4β2 than in α3β4 nAChRs (28 ± 5% vs 13 ± 2%, respectively, of ACh (EC_{50})-induced peak current). Detailed examination of the agonist effect of (+)-**1** on α4β2 nAChRs revealed that the compound behaved as a weak partial agonist with an intrinsic activity of 17 ± 0.7% versus a full agonist ACh (1 mM) and EC_{50} of 5.5 μM. In addition, ACh (EC_{50})-induced currents mediated by α4β2 and α3β4 nAChRs were not inhibited in the presence of (+)- or (−)-**1** at the 1−10 μM concentration range. When (+)-**1** concentration was increased

Table 3. Agonist/Antagonist Activity of Test Compounds in Nicotine Rat Discrimination

compd (dose mg/kg)	agonist effects[a]		antagonist effects[b]
	% nicotine lever responding	response rate	% nicotine lever responding
vehicle	2.7 ± 1.2	1.0 ± 0.2	
(*S*)-(−)-nicotine (0.4)	98.3 ± 0.7[c]	1.0 ± 0.1	
(±)-**1** (3)	17 ± 7.7	0.4 ± 0.1[c]	84 ± 16
(+)-**1** (0.56)	44.5 ± 9.5[c]	0.2 ± 0.1[c]	97 ± 0.25[d]
(−)-**1** (3)	23.8 ± 16	1.1 ± 0.2	84 ± 9.5

[a] Following successful acquisition of the discrimination, stimulus substitution tests with test compounds were conducted during 15-min test sessions 10 min after sc injection. [b] Antagonist testing was conducted by pretreating rats with the target dose followed 10 min later with 0.4 mg/kg of (−)-nicotine. [c] $P < 0.05$ from vehicle. [d] For antagonist studies with (+)-**1**, the compound was given at 0.3 mg/kg.

up to 40 μM in the experiments on $\alpha4\beta2$ nAChRs, the compound inhibited ACh-induced currents in average by 10%.

Even though (+)-**1** has a K_i essentially identical to that of (*S*)-(−)-nicotine (**2**), its pharmacological profile differs from that of (*S*)-(−)-nicotine. It depressed spontaneous activity and produced hypothermia, although it was less potent than (*S*)-(−)-nicotine. However, these effects were not blocked by the nicotinic antagonist mecamylamine. On the basis of these findings, it is highly likely that the effects of (+)-**1** on spontaneous activity and body temperature are not produced through actions at nAChRs. Compound (+)-**1** failed to produce antinociception in either tail-flick or hot-plate assays at 1 mg/kg, a dose that (*S*)-(−)-nicotine produces robust antinociception. The inability of (+)-**1** to produce antinociceptive effects is not likely a biodispositional problem, since an intrathecal injection of (+)-**1** at a dose of 10 μg/mouse was also ineffective in the tail-flick test (data not shown). In contrast to nicotine, which fully substituted for itself (Table 3), (±)-**1** and (+)-**1** failed to fully substitute for nicotine (0.4 mg/kg) in rat drug discrimination. At a slightly higher dose (1 mg/kg), (+)-**1** produced lethal effects in the two rats to which it was administered. Higher dose were therefore not tested. Moreover, (+)-**1** decreased overall response rates compared to vehicle ($p > 0.05$; Table 3). In addition, (±)-**1** and its isomers given at the highest inactive dose failed to significantly block nicotine discrimination.

Not surprising (−)-1 with the K_i of 346 nM was inactive in all four mouse behavioral assays. It was also inactive when given intrathecally (10 μg/mouse) in the tail-flick test. It failed to generate nicotine-like responding in rat drug discrimination and did not block the nicotine cue. Surprisingly, (−)-**1** was highly potent in antagonizing nicotine-induced antinociception in the tail-flick test ($AD_{50} = 0.07$ μg/kg). Compound (−)-**1** also antagonized the antinociceptive effects of nicotine in the hot-plate test, showing an AD_{50} of 0.8 μg/kg. Compound (−)-**1** did not antagonize nicotine effects of body temperature.

