Expedited Articles

Novel 3-Pyridyl Ethers with Subnanomolar Affinity for Central Neuronal Nicotinic Acetylcholine Receptors

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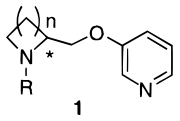
Recent evidence indicating the therapeutic potential of cholinergic channel modulators for the treatment of central nervous system (CNS) disorders as well as the diversity of brain neuronal nicotinic acetylcholine receptors (nAChRs) have suggested an opportunity to develop subtype-selective nAChR ligands for the treatment of specific CNS disorders with reduced side effect liabilities. We report a novel series of 3-pyridyl ether compounds which possess subnanomolar affinity for brain nAChRs and differentially activate subtypes of neuronal nAChRs. The synthesis and structure−activity relationships for the leading members of the series are described, including A-85380 (**4a**), which possesses ca. 50 pM affinity for rat brain [^{3}H]-(−)-cytisine binding sites and 163% efficacy compared to nicotine to stimulate ion flux at human $\alpha4\beta2$ nAChR subtype, and A-84543 (**2a**), which exhibits 84-fold selectivity to stimulate ion flux at human $\alpha4\beta2$ nAChR subtype compared to human ganglionic type nAChRs. Computational studies indicate that a reasonable superposition of a low energy conformer of **4a** with (*S*)-nicotine and (−)-epibatidine can be achieved.

The hypothesis that cholinergic dysfunction contributes to cognitive impairments in patients with Alzheimer's disease (AD)[1] has prompted considerable exploration of potential therapies designed to replace lost cholinergic function, including acetylcholine (ACh) precursor loading, inhibition of ACh catabolism, and cholinomimetic treatments.[2] ACh receptors can be divided into two families, i.e., muscarinic and nicotinic. Whereas considerable effort has been directed toward discovery of muscarinic agents with improved safety profiles and bioavailability compared to classical agents, targeting of neuronal nicotinic acetylcholine receptors (nAChRs) has received less attention. However, the observation of decreased nAChR density in AD, the ability of nicotine to upregulate nAChRs, the properties of nicotine as a cognitive-enhancing agent in animals and humans, and the reported neuroprotective effects of nicotine support the attractiveness of this approach for the potential treatment of AD.[3]

Neuronal nAChRs are widely distributed throughout the central and peripheral nervous systems where they modulate a number of CNS functions including neutotransmittor release and the control of cerebral blood flow.[3−8] A major subtype in brain is composed of the $\alpha4\beta2$ subunit combination,[9] whereas ganglionic-type nAChRs are thought to contain $\alpha3$ in combination with $\beta2$ or $\beta4$ and possibly $\alpha5$.[10] Since ganglionic-type nAChRs are believed to at least partially mediate the cardiovascular and gastrointestinal liabilities of nicotine,[11,12] an important objective of pharmaceutical research targeting the neuronal nAChRs would be to achieve selectivity for central versus ganglionic nAChRs.



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n = 1 or 2
R = H or Me
* = *R* or *S*

Figure 1. Generic structure of synthesized analogs.

Recent advances in the search for novel nAChR ligands include the discovery of ABT-418,[13,14] currently in development for treatment of AD, and epibatidine, a potent analgesic compound with subnanomolar affinity for nAChRs.[15] In the present report is disclosed a new series of 3-pyridyl ether compounds **1** (Figure 1), which generally possess subnanomolar affinity for brain nAChRs. These compounds are structurally dissimilar to previously known nAChR ligands and have provided structural leads to a new series of nAChR ligands.

Methods

Chemistry. Throughout, compounds with the **a** designation are of the *S* stereochemical series, whereas the **b** designation signifies *R* stereochemistry. Compounds **2a**−**5a** and **2b**−**5b** (Table 1) were prepared and characterized by ^{1}H-NMR, MS, and elemental analysis prior to biological evaluation. Preparative methods for these compounds are summarized in Scheme 1. The key ether-forming step for all analogs was carried out under Mitsunobu conditions starting with an appropriately protected imino alcohol (**7a, 7b, 8a, 8b, 9a,** or **10**) and 3-pyridinol. *N*-Protected prolinol derivatives **8a** and **8b** were prepared, respectively, from (*S*)- and (*R*)-proline according to literature procedures,[16,17] for which it is established that the transformations occur without racemization.

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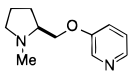
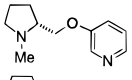
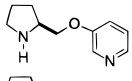
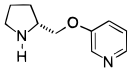
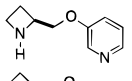
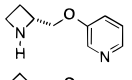
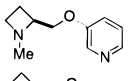
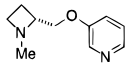
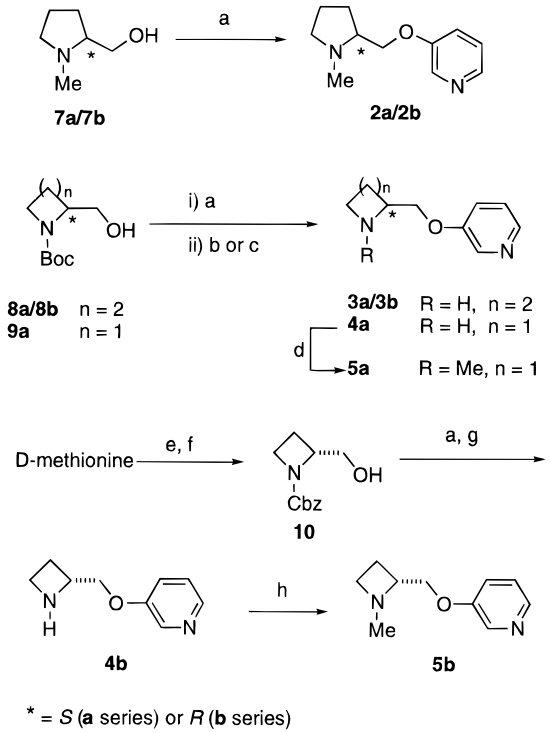
Table 1. Radioligand Binding and Functional Properties of Cholinergic Channel Ligands[a]

Compound	Structure	[^{3}H]cytisine binding K_i(nM)	$^{86}Rb^+$ Flux Human α4β2 K177 Cells EC_{50} (μM)	% Max	$^{86}Rb^+$ Flux Human α3βx IMR-32 Cells EC_{50} (μM)	% Max[b]
2a (A-84543)		0.15 ± 0.01	0.75 ± 0.2	100 ± 6	63 ± 12	100 ± 4
2b		19.7 ± 4.4	110 ± 20 (IC_{50})	< 10%	54 ± 8 (IC_{50})	< 20%
3a		0.16 ± 0.06	4 ± 1	100 ± 11	12 ± 4	98 ± 11
3b		0.14 ± 0.03	4.3 ± 1.2	120 ± 14	5.8 ± 2	100 ± 9
4a (A-85380)		0.052 ± 0.001	0.68 ± 0.1	163 ± 27	0.7 ± 0.1	113 ± 12
4b		0.05 ± 0.02	0.4 ± 0.1	159 ± 18	1.1 ± 0.5	116 ± 12
5a		0.45 ± 0.019	3.7 ± 2	116 ± 12	30 ± 3	74 ± 8
5b		3.5 ± 0.8	35 ± 8	103 ± 9	38 ± 6	39 ± 6
(*S*)-nicotine		1 ± 0.1	5 ± 1	(100)	21 ± 3	(100)
(±) epibatidine		0.043 ± 0.006	0.017 ± 0.006	156 ± 20	0.007±0.001	156 ± 12

[a] Values represent mean ± S.E.M., n = 3-5. [b] % Max represents the maximal efficacy of the compounds relative to 100 μM (*S*)-nicotine.

