JOC Article

Synthesis of 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane, 2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane, and 2-(Pyridin-3-yl)-1-azabicyclo[3.2.1]octane, a Class of Potent Nicotinic Acetylcholine Receptor–Ligands

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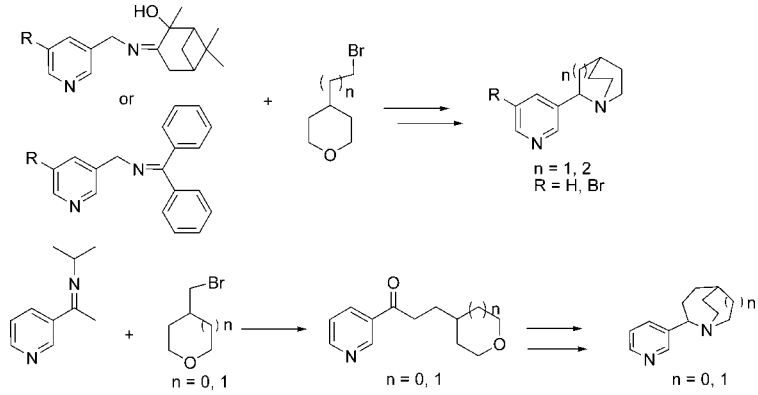

In an attempt to generate nicotinic acetylcholine receptor (nAChR) ligands selective for the α4β2 and α7 subtype receptors we designed and synthesized constrained versions of anabasine, a naturally occurring nAChR ligand. 2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane, 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane, and several of their derivatives have been synthesized in both an enantioselective and a racemic manner utilizing the same basic synthetic approach. For the racemic synthesis, alkylation of *N*-(diphenylmethylene)-1-(pyridin-3-yl)methanamine with the appropriate bromoalkyltetrahydropyran gave intermediates which were readily elaborated into 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane and 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane via a ring opening/aminocyclization sequence. An alternate synthesis of 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane via the alkylation of *N*-(1-(pyridin-3-ylethylidene)propan-2-amine has also been achieved. The enantioselective syntheses followed the same general scheme, but utilized imines derived from (+)- and (−)-2-hydroxy-3-pinanone. Chiral HPLC shows that the desired compounds were synthesized in >99.5% ee. X-ray crystallography was subsequently used to unambiguously characterize these stereochemically pure nAChR ligands. All compounds synthesized exhibited high affinity for the α4β2 nAChR subtype ($K_i \leq 0.5$–15 nM), a subset bound with high affinity for the α7 receptor subtype ($K_i \leq 110$ nM), selectivity over the α3β4 (ganglion) receptor subtype was seen within the 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane series and for the muscle (α1βγδ) subtype in the 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane series.

Introduction

Nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels, and are widely distributed and abundant in the mammalian central nervous system (CNS) and peripheral nervous system (PNS). The two most prevalent nAChR subtypes in the CNS are α4β2 and α7.[1] Ligands for these receptors have been recognized as possessing potential for treatment of a variety of conditions and disorders with substantial unmet medical needs, including schizophrenia,

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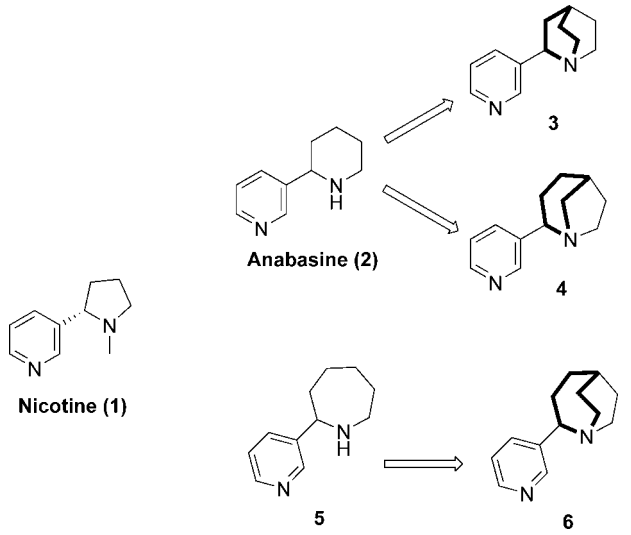
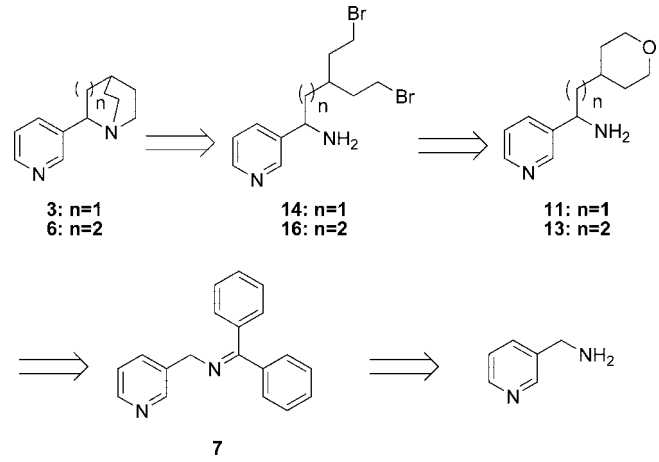


FIGURE 1. Design of constrained analogues.

various pain states, neurodegenerative diseases, and cognitive disorders.[2–19]

S-(−)-Nicotine (**1**), Figure 1, the principal alkaloid in tobacco and the prototypical nAChR ligand, possesses high affinity for the $\alpha4\beta2$ nAChR ($K_i \sim 2$nM).[20] It is also recognized as a nonselective agonist, with activity at multiple nAChR subtypes.[20,21] This lack of selectivity, particularly with respect to ganglionic $\alpha3\beta4$ nAChR subtypes, is assumed to be responsible for undesirable side effects associated with nicotine substitution therapy (in smoking cessation medications).[21] Our goal was therefore to create ligands with enhanced selectivity over the ganglionic nAChRs to minimize the potential for adverse side effects. The lack of available crystal structures of the nicotinic receptors necessitated ligand-based design, in which compounds possessing pharmacophoric elements consistent with nicotinic activity serve as the basis for creation of new ligands.[22]

SCHEME 1. Retrosynthetic Analysis of 2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octanes and 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonanes



Introduction of conformational constraint is an often used technique in medicinal chemistry to enhance selectivity. Anabasine (**2**) and 2-pyridinylazepane (**5**), close structural relatives to nicotine, were both reported to have K_i values at $\alpha4\beta2$ nAChRs of 20 nM or less,[23] and appeared to be suitable candidates for this strategy. In addition, the 1-azabicyclo[2.2.2]octane moiety appears in numerous nicotinic ligands, particularly those with high affinity and selectivity at $\alpha7$ nAChRs.[17,18] We became interested in exploring the pharmacological profile of 2-(pyridine-3-yl)-1-azabicyclo[2.2.2]octane (**3**) and 2-(pyridine-3-yl)-1-azabicyclo[3.2.1]octane (**4**), which we envisioned as constrained analogues of **2**, wherein the piperidine ring is incorporated into a bridged azabicycle. Also of interest was the related 2-(pyridine-3-yl)-1-azabicyclo[3.2.2]nonane **6**.

A literature survey revealed that target compounds **3** and **6** had been previously claimed in patents[24,25] or reported in the literature,[26,27] albeit without pharmacological data. We felt that the reported syntheses were cumbersome, lengthy, or not suitable for our needs. We therefore designed syntheses of these targets which were facile and straightforward. We now report the results of our racemic and enantioselective synthetic approaches to 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane (**3**), 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (**6**), 2-(pyridin-3-yl)-1-azabicyclo-[3.2.1]octane (**4**) and a number of other novel derivatives bearing substituents on the pyridinyl ring.

Retrosynthetic analysis (Scheme 1) of compounds **3** and **6** suggested that they could be synthesized via an intramolecular bis-aminocyclization of a dibromide (**14** or **16**), which should be readily available from the HBr-promoted ring opening of

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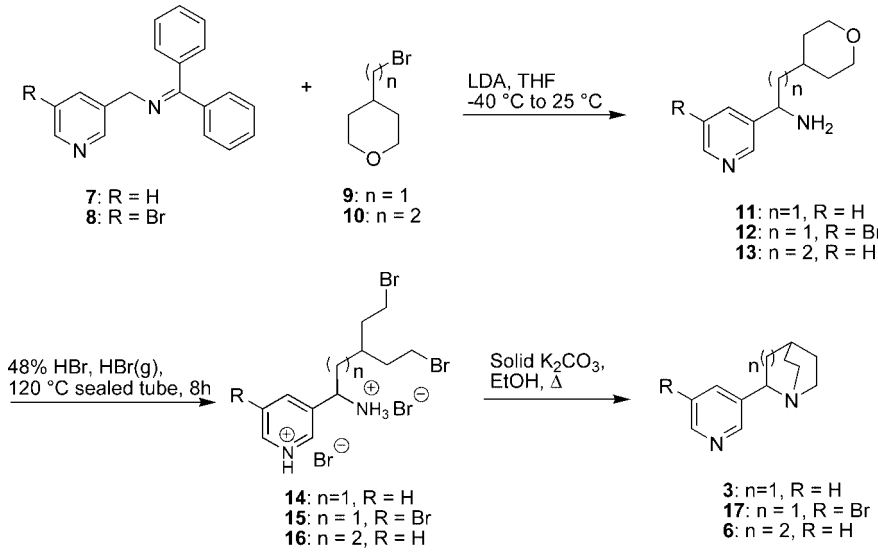
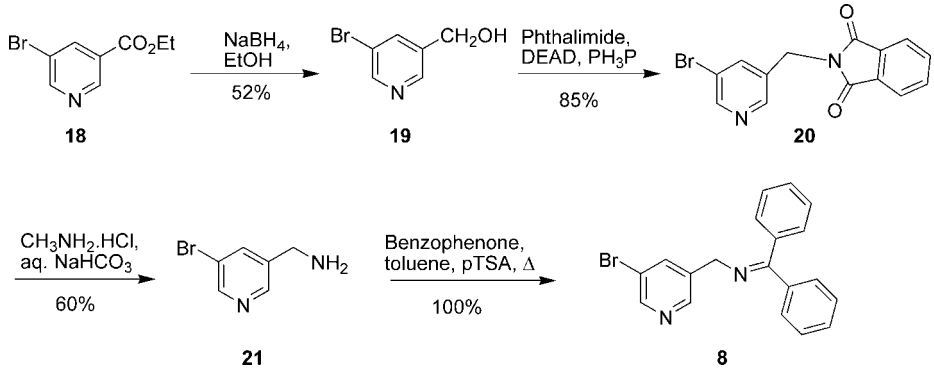
SCHEME 2. Synthesis of 2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane (3) and 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (6)