The enantiomers of **1** represent intriguing probes for nicotinic receptors for several reasons. Certainly, the enantioselectivity exhibited by (+)- and (−)-**1** far exceeds that of previously reported nicotinic ligands such as nicotine and epibatidine and serves as a guide for gaining greater insight into the receptor pharmacophore. While (+)-**1** retains the ability to bind to the epibatidine-binding site (assumed to be an $\alpha4\beta2$ subtype), it lacks sufficient intrinsic efficacy to activate either $\alpha4\beta2$ and $\alpha3\beta4$ receptors to a sufficient degree to produce the full spectrum of nicotine pharmacological effects. In addition, it failed to antagonize several of nicotine's behavioral effects and in vitro receptor activation. It is possible that (+)-**1** is involved in a different mechanism of nicotinic receptor modulation not detected in our experimental models. However, (−)-**1** represents a paradox in that it has little affinity for the epibatidine-binding site, fails to activate or block either $\alpha4\beta2$ and $\alpha3\beta4$ receptors, yet it is highly effective in blocking nicotine-induced antinociception. These observations underscore previous findings that indicate receptor subtypes other than $\alpha4\beta2$ participate in antinociceptive effects in the tail-flick procedure. The failure of (−)-**1** to alter ACh-induced currents in $\alpha4\beta2$-containing cells argues against allosteric modulation. On the other hand, it is possible that (−)-**1** is acting at a non-epibatidine-sensitive receptor subtype to antagonize nicotine's effects in the tail-flick procedure. If such a receptor subtype exists, then it appears to play a weaker role in antinociception measured by the hot-plate test. There are several possible explanations for the apparent lack of correlation between affinity/activity at $\alpha4\beta2$ and $\alpha3\beta4$ nAChR subtypes and its in vivo efficacy. One is that (−)-**1** antagonized nicotine-induced antinociception in the tail-flick by binding to other nAChRs subtypes such as $\alpha7$ nicotinic receptors. However, we showed that (−)-**1** does not compete with high-affinity $\alpha7$ subtypes ruling out such possibility. Another explanation is that (−)-**1** binds to a receptor population different from epibatidine. In the binding assays, we are limited to the subtype binding profile of [^{3}H] epibatidine, and our tissue homogenate contains predominantly the $\alpha4\beta2$ nAChR subtypes. Thus, (−)-**1** may have an nAChR subtype binding profile different from epibatidine. Finally, compounds may have differential binding affinity to the various conformations of nicotinic receptors (desensitized or inactive state for example) or simply bind to nonnicotinic receptors. It is worth mentioning that the other nAChR ligands characterized by high binding affinity to native $\alpha4\beta2$* receptors and low efficacies at nAChRs possess interesting in vivo profiles, yet their mechanism of action is not fully understood. Future exploration of this novel nicotine modulator will be required in order to understand its pharmacological properties.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz (Bruker AVANCE 300) or 500 MHz (Varian 500) spectrometer. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal $(CH_3)_4Si$ (δ 0.0). Melting points were determined on a Bristoline apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). Thin-layer chromatography was carried out on EMD silica gel 60 TLC plates. Visualization was accomplished under UV or in an iodine chamber. Microanalyses were carried out by Atlantic Microlab Inc. The compounds were purified by flash chromatography on silica gel 60 (230−400 mesh) or RediSep columns by running CombiFlash Companion Isco system. All moisture-sensitive reactions were performed under a positive pressure of nitrogen.

***Trans*-8-[(*R*)-Phenylethylamino]cyclooct-4-enol (6 and 7).** A solution of 9-oxabicyclo[6.1.0]non-4-ene (**5**, 30.60 g, 0.246 mol) and (*R*)-(+)-methylbenzylamine (50.8 mL, 0.394 mol) in methanol (12 mL) was placed in a sealed tube and was stirred at 120 °C for 72 h, then cooled to room temperature. The CH_3OH and excess methylbenzylamine were evaporated under reduced pressure. Recrystallization of the residue in hexane followed by flash chromatography [silica, 100% EtOAc followed by CH_2Cl_2/CH_3OH (9:1)] of the resulting concentrated filtrate afforded overall 20.12 g (33%) of (+)-**6** as white crystals and 20.57 g (34%) of (−)-**7** as a colorless viscous oil.

