Conformationally Constrained Nicotines: Polycyclic, Bridged, and Spiro-Annulated Analogues as Novel Ligands for the Nicotinic Acetylcholine Receptor

Thomas Ullrich,*,[†] Sylvia Krich,[†] Dieter Binder,[†] Kurt Mereiter,[‡] David J. Anderson,[§] Michael D. Meyer,[§] and Michael Pyerin[†]

Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/E163, A-1060 Vienna, Austria, Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/E164, A-1060 Vienna, Austria, and Neurological and Urological Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, Department 47W, Building AP-9A/311, 100 Abbott Park Road, Abbott Park, Illinois 60064-6125

A set of novel nicotine-related, conformationally constrained compounds, including tetracyclic, bridged (**4**), and tricyclic, spiro-annulated (**5**) structures, were synthesized in a straightforward manner and optically resolved in a convenient fashion with (+)- and (−)-*O,O′*-di-*p*-toluoyltartaric acids. Absolute configurations were determined by X-ray crystallography. These compounds were evaluated for their ability to displace [³H]cytisine in a rat forebrain preparation and compared to (−)-nicotine. Three substances emerged with high affinity in the low nanomolar range. Moreover, one of these compounds ((+)-**5b**) showed not only high binding affinity ($K_i =$ 4.79 nM) but also significant enantioselectivity over its antipode ($K_i = 148$ nM), supporting the hypothesis that conformational restraint can lead to high-affinity ligands, which are stereochemically discriminated by the nicotinic acetylcholine receptor and may feature optimum locations of the active sites of the pharmacophore.

Introduction

Central nicotinic acetylcholine receptors (nAChRs) have been implicated in a number of cognitive and learning processes, making them a potential target for the treatment of Alzheimer's and other neurodegenerative diseases.[1] Other findings suggest that activation of these receptors also plays a critical role in the antinociceptive effects of cholinergic channel modulators.[2] Alzheimer's disease has received the most attention as a therapeutic target for nicotinic drugs, as nicotinic receptor binding was found to be significantly reduced in distinct brain regions of Alzheimer's patients.[3] Because the identification of various adverse physiological effects[3,4] of the alkaloid (*S*)-nicotine (**1**, Chart 1), synthetic modifications of its structure have been performed in order to improve potency and selectivity while reducing the toxicity.

A worldwide search for nAChR agonists for the α4β2 receptor, the predominant nAChR subtype in the brain, has already led to a number of promising substances, many of them closely related to nicotine.[5] In particular, nicotine analogues with rigid structures have become interesting targets stimulated by recent findings related to the highly active alkaloid, epibatidine.[6] Glassco et al.[7] and several others[8] pursued the concept of conformational restriction in nicotine with the objective of forcing

Chart 1. Nicotine (**1**) and Selected Conformationally Restricted Analogues
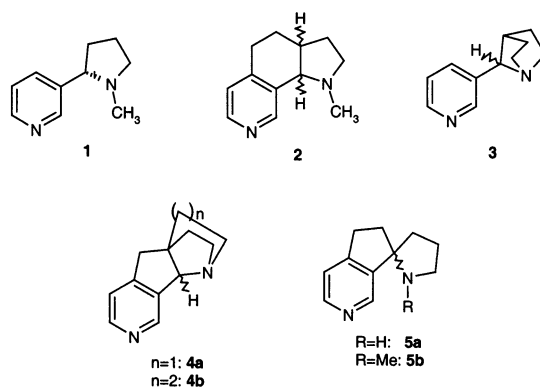
both pharmacophore nitrogen atoms into well-defined angles ("up" and "down" conformations), which would help in elucidating the "active" conformation of nicotine on one hand and obtaining a tool to study receptor subtype specificity on the other hand. These endeavors led to, among others, the class of hexahydropyrroloisoquinolines (**2**). The correct stereochemistry began to play an increasingly decisive role: while the relatively low enantioselectivity of nicotine (the affinity of (*S*)-nicotine is 10–100 times higher than that of (*R*)-nicotine)[9] has been an intriguing phenomenon for many years,[10] the premise that conformational restraint of nicotine should enhance enantioselectivity has been well-established.[11]
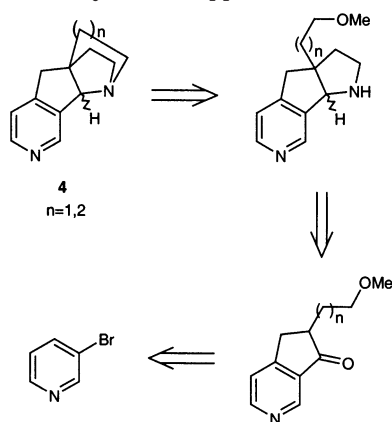
The (−)-enantiomer of **2** shows low relative affinity ($K_i = 605$ nM) for the nAChR [³H]nicotine binding site, whereas the (+)-enantiomer fails to displace the radioligand even at 10 μM concentrations.[8] Looking for similar enantioselectivities but higher binding affinities,