SCHEME 3. Synthesis of *N*-(Diphenylmethylene)-1-(5-bromopyridin-3-yl)methanamine (8)



the tetrahydropyran rings in **11** or **13**, respectively.[28,29] It was anticipated that the desired tetrahydropyrans could be prepared by alkylation of the imine **7** via abstraction of the benzylic proton with LDA, an approach that has been successfully employed by others[30–32] as well as in our own laboratories.[33–35]

Discussion

Alkylation of imine **7**[35] (available from condensation of benzophenone and 3-aminomethylpyridine) was accomplished in good yield by treatment with LDA and the appropriate bromide (**9**[36,37] or **10**,[38] Scheme 2). The resulting tetrahydropyrans (**11** and **13**) were reacted with concentrated HBr in the presence of excess HBr gas at 120 °C in a sealed tube for 8 h, affording dibromides **14** and **16** as the dihydrobromide salts. Subsequent heating of the crude reaction products in EtOH in the presence of K_2CO_3 gave the desired cyclized compounds (**3** and **6**) in good yield.

Bolstered by this initial success, we next applied this methodology to the preparation of the analogous 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octanes and 2-(pyridin-3-yl)-1-azabicyclo-[3.2.2]nonanes bearing a bromine substituent at the 5-position of the pyridine ring (**17**), believing that the bromine substituent could subsequently serve to introduce other functionalities at that position. Preparation of the required imine **8** began with reduction of ethyl 5-bromo-3-nicotinate (**18**) with $NaBH_4$ in EtOH at 60 °C to give alcohol **19**[39] in 52% yield. Reaction of this alcohol with phthalimide under Mitsunobu conditions gave phthalimide **20** in 85% yield. This was subsequently deprotected with methylamine under aqueous conditions at 60 °C to give the desired 5-bromo-3-aminomethylpyridine (**21**)[40] in 60% yield. Condensation of **21** with benzophenone under standard conditions gave imine **8** in quantitative yield (Scheme 3). Alkylation of imine **8**, to give compound **12**, and subsequent ring opening

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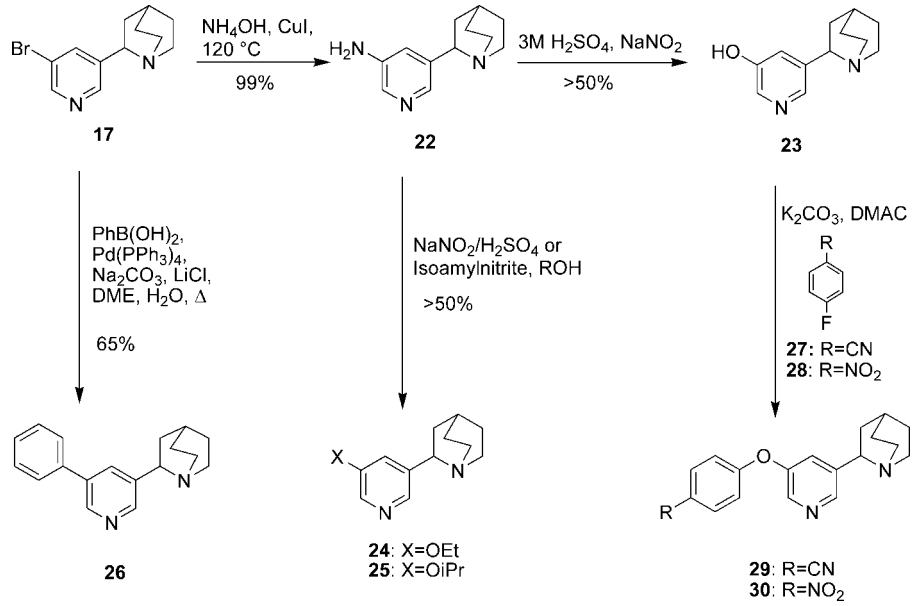
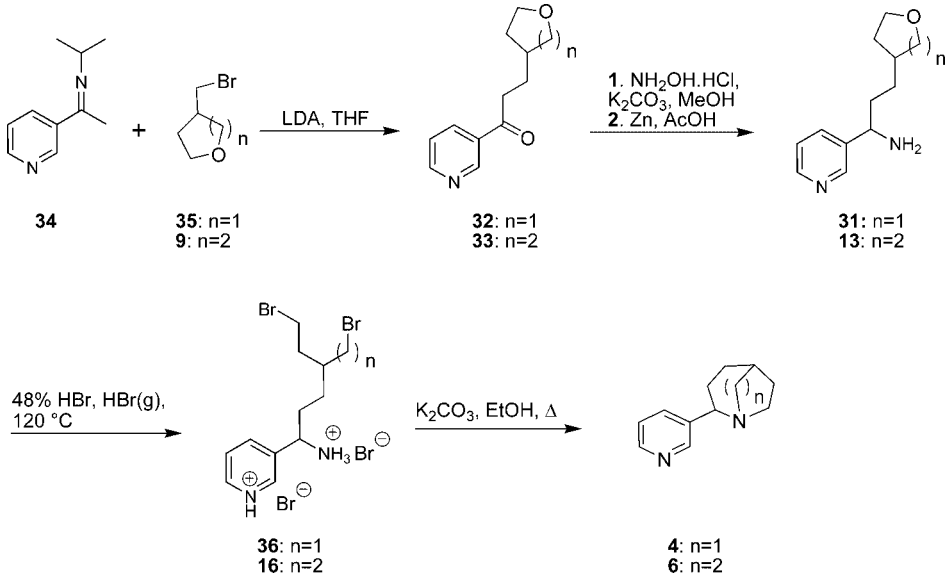
SCHEME 4. Synthesis of Analogues of 17



SCHEME 5. Synthesis of 2-(Pyridin-3-yl)-1-azabicyclo[3.2.1]octane (4) and 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (6)



(producing **15**) and cyclization, utilizing chemistry previously described, produced compound **17**.

SAR around the pyridinyl−quinuclidine scaffold of **3** could be explored if there was a convenient synthetic handle that could be elaborated readily. This was achieved in one instance by converting **17** into a number of analogues by using the Br at the 5′-position of pyridine as the synthetic handle for elaboration (Scheme 4). Heating bromide **17** in 30% aqueous NH_4OH containing catalytic CuI in a sealed tube at 120 °C for 8 h afforded 2-(5-aminopyridin-3-yl)-1-azabicyclo[2.2.2]octane (**22**). Diazotization with isoamyl nitrite in the presence of ethanol or 2-propanol gave aryl ethers **24** and **25**, respectively, in moderate yield (∼50%). Hydrolysis of the intermediate diazonium ion (**22** + $NaNO_2$ and H_2SO_4, then heat) gave the pyridinol **23**, which was subsequently reacted with 4-fluorobenzonitrile (**27**) or 4-fluoronitrobenzene (**28**), in the presence of K_2CO_3, to give **29** and **30**, respectively (synthesis and spectral data for **29** and **30** can be found in the Supporting Information). Reaction of **17** with phenylboronic acid under Suzuki[41] conditions gave **26** in 65% yield.

We next chose to apply a slight modification of this methodology to the preparation of **4**, in which the azabicyclic ring system is constrained by a one-carbon bridge (Scheme 5). It was recognized that both **4** and the previously prepared **6** could be obtained via a modification of the initial route. In this case, choice of either a halomethyltetrahydrofuran or a halomethyltetrahydropyran alkylating species would determine the product ring system. A similar sequence was envisioned to that in Scheme 1, but in this instance, imine **34**,[42] derived from 3-acetylpyridine, would be utilized.