Scheme 1[a]



[a] (a) 3-Pyridinol, diethyl azodicarboxylate, triphenylphosphine, THF; (b) TFA, CH_2Cl_2; (c) HCl, EtOH; (d) aqueous HCHO, $NaBH_3CN$; (e) refs 18−20; (f) BH_3, THF; (g) H_2, Pd/C; (h) $(HCHO)_n$; H_2, Pd/C.

Azetidine **9a** was prepared in analogous fashion from (*S*)-azetidine-2-carboxylic acid. For the preparation of **10**, the precursor (*R*)-*N*-benzyloxycarbonyl-azetidine-2-carboxylic acid was synthesized from the corresponding free amino acid, which was in turn derived from D-methionine according to literature procedures.[18,19] It should be noted that the (*R*)-azetidine-2-carboxylic acid obtained from this procedure was not optically pure. Therefore, the pure (*R*)-enantiomer was isolated as the *N*-Cbz derivative according to a literature resolution protocol.[20] The optical purity was established after conversion to **5b**, which was found by chiral HPLC assay to possess 99% ee.[21] Following Mitsunobu couplings, *N*-Cbz- or *N*-Boc-protected derivatives were deprotected by standard methods. *N*-Methyl-azetidines were prepared by reductive methylation of the secondary amines with formaldehyde. Final compounds were isolated and characterized as dihydrochloride or fumarate salts.

Biological Assays. The binding affinity of each compound to central nAChRs was determined by measuring the displacement of [^{3}H]-(−)-cytisine from a preparation of whole rat brain according to the procedure of Pabreza et al.[22] [^{3}H]-(−)-Cytisine has been shown to label primarily a receptor subtype in rat brain composed of α4 and β2 subunits.[9] Compounds also were evaluated for their ability to stimulate $^{86}Rb^+$ efflux from cell preparations containing different subtypes of nAChRs. Ion flux at human α4β2 receptors was assessed using a human cell line (K177) in which these receptors have been stably expressed.[14] $^{86}Rb^+$ efflux from the human neuroblastoma-derived IMR-32 cell line, which expresses ganglionic-like nAChRs, was investigated using the procedure described previously.[23]

Molecular Modeling. Molecular modeling was performed with SYBYL.[24] Conformations for (*S*)-nicotine, (−)-epibatidine, and compound **4a** were generated with DGEOM and minimized with MMP2.[25] The missing parameters were estimated by *ab initio* calculations as follows: Model compounds were studied with the torsion angle of interest at 0°, 30°, 60°, and 120°; these structures were optimized at the STO-3G level; then energies were calculated at the 6−31G* level; and the results fitted to the needed parameters to reproduce the barrier heights. The following V1 V2 and V3 torsional parameters were estimated: 12-2-37-2, 0 10 0; 12-2-37-20, 0 10 0; 6-2-2-37, 0 15 0. The following in-plane bending parameter was estimated: 12-2-37, 0.4 116.54.

For nicotine and epibatidine, 250 conformations were generated, whereas 500 conformations were generated for compound **4a**. Unique conformations were recognized as those which differed in one or more interatomic distances by more than 0.2 Å. By this criterion, there are eight low-energy conformations of epibatidine and nicotine, whereas 57 conformations of **4a** were obtained with MM2 energies up to 2.5 kcal above the minimum. The conformations of epibatidine and nicotine occur in pairs, of approximately equal energy, that differ by approximately 180° in the rotation of the pyridyl ring.

Potential superpositions were generated with DISCO[26] as implemented in SYBYL, using (−)-epibatidine as the reference. Two types of models were investigated. The first required the inclusion of the pyridyl nitrogen atom, its complementary site point, and the sp^3 nitrogen atom and its complementary site point, whereas the second omitted the requirement for the site point complementary to the sp^3 nitrogen.

Results and Discussion

Binding Data. In binding assays, prototypical nAChR ligands exhibit diverse structure−activity patterns with respect to *N*-substitution and stereochemistry. For example, (*S*)-nicotine possesses 19-fold higher affinity than (*S*)-nornicotine for central neuronal nAChRs. In contrast, *N*-Me-(−)-epibatidine is approximately 2-fold weaker than (−)-epibatidine,[27] and *N*-Me-(+)-anatoxin is several hundred fold weaker than (+)-anatoxin.[28] With respect to stereoselectivity, (*S*)-nicotine possesses 14-fold higher affinity than (*R*)-nicotine, and (+)-anatoxin is also highly stereoselective, whereas nornicotine,[13,29] epibatidine,[15] and *N*-Me-epibatidine[27] show little stereoselectivity.

In Table 1, pyrrolidine and azetidine analogs are varied with respect to stereochemistry and *N*-substitution. The binding data indicate that most of the analogs possess subnanomolar affinities for central nAChRs. Of particular note are compounds **4a** (A-85380, $K_i = 52$ pM) and **4b** ($K_i = 50$ pM), which possess affinity comparable to that of epibatidine, the most potent nAChR ligand reported to date.

The effect of *N*-methylation for the compounds in Table 1 is different from that found in the nicotine series. Thus, the (*S*)-*N*-H-pyrrolidine analog **3a** has affinity that is comparable to that of the corresponding (*S*)-*N*-Me analog **2a**; for the corresponding azetidines, the (*S*)-*N*-H compound **4a** binds nearly 9-fold more tightly than the (*S*)-*N*-Me congener **5a**. This trend with respect to *N*-methylation resembles the pattern observed for (−)-epibatidine more closely than that for (*S*)-nicotine. With respect to stereoselectivity, the trends are similar to those found for nicotine and nornicotine. Thus, the (*S*)-*N*-Me compounds have higher affinity than their (*R*)-enantiomers (**2a** vs **2b** and **5a** vs **5b**), and the desmethylpyrrolidine enantiomers show little stereoselectivity (**3a** vs **3b** and **4a** vs **4b**). Further pharmacological characterization of compound **4a**, including binding affinity in other receptor systems, is the subject of a separate report.[30]

Functional Activity. The ability of the analogs to activate nAChRs was investigated using cell lines that express the human α4β2 subunit combination (K177 cells) or a human ganglionic-like (α3βx) nAChR (IMR-32 cells). With the exception of (*R*)-*N*-Me-pyrrolidine **2b** and (*R*)-*N*-Me-azetidine **5b**, all of the analogs stimulated cation efflux with high efficacy at both receptor subtypes, and in several cases the maximum stimulation exceeded that of nicotine. Most notably, both the (*S*)- and the (*R*)-*N*-H-azetidines (**4a** and **4b**) exhibit exceptionally high efficacy at the α4β2 subtype, stimulating a maximum response >160% that of nicotine, and comparable to that of (±)-epibatidine. Moreover, compounds **4a** and **4b** also exhibited exceptionally high potency at both receptor subtypes. Thus, compound **4a** is, respectively, 7- and 30-fold more potent than (*S*)-nicotine to stimulate cation efflux mediated by the human α4β2 and α3βx receptors. It is noteworthy, however, that although compounds **4a** and **4b** are equipotent to (±)-epibatidine to interact with the [^{3}H]-cytisine binding site on the α4β2 subtype, these compounds are 24−40-fold less potent to activate this subtype. The reasons for this difference are under investigation.