* To whom correspondence should be addressed. Tel: +43(1)86634-436. Fax: +43(1)86634-285. E-mail: thomas.ullrich@pharma.novartis.com.
† Institute of Applied Synthetic Chemistry, Vienna University of Technology.
‡ Institute of Chemical Technologies and Analytics, Vienna University of Technology.
§ Abbott Laboratories.

Scheme 1. Retrosynthetic Approach to Racemic **4**

Scheme 2[a]

[a] Reagents: (i) HC(OMe)$_3$, H$_2$SO$_4$ (catalytic), MeOH. (ii) Pyrrolidine, NH$_4$Cl (catalytic), reflux. (iii) (a) LDA, BrCH$_2$Cl, THF; (b) NaI, acetone. (iv) (a) Zn, LiCl, Cu, THF; (b) 3-bromopyridine, ClCOOEt, THF, −40 °C; (c) sulfur, xylene, reflux. (v), *n*-BuLi, THF, −78 °C. (vi) LDA, ICH$_2$CN, THF, −78 °C. (vii) Raney-cobalt, MeOH, 50 °C. (viii) (a) 62% HBr, reflux; (b) Na$_2$CO$_3$, H$_2$O, reflux.
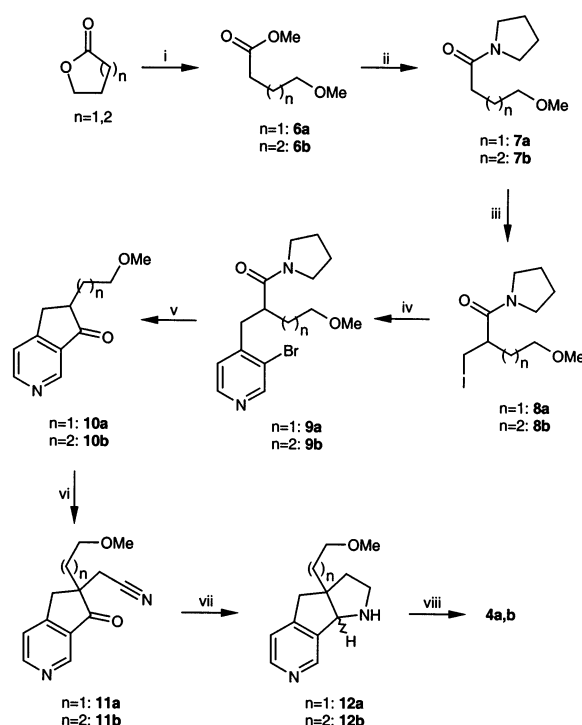
there has been a continuing effort in our group to extend the concept of conformational restriction in nicotinoid molecules either by imposing more rigidity on the nicotinic ligands or by achieving constraint in different molecule locations. The goal of our endeavors was to eventually find a structure, which is deprived of flexibility, binds with high affinity to the receptor, and is essentially more active than its stereoisomer. Without taking advantage of the possible predictability of binding provided by several pharmacophore models,[5,12] we found Glassco's research on isoquinolines (**2**) an intriguing concept and decided to focus on its structural variation. Recently, we have reported an enantioselective synthesis of azabicyclo[2.2.1]heptanes (**3**)[13] in which the pyrrolidine ring of nicotine is conformationally constrained into a bicyclic ring system. In the course of the present studies, we developed a synthetic route to combine the structural features of **3** with those of **2**, resulting in a novel class of tetracyclic nicotine-like compounds **4**. This novel chemical entity features a five-membered central ring (to keep the flexibility of the molecule at a minimum) and a bridge of variable chain length (*n* = 1, 2).

In yet another approach, closely related to the synthesis of **4**, it was our objective to create a second set of conformationally restricted molecules by introducing spiro-connection between the pyrrolidine ring and the pyridine-bearing unit. This approach led to compounds **5**, which represent, to the best of our knowledge, the first spiro-annulated nicotine analogues ever reported.