Alkylation[42] of imine **34** with 3-(bromomethyl)tetrahydrofuran (**35**),[43] followed by aqueous workup to hydrolyze the imine, gave 1-(pyridin-3-yl)-3-(tetrahydrofuran-3-yl)propan-1-

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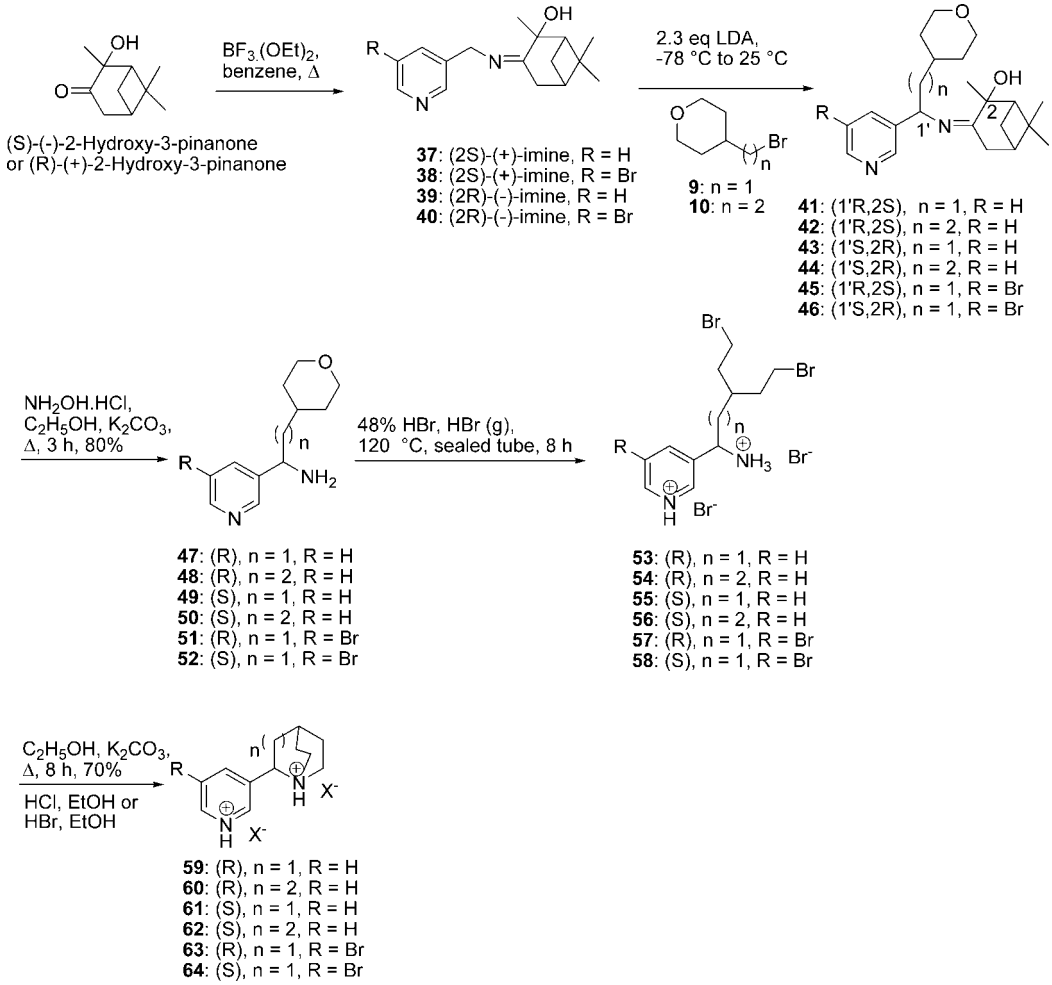
SCHEME 6. Enantioselective Synthesis of Azabicyclo[3.2.2]octanes and Azabicyclo[3.2.2]nonanes (59−64)



one (**32**) in good yield (Scheme 5). Oxime formation under standard conditions, followed by reduction with zinc and acetic acid, afforded **31** in high yield (90%). The tetrahydrofuran ring was cleaved by heating with HBr, as described previously, to give the dibromo intermediate **36**. Subsequent heating with K_2CO_3 in EtOH gave the desired **4**, as an inseparable mixture of *exo* and *endo* diastereomers, in good yield. When bromide **9** was used to alkylate **34**, ketone **33** was produced in ∼90% yield after purification. Conversion of **33** to the oxime and reduction as before afforded intermediate **13**, thus completing a formal synthesis of **6**.

The Enantioselective Synthesis of 2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octanes and 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]-nonanes. It has been well established in the field of drug design that the enantiomers of a given racemate often differentiate from one another on the basis of potency, selectivity, or efficacy at biologic targets. This is exemplified by nicotine itself. (*S*)-Nicotine (**1**) has high affinity for α4β2 (K_i = 2 nM) and moderate affinity for α7 receptors (K_i > 700 nM), whereas (*R*)-nicotine possesses much lower affinity (K_i = 38 nM) for α4β2 and virtually no affinity for α7.[44–46] Since a similar possibility existed for enhanced affinity and/or selectivity residing in a single enantiomer of the 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octanes and 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonanes, we were interested in developing enantioselective versions of the syntheses in Schemes 2 and 5.

There are several examples in the literature where alkylation of imines derived from enantiomerically pure chiral ketones has afforded acyclic quaternary α-amino acids with high enantioselectivities,[47–49] and Crooks et al. have used this technique to synthesize anabasine analogues and derivatives.[50] Recognizing the potential of this modification to control the stereochemical outcome in the key alkylation step, we chose to use the (+)- and (−)-antipodes of 2-hydroxy-3-pinanone to synthesize the desired imines. Imine **37** was synthesized in 52% yield from (−)-2-hydroxy-3-pinanone and 3-aminomethylpyridine, by refluxing the mixture in the presence of $BF_3 \cdot Et_2O$ in

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SCHEME 7. Proposed Mechanism Involving Pyridyne Intermediate

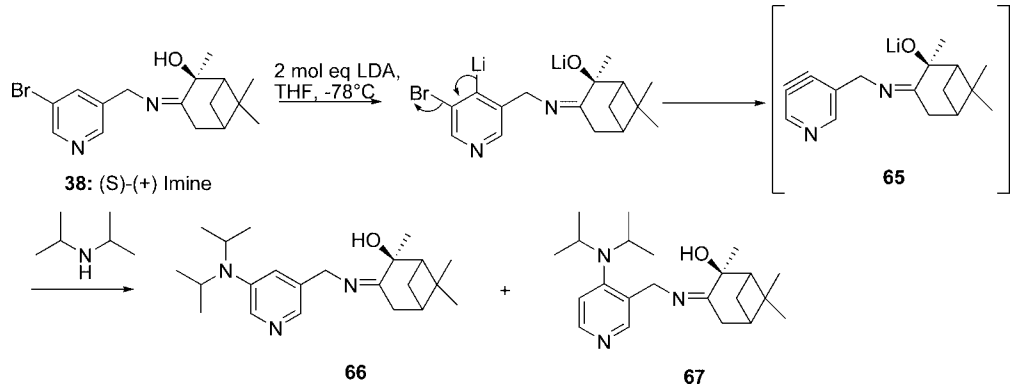

TABLE 1. In Vitro Activity of nAChR Ligands

compd	α4β2 K_i (nM)[a]	α7 K_i (nM)[b]	α4β2 E_{max} (%)[c]	α4β2 EC_{50} (nM)	α3β4 E_{max} (%)[d]	α1βγδ EC_{50} (nM)	α1βγδ E_{max} (%)[e]	α1βγδ EC_{50} (nM)
3	1.0	24.3	40	297	85	1100	130	55
59	0.5	105	S.P. <20[f]		125	375	169	50
61	3.0	40			110	8000	226	362
17	15.0	55000	26	3890	108	2000	116	650
63	0.3							
64	2.0	66						
24	1.0	400000	40	3	52	10000	161	400
25	0.5	3900	45		55	10000	110	3000
26	10.0	4900						
29	2.0	410						
30	3.0							
4	2.5		22	100				
6	0.7	10.9			97	1000	13	100000
60	0.5	19.8	47	120000	63	4620	12	100000
62	3.0	5.0					10	100000

[a] [^{3}H]Nicotine; α4β2 nAChR in rat cortex. [b] Inhibtion of radiolabeled [^{3}H]MLA binding to rat hippocampus receptors. [c] Transfected SH-EP 1 cells, $^{86}Rb^{2+}$ efflux. [d] PC12 cells, $^{86}Rb^{2+}$ efflux. [e] TE-671 cells, $^{86}Rb^{2+}$ efflux. [f] S.P. = single-point response.

benzene for 16 h (Scheme 6). The (+)-2-hydroxy-3-pinanone was likewise used to make imine **39**. Deprotonation of imines **37** and **39** with LDA and alkylation with bromides **9** or **10** at −78 °C in THF gave imines **41**–**44** in 60–70% yield. Imines **41**–**44** were treated with hydroxylamine in ethanol to cleave the chiral auxiliary, affording amines **47**–**50** in good yield. Amines **47**–**50** were then reacted with concentrated HBr in the presence of excess HBr gas at 120 °C in a sealed tube for 8 h, affording dibromides **53**−**56** as the dihydrobromide salts. Subsequent heating of the crude reaction products with K_2CO_3 in EtOH gave the desired cyclized compounds **59**–**64**. We did not determine the enantioselectivity of the alkylation reaction or the enantiomeric excess for intermediates in the sequence. Instead, evidence of the extremely high enantioselectivity of the key alkylation step was made by inference, as the final products **59**–**64** were shown to be essentially single enantiomers by chiral LC analysis. Since minimal purification was performed on intermediates, it is unlikely that the enantiomeric ratio was significantly enhanced in steps subsequent to the alkylation.