Several of the compounds exhibit significant nAChR subtype selectivity at the functional level with respect to either efficacy or potency. (*S*)-*N*-Me-pyrrolidine **2a** is 84-fold more potent to stimulate the α4β2 subtype than α3βx, and (*S*)-*N*-Me-azetidine **5a** was both more potent and more efficacious at the α4β2 subtype. Also, the efficacy of (*R*)-*N*-Me-azetidine **5b** was markedly lower at the α3βx subtype (39%) than at the α4β2 subtype (103%). The corresponding desmethyl compounds were much less selective; thus, *N*-methylation had the effect of improving selectivity for the α4β2 subtype in both the (*S*)-pyrrolidine and the (*S*)-azetidine series.

Since (*R*)-*N*-Me-pyrrolidine **2b** displayed very low efficacy (<20%) at both subtypes, it was tested for antagonist properties in both preparations. At the α4β2 subtype, **2b** antagonized the stimulatory effect of 100 μM (*S*)-nicotine ($IC_{50} = 110$ μM). By comparison, the competitive nicotinic antagonist dihydro-β-erythroidine, which possesses similar binding affinity to that of **2b**, was nevertheless considerably more potent in inhibiting the (*S*)-nicotine response ($IC_{50} = 1.9$ μM).[14] At α3βx, compound **2b** antagonized cation efflux mediated by 100 μM (*S*)-nicotine with an IC_{50} value of 54 μM. Thus, compound **2b** represents a novel structural class of nAChR antagonists.

Computational Studies. An interesting question regarding this series of compounds is whether they can interact with the nicotinic receptor similarly to nicotine and/or epibatidine. The classical Beers and Reich model proposes that the essential elements of the nicotinic pharmacophore are a hydrogen bond acceptor (i.e. the pyridine lone pair of nicotine) and a charged species, e.g. a protonated or quaternary nitrogen approximately 5.9 Å from the hydrogen bond acceptor.[31] Subsequently, Sheridan performed ensemble distance geometry with several known ligands, in which the pharmacophoric elements selected for superposition were those that correspond to the two nitrogen atoms of nicotine and a pyridine ring centroid.[32] Both the Beers and Reich and the Sheridan models suggested an internitrogen distance for nicotine of around 4.8 Å. The subsequent discovery of (±)-epibatidine as an exceptionally high-affinity ligand for nAChRs prompted the more recent proposal[33] that the optimal internitrogen distance for high affinity binding may be closer to 5.5 Å. This hypothesis was supported by the finding that, of the compounds studied, those having minimum-energy conformations with internitrogen distances either shorter or longer than 5.5 Å had substantially weaker affinities than (±)-epibatidine. For example, (±)-isonornicotine,

Table 2. Relative Energies, Root Mean Square (RMS) Deviations, and Overlap Values for Three Models Obtained from DISCO Analysis of (−)-Epibatidine (as Reference Compound), (*S*)-Nicotine, and Compound **4a**

model	N−N distance in epibatidine (Å)	energy (kcal/mol, MM2)			RMS (Å)[a]		Overlap (Å^3)[b]	
		(−)-epibatidine	(*S*)-nicotine	**4a**	(*S*)-nicotine	**4a**	(*S*)-nicotine	**4a**
1	4.6	0.00	0.00	1.34	0.70	0.61	84.38	100.88
2	4.6	0.00	0.02	1.31	1.34	0.72	70.38	91.50
3	5.6	0.01	0.02	0.16	0.65	0.42	91.75	94.00

[a] RMS deviations of the coordinates of the four pharmacophore elements from those of the corresponding features of the reference compound; lower RMS values imply better fit. [b] Extent of overlap with the reference compound.

with an internitrogen distance of 5.74 Å, has 133-fold lower affinity than (±)-epibatidine. We have performed calculations on compound **4a**, which possesses affinity comparable to that of (±)-epibatidine. The minimum-energy conformer possessed an internitrogen distance of 6.1 Å, which is somewhat longer than that proposed by the models discussed above.

Since compound **4a** is a flexible molecule, it is reasonable to consider other conformations with energies higher than the minimum. In the following analysis, we consider whether (*S*)-nicotine, (−)-epibatidine (natural isomer), and compound **4a** are able to achieve a reasonable unified superposition of putative pharmacophoric elements. A key issue is the selection of pharmacophoric elements to be superimposed. In the primary analysis, the points included are the sp^3 nitrogen, its complementary anionic site point, the pyridine nitrogen, and its complementary hydrogen-bond donor site point. The existence of an anionic binding site at the nicotinic receptor is controversial,[34,35] and in the case of acetylcholinesterase, interaction of the quaternary ammonium group of acetylcholine with several aromatic residues, possibly through a cation−π interaction, appears to be operative as the principal stabilizing interaction.[36,37] Therefore, an additional analysis was conducted in which consideration of a specific anionic site point was not included.

In the four-point analysis**,** DISCO found 12 pharmacophore models at a tolerance of 1.5 Å. Visual inspection revealed that these models can be represented by three classes. The first two classes differ from each other with respect to which of two possible site points on the sp^3 nitrogen of epibatidine was superimposed with sitepoints from the other ligands, and the third class differed from the first with respect to an approximate 180° rotation of the bond connecting the pyridine ring to the azabicyclic moiety. Table 2 shows the details of the best model of each class, with pictorial representations shown in Figure 2. In models 1 and 2, the pyridine ring of the reference epibatidine conformer is rotated so that its nitrogen atom is proximal to the sp^3 nitrogen (N−N distance of 4.6 Å). Only a comparatively high energy conformation of compound **4a** is accommodated by the first model (MM2 ΔE, 1.34 kcal/mol; Tripos force field ΔE, 2.60 kcal/mol, Figure 2a). Model 2 also required a higher energy conformation of **4a**. In addition, the superposition of nicotine was such that its pyridine ring does not overlay the aromatic rings of the other two compounds (Figure 2b). For model 3, a lower energy conformation of compound **4a** is possible, while the root-mean-square superposition and overlap volume of nicotine with epibatidine are comparable to those of the first model. The N−N distance for **4a** in model 3 is 6.3 Å. Since the four points in this model are approximately in a plane, the enantiomers of the compounds, which also possess high affinity for the nicotinic receptor, are accommodated as well.