Chemistry

(a) Synthesis of Bridged Analogues 4a,b. Following a basic concept, compound class **4** was aimed to be synthesized as a mixture of stereoisomers that would easily undergo optical resolution, due to the high strain of the molecule. As it was neither known nor anticipated which of the isomers would elicit any activity in biological assays, an early determination of the stereochemistry appeared disadvantageous. Optical resolution at the final stage of the pathway, on the other hand, would provide quick availability of any desired isomer.

The retrosynthetic approach toward racemic compounds **4** was based on successive ring closure steps, starting with a commercial pyridine derivative and approaching the final azabicyclic system step by step (Scheme 1). The variable chain length (*n* = 1, 2) that determined the size of the bicyclic ring had to be

introduced early in the synthesis. For this reason, the multifunctional precursors **8** (Scheme 2) were built up in an efficient pathway that took its course from a methanolysis of γ-butyrolactone and δ-valerolactone,[14] respectively. Thus, the chain length present in the azabicyclic unit rooted in the commercial starting material, and its variation at a later stage was not possible. After esters **6** were aminolyzed with neat pyrrolidine, an iodomethyl substituent had to be introduced into the α-position of amides **7**, which appeared to be the bottleneck of the pathway. Lithiation of **7** with LDA in tetrahydrofuran (THF) and direct treatment with diiodomethane[15] resulted in poor yields, due to side reactions, such as elimination and dimerization. Circumvention of this problem was achieved by reacting the lithium enolate with bromochloromethane, giving reasonable yields of chloromethyl-substituted intermediate, and conversion into iodides **8** was easily accomplished under Finkelstein conditions.

Chemo- and regioselective 1,4-addition of soft nucleophiles to pyridinium salts (Knochel reaction) has been extensively reported in the literature.[16a−c] Thus, iodides **8** had to be transformed into activated, mixed zinc, copper organometallic species and were in situ combined with 3-bromopyridinium ethylformate at low temperatures. The dihydropyridines formed quantitatively, according to thin-layer chromatography (TLC), and were aromatized without prior purification, employing elemental sulfur in refluxing xylene.[16c] In good overall yields (50−60%), 4-substituted pyridines **9** were obtained . Metal−halogen exchange of the 3-bromo substituent was accomplished with *n*-BuLi and led to immediate and chemoselective, intramolecular cycliza-
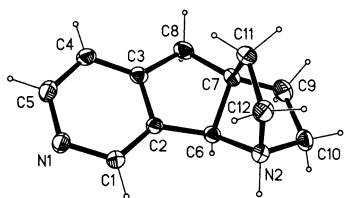
Figure 1. Thermal ellipsoid plot (20% ellipsoids) of (*R*)-(−)-**4a** in its crystalline salt **16**. Crystallographic atom numbering.
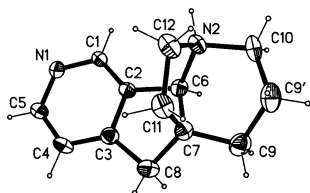

Figure 2. Thermal ellipsoid plot (20% ellipsoids) of (4a*S*)-(+)-**4b** in its crystalline salt **17**. Crystallographic atom numbering.

tion with the amide unit, affording the first ring closure in the synthetic route to give pyrindinones **10**. For this step, THF was first chosen as an appropriate solvent and gave good yields (68%) of **10b**, whereas **10a** could only be isolated among a number of byproducts. Compound **10a**, however, was obtained in equally good yields when THF was substituted for toluene to modulate the reactivity of *n*-BuLi. α-Substitution of the ketones with iodoacetonitrile was achieved after forming the lithium enolate with LDA, and catalytic hydrogenation of nitriles **11** led to a reaction cascade, assumably via subsequent, stereoselective formation of a primary amine and a cyclic hemiaminal, followed by reduction to the secondary amine. Whereas employment of Raney nickel gave inferior results, Raney cobalt, prepared from a commercially available Co−Al alloy,[17] furnished yields between 40 and 50%. Thus, only cis-annulated pyrrolidines **12** were obtained, with no traces of trans products determined. The mixtures of both diastereomers, respectively, underwent ether cleavage under acidic conditions followed by alkaline treatment under heating, upon which the last cyclization to the azabicyclic ring systems **4** took place.[13] The five-membered ring in **4a** (from methoxyethyl substitution) formed as easily as its six-membered analogue in **4b** (from methoxypropyl substitution), despite the considerably higher ring strain, and little material was lost due to the harsh reaction conditions.