(1*S*,8*S*)-(+)-*trans*-8-[(*R*)-Phenylethylamino)cyclooct-4-enol (6). $[\alpha]^{25}_D$ +104.5 (*c* 1.38, $CHCl_3$); mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 7.15−7.38 (m, 5H), 5.35−5.60 (m, 2H), 3.92 (q, $J = 6.6$ Hz, 1H), 3.31 (dt, $J = 3.0$, 6.6 Hz, 1H), 3.29 (s, 1H), 2.20−2.45 (m, 2H), 1.90−2.15 (m, 6H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.30 (m, 1H), 1.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 144.42, 130.41, 128.48, 127.96,

127.19, 126.96, 71.52, 57.65, 56.24, 34.52, 32.46, 24.76, 23.01, 22.93; MS (ESI) *m*/*z* ($M^+ + 1$) calcd 246.4, obsd 246.5.

(1*R*,8*R*)-(−)-*trans*-8-[(*R*)-Phenylethylamino]cyclooct-4-enol (7). $[\alpha]^{25}_D$ −20.1 (*c* 3.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.16−7.38 (m, 5H), 5.60−5.75 (m, 1H), 5.44 (m, 1H), 3.74 (q, *J* = 6.6 Hz, 1H), 3.31 (dt, *J* = 3.0, 7.5 Hz, 1H), 2.58 (m, 1H), 2.10−2.40 (m, 5H), 1.95 (m, 1H), 1.74 (m, 1H), 1.20−1.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 145.55, 130.78, 128.71, 128.24, 127.44, 126.56, 71.76, 58.81, 57.87, 34.98, 33.47, 23.50, 23.12, 22.87; MS (ESI) *m*/*z* ($M^+ + 1$) calcd 245.4, obsd 245.6.

(1*S*,2*S*,6*S*)-(+)-9-[(*R*)-Phenylethyl]-9-azabicyclo[4.2.1]nonan-2-ol (8a). To a solution of mercuric acetate (98%, 3.32 g, 0.01 mol) in THF (30 mL) and water (30 mL) at 0 °C was added (1*S*,8*S*)-(+)-*trans*-8-[(*R*)-phenylethylamino]cyclooct-4-enol (**6**) (2.45 g, 0.01 mol) in THF (20 mL). The mixture was stirred at 0 °C for 5 h, and then 3 M NaOH (10.0 mL) was added followed by sodium borohydride (99%, 390 mg, 10.2 mmol) in 3 M NaOH (10.0 mL). After stirring for 30 min while warming to room temperature, the solution was diluted with brine, and the THF layer was separated. The aqueous layer was extracted with ether (2 × 40 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Flash chromatography [silica, CH_2Cl_2/CH_3-OH (10:1)] of the residue afforded 1.49 g (61%) of **8a** as a colorless viscous oil along with 0.23 g (7.6%) of **9a** as a side product. $[\alpha]^{25}_D$ +20.5 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.10−7.40 (m, 5H), 3.65−3.80 (m, 2H), 3.47 (t, *J* = 8.1 Hz, 1H), 3.25 (t, *J* = 6.2 Hz, 1H), 2.05 (m, 1H), 1.71−1.90 (m, 3H), 1.48−1.70 (m, 4H), 1.36−1.47(m, 2H), 1.20−1.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 146.93, 128.30, 127.31, 126.75, 73.65, 66.15, 61.26, 57.37, 36.39, 33.51, 33.17, 22.98, 22.64, 20.30; MS (ESI) *m*/*z* ($M^+ + 1$) calcd 246.4, obsd 246.5.

(1*R*,2*R*,6*R*)-9-[(*R*)-Phenylethyl]-9-azabicyclo[4.2.1]nonan-2-ol (8b). Compound **8b**, a colorless viscous oil, was prepared from (1*R*,8*R*)-(−)-**7** in 60% yield in a manner analogous to that of **8a**, along with 9.2% of **9b** as a side product. $[\alpha]^{25}_D$ −9.2 (*c* 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.10−7.40 (m, 5H), 3.68−3.83 (m, 2H), 3.47 (t, *J* = 6.3 Hz, 1H), 3.25 (t, *J* = 8.4 Hz, 1H), 1.95−2.05 (m, 2H), 1.25−1.92 (m, 11H), 1.10−1.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 146.92, 128.23, 127.22, 126.62, 74.11, 64.48, 61.33, 59.12, 35.93, 33.17, 23.26, 22.85, 20.42; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 246.4, obsd 246.5.