When the analysis is conducted superimposing only three points (anionic site omitted), solutions were found that correspond closely to those represented in Table 2 and Figure 2, as expected. The question is whether removal of the additional constraint permitted additional unique solutions that should be considered. The results show that, in the case where the epibatidine reference conformer corresponds to that of models 1 and 2 above, no conformer of compound **4a** with MM2 energy lower than 1.34 kcal was found. The epibatidine conformer corresponding to model 3 yielded a solution set containing conformers of compound **4a** with energies of 0, 0.16, 0.65, and 0.67 kcal and higher. Among the lower energy members, the RMS distances and overlap were most favorable for the 0.16 kcal conformer. In model 3, the 0.02 kcal conformer of nicotine is superimposed on epibatidine with RMS distance (0.44 Å) and overlap (105.25 Å^3) that were slightly more favorable compared to the values shown in Table 2, but the general features of the superposition are similar to that shown in Figure 2c. Thus, with the basis set comprised of epibatidine, nicotine, and compound **4a**, the three-point and four-point analyses yielded comparable results.

Therefore, it is at least plausible that nicotine, epibatidine, and **4a** interact similarly with residues in the nAChR binding site. Further evaluation of these models for their ability to accommodate other known nicotinic ligands will be necessary to further distinguish between them and to gain support for the validity of any one of them. Such studies will be aided by the availability of functional data, which will help to characterize ligands which may interact with the receptor in distinct binding modes (e.g. agonists vs antagonists).

Summary

We have demonstrated 3-pyridyl ether compounds are potent nAChR ligands which possess subnanomolar affinity for brain nAChRs and differentially activate subtypes of neuronal nAChRs. A-85380 (**4a**), which possesses ca. 50 pM affinity for rat brain [^{3}H]-(−)-cytisine binding sites and 163% efficacy compared to nicotine to stimulate ion flux at human $\alpha4\beta2$ nAChR subtype and is not stereoselective in the assays examined. A-84543 (**2a**) exhibits 84-fold selectivity to stimulate ion flux at human $\alpha4\beta2$ nAChR subtype compared to human ganglionic type nAChRs and is stereoselective. Computer-modeling studies indicate that a reasonable superposition of a low-energy conformer of **4a** with (*S*)-nicotine and (−)-epibatidine can be achieved. SAR studies are now in progress to further develop this series as novel, highly potent nAChR ligands.

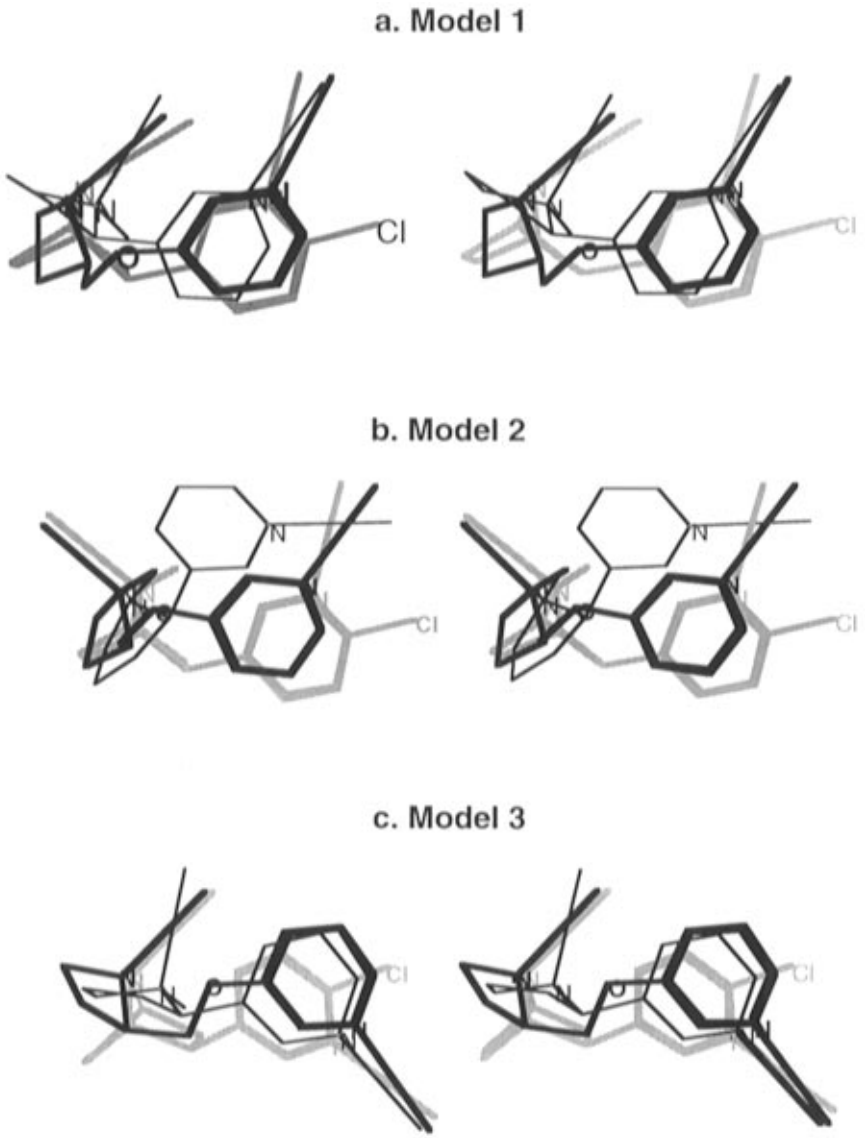


Figure 2. Stereoviews of three different four point models of **4a** (thick black) superimposed with (−)-epibatidine (gray) and (*S*)-nicotine (thin black).

Experimental Section

Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz) or a General Electric GN-300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Mass spectra were obtained with a Hewlett-Packard HP5965 spectrometer. The above determinations were performed by the Analytical Research Department, Abbott Laboratories, and elemental analyses were performed by Robertson Microlit Laboratiories, Inc., Madison, New Jersey.

Thin-layer chromatography (TLC) was carried out using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Flash chromatography was carried out using Merck silica gel 60, 200−400 mesh.

Melting points are uncorrected and were determined on a Buchi melting point apparatus. Optical rotation data was obtained on a Perkin-Elmer Model 241 polarimeter. All reactions were performed under anhydrous conditions unless otherwise noted.

The following abbreviations are used in the Experimental Section: THF for tetrahydrofuran, D_2O for deuterium oxide, $CDCl_3$ for deuteriochloroform, DMSO-d_6 for deuteriodimethyl sulfoxide, BOC for *tert*-butoxycarbonyl, Cbz for benzyloxycarbonyl, $CHCl_3$ for chloroform, EDC for 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide, TFA for trifluoroacetic acid, DEAD for diethyl azodicarboxylate, HOBt for 1-hydroxybenzotriazole.

(*S*)-1-Methyl-2-pyrrolidinemethanol and (*S*)-2-azetidinecarboxylic acid were purchased from Aldrich Chemical Co. and used without further purification. (*R*)-1-Methyl-2-pyrrolidinemethanol was purchased from Fluka. (*S*)-1-(*tert*-Butoxycarbonyl)-2-pyrrolidinemethanol and (*R*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol were prepared according to the literature procedure[16,17] starting from commercially available D-proline and L-proline, which were purchased from Aldrich.