Although the chemistry proved to be relatively straightforward when the 5-position of pyridine was unsubstituted, the presence of a bromo substituent in **38** and **40** complicated matters. The yields observed for alkylation products **45** and **46** were approximately 10%, with the majority of the isolated product **66** and **67** arising from a side reaction involving LDA (Scheme 7). These presumably arise via the pyridyne intermediate **65**.

The absolute configurations for products **59**−**64** were assigned on the basis of X-ray crystallographic analysis. Compounds **59**−**62** exhibited two crystallographically independent anion/cation pairs in the asymmetric unit along with a single water molecule. The crystal structures can be found in the Supporting Information (Figures S2, S3, S4, and S5).

A summary of biological data for our targeted compounds is shown in Table 1. All compounds tested had α4β2 K_i < 15nM. Several compounds, **3**, **6**, **59**–**62**, and **64**, also bound to the α7 receptor with high affinity. Unfortunately only the 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane series (**6**, **60**, and **62**) had little or no efficacy at α1βγδ (muscle). In sharp contrast the 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane series is extremely potent at α1βγδ, the reason for this difference between these two series is unknown. However, we do see selectivity within the 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane series for α3β4 (ganglion) with compound **59** (*R* isomer) >10 times the potency of compound **61** (*S* isomer). Binding at the α7 receptor within the 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octane series drops off quickly with susbstitution at the 5′-position on the pyridine (**17**, **24**, **25**, **26**, **29**, and **30**) presumably due to unfavorable interactions with the receptor.

Summary

In summary, we have developed facile methods for the synthesis of a class of high-affinity nAChR ligands, the 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonanes, 2-(pyridin-3-yl)-1-azabicyclo[2.2.2]octanes, and 2-(pyridin-3-yl)-1-azabicyclo[3.2.1]octanes. The general approach of alkylation of a pyridine-containing imine, cyclic

ether cleavage, and bis-aminocyclization was also tolerant to the incorporation of a bromo substituent in the 5-pyridinyl position, allowing elaboration to a number of novel analogues. All compounds have been evaluated for activity at nAChRs, and displayed high affinity at the α4β2 receptor (<15 nM). Pharmacological data for several of these analogues have been previously reported as well as in this paper.[51,52] Compounds **60** and **62** exhibit high affinity for both the α4β2 and α7 receptors. The *R*-enantiomer (**60**) shows some preference for α4β2 over α7, while the *S*-enantiomer (**62**) binds with equal affinity (<10 nM) to the two receptor subtypes. However, more pertinent to a possible side effect profile, compound **60** is significantly less active than compound **62** at human muscle and ganglionic nAChR subtypes. Data for other compounds will be reported in due course.

Experimental Section

Alkylation Procedure A (Preparation of Amines 11, 12, and 13). 1-(Pyridin-3-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-amine (13). To a stirred solution of **7** (2.0 g, 7.3 mmol) in 50 mL of dry THF at −78 °C was added a solution of LDA [prepared from diisopropylamine (0.96 g, 9.6 mmol) and *n*-BuLi (3.8 mL of 2.5 M solution in hexanes, 9.5 mmol) at 0 °C in dry THF (10 mL) under N_2] dropwise via cannula over 5 min. After stirring for 10 min at −78 °C, the reaction mixture was warmed to −40 °C, and 4-(2-bromoethyl)tetrahydropyran (**10,** 1.56 g, 8.08 mmol) in 15 mL of dry THF was added. The reaction mixture was stirred for an additional 12 h, and then quenched with 20 mL of 2 N HCl. The reaction mixture was stirred for an additional 45 min and extracted with EtOAc (4 × 25 mL) to remove the liberated benzophenone. The acidic solution was then basified by the addition of solid $NaHCO_3$ (pH 8–9) and extracted with $CHCl_3$ (5 × 25 mL). The combined organic extracts were dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to afford a viscous brown liquid, which was purified by column chromatography (MeOH/$CHCl_3$, 9:1) to afford compound **13** as a viscous, light brown oil (1.2 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46–8.58 (m, 2H), 7.64–7.72 (m, 1H), 7.22–7.32 (m, 1H), 3.80–4.00 (m, 3H), 3.34–3.48 (t, *J* = 14.1 Hz, 2H), 1.00–1.80 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 141.4, 133.7, 123.5, 67.9, 54.1, 36.3, 34.9, 33.5, 33.1, 33.0.

1-(Pyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (11). By using the procedure described above and replacing **10** with 4-(bromomethyl)tetrahydropyran (**9**),[36,37] 1-(pyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (**11**) was obtained from imine **7** in 90% yield. Purity was determined to be ≥95% by ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52–8.53 (d, *J* = 4.0 Hz, 1H), 8.50–8.52 (dd, *J* = 6.0 Hz, 1H), 7.62–7.65 (m, 1H), 7.26–7.70 (m, 1H), 4.52–4.57 (t, *J* = 14.0 Hz, 1H), 3.80–4.00 (m, 2H), 3.34–3.48 (m, 2H), 1.00–1.80 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 147.7, 138.9, 122.9, 56.3, 49.4, 41.9, 32.4, 26.8, 26.0, 21.0, one quaternary carbon was not observed.

1-(5-Bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (12). Alkylation of imine **8** (1.0 g, 2.9 mmol) with 4-(bromomethyl)tetrahydropyran (**9**)[36,37] (0.5 g, 2.9 mmol) afforded 1-(5-bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine **12** (0.74 g, 90%). This material was 85% pure by ^{1}H NMR and was used crude in subsequent reactions. Further purification could be achieved by distillation of the crude product under reduced pressure in a Kugelrohr apparatus, resulting in material of ≥99% purity as determined by GC-MS. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57–8.56 (d, *J* = 2.1 Hz, 1H), 8.45–8.44 (d, *J* = 2.1 Hz, 1H), 7.86–7.84 (t, *J* = 2.1 Hz, 1H), 4.09–4.06 (t, *J* = 6.8 Hz, 1H), 3.95–3.90 (m, 2H), 3.36–3.29 (t, *J* = 11.7 Hz, 2H), 2.19 (br, 2H), 1.66–1.27 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 146.6, 133.0, 136.6, 121.1, 67.7, 50.3, 46.1, 33.3, 32.8, 31.8.

Alkylation Procedure B (Preparation of Amines 13 and 31). 1-(Pyridin-3-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-amine (13). A solution of LDA [prepared from diisopropylamine (1.0 mL; 7.3 mmol) and *n*-BuLi (2.9 mL of a 2.5 M solution in hexane, 7.25 mmol) at 0 °C in dry THF (10 mL) under N_2] was added dropwise to a solution of isopropyl(1-pyridin-3-ylethylidene)amine **34**[42] (1.2 g, 7.3 mmol) in dry THF (10 mL) at 0 °C under N_2. After 45 min, 4-(2-bromomethyl)tetrahydropyran (**9**, 1.3 g, 7.3 mmol) in 10 mL dry THF, was added to the reaction mixture. The reaction mixture was warmed to ambient temperature, stirred for another 12 h, quenched with 10 mL of saturated aqueous NH_4Cl solution, and stirred for a further 45 min. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a light brown residue. This was purified by column chromatography eluting with acetone in $CHCl_3$ (3:7), to yield 1-(pyridin-3-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propan-1-one (**33**, 1.4 g, 90%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (m, 1H), 8.76–8.84 (m, 1H), 8.20–8.28 (m, 1H), 7.40–7.45 (m, 1H), 3.90–4.15 (m, 2H), 3.30–3.45 (m, 2H), 3.02–2.92 (m, 2H), 1.20–1.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 153.5, 149.6, 135.3, 132.1, 123.6, 67.9, 35.6, 34.5, 32.9, 30.7.

Solid K_2CO_3 (4.4 g, 32 mmol) was added to a stirred suspension of hydroxylamine hydrochloride (2.2 g, 32 mmol) in 20 mL of MeOH at 0 °C. Intermediate **33** (1.4 g, 6.4 mmol) in MeOH (5 mL) was added and the reaction mixture was stirred for 2 h, then filtered and concentrated in vacuo. Zinc dust (6.50 g, 100 mmol) was added, over a 15 min period, to a suspension of the crude oxime (obtained as a mixture of cis- and trans-isomers) in 20 mL of EtOH (95%) and 8 mL of acetic acid. The reaction was stirred for 4 h, then filtered through a pad of diatomaceous earth, washing with EtOH (50 mL). The filtrate was evaporated under reduced pressure to afford a white solid, which was basified with NaOH (∼10 mL, 50% aqueous, pH 9–10) and extracted with $CHCl_3$ (6 × 25 mL). The combined $CHCl_3$ extracts were dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to afford a viscous oil (0.70 g, 93% yield). ^{1}H ^{13}C NMR spectra were identical with those generated from **13** from the Alkylation Procedure A.

1-(Pyridin-3-yl)-3-(tetrahydrofuran-3-yl)propan-1-amine (31). By using the procedure described above for **13**, amine **31** was synthesized from **32**, hydroxylamine, and Zn dust in 90% yield as a pair of diastereomers and was taken as such to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58–8.48 (m, 2H), 7.68–7.64 (m, 1H), 7.30–7.24 (m, 1H), 3.96–3.66 (m, 3H), 3.33–3.22 (m, 1H), 2.18–21.95 (m, 2H), 1.75–1.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148.5, 141.3, 133.8, 123.6, 73.2, 67.8, 54.1, 39.2, 38.3, 32.3, 29.9.