(1*S*,6*S*)-9-[(*R*)-Phenylethyl]-9-azabicyclo[4.2.1]nonan-2-one (10a). To a cooled (−78 °C) solution of oxalyl chloride (4.5 mL, 9.0 mmol, 2 M in CH_2Cl_2) in CH_2Cl_2 (15 mL) under nitrogen was added dimethyl sulfoxide (1.28 mL, 18.0 mmol) dropwise. The resulting solution was allowed to stir at −78 °C for an additional 10 min before the addition of **8a** (1.47 g, 0.006 mol) dissolved in methylene chloride (10 mL). The mixture was stirred at −78 °C for 30 min, and then triethylamine (5.0 mL, 36 mmol) was added. The mixture was stirred overnight while warming up to room temperature. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography [silica, EtOAc/hexanes (1:4)] of the residue afforded 1.24 g (85%) of **10a** as a light yellow, viscous oil: $[\alpha]^{25}_D$ +107 (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.12−7.40 (m, 5H), 3.93 (q, *J* = 6.6 Hz, 1H), 3.73 (dd, *J* = 1.8, 9.9 Hz, 1H), 3.52 (m, 1H), 2.82 (dt, *J* = 3.6, 14 Hz, 1H), 2.40 (dd, *J* = 5.7, 15 Hz, 1H), 2.10−2.30 (m, 1H), 1.45−1.98 (m, 7H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 218.30, 145.48, 128.55, 127.13, 127.09, 70.18, 59.64, 59.37, 43.10, 34.15, 30.16, 27.90, 22.75, 20.00; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 244.3, obsd 244.5.

(1*R*,6*R*)-9-[(*R*)-Phenylethyl]-9-azabicyclo[4.2.1]nonan-2-one (10b). Compound **10b**, which was prepared from **8b** in 85% yield in a manner analogous to that of **10a**, is a light yellow, viscous oil: $[\alpha]^{25}_D$ −20.7 (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.12−7.40 (m, 5H), 3.80 (q, *J* = 6.6 Hz, 1H), 3.55−3.73 (m, 2H), 3.01 (dt, *J* = 2.7, 13.7 Hz, 1H), 2.32 (dd, *J* = 5.7, 14.4 Hz, 1H), 2.07−2.24 (m, 1H), 1.45−1.95 (m, 7H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 218.31, 145.61, 128.46, 127.17, 127.10, 69.94, 61.56, 60.65, 42.52, 35.41, 30.88, 27.21, 22.62, 20.08; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 244.3, obsd 244.5.

(1*S*,6*S*)-3-Allyl-9-[(*R*)-phenylethyl)-9-azabicyclo[4.2.1]nonan-2-one (11a). To a cooled (−78 °C) solution of potassium bis-(trimethylsilyl)amide (95%, 3.54 g, 0.017 mol) in THF (25 mL) under nitrogen was added **10a** (3.16 g, 0.013 mol) dissolved in THF (20 mL) dropwise. The resulting solution was allowed to stir at −78 °C for an additional 10 min before 1.0 M triethylboron (16.9 mL, 16.9 mmol) was added dropwise over 10 min, then allyl bromide (99%, 1.47 mL, 16.9 mmol) was added all at once. The mixture was stirred at −78 °C for 30 min, then warmed to room temperature and stirred at room temperature for 24 h. Water (30 mL) was added, and the mixture was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Flash chromatography [silica, EtOAc/hexanes (1:4)] of the residue afforded 2.47 g (77%) of **11a** as a light yellow, viscous oil along with 0.42 g of **10a** recovered. ^1H NMR ($CDCl_3$) δ 7.15−7.40 (m, 5H), 5.77 (m, 1H), 5.02 (dd, *J* = 0.6, 12.6 Hz, 2H), 3.84 (q, *J* = 6.6 Hz, 1H), 3.62 (dd, *J* = 0.9, 9.6 Hz, 2H), 3.12 (m, 1H), 2.46 (m, 1H), 1.42−2.20 (m, 9H), 1.36 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 218.50, 145.56, 137.21, 128.69, 127.29, 127.25, 116.44, 70.76, 60.50, 59.94, 48.89, 35.33, 35.04, 31.23, 27.67, 26.03, 22.74; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 284.4, obsd 284.6.