3-((1-Methyl-2(*S*)-pyrrolidinyl)methoxy)pyridinefumarate (2a). To a solution of triphenylphosphine (1.71 g, 6.5 mmol) in THF (30 mL) at −15 °C was added DEAD (1.02 mL, 6.5 mmol) dropwise with stirring. Then, (*S*)-1-methyl-2-pyrrolidinemethanol **7a** ($[\alpha]^{19}_D$ −49.5° (*c* 5, MeOH)) (5.0 g, 4.34 mmol) and 3-hydroxypyridine (0.43 g, 4.5 mmol) were added, and the mixture was kept at −20 °C overnight. After evaporation of the solvent, the residue was dissolved in methylene chloride and washed with 1 *N* HCl. The aqueous layer was adjusted to basic pH with aqueous sodium bicarbonate and extracted with methylene chloride. The organic extract was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography. Elution with $CHCl_3$/MeOH (10:1) provided the product (260 mg, 31%): MS (DCI/NH_3) *m*/*e* 193 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (t, J = 1.5 Hz, 1H), 8.22 (t, J = 3 Hz, 1H), 7.24−7.2 (m, 2H), 4.14−4.05 (dd, J = 9, 6 Hz, 1H), 4.00−3.93 (dd, J = 9, 6 Hz, 1H), 3.24−3.14 (m, 1H), 2.81−2.7 (m, 1H), 2.54 (s, 3H), 2.44−2.31 (m, 1H), 2.14- 2.00 (m, 1H), 1.96−1.71 (m, 3H).

The compound from above was dissolved in anhydrous MeOH and brought to 0 °C with stirring. Fumaric acid was dissolved in MeOH with sonication and added dropwise to the solution containing the amine. The mixture was warmed to room temperature with stirring. After 30 min the solvent was evaporated *in vacuo*, and the remaining solid was vacuum filtered. The solid was then recrystallized from MeOH/Et_2O to give the desired product as a white powder (262 mg, 21%): mp 124−125 °C; $[\alpha]^{25}_D$ −3.9° (*c* 1, MeOH); MS (DCI/NH_3) *m/e* 193 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.43 (br s, 1H), 8.33 (d, $J = 4.5$ Hz, 1H), 7.88−7.84 (m, 1H), 7.3 (dd, $J = 8.82, 5.15$ Hz, 1H), 6.58 (s, 2H), 4.59 (dd, $J = 11, 3$ Hz, 1H), 4.42 (dd, $J = 11, 5.88$ Hz, 1H), 4.05−3.9 (m, 1H), 3.82−3.74 (m, 1H), 3.34−3.22 (m, 1H), 3.05 (s, 3H), 2.47−2.37 (m, 1H), 2.30−2.06 (m, 3H). Anal. ($C_{11}H_{16}N_2O \cdot C_4H_4O_4$) C, H, N.

3-((1-Methyl-2(*R*)-pyrrolidinyl)methoxy)pyridine Dihydrochloride (2b). To a solution of triphenylphosphine (509 mg, 1.94 mmol) in THF (10 mL) at room temperature was added DEAD (0.35 mL, 1.94 mmol) dropwise with stirring. After stirring at room temperature for 30 min, (*R*)-1-methyl-2-pyrrolidinemethanol (**7b,** $[\alpha]^{20}_D$ −31 ± 2° (*c* 1, toluene)) (150 mg, 1.30 mmol) and 3-hydroxypyridine (185 mg, 1.94 mmol) were added to the reaction mixture. The resultant solution was then stirred at room temperature overnight. After all of the starting material was consumed, the organic solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography. Elution with $CHCl_3$/MeOH (10:1) provided the product (76 mg, 21%): MS (DCI/NH_3) *m/e* 193 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (t, $J = 1.5$ Hz, 1H), 8.22 (t, $J = 3$ Hz, 1H) 7.24−7.2 (m, 2H), 4.14−4.05 (dd, $J = 9, 6$ Hz, 1H), 4.00−3.93 (dd, $J = 9, 6$ Hz, 1H), 3.24−3.14 (m, 1H), 2.81−2.7 (m, 1H), 2.54 (s, 3H), 2.44−2.31 (m, 1H), 2.14−2.00 (m, 1H), 1.96−1.71 (m, 3H).

The compound from above (76 mg, 0.4 mmol) was dissolved in ethanol. Hydrochloric acid in diethyl ether was added dropwise to a stirring solution of base at ambient temperature. The resultant white precipitate was then collected by evaporation of solvent and triturated with three portions of diethyl ether producing (53 mg, 50%) a hygroscopic solid: $[\alpha]^{25}_D$ +6.54 ° (*c* 1, MeOH); MS (DCI/NH_3) *m/e* 193 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.43 (br s, 1H), 8.33 (d, $J = 5.6$ Hz, 1H), 7.88−7.82 (m, 1H), 7.72 (dd, $J = 8.50, 5.15$ Hz, 1H), 4.59 (dd, $J = 11, 3$ Hz, 1H), 4.42 (dd, $J = 11.4, 6.2$ Hz, 1H), 4.17−4.25 (m, 1H), 4.05−3.9 (m, 1H), 3.82−3.74 (m, 1H), 3.34−3.22 (m, 1H), 3.04 (s, 3H), 2.42−2.36 (m, 1H), 2.26−2.06 (m, 3H). Anal. ($C_{11}H_{16}N_2O \cdot HCl \cdot 0.2\ H_2O$) C, H, N.

3-(2-(*S*)-Pyrrolidinylmethoxy)pyridine Fumarate (3a). To a solution of triphenylphosphine (1.97 g, 7.5 mmol) in THF (30 mL) at room temperature was added DEAD (1.13 mL, 7.5 mmol) dropwise with stirring. After stirring at room temperature for 30 min, (*S*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol **8a**[16,17] (1 g, 5.0 mmol) and 3-hydroxypyridine (713 mg, 7.5 mmol) were added to the reaction mixture. The resultant solution was stirred at room temperature for 16 h. After all the starting material was consumed, the organic solvent was evaporated *in vacuo*. The residue was purified by flash silica gel column chromatography. Elution with $CHCl_3$/MeOH (10:1) provided 3-((1-(*tert*-butoxycarbonyl)-2(*S*)-pyrrolidinyl)methoxy)pyridine (2 g, contaminated with PPh_3O): MS (DCI/NH3) *m/e* 279 $(M + H)^+$.

To a solution of the compound from above in CH_2Cl_2 (12 mL) was added TFA (12 mL). The resultant solution was stirred at room temperature for 3 h. Evaporation of both solvent and TFA gave a brown oil which was basified with saturated ammonium hydroxide solution. This oil was purified by flash silica gel column chromatography. Elution with $CHCl_3$/MeOH/NH_4OH (10:1:0.1) provided the desired product (280 mg, 31%): MS (DCI/NH_3) *m/e* 179 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.33 (br s, 1H), 8.22 (m, 1H), 7.22 (m, 2H), 3.82−4.03 (m, 2H), 3.50−3.61 (m, 1H), 2.92−3.10 (m, 2H), 1.70−2.10 (m, 4H), 1.51−1.66 (m, 1H).