1-(Pyridin-3-yl)-3-(tetrahydrofuran-3-yl)-propan-1-one (32). By using the procedure described above for **33**, ketone **32** was synthesized from **34** and 3-(bromomethyl)tetrahydrofuran (**35**).[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14–9.18 (m, 1H), 8.74–8.80 (m, 1H), 8.14–8.24 (m, 1H), 7.38–7.44 (m, 1H), 3.82–3.96 (m, 2H), 3.70–3.80 (m, 1H), 3.82–4.20 (m, 1H), 2.98–3.24 (m, 2H), 2.20–2.34 (m, 1H), 2.02–2.16 (m, 1H), 1.78–1.87 (m, 2H), 1.50–1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 153.5, 149.5, 135.3, 131.9, 123.6, 73.1, 67.8, 38.7, 37.5, 32.2, 27.2.

Procedures for Ether Cleavage and Amine Cyclization (Compounds 3, 6, 17, and 4). 2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (6). HBr gas was passed through a solution of amine **13** (1.80 g, 8.73 mmol) in 48% HBr (10 mL) in a high-pressure reaction tube until the solution was saturated. The pressure tube was then sealed and heated in an oil bath at 120 °C for 12 h. The reaction mixture was cooled in an ice–water bath, and the contents transferred to a round-bottomed flask. Repeated azeotropic distillation with EtOH

(51) Bencherif, M.; Schmitt, J. D.; Bhatti, B. S.; Crooks, P.; Caldwell, W. S.; Lovette, M. E.; Fowler, K.; Reeves, L.; Lippiello, P. M. *J. Pharmacol. Exp. Ther.* **1998**, *284* (3), 886–894.

(52) Caldwell, W. S.; Bencherif, M.; Dull, G. M.; Crooks, P. A.; Lippiello, P. M.; Bhatti, B. S.; Deo, N. M.; Ravard, A. PCT Int. Appl., WO A1 9900385, 1999.

under reduced pressure removed the HBr, leaving a yellow solid (**17**). This was taken up in EtOH (150 mL), and the solution was heated under reflux in the presence of solid K_2CO_3 (5 g) for 10 h. The reaction mixture was filtered through a diatomaceous earth plug, which was washed with 50 mL of EtOH. The EtOH filtrates were combined and concentrated under reduced pressure to give a white solid, which was then dissolved in 100 mL of $CHCl_3$. The resulting solution was passed through a pad of silica gel, eluting with additional $CHCl_3$. The light brown liquid obtained after the removal of $CHCl_3$ was distilled under reduced pressure (110–112 °C at 4 mmHg), using a Kugelrohr distillation apparatus. This afforded 2-(pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (**6**) as a colorless liquid (1.3 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62–8.64 (d, J = 6 Hz, 1H), 8.42–8.50 (m, 1H), 7.72–7.82 (m, 1H), 7.22–7.30 (m, 1H), 3.98–4.08 (dd, J = 15 Hz, 1H), 3.22–3.98 (m, 1H), 3.08–3.21 (m, 1H), 2.82–3.08 (m, 2H), 1.60–2.10 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 143.9, 142.3, 132.5, 127.6, 66.8, 50.3, 40.9, 32.3, 25.8, 24.7, 24.3, 20.6; GC-MS M^+ 202. The free base was dissolved in HCl-saturated EtOH and sonicated for 5 min. Solvent was removed in vacuo to yield a solid residue that was recrystallized from 2-propanol to afford the di-HCl salt monohydrate as a brown crystalline solid (mp 270–272 °C). ^{1}H NMR (300 MHz, D_2O) δ 8.82 (s, 1H), 8.76–8.78 (d, J = 6 Hz, 1H), 8.60–8.63 (d, J = 9 Hz, 1H), 7.96–8.00 (t, J = 12 Hz, 1H), 4.80–4.84 (d, J = 12 Hz, 1H), 3.40–3.80 (m, 2H), 3.20–3.40 (m, 1H), 3.10–3.23 (m, 1H), 2.20–2.50 (m, 2H), 1.92–2.26 (m, 6H), 1.74–1.88 (m, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 169.4, 147.3, 136.1, 132.4, 124.5, 67.2, 49.1, 41.7, 31.8, 25.2, 24.1, 23.8, 20.1; GC-MS M^+ 202. Anal. Calcd for $C_{13}H_{18}N_2 \cdot 2HCl$: C, 56.25; H, 7.27; N, 10.18. Found: C, 53.63; H, 7.12; N, 9.59. (Consistent with 1 mol equiv of water.) The following conditions were used to determine retention times for each enaniomer: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention times 7.4 and 8.4 min.

2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane (3). Compound **3** (0.94 g, 86% yield) was obtained by using the above sequence, starting with amine **11** (1.2 g, 5.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67–8.66 (d, J = 2.0 Hz, 1H), 8.47–8.49 (m, 1H), 7.73–7.77 (m, 1H), 7.24–7.28 (m, 1H), 3.99–4.04 (t, J = 9.0 Hz, 1H), 2.89–3.20 (m, 2H), 2.75–3.20 (q, J = 7.5 Hz, 2H), 2.15–2.23 (m, 1H), 1.90–1.98 (m, 1H), 1.40–1.80 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 147.1, 138.9, 134.9, 122.9, 56.3, 49.4, 42.0, 32.4, 26.8, 25.9, 21.8; GC-MS M^+ 188. Dihydrochloride salt, monohydrate (mp 197–200 °C): ^{1}H NMR (300 MHz, D_2O) δ 9.00 (s, Hz, 1H), 8.80–8.83 (d, J = 9.0 Hz, 1H), 8.60–8.84 (m, 1H), 7.88–8.24 (m, 1H), 4.98–5.06 (t, J = 9.0 Hz, 1H), 3.68–3.80 (m, 1H), 3.45–3.52 (m, 2H), 3.15–3.23 (m, 1H), 2.30–2.50 (m, 3H), 1.92–2.22 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 150.0, 149.7, 144.8, 134.7, 129.0, 61.3, 51.8, 44.7, 30.4, 25.2, 24.7, 23.0 (one more than theoretical); GC-MS M^+ 188. Anal. Calcd for $C_{12}H_{16}N_2 \cdot 2HCl$: C, 55.17; H, 6.89; N, 10.72. Found: C, 50.91; H, 7.12; N, 9.80. (Consisent with 1 mol equiv of water.) The following conditions were used to determine retention times for each enatiomer: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention times 7.8 and 10.9 min.

2-(5-Bromopyridin-3-yl)-1-azabicyclo[2.2.2]octane (17). By using the procedure described above, **17** (132 mg, 75%) was synthesized from 1-(5-bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (**12**, 0.19 g, 0.66 mmol). The free base was converted to the dihydrobromide salt, which was obtained as white needles (sublimed at 198–200 °C, dec at 210 °C). ^{1}H NMR (300 MHz, D_2O) δ 8.75 (d, J = 1.8 Hz, 1H), 8.67 (d, J = 1.8 Hz, 1H), 8.44–8.42 (t, J = 1.8 Hz, 1H), 4.84–4.78 (t, J = 6.8 Hz, 1H), 3.62–3.51 (m, 1H), 3.40–3.24 (m, 1H), 3.20–3.10 (m, 2H), 2.30–2.11, (m, 3H), 2.00–1.79 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 148.7, 147.1, 141.3, 137.5, 120.7, 55.9, 49.4, 42.0, 32.6, 26.7, 25.9, 21.8. Anal. Calcd for $C_{12}H_{15}N_2Br \cdot 2HBr$: C, 33.60; H, 3.99; N, 6.53; Br, 55.88. Found: C, 33.70; H, 4.21; N, 6.25; Br, 55.60.

2-(Pyridin-3-yl)-1-azabicyclo[3.2.1]octane (4). By using the procedure described above, **4** (1.37 g, 88%) was synthesized from 1-pyridin-3-yl-3-(tetrahydrofuran-3-yl)propylamine (**31**, 1.7 g, 8.2 mmol) as an approximately 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72–8.74 (m, $^1/_2$H), 8.60–8.63 (m, $^1/_2$H), 8.42–8.48 (m, 1H), 7.82– 7.85 (m, $^1/_2$H), 7.72–7.78 (m, $^1/_2$H), 7.20–7.30 (m, 1H), 3.90–3.98 (m, 1H), 3.00–3.20 (m, 2H), 2.52–2.86 (m, 2H), 1.50–2.31 (m, 7H). Dihydrochloride salt: ^{1}H NMR (300 MHz, D_2O) δ 8.52–8.60 (m, 1H), 8.42–8.48 (m, 1H), 7.85–7.88 (m, 1H), 7.38–7.46 (m, 1H), 4.70–4.7.45 (m, 1H), 3.20–3.80 (m, 3H), 2.60–3.20 (m, 1H), 2.60–2.80 (m, 1H), 1.6–2.48 (m, 6H); ^{13}C NMR (75 MHz, D_2O) δ 152.9, 152.4, 151.8, 141.1, 140.6, 133.5, 127.7, 127.6, 67.0, 65.1, 63.3, 56.0, 55.1, 49.2, 36.3, 35.8, 30.6, 29.6, 29.3, 29.2, 23.3, 21.2; GC-MS M^+ 188. GC-MS of the free base regenerated from the salt confirms the presence of two diastereomers in the ratio of 26:74, which indicates that during the crystallization of the salt, differential solubility resulted in enrichment in one of the diastereomers. Anal. Calcd for $C_{12}H_{16}N_2 \cdot 2HCl$: C, 54.43; H, 7.00; N, 10.58. Found C, 54.44; H, 7.09; N, 10.47. (Consistent with correction for 0.2 mol equiv of H_2O.)