(1*R*,6*R*)-3-Allyl-9-[(*R*)-phenylethyl]-9-azabicyclo[4.2.1]nonan-2-one (11b). Compound **11b** was prepared from **10b** in 82% yield in a manner analogous to that described for **11a** as a light yellow, viscous oil: ^1H NMR ($CDCl_3$) δ 7.15−7.40 (m, 5H), 5.75 (m, 1H), 4.98−5.20 (m, 2H), 3.85 (m, 1H), 3.65 (q, *J* = 6.6 Hz, 1H), 3.50 (m, 1H), 2.70−3.00 (m, 2H), 2.47 (m, 1H), 1.40−2.25 (m, 8H), 1.34 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 216.95, 145.63, 136.72, 128.62, 127.28, 127.19, 116.47, 71.70, 62.08, 62.00, 52.01, 35.98, 31.46, 30.78, 27.43, 23.19, 22.81; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 284.4, obsd 284.6.

(1*S*,6*S*)-3-Allyl-9-[(*R*)-phenylethyl]-9-azabicyclo[4.2.1]nonane-2-carbonitrile (12a). To a stirred, cooled (0 °C) solution of **11a** (2.83 g, 0.01 mol) and tosylmethyl isocyanide (3.90 g, 20.0 mmol) in ethylene glycol dimethyl ether (DME) (50 mL) and methanol (0.82 mL) was added potassium *tert*-butoxide (95%, 5.90 g, 0.05 mol) all at once. The resulting solution was heated to 50 °C and stirred for 36 h. The mixture was then cooled in an ice bath, and 2 N HCl was added until a pH of 8 was obtained. Most of the DME was evaporated under reduced pressure, and the mixture was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (silica, 100% CH_2Cl_2) of the residue afforded 2.28 g (77%) of **12a** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.15−7.45 (m, 5H), 5.65−5.85 (m, 1H), 4.90−5.20 (m, 2H), 3.40−3.95 (m, 3H), 1.82−2.50 (m, 6H), 1.20−1.70 (m, 9H); MS (APCI) *m*/*z* ($M^+ + 1$) calcd 295.4, obsd 295.3.

(1*R*,6*R*)-3-Allyl-9-[(*R*)-phenylethyl]-9-azabicyclo[4.2.1]nonane-2-carbonitrile (12b). Compound **12b**, which was prepared from **11b** in 79% yield in a manner analogous to that of **12a**, is a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.10−7.40 (m, 5H), 5.75 (m, 1H), 5.00−5.20 (m, 2H), 3.55−4.00 (m, 2H), 3.18−3.40 (m, 1H), 2.00−2.50 (m, 5H), 1.55−1.95 (m, 2H), 1.25−1.53 (m, 8H); MS (APCI) *m*/*z* ($M^+ + 1$) calcd 295.4, obsd 295.3.

(1*S*,6*S*)-3-Allyl-9-[(*R*)-phenylethyl]-9-azabicyclo[4.2.1]nonane-2-carbaldehyde (13a). To a stirred, cooled (0 °C) solution of **12a** (2.94 g, 0.01 mol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise 1.0 M diisobutylaluminum hydride (12.0 mL, 12.0 mmol) in CH_2Cl_2. The mixture was stirred at 0 °C for 2 h and then warmed to room temperature and stirred for 3 h. The mixture was again cooled to 0 °C, and water (10 mL) and 2 N HCl (0.5 mL) were added. The mixture was stirred at room temperature for 1 h, then filtered through Celite and thoroughly washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography [silica, EtOAc/hexanes (1:4)] of the residue provided 2.26 g (76%) of **13a** as viscous, light yellow oil: ^1H NMR ($CDCl_3$) δ 9.23 (s, 1H), 7.15−7.40 (m, 5H),

5.65−6.18 (m, 1H), 4.95−5.25 (m, 2H), 3.40−3.70 (m, 2H), 1.20−2.40 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 205.38, 145.54, 136.66, 128.35, 127.85, 127.13, 116.98, 64.32, 62.27, 61.55, 60.73, 40.81, 37.58, 36.37, 34.68, 28.71, 27.36, 20.75; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 298.4, obsd 298.5.