The free base (281 mg, 1.57 mmol) was dissolved in anhydrous MeOH and brought to 0 °C with stirring. Excess fumaric acid was dissolved in MeOH with sonication and added dropwise to the base. The mixture was warmed to room temperature with stirring. After 30 min the solvent was evaporated *in vacuo*, and the remaining solid was triturated with anhydrous diethyl ether. The product was obtained as a hygroscopic solid (218 mg, 47%): mp 92−95 °C; $[\alpha]^{25}_D$ −15.0° (*c* 0.35, MeOH); MS (DCI/NH_3) *m/e* 179 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.38 (m, 1H), 8.30 (m 1H), 7.76−7.72 (m, 1H), 7.72−7.62 (m, 1H), 6.57 (s, 2H), 4.60−4.50 (m, 1H), 4.35−4.25 (m, 1H), 4.10−4.08 (m, 1H), 3.42 (t, $J = 7.5$ Hz, 2H), 2.37−2.23 (m, 1H), 2.23−2.06 (m, 2H), 2.06−1.98 (m, 1H). Anal. ($C_{10}H_{14}N_2O \cdot C_2H_4O_2 \cdot 0.9\ H_2O$) C, H, N.

3-(2(*R*)-Pyrrolidinylmethoxy)pyridine Dihydrochloride (3b). To a solution of triphenylphosphine (1.24g, 4.74 mmol) in THF (20 mL) at room temperature was added DEAD (0.746 mL, 4.74 mmol) dropwise with stirring. After stirring at room temperature for 30 min, (*R*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol **8b**[16,17] (350 mg, 3.16 mmol) and 3-hydroxypyridine (450 mg, 4.74 mmol) were added to the reaction mixture. The resultant solution was then stirred at room temperature overnight. After all of the starting material was consumed, the organic solvent was evaporated *in vacuo*. The residue was purified by flash silica gel column chromatography. Elution with $CHCl_3$/MeOH (10:1) provided 518 mg of the product contaminated with diethylhydrazine dicarboxylate: MS (DCI/NH_3) *m/e* 279 $(M + H)^+$.

To a solution of the compound from above (115 mg, 0.42 mmol) in CH_2Cl_2 (2 mL) solution was added TFA (2 mL). The resultant solution was stirred at room temperature for 2.5 h. Evaporation of both solvent and trifluoroacetic acid gave a brown oil which was basified with saturated ammonium hydroxide solution. This oil was purified by flash silica gel column chromatography. Elution with $CHCl_3$/MeOH (10:1.5) provided the desired product (67 mg, 96%): MS (DCI/NH_3) *m/e* 179 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.33 (br s, 1H), 8.22 (m, 1H), 7.22 (m, 2H), 3.82−4.03 (m, 2H), 3.50−3.61 (m, 1H), 2.92−3.10 (m, 2H), 1.70−2.10 (m, 4H), 1.51−1.66 (m, 1H).

The compound from above (67 mg, 0.4 mmol) was dissolved in ethanol, and hydrochloric acid in diethyl ether was added dropwise at ambient temperature. The resultant white precipitate was then collected by evaporation of solvent followed by trituration with three portions of diethyl ether yielding a hygroscopic solid (53 mg, 55%): $[\alpha]^{25}_D$ +7.5° (*c* 1.2, MeOH); MS (DCI/NH_3) *m/e* 179 $(M + H)^+$; ^1H NMR (D_2O, 300 MHz) δ 8.43 (br s, 1H), 8.34 (br s 1H), 7.85 (dd, $J = 8.80, 2.90$ Hz, 1H), 7.72 (dd, $J = 8.80, 5.15$ Hz, 1H), 4.54 (dd, $J = 11, 3.3$ Hz, 1H), 4.32 (dd, $J = 10.6, 3.3$ Hz, 1H), 4.10−4.19 (m, 1H), 3.42 (t, $J = 7.5$ Hz, 1H), 2.27−2.35 (m, 1H), 2.06−2.21 (m, 2H), 1.90−2.02 (m, 1H). Anal. ($C_{10}H_{14}N_2O \cdot 2.4HCl$) C, H, N.

3-(2(*S*)-Azetidinylmethoxy)pyridine Dihydrochloride (4a). (a) (*S*)-1-(*tert*-Butoxycarbonyl)-2-azetidinemethanol (9a). To an ice-cooled solution of (*S*)-2-azetidinecarboxylic acid ($[\alpha]^{20}_D$ −120° (*c* 3.6, H_2O)) (10.15 g, 100.39 mmol) in 1, 4-dioxane:water (300 mL, 1:1) was added di-*tert*-butyl dicarbonate (28.48 g, 130.51 mmol) at 0 °C, followed by 4-methylmorpholine (11.68 g, 115.45 mmol). The reaction mixture was stirred for 18 h, with gradual warming to room temperature. The reaction mixture was then poured into a saturated solution of sodium bicarbonate (250 mL) at 0 °C and washed with ethyl acetate (3 × 250 mL). The aqueous layer was then acidified with potassium hydrogen sulfate to pH = 1 and extracted with ethyl acetate (3 × 300 mL). These extracts were then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting semisolid (*S*)-1-(*tert*-butyloxycarbonyl)azetidine-2-carboxylic acid[38] was carried forward without further purification: MS (DCI/NH_3) *m/e* 202 $(M + H)^+$, 219 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.0 (br s, 1H), 4.81−4.76 (t, $J = 15$ Hz, 1H), 3.99−3.83 (m, 2H), 2.62−2.38 (m, 2H), 1.48 (s, 9H).

To a solution of the compound from above (9.39 g, 46.72 mmol) in THF (100 mL) was added borane/THF complex (1 M, 210 mL, 4.5 equiv) at 0 °C under nitrogen. The mixture was allowed to gradually warm to room temperature and was stirred for 48 h. A 10% aqueous potassium hydrogen sulfate solution (60 mL) was added gradually, and the volatile components were then evaporated *in vacuo*. The remaining slurry was extracted with EtOAc (3×). The organic phase was then washed with a saturated solution of sodium hydrogen carbonate (3 × 75 mL), dried ($MgSO_4$), filtered, and concen-

trated *in vacuo*, yielding **9a** (8.4 g, 96% yield) as a colorless oil. This material was carried forward without further purification: MS (DCI/NH_3) *m/e* 188 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.49−4.40 (ddd, J = 9.0, 9.0, 3.0 Hz, 1H), 3.95−3.68 (m, 4H), 2.23−2.12 (m, 1H), 1.99−1.87 (m, 1H), 1.46 (s, 9H).