Procedures for Preparation of Analogues 22–26, 29, and 30. 2-(5-Aminopyridin-3-yl)-1-azabicyclo[2.2.2]octane (22). 2-(5-Bromopyridin-3-yl)-1-azabicyclo[2.2.2]octane **17** (1.0 g, 3.8 mmol) and concentrated aqueous NH_4OH (150 mL) were added to a pressure tube containing CuI (75 mg, 10 mol %). The tube was sealed and heated at 120 °C for 16 h. The tube was cooled to room temperature, and the reaction mixture was concentrated by rotary evaporation at 60 °C (bath temperature). The resulting solid was dissolved in CH_3OH and filtered through diatomaceous earth to remove copper salts. The solvent was removed by rotary evaporation, and the residue was purified on silica gel, eluting with a $CH_3OH-CHCl_3$ gradient (0–20% CH_3OH) to give **22** as an orange solid (0.74 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.96–7.97 (d, J = 2.7 Hz, 1H), 7.09 (m, 1H), 3.97–3.91 (t, J = 8.7 Hz, 1H), 3.62 (m, 2H), 3.20–2.98 (m, 2H), 2.82–2.68 (m, 2H), 2.20–2.05 (m, 1H), 1.85–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 135.6, 120.9, 56.2, 49.4, 42.0, 32.3, 26.8, 25.9, 21.8, two quaternary carbons were not observed; mp 165 °C. The free base was dissolved in HCl-saturated EtOH (20 mL) and sonicated for 10 min. Solvent was removed in vacuo to yield a solid that was recrystallized from 2-propanol to afford the di-HCl salt as a yellow crystalline solid. ^{1}H NMR (300 MHz, D_2O) δ 8.15 (s, 1H), 8.02 (s, 1H), 7.80 (s, 1H), 4.84–4.78 (t, J = 6.6 Hz, 1H), 3.62–3.51 (m, 1H), 3.40–3.24 (m, 1H), 3.20–3.10 (m, 2H), 2.30–2.11 (m, 3H), 2.00–1.79 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 147.5, 134.0, 129.5, 129.1, 127.9, 57.4, 48.9, 41.9, 27.2, 22.1, 21.5, 19.8; mp 276–279 °C; GC-MS M^+ 203. Anal. Calcd for $C_{12}H_{17}N_3 \cdot 2HCl$: C, 51.35; H, 7.00; N, 14.97; Cl, 25.26. Found C, 51.30; H, 6.98; N, 14.70; Cl, 25.10. (Consistent with 0.25 mol equiv of H_2O.)

2-(5-Ethoxypyridin-3-yl)-1-azabicyclo[2.2.2]octane (24). To a stirred solution of **22** (25 mg of di-HCl salt, 0.091 mmol) in dry EtOH (3 mL) was added isoamyl nitrite (0.1 mL, 0.74 mmol) and the mixture was heated at reflux for 2 h. The mixture was then cooled to ambient temperature, and the solvent was removed in vacuo to yield a viscous, brown oil, which solidified upon addition of dry ether. The product thus obtained was dissolved in $CHCl_3$ and kept overnight at 4 °C to induce crystallization. The resulting solids were filtered, washed with ether, and dried under vacuum to yield **24** as its di-HCl salt (10 mg, 51%), as colorless needles. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (s, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 5.08–5.02 (m, 1H), 4.35 (m, 2H), 3.75–3.65 (m, 1H), 3.42–3.35 (m, 1H), 3.20–3.14 (m, 2H), 2.38–2.30, (m, 3H), 2.15–1.80 (m, 4H), 1.42–1.38 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.6, 136.9, 135.5, 132.8, 132.3, 67.3, 58.7, 49.6, 42.8, 28.4, 23.3, 22.9, 21.7, 14.6; GC-MS M^+ 232.

2-(5-Isopropoxypyridin-3-yl)-1-azabicyclo[2.2.2]octane (25). By using the procedure described above for **24**, compound **25** (as its di-HCl salt) was synthesized from **22** (28 mg, 55%). ^{1}H NMR (300

MHz, D_2O) δ 8.38–8.35 (m, 2H), 7.60 (s, 1H), 4.88–4.76 (m, 2H), 3.72–3.60 (m, 1H), 3.56–3.42 (m, 1H), 3.36–3.14 (m, 2H), 2.40–2.31, (m, 3H), 2.15–1.92 (m, 4H), 1.40 (d, J = 3.6 Hz, 6H); GC-MS M^+ 246. Anal. Calcd for $C_{15}H_{22}N_2O \cdot 2HCl$: C, 56.43; H, 37.58; N, 8.77; Cl, 22.21. Found: C, 56.39; H, 7.65; N, 8.62; Cl, 22.05.

2-(5-Phenylpyridin-3-yl)-1-aza-bicyclo[2.2.2]octane (26). DME (5.0 mL) and H_2O (2.0 mL) were added to a vial containing **17** (100 mg, 0.375 mmol), phenylboronic acid (92 mg, 0.75 mmol), $Pd(PPh_3)_4$ (22 mg, 5 mol %), and Na_2CO_3 (80 mg, 0.75 mmol). The vial was purged with argon (evacuated and filled 3 times), capped, and then heated under reflux for 12 h. The vial was cooled to ambient temperature, and the solvent was removed in vacuo. The crude residue was suspended in saturated NH_4Cl solution (25 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a viscous oil. Purification on an ISCO Combiflash silica gel column, eluting with a CH_2Cl_2:EtOAc gradient (0–100%), afforded **26** as a yellow oil (65 mg, 65%). ^{1}H NMR (300 MHz, D_2O) δ 9.05 (s, 1H), 8.85 (s, 1H), 8.75 (s, 1H), 7.70–7.65, (m, 2H), 7.58–7.50 (m, 3H), 5.02–4.96 (t, J = 6.6 Hz, 1H), 3.60–3.50 (m, 1H), 3.38–3.32 (m, 1H), 3.22–3.14 (m, 2H), 2.40–2.31 (m, 3H), 2.05–1.89 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 150.0, 149.7, 144.9, 134.7, 128.9, 61.3, 51.9, 44.7, 30.5, 25.2, 24.7, 23.0. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.62; N, 10.59. Found: C, 81.50; H, 7.20; N, 10.87; LC-MS $(M + H)^+$ 265.2.

5-(1-Azabicyclo[2.2.2]oct-2-yl)pyridin-3-ol (23). To a solution of compound **22** (87 mg of di-HCl salt, 0.32 mmol) in 2 mL of 3 M sulfuric acid, cooled in an ice bath, was added sodium nitrite (33 mg, 0.47 mmol) in two portions over several minutes. The mixture was stirred for 30 min, then placed in a hot-water bath at 55 °C for 45 min. The mixture was cooled, adjusted to pH ~8, and concentrated under reduced pressure. The residue was triturated with hot CH_3OH (2 × 10 mL), and the extracts filtered and concentrated to give ~50 mg (82%) of crude product **23**. This material was not characterized, but used directly to produce compounds **29** and **30**.

Typical Procedure for the Enatioselective Synthesis of Azabicyclo[3.2.2]nonanes and Azabicyclo[2.2.2]octanes. Typical Procedure for Formation of Imines 37–40. 2,6,6-Trimethyl-3-(pyridine-3-ylmethylimino)bicycle[3.1.1]heptan-2-ol (37).[53,54] To a stirred solution of (−)-2-hydroxy-3-pinanone (10.0 g, 59.4 mmol) in 500 mL of benzene was added pyridinylmethylamine (6.66 mL, 65.4 mmol) in one portion. Boron trifluoride diethyl etherate (0.70 mL, 5.90 mmol) was added in one portion and the reaction was heated at reflux for 5 h under N_2 and then stirred at room temperature for an additional 16 h. The solvents were then removed in vacuo, and the resulting residue was stirred in 100 mL of saturated aqueous $NaHCO_3$ for 1 h and extracted with $CHCl_3$ (3 × 100 mL). The extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting dark brown oil was purified via chromatography, eluting with a gradient of $CHCl_3$ to 20% MeOH−$CHCl_3$. The yellow oil was dissolved in 50 mL of hot EtOAc and placed in the freezer at −4 °C for 16 h. The resulting solid was filtered, washed with cold EtOAc, and dried under high vacuum to yield off-white crystals **37** (8.0 g, 53%).