(1*R*,6*R*)-3-Allyl-9-(1-phenylethyl)-9-azabicyclo[4.2.1]nonane-2-carbaldehyde (13b). Compound **13b**, which was prepared from **12b** in 78% yield in a manner analogous to that of **13a**, is a light yellow, viscous oil: ^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H), 7.15−7.40 (m, 5H), 5.75 (m, 1H), 4.90−5.10 (m, 2H), 3.84 (dd, J = 2.4, 10.2 Hz, 1H), 3.59 (q, J = 6.6 Hz, 1H), 3.26 (m, 1H), 2.25−2.45 (m, 2H), 2.10 (m, 1H), 1.32−2.00 (m, 9H), 1.21 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.58, 146.44, 136.40, 128.27, 127.12, 126.72, 116.95, 63.85, 62.04, 61.73, 59.48, 40.68, 36.81, 36.40, 34.52, 27.54, 27.21, 23.18; MS (ESI) *m*/*z* ($M^+ + 1$) calcd 298.4, obsd 298.4.

(1*S*,6*S*)-9-[(*R*)-Phenylethyl]-pyrido[3,4-*b*]homotropane (14a). To a stirred, cooled (0 °C) solution of **13a** (2.97 g, 0.01 mol) in anhydrous CH_2Cl_2 (20 mL) under nitrogen was added trifluoroacetic acid (0.80 mL, 10.5 mmol). After stirring at 0 °C for 10 min, the solution was cooled to −78 °C, and then ozone was bubbled through the solution over 20−30 min until a light blue color appeared. After the solution stirred 2 min longer, the ozone was removed. The excess ozone in the solution was evacuated with nitrogen for about 10 min until the light blue color disappeared. Methyl sulfide (4.4 mL) was added, and the mixture was stirred for 2 h while warming up to room temperature and stirred 1 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was dissolved in 60 °C acetic acid (10 mL), which was added dropwise to a 105 °C solution of hydroxylamine hydrochloride (3.47 g, 0.05 mol) in acetic acid (25 mL). The mixture was stirred at 105 °C for 30 min under nitrogen; the color of solution changed to deep brown. The solution was cooled to room temperature and poured into ice-cold ether (80 mL), basified with 29% ammonium hydroxide and then saturated K_2CO_3 to pH 8. The ether layer was separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (silica, 100% EtOAc) of the residue afforded 0.78 g (28%) of **14a** as a light yellow, viscous oil which solidified on standing. $[\alpha]^{25}_D$ +46.6 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.36 (d, J = 4.8 Hz, 1H), 7.13−7.33 (m, 5H), 7.10 (d, J = 4.8 Hz, 1H), 4.49 (dd, J = 0.9, 9.3 Hz, 1H), 3.20−3.40 (m, 2H), 3.05 (dt, J = 3.6, 12.9 Hz, 1H), 2.48−2.72 (m, 2H), 2.11 (m, 1H), 1.65−2.00 (m, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.13−1.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 149.9, 149.57, 148.45, 145.68, 139.38, 128.45, 127.20, 126.87, 124.98, 61.38, 58.08, 55.85, 32.18, 31.30, 28.73, 24.87, 23.08; MS (ESI) *m*/*z* ($M^+ + 1$) calcd 279.4, obsd 279.4.

(1*R*,6*R*)-9-[(*R*)-Phenylethyl]pyrido[3,4-*b*]homotropane (14b). Compound **14b**, which was prepared from **13b** in 26% yield in a manner analogous to that of **14a**, is a light yellow, viscous oil which solidified on standing. $[\alpha]^{25}_D$ +93 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.29(d, J = 4.8 Hz, 1H), 7.43 (s, 1H), 7.18−7.33 (m, 3H), 7.02−7.13 (m, 3H), 3.80−3.97 (m, 2H), 3.28 (q, J = 6.3 Hz, 1H), 3.08 (dt, J = 3.6, 12.9 Hz, 1H), 2.70 (dt, J = 3.3, 15.6 Hz, 1H), 2.18−2.48 (m, 2H), 2.11 (t, J = 12.9 Hz, 1H), 1.68−1.95 (m, 2H), 1.55 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 150.18, 149.60, 148.34, 145.18, 139.69, 128.45, 127.46, 127.12, 124.58, 61.79, 57.59, 55.76, 32.32, 30.89, 29.17, 24.87, 23.66; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 279.4, obsd 279.6.