(b) Compound 4a. A solution of compound **9a** (2.8 g, 14.97 mmol) in THF (40 mL) was stirred at 0 °C under a nitrogen atmosphere. To this solution was added DEAD (3.54 mL, 22.46 mmol) followed by triphenylphosphine (4.78 g, 22.46 mmol), and the mixture was stirred for 10 min. 3-Hydroxypyridine (2.14 g, 22.46 mmol) was then added to the reaction mixture with additional THF (40 mL). After 18 h, additional 3-hydroxypyridine (0.1 g, 1.05 mmol) was added and the mixture was stirred for 24 h. The reaction mixture was concentrated *in vacuo*, and the crude mixture was then acidified (pH < 2) with a 10% solution of potassium hydrogen sulfate (80 mL) and washed with ethyl acetate (3 × 75 mL). The aqueous portion was then basified with a saturated solution of potassium carbonate (pH = 10) and extracted with ethyl acetate (4 × 75 mL). These extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a red-brown oil. The crude product was purified on flash silica gel column chromatography. Elution with EtOAc/hexane (2:1) provided a light yellow oil (927 mg, 24% yield): MS (DCI/NH_3) *m/e* 265 $(M + H)^+$, 282 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 8.36 (dd, J = 3.7, 0.7 Hz, 1H), 8.23 (dd, J = 4.0, 1.5 Hz, 1H), 7.25−7.22 (m, 2H), 4.56−4.48 (m, 1H), 4.34 (dd, J = 10, 4.9 Hz, 1H), 4.15 (dd, J = 10, 2.9 Hz, 1H), 3.90 (dd, J = 8.2, 6.8 Hz, 2H), 2.42−2.25 (m, 2H), 1.42 (s, 9H).

To a solution of the compound from above (286 mg, 1.08 mmol) in absolute ethanol (4 mL) at 0 °C under nitrogen was added a saturated solution of hydrogen chloride in ethanol (4 mL). The reaction mixture was stirred for 18 h while gradually warming to room temperature. The mixture was then concentrated *in vacuo*, and the product was dissolved in absolute ethanol and triturated with diethyl ether. Two recrystallizations from ethanol and diethyl ether yielded a white powder (174 mg, 81% yield): mp 135−137 °C; $[\alpha]^{25}_D$ = − 5.0° (*c* 0.4, MeOH); MS (DCI/NH_3) *m/e* 165 $(M + H)^+$, 182 $(M + NH_4)^+$; ^{1}NMR (D_2O, 300 MHz) δ 8.59 (d, J = 2.9 Hz, 1H), 8.47 (d, J = 5.8 Hz, 1H), 8.23 (ddd, J = 9.0, 2.6, 1.1 Hz, 1H), 5.05−4.97 (m, 1H), 4.58 (d, J = 4.0 Hz, 2H), 4.22−4.05 (m, 2H), 2.72 (dd, J = 16.9, 8.45 Hz, 2H). Anal. ($C_9H_{12}N_2O$·2.HCl·0.2H_2O) C, H, N.

3-((1-Methyl-2(*S*)-azetidinyl)methoxy)pyridine Dihydrochloride (**5a**). To a solution of Boc-protected **4a** from above (550 mg, 1.89 mmol) in methylene chloride (3 mL) at 0 °C under nitrogen was added TFA in methylene chloride (5 mL, 1:1). The mixture was stirred for 18 h, gradually warming to room temperature. The reaction mixture was then concentrated *in vacuo* and dissolved in absolute ethanol (5 mL). Formalin (37%, 0.75 mL) was added, and the acidity was adjusted to pH 5 with the addition of acetic acid and sodium acetate. The reaction mixture was stirred for 15 min, and sodium cyanoborohydride (180 mg, 2.86 mmol) was added. A small amount of bromocresol green was added to the reaction mixture as indicator. The mixture was allowed to stir for 18 h, after which time the reaction was complete as monitored by TLC. The reaction mixture was then acidified (pH = 1) with a saturated solution of potassium hydrogen sulfate, and the volatiles were evaporated *in vacuo*. The aqueous phase was then washed with ethyl acetate (3 × 20 mL), basified (pH = 10) with potassium carbonate, and extracted with ethyl acetate (4 × 20 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* (274 mg, 81% yield). The crude product was then purified on flash silica gel column chromatography. Elution with $CHCl_3$/MeOH/NH_4OH (800:15:1.5) provided the product as a colorless oil (147 mg, 44% yield). This oil was dissolved in absolute ethanol (1.5 mL) and treated with a saturated solution of hydrogen chloride in diethyl ether. After one recrystallization from ethanol and diethyl ether, pure product was obtained as fine hygroscopic needles (47 mg, 12% from ((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)methoxy)-pyridine): $[\alpha]^{25}_D$ −21.4° (*c* 0.5, MeOH); MS (CI/NH_3) *m/e* 179 $(M + H)^+$, 196 $(M + NH_4)^+$; ^1H NMR (D_2O/300 MHz) δ 8.53 (d, J = 2.2Hz, 1H), 8.41 (d, J = 5.5 Hz, 1H), 8.07 (dd, J = 8.8, 3.0 Hz, 1H), 7.89 (dd, J = 8.8, 5.4 Hz, 1H), 4.90−4.80 (m, 1H), 4.61 (dd, J = 11.8, 2.9 Hz, 1H), 4.53 (dd, J = 11.8, 5.3 Hz, 1H), 4.30 (ddd, J = 9.9, 9.9, 5.1 Hz, 1H), 4.02 (dd, J = 19.5, 9.4 Hz, 1H), 3.00 (s, 3H), 2.77−2.60 (m, 2H). Anal. (C_{10}-$H_{14}N_2O$·2.0HCl·0.7H_2O) C, H, N.

3-(2(*R*)-Azetidinylmethoxy)pyridine Dihydrochloride (4b). (a) (*R*)-1-(Benzyloxycarbonyl)-2-azetidinemethanol (10). 1-(*p*-Tolylsulfonyl)azetidine-2-carboxylic acid was prepared from D-methionine by the method of Miyoshi *et al.*[18] Analysis of enantiomeric purity was carried out by conversion to the α-methylbenzylamide [EDC (1.2 equiv), HOBt (2.3 equiv), and α-methylbenzylamine (1.2 equiv)] and evaluation by ^{1}H-NMR, which indicated a ca. 4:1 mixture of enantiomers. This mixture (1.48 g, 5.8 mmol) was slurried in liquid NH_3 (25 mL) at −78 °C, and sodium metal was added until a dark blue color persisted for 30 min. Solid ammonium chloride was added until the blue color disappeared. The cold bath was replaced with a water bath as the ammonia was allowed to evaporate. The remaining white solid was carefully dissolved in H_2O (30 mL) and HOAc to adjust the mixture to pH 7.0. 1,4-Dioxane (30 mL) and *N*-((benzyloxycarbonyl)oxy)succinimide (2.1 g, 8.7 mmol) were added, and the mixture was stirred for 2 h. The biphasic mixture was partitioned between saturated K_2CO_3 and Et_2O, and the phases were separated. The aqueous phase was acidified with concentrated HCl and then extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified on flash silica gel column chromatography. Elution with $CHCl_3$/MeOH/HOAc (95:5:0.5) provided a colorless oil (955 mg, 70%): MS (CI/NH_3) *m/e* 236 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.40 (m, 5H), 5.65 (s, 2H), 4.78−4.87 (m, 1H), 3.98−4.07 (m, 2H), 2.47−2.60 (m, 2H).