Typical Procedure for Alkylation of Imines 37–40. (1′*R*,2*S*)-2,6,6-Trimethyl-3-[1-pyridin-3-yl-3-(tetrahydropyran-4-yl)propylimino]bicyclo[3.1.1]heptan-2-ol (42). LDA was prepared from BuLi (2.5 M, 6.23 mL, 15.6 mmol) and diisopropylamine (2.19 mL, 15.6 mmol) in dry THF (20 mL) at 0 °C. The solution was warmed to room temperature and stirred for 30 min. The LDA solution was added dropwise via cannula to a solution of **37** (2.0 g, 7.8 mmol) in dry THF (80 mL) at −78 °C and stirred for 60 min, at which point 4-(2-bromoethyl)tetrahydropyran (**10**, 2.69 g, 14.0 mmol) was added. The solution was warmed to ambient temperature and stirred for 16 h. Saturated aqueous NH_4Cl (100 mL) was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated. The resulting material was purified via chromatography eluting with 25% acetone/$CHCl_3$ to yield **42** (1.85 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (m, 2H), 8.18 (br, 1H), 7.38–7.42 (m, 1H), 4.56–4.66 (t, J = 6.6 Hz, 1H), 3.88–4.00 (m, 2H), 3.30–3.44 (dt, J = 6.6 Hz, 2H), 2.88–2.92 (d, J = 24 Hz, 1H), 2.56–2.60 (d, J = 24 Hz, 1H), 2.22–2.38 (m, 2H), 2.02–2.12 (m, 3H), 1.80–1.92 (m, 3H), 1.40–1.65 (m, 3H), 1.15–1.38 (m, 8H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148.3, 138.9, 134.5, 123.6, 67.9, 60.9, 49.9, 38.2, 38.2, 35.6, 34.8, 33.5, 33.5, 33.4, 33.1, 33.0, 28.4, 27.9, 27.2, 22.9; $[\alpha]^{25}_D$ +30.0 (*c* 1.02, MeOH).

(2*S*,*Z*)-3-((*R*)-1-(5-Bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (45). Following the procedure described above for **42**, LDA (2.1 mol equiv), **9** (1.8 mol equiv), and **38** (3.0 g, 8.9 mmol) in 50 mL of dry THF afforded **45** (1.73 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52–8.51 (d, J = 3.0 Hz, 1H), 8.42–8.41 (d, J = 3.0 Hz, 1H), 7.84–7.82 (d, J = 0.6 Hz, 1H), 4.32–4.40 (dd, J = 12.0 Hz, 1H), 3.84–3.80 (m, 4H), 3.18–3.33 (m, 2H), 2.62–2.58 (m, 1H), 2.30–2.38 (m, 1H), 2.10–2.20 (m, 1H), 1.98–1.92 (t, J = 9.0 Hz, 1H), 1.92–1.82 (m, 1H), 1.80–1.62 (m, 4H), 1.52–1.00 (m, 9H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.2 139.0, 136.0, 120.6, 68.0, 67.9, 67.7, 61.5, 39.4, 38.3, 38.2, 35.6, 34.8, 33.3, 33.1, 32.2, 30.7, 28.4, 27.9, 27.2, 22.9; $[\alpha]^{20}_D$ +15 (*c* 1.0,$CHCl_3$).

(2*R*,*Z*)-3-((*S*)-1-(5-Bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (46). Following the procedure described above for **42**, LDA (2.1 mol equiv), **9** (1.8 mol equiv), and **40** (3.0 g, 8.9 mmol) in 50 mL of dry THF afforded **45** (1.6 g, 42%). $[\alpha]^{20}_D$ −15 (*c* 1.0, $CHCl_3$).

Typical Procedure for Hydrolysis of Imines 41–46 To Yield Amines 47–52. (*R*)-1-Pyridin-3-yl-3-(tetrahydropyran-4-yl)propylamine (48). A solution of **42** (1.85 g, 5.0 mmol) and hydroxylamine hydrochloride (2.00 g, 28.8 mmol) in EtOH (20 mL) was heated at reflux for 16 h. The mixture was then cooled to room temperature, filtered through diatomaceous earth, washed with EtOH, concentrated, and purified via chromatography, using 10–20% MeOH/$CHCl_3$ with 1% NH_4OH, to yield **48** (0.88 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.55 (d, J = 5 Hz, 1H), 7.93 (d, J = 10 Hz, 1H), 7.33–7.43 (m, 1H), 4.23–4.30 (m, 1H), 3.90–3.94 (dd, J = 10 Hz, 2H), 3.64–3.70 (m, 1H). 3.33–3.43 (t, J = 10 Hz, 2H), 2.22 (m, 2H), 2.02 (m, 3H), 1.65 (m, 4H), 1.05 (m, 1H); $[\alpha]^{25}_D$ +5.0 (*c* 1.0, MeOH).

Compounds **47** and **49**–**52** were synthesized following the procedure outlined above and the desired material for each reaction was isolated and used directly in the cyclization reaction described in detail below.

(*R*)-1-(Pyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (47). A solution of **41** (1.40 g, 3.92 mmol) and 20 mL of ethanolic hydroxylamine hydrochloride solution were reacted together as described for **48** to give **47** (650 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56–8.55, d (d, J = 3.0 Hz, 1H), 8.51–8.49 (dd, J = 2.4, 7.2 Hz, 1H), 7.71–7.64, (m, 1H), 7.32–7.24, (m, 1H), 4.10–4.02 (t, J = 7.5 Hz, 1H), 3.98–3.88, (m, 2H), 3.38–3.28 (dt, J = 2.1, 12.6 Hz, 2H), 1.90–1.22, (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.5, 133.7, 123.6, 67.8, 50.7, 46.6, 33.3, 32.9, 31.9; $[\alpha]^{20}_D$ +3.50 (*c* 1.0, $CHCl_3$).

(*S*)-1-Pyridin-3-yl-3-(tetrahydropyran-4-yl)propylamine (50). A solution of **44** (1.5 g, 4.0 mmol) and 20 mL of ethanolic hydroxylamine hydrochloride solution were reacted together as described for **48** to give **50** (0.67 g, 75%).

(*S*)-1-(Pyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (49). A solution of **43** (1.20 g, 3.37 mmol) and 20 mL of ethanolic hydroxylamine hydrochloride solution were reacted together as described for **48** to give **49** (520 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56–8.55 (d, J = 2.0 Hz, 1H), 8.51–8.49 (dd, J = 1.7,

(53) Swango, J. H.; Bhatti, B. S.; Qureshi, M. M.; Crooks, P. A. *Chirality* **1999**, *11* (4), 316–318.

(54) Ayers, J. T.; Sonar, V. N.; Parkin, S.; Dwoskin, L. P.; Crooks, P. A. *Acta Crystallogr., Sect. E* **2005**, *61*, o2682–o2684.

6.6 Hz, 1H), 7.70–7.64 (m, 1H), 7.32–7.24 (m, 1H), 4.10–4.02 (t, $J = 7.2$ Hz, 1H), 3.98–3.88 (m, 2H), 3.38–3.28 (dt, $J = 2.0$, 11.5 Hz, 2H), 1.70–1.22 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 147.7, 138.9, 134.9, 122.9, 56.3, 49.5, 41.9, 32.4, 26.8, 25.9, 21.8; $[\alpha]^{20}_D$ −5.18 (*c* 1.35, $CHCl_3$).

(*R*)-1-(5-Bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (51). A solution of **45** (1.3 g, 3.0 mmol) and 20 mL of ethanolic hydroxylamine hydrochloride solution were reacted together as described for **48** to give **51** (640 mg, 75%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57–8.56 (d, $J = 6$ Hz, 1H), 8.45–8.44 (d, $J = 6$ Hz, 1H), 7.85–7.84 (m, 1H), 4.08–4.03 (t, $J = 7.5$ Hz, 1H), 3.96–3.95 (m, 1H), 3.92–3.90 (m, 1H), 3.38–3.30 (m, 2H), 1.72–1.28 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 146.5, 143.6, 136.5, 121.0, 67.7, 50.3, 50.2, 46.5, 33.3, 32.7, 31.3; $[\alpha]^{20}_D$ +4.5 (*c* 1.0, $CHCl_3$).

(*S*)-1-(5-Bromopyridin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanamine (52). A solution of **46** (1.4 g, 3.2 mmol) and 20 mL of ethanolic hydroxylamine hydrochloride solution were reacted together as described for **48** to give **51** (0.74 g, 80%). $[\alpha]^{20}_D$ −4.5 (*c* 1.0, $CHCl_3$).

Typical Cyclization Reaction for Formation of 59–64. (*R*)-2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane dihydrochloride (60). HBr gas was passed through a solution of amine **48** (0.88 g, 4.0 mmol) in 48% HBr (20 mL) in a high-pressure reaction tube until the solution was saturated. The pressure tube was sealed and heated in an oil bath at 120 °C for 8 h. The reaction mixture was cooled in an ice–water bath, and the contents transferred to a round-bottomed flask. Repeated azeotropic distillation with EtOH under reduced pressure removed the HBr, leaving a yellow solid (**54**). This was taken up in ethanol (250 mL) and heated under reflux in the presence of solid K_2CO_3 (20 g) for 16 h. The reaction mixture was filtered through a diatomaceous earth plug, which was washed with 50 mL of EtOH. Rotary evaporation of the EtOH from the filtrates left a white solid, which was purified via column chromatography, eluting with 10% MeOH/$CHCl_3$ with 1% NH_4OH, followed by Kugelrohr distillation (110–112 °C at 4 mmHg), to yield 528 mg of the desired free base as a yellow oil (65%). The free base was dissolved in HCl-saturated ethanol and sonicated for 5 min. Solvent was removed in vacuo to yield a solid residue that was recrystallized from 2-propanol to afford the di-HCl salt monohydrate as a brown crystalline solid (mp 258–260 °C). ^{1}H NMR (300 MHz, D_2O) δ 8.82 (s, 1H), 8.76–8.78 (d, $J = 6$ Hz, 1H), 8.60–8.63 (d, $J = 9$ Hz, 1H), 7.96–8.00 (t, $J = 12$ Hz, 1H), 4.80–4.84 (d, $J = 12$ Hz, 1H), 3.40–3.80 (m, 2H), 3.20–3.40 (m, 1H), 3.10–3.23 (m, 1H), 2.20–2.50 (m, 2H), 1.92–2.26 (m, 6H), 1.74–1.88 (m, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 169.4, 147.3, 136.1, 132.4, 124.5, 67.2, 49.1, 41.7, 31.8, 25.2, 24.1, 23.8, 20.1; GC-MS M^+ 202. Mp 211–215 °C; $[\alpha]^{25}_D$ + 4.0 (*c* 1.0, MeOH). Anal. Calcd for $C_{13}H_{18}N_2 \cdot 2HCl$: C, 56.25; H, 7.27; N, 10.18. Found: C, 53.63; H, 7.12; N, 9.59. (Consistent with 1 mol equiv of water.) The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength, tetention time $t_{60} = 7.4$ min. There was no detectable compound **62**.