(1*S*,6*S*)-(−)-Pyrido[3,4-*b*]homotropane[(−)-1] Dihydrochloride. To a solution of **14a** (141 mg, 0.506 mmol) and dry ammonium formate (638 mg, 10.12 mmol) in absolute methanol (5 mL) was added dry 10 wt % Pd/C (141 mg). The mixture was stirred at room temperature under nitrogen for 24 h and then filtered through Celite and thoroughly washed with methanol. The filtrate was evaporated under reduced pressure. Flash chromatography [silica, $CH_2Cl_2/CH_3OH/29\%NH_3{\cdot}H_2O$ (90:18:2)] of the resulting residue afforded 68 mg (77%) of (−)-**1** as a white solid. $[\alpha]^{25}_D$ (*c* 2.90, $CHCl_3$) −38.4; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 4.8 Hz, 1H), 8.30 (s, 1H), 7.06 (d, J = 4.8 Hz, 1H), 4.36 (dd, J = 2.1, 11.1 Hz, 1H), 3.81 (m, 1H), 3.08 (dt, J = 3.3, 14.4 Hz, 1H), 2.70 (dt, J = 3.6, 15.9 Hz, 1H), 2.45 (m, 1H), 2.00−2.20 (m, 2H), 1.73−1.98 (m, 3H), 1.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 149.28, 148.48, 148.13, 143.72, 125.57, 60.80, 58.34, 34.17, 31.99, 31.68, 30.13; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 175.3, obsd 175.6.

To a stirred solution of (−)-**1** free base (62 mg, 0.333 mmol) in CH_2Cl_2 (10 mL) and CH_3OH (2 mL) at 0 °C was added HCl (1 M in ether, 1.3 mL) dropwise. The mixture was warmed to room temperature and stirred at room temperature for 1 h. The solvent and excess HCl were evaporated and then kept under vacuum overnight to provide 86 mg (98%) of (−)-**1**·2HCl. $[\alpha]^{25}_D$ (*c* 0.85, CH_3OH) −48.3; Anal. Calcd for ($C_{11}H_{16}Cl_2N_2$): C, H, N.

(1*R*,6*R*)-(+)-Pyrido[3,4-*b*]homotropane [(+)-1] Dihydrochloride. To a solution of **14b** (300 mg, 1.08 mmol) and dry ammonium formate (1.36 g, 0.022 mol) in absolute methanol (10 mL) was added dry 10 wt % Pd/C (300 mg). The mixture was stirred at room temperature under nitrogen for 24 h and then filtered through Celite and thoroughly washed with methanol. The filtrate was evaporated under reduced pressure. Flash chromatography [silica, $CH_2Cl_2/CH_3OH/29\%NH_3{\cdot}H_2O$ (90:18:2)] of the resulting residue afforded 146 mg (78%) of (+)-**1** as a white solid. $[\alpha]^{25}_D$ (*c* 1.34, $CHCl_3$) +38.3; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 4.8 Hz, 1H), 8.30 (s, 1H), 7.07 (d, J = 4.8 Hz, 1H), 4.40 (dd, J = 2.1, 11.1 Hz, 1H), 3.85 (m, 1H), 3.09 (dt, J = 3.6, 14.4 Hz, 1H), 2.72 (dt, J = 3.6, 15.9 Hz, 1H), 2.60 (s, 1H), 2.46 (m, 1H), 2.17 (m, 1H), 1.73−1.98 (m, 3H), 1.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 149.34, 148.70, 148.29, 143.14, 125.68, 60.78, 58.44, 33.89, 31.97, 31.66, 30.06; MS (APCI) *m*/*z* ($M^+ + 1$) calcd 175.3, obsd 175.3.

To a stirred solution of (+)-**1** freebase (134 mg, 0.769 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (4 mL) at 0 °C was added HCl (1 M in ether, 3.1 mL) dropwise. The mixture was warmed to room temperature and stirred at room temperature for 1 h. The solvent and excess HCl were evaporated and then kept under vacuum overnight to provide 189 mg (99.5% yield) of (+)-**1**·2HCl. $[\alpha]^{25}_D$ (*c* 0.76, CH_3OH) +48.5; Anal. Calcd ($C_{11}H_{16}Cl_2N_2$): C, H, N.

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Supporting Information Available: Crystal data, structural refinement analysis, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters of **6** and elemental analysis data for compounds (+)- and (−)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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