The mixture of (*R*)- and (*S*)-1-(benzyloxycarbonyl)azetidine-2-carboxylic acid from above (932 mg, 3.96 mmol) was dissolved in MeOH (20 mL) and L-tyrosine hydrazide (773 mg, 3.96 mmol) added. The slurry was heated at reflux for 10 min, allowed to cool to ambient temperature, and then filtered. The filter cake was dissolved in 6 N HCl and extracted with EtOAc (2×). The organic fractions were combined, dried ($MgSO_4$), and concentrated to give the (*R*)-enantiomer as a colorless oil (403 mg, 55%): $[\alpha]^{20}_D$ +104.7° (*c* 4.0, $CHCl_3$) (lit.[20] $[\alpha]^{20}_D$ +98.5° (c 3.9, $CHCl_3$)).

(*R*)-1-(Benzyloxycarbonyl)azetidine-2-carboxylic acid (2.0 g, 8.6 mmol) in THF (35 mL) was cooled to 0 °C, and 1.0 M BH_3·THF (12.9 mL, 12.9 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature and was stirred for 2.5 h. A solution of 2 N HCl was carefully added, and the heterogeneous mixture was allowed to stir for 1 h. The slurry was extracted with CH_2Cl_2, and the organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified on flash silica gel column chromatography. Elution with EtOAc/hexane (1:1) provided **10** as a colorless oil (1.46 g, 77%): $[\alpha]^{20}_D$ = +15.5° (*c* 1.2, $CHCl_3$); MS (CI/NH_3) *m/e* 222 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.41 (m, 5H), 5.12 (s, 2H), 4.47−4.58 (m, 1H), 3.72−4.01 (m, 4H), 2.18−2.29 (m, 1H), 1.93−2.08 (m, 1H).

(b) Compound 4b. DEAD (1.2 mL, 7.9 mmol) was added to a stirred solution of Ph_3P (2.1 g, 7.9 mmol) in THF (60 mL) at 0 °C. After 15 min, compound **10** (1.46 g, 6.6 mmol) in THF (6.6 mL) was added followed by 3-hydroxypyridine (690 mg, 7.3 mmol). After stirring for 18 h at ambient temperature the solvent was removed and the residue was dissolved in CH_2-Cl_2, washed with saturated K_2CO_3, dried ($MgSO_4$), and concentrated. The crude product was then purified on flash silica gel column chromatography. Elution with EtOAc/hexane (1:2) provided a mixture (2.8 g) of (*R*)-1-(benzyloxycarbonyl)-3-((2-azetidinylmethyl)oxy)pyridine and Ph_3PO: MS (CI/NH_3) *m/e* 299 $(M + H)^+$. A sample (1.6 g) of this mixture was dissolved in EtOH (25 mL) and stirred in the presence of 10% Pd/C (320 mg) under an atmosphere of H_2 (1 atm) for 4 h. The reaction was filtered and concentrated. The residue was purified by flash silica gel column chromatography. Elution with $CHCl_3$/MeOH/NH_4OH (90:10:0 to 90:10:0.5) provided an amber oil (465 mg, 75%): $[\alpha]^{20}_D$ +5.8° (*c* 1.6, $CHCl_3$); MS (CI/NH_3) *m/e* 165 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.33

(dd, J = 1.5, 2.2 Hz, 1H), 8.22 (dd, J = 2.9, 3.0 Hz, 1H), 7.21−7.24 (m, 2H), 4.26−4.35 (m, 1H), 4.00−4.10 (m, 2H), 3.73 (dd, J = 7.7, 8.5 Hz, 1H), 3.45−3.51 (m, 1H), 2.22−2.46 (m, 2H).

(*R*)-3-(2-Azetidinylmethoxy)pyridine (450 mg, 2.74 mmol) was slurried in Et_2O (20 mL) and MeOH (~2 mL), and then Et_2O saturated with HCl gas was added at ambient temperature. The solvent was removed, and the remaining solid was recrystallized from MeOH/Et_2O to afford product as a deliquescent white solid (206 mg, 31%): mp 138−140 °C; $[\alpha]^{20}_D$ = +9.8° (*c* 0.5, MeOH); MS (CI/NH_3) *m/e* 165 $(M + H)^+$; ^{1}H NMR (D_2O, 300 MHz) δ 8.59 (d, J = 2.8 Hz, 1H), 8.46 (d, J = 5.7 Hz, 1H), 8.21 (ddd, J = 1.2, 2.8, 9.0 Hz, 1H), 7.99 (dd, J = 5.7, 9.0 Hz, 1H), 4.96−5.03 (m, 1H), 4.57 (d, J = 4.4 Hz, 2H), 4.05−4.21 (m, 2H), 2.71 (dd, J = 8.5, 17.3 Hz, 2H). Anal. ($C_9H_{11}N_2O\cdot 2HCl\cdot 0.2H_2O$) C, H, N.

3-((1-Methyl-2(*R*)-azetidinyl)methoxy)pyridine Dihydrochloride (5b). (*R*)-1-(benzyloxycarbonyl)-3-(2-azetidinylmethoxy)pyridine from above (1.2 g, contaminated with Ph_3PO) and paraformaldehyde (375 mg, 12.5 mmol) in EtOH (8 mL) was stirred in the presence of 10% Pd/C (80 mg) under 1 atm of H_2 for 6 h. The mixture was filtered and the filtrate concentrated. The residue was purified on flash silica gel column chromatography. Elution with $CHCl_3$/MeOH (90:10) afforded a colorless oil (250 mg, 50% yield from (*R*)-1-(benzyloxycarbonyl)-2-azetidinemethanol): $[\alpha]^{20}_D$ +58° (*c* 1.5, $CHCl_3$); MS (CI/NH_3) *m/e* 179 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (dd, J = 1.8, 1.8 Hz, 1H), 8.21 (dd, J = 2.9, 3.3 Hz, 1H), 7.20−7.22 (m, 2H), 4.02 (d, J = 5.5 Hz, 2H), 3.35−3.49 (m, 2H), 2.83−2.91 (m, 1H), 2.40 (s, 3H), 2.05−2.13 (m, 2H).

(*R*)-3-((1-Methyl-2-azetidinyl)methoxy)pyridine (220 mg, 1.23 mmol) was slurried in Et_2O (10 mL) and treated with Et_2O saturated with HCl gas. The solvent was removed and the remaining solid triturated with EtOAc (4×) to afford a deliquescent white solid (220 mg, 83%): mp 111−113 °C; $[\alpha]^{25}_D$ = +25.1° (*c* 0.5, MeOH); MS (CI/NH_3) *m/e* 179 $(M + H)^+$; ^{1}H NMR (D_2O, 300 MHz) δ 8.43 (d, J = 2.9 Hz, 1H), 8.32 (d, J = 5.0 Hz, 1H), 7.81 (ddd, J = 1.1, 2.9, 8.6 Hz, 1H), 7.68 (dd, J = 5.0, 8.6 Hz, 1H), 4.79−4.88 (m, 1H), 4.45−4.59 (m, 2H), 4.25−4.34 (m, 1H), 4.01 (dd, J = 9.4, 19.7 Hz, 1H), 3.00 (s, 3H), 2.56−2.77 (m, 2H). Anal. ($C_{10}H_{14}N_2O\cdot 0.5HCl\cdot 0.6H_2O$) C, H, N.

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