(*R*)-2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane Dihydrochloride (59). By using the procedure described above for compound **60**, compound **59** (223 mg of di-HCl salt, 88%) was synthesized from compound **47** (0.20 g, 0.97 mmol). ^{1}H NMR (300 MHz, D_2O) δ 9.00 (s, 1H), 8.80–8.83 (d, $J = 9$ Hz, 1H), 8.60–8.84 (m, 1H), 7.88–8.24 (m, 1H), 4.98–5.06 (t, $J = 18$ Hz, 1H), 3.68–3.80 (m, 1H), 3.45–3.52 (m, 2H), 3.15–3.23 (m, 1H), 2.30–2.50 (m, 3H), 1.92–2.22 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 152.8, 152.5, 141.2, 133.1, 127.7, 61.7, 51.7, 44.4, 30.4, 25.2, 24.7, 23.1; mp 211–215 °C; $[\alpha]^{25}_D$ + 59.8 (*c* 0.98, MeOH). Anal. Calcd for $C_{12}H_{16}N_2.2HCl$: C, 55.17; H, 6.89; N, 10.72. Found: C, 51.07; H, 7.24; N, 9.94. (Consistent with 1 mol equiv of water.) The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention time $t_{59} = 7.8$. There was no detectable compound **61**. (*R*)-2-(Pyridin-3-yl)quinuclidine (**59**) (free-base): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67–8.66 (t, $J = 1.0$ Hz, 1H), 8.49–8.47 (dd, $J = 3.0$ Hz, 1H), 7.77–7.73 (m, 1H), 7.28–7.24 (m, 1H), 4.06–4.00 (t, $J = 9.0$ Hz, 1H), 3.19–2.99 (m, 2H), 2.76–2.71 (q, $J = 7.5$ Hz, 2H), 2.05 (s, 1H), 1.96–1.92 (m, 1H), 1.77–1.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 147.7, 138.9, 134.8, 122.9, 56.3, 49.4, 41.9, 32.4, 26.7, 25.9, 21.8; $[\alpha]^{25}_D$ +59.8 (*c* 0.97, $CHCl_3$).

(*S*)-2-(Pyridin-3-yl)-1-azabicyclo[2.2.2]octane dihydrochloride (61). By using the procedure described above for compound **60**, compound **61** (213 mg of di-HCl salt, 84%) was synthesized from **49** (0.20 g, 0.97 mmol). ^{1}H NMR (300 MHz, D_2O) δ 9.00 (s, 1H), 8.80–8.83 (d, $J = 9$ Hz, 1H), 8.60–8.84 (m, 1H), 7.88–8.24 (m, 1H), 4.98–5.06 (t, $J = 18$ Hz, 1H), 3.68–3.80 (m, 1H), 3.45–3.52 (m, 2H), 3.15–3.23 (m, 1H), 2.30–2.50 (m, 3H), 1.92–2.22 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 150.0, 149.7, 144.8, 134.7, 129.0, 61.3, 51.8, 44.7, 30.4, 25.2, 24.7, 23.0; mp 203–205 °C; $[\alpha]^{25}_D$ −49.2 (*c* 1.18, MeOH). Anal. Calcd for $C_{12}H_{16}N_2.2HCl$: C, 55.17; H, 6.89; N, 10.72. Found: C, 51.50; H, 7.20; N, 9.97. (Consistent with 1 mol equiv of water.) The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention times $t_{61} = 10.9$. There was no detectable compound **59**.

(*S*)-2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane dihydrochloride (62). By using the procedure described above for compound **60**, compound **62** (123 mg of di-HCl salt, 45%) was synthesized from **50** (0.65 g, 4.0 mmol). ^{1}H NMR (300 MHz, D_2O) δ 8.82 (s, 1H), 8.76–8.78 (d, $J = 6.0$ Hz, 1H), 8.60–8.63 (d, $J = 9.0$ Hz, 1H), 7.96–8.00 (t, $J = 6.0$ Hz, 1H), 4.80–4.84 (d, $J = 12.0$ Hz, 1H), 3.40–3.80 (m, 2H), 3.20–3.40 (m, 1H), 3.10–3.23 (m, 1H), 2.20–2.50 (m, 2H), 1.92–2.26 (m, 6H), 1.74–1.88 (m, 1H); mp 258–260 °C; $[\alpha]^{25}_D$ −4.0 (*c* 1.0, MeOH). Anal. Calcd for $C_{13}H_{18}N_2.2HCl$: C, 56.25; H, 7.27; N, 10.18. Found: C, 53.53; H, 7.02; N, 9.69. (Consistent with 1 mol equiv of water.) The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention time $t_{60} = 7.4$, $t_{62} = 8.4$ min, ratio (0.3:99.7), ee 99.4%.

(*R*)-2-(5-Bromopyridin-3-yl)-1-azabicyclo[2.2.2]octane dihydrobromide (63). By using the procedure described above for compound **60**, compound **63** (43 mg of di-HBr salt, 80%) was synthesized from **51** (50 mg, 0.17 mmol). ^{1}H NMR (300 MHz, D_2O) δ 8.75 (d, $J = 1.8$ Hz, 1H), 8.67 (d, $J = 1.8$ Hz, 1H), 8.44–8.42 (t, $J = 1.8$ Hz, 1H), 4.84–4.78 (t, $J = 6.8$ Hz, 1H), 3.62–3.51 (m, 1H), 3.40–3.24 (m, 1H), 3.20–3.10 (m, 2H), 2.30–2.11, (m, 3H), 2.00–1.79 (m, 4H); mp 196–201 °C; $[\alpha]^{25}_D$ + 39.0 (*c* 1.02, MeOH). Anal. Calcd for $C_{12}H_{15}N_2Br \cdot 2HBr$: C, 33.60; H, 3.99; N, 6.53; Br, 55.88. Found: C, 33.82; H, 4.07; N, 6.48; Br, 55.71.

(*R*)-2-(5-Bromopyridin-3-yl)quinuclidine (63) (free-base). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.54 (s, 1H), 7.93–7.92 (d, $J = 0.9$ Hz, 1H), 4.04–3.98 (t, $J = 9.0$ Hz 1H), 3.19–2.98 (m, 2H), 2.81–2.70 (m, 2H), 1.99–1.90 (m, 1H), 1.71–1.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 147.0, 140.9, 137.6, 120.7, 55.9, 49.3, 42.0, 32.4, 26.6, 25.8, 21.7; $[\alpha]^{25}_D$ +49.8 (*c* −1.27, $CHCl_3$). Anal. Calcd for $C_{12}H_{15}N_2Br \cdot 2HBr$: C, 33.60; H, 3.99; N, 6.53; Br, 55.88. Found: C, 33.58; H, 4.05; N, 6.47; Br, 55.93. The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention times $t_{63} = 11.0$ min. There was no detectable compound **64**.

(*S*)-2-(5-Bromopyridin-3-yl)-1-azabicyclo[2.2.2]octane dihydrobromide (64). By using the procedure described above for compound **60**, compound **64** (58 mg, 85%) was synthesized from **52** (65 mg, 0.23 mmol). ^{1}H NMR, (300 MHz, D_2O) δ 8.63 (d, $J = 1.8$ Hz, 1H), 8.56 (d, $J = 1.8$ Hz, 1H), 4.84–4.78 (t, $J = 6.8$ Hz, 1H), 3.62–3.51 (m, 1H), 3.40–3.24 (m, 1H), 3.20–3.10 (m, 2H), 2.30–2.11, (m, 3H), 2.00–1.79 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 148.7, 147.1, 141.3, 137.5, 120.7, 55.9, 49.4, 42.0, 32.6, 26.7,

25.9, 21.8; mp 207 °C; $[\alpha]^{25}_{D}$ −39.2 (*c* 1.01, MeOH). Anal. Calcd for $C_{12}H_{15}N_2Br \cdot 2HBr$: C, 33.60; H, 3.99; N, 6.53; Br, 55.88. Found: C, 33.82; H, 4.07; N, 6.48; Br, 55.71. The following conditions were used to determine enatiomeric purity: Chiralpack AD 0.46 × 25 cm column, 85% hexane, 15% EtOH, flow rate 1.0 mL/min, 210–400 nm detector wavelength; retention times t_{64} = 18.7 min. There was no detectable compound **63**.

Solid-State Structure Analysis. Crystals of **59**–**62** suitable for X-ray analysis were obtained as previously described. See the Supporting Information for complete details of the X-ray crystallographic studies.

Supporting Information Available: General information and experimental procedures for preparation of starting materials; ^{1}H NMR and ^{13}C NMR spectra for all new compounds; X-ray crystallographic data for **59**–**62**. This material is available free of charge via the Internet at http://pubs.acs.org.

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