Compounds **4a**,**b** (as mixtures of two diastereomers, respectively) were optically resolved by salt formation with chiral *O,O′*-di-*p*-toluoyltartaric acid and fractional recrystallization. In both cases, an optical purity of the free base of >95% de was observed by employment of (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate as an appropriate ¹H NMR shift reagent.[18] Absolute configurations were determined by single-crystal X-ray diffraction analysis for (−)-**4a** via its (2*R*,3*R*)-(−)-*O,O′*-di-*p*-toluoyltartrate **16** (Figure 1) and for (+)-**4b** via its (2*S*,3*S*)-(+)-*O,O′*-di-*p*-toluoyltartrate **17** (Figure 2). In the crystal structure images, the high conformational strain of the molecules becomes evident, and the spatial arrangement of the bridged unit can be easily contemplated. The absolute configuration of (−)-**4a** was found to be *R*; hence, the *S* configuration was assigned to its

Scheme 3. Retrosynthetic Approach to Racemic **5a**
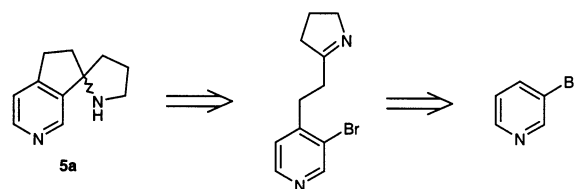
Scheme 4[a]
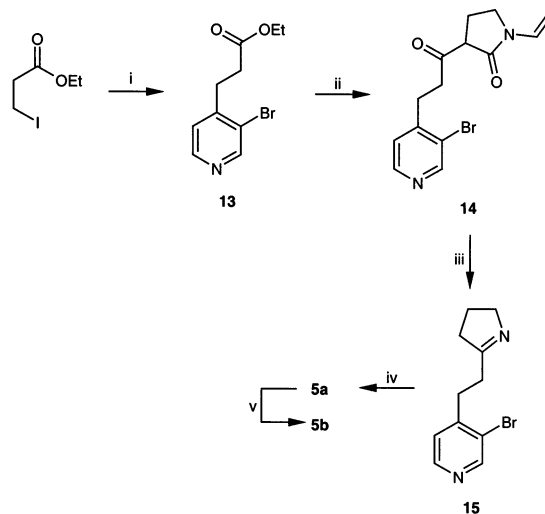
[a] Reagents: (i) (a) Zn, LiCl, Cu, THF; (b) 3-bromopyridine, ClCOOEt, THF, −40 °C; (c) sulfur, xylene, reflux. (ii) *N*-Vinylpyrrolidone, NaH, THF, °C. (iii) (a) 6 N HCl; (b) Na₂CO₃. (iv) *n*-BuLi, THF, −78 °C. (v) HCHO, NaBH₃CN, CH₃CN.

enantiomer (+)-**4a**. The absolute configuration of (+)-**4b** was found to be 4a*S*; hence, the 4a*R* configuration was assigned to its stereoisomer (−)-**4b**.

(b) Synthesis of Spiro-Annulated Analogues 5a,b. In a similar manner, the spiro-system present in compounds **5** was designed in a straightforward, symmetric sequence, with 3-bromopyridine as the starting material. In this approach, spiro-annulation was generated from a pyrroline key intermediate (Scheme 3).

In analogy with the pathway described above, a β-iodocarboxylic acid derivative was introduced into position 4 of 3-bromopyridine via 1,4-addition under the same experimental conditions as described above (Scheme 4). Ethyl ester **13** was then transformed in two steps into a cyclic imine that was considered essentially reactive toward intramolecular reaction with an organolithium species: Pyrroline **15** was obtained following conditions described by Haslego et al.[19] In this manner, reaction with deprotonated *N*-vinylpyrrolidone led to β-ketolactam **14**, which was not isolated but directly *N*-dealkylated with HCl under concomitant lactam hydrolysis and decarboxylation, yielding a γ-aminoketone that finally cyclized upon basification. Pyrroline **15** was simply treated with *n*-BuLi in toluene to trigger metal−halogen exchange and intramolecular addition across the C−N double bond. Spiro-compound **5a** was obtained in moderate yield as a racemate, which could be optically resolved again by salt formation with chiral *O,O′*-di-*p*-toluoyltartaric acid and fractional recrystallization. For both enantiomers, an optical purity of the free base of >95% ee was observed after derivatization with (*S*)-(−)-phenylethylisocyanate and ¹H NMR analysis of the resulting ureas. *N*-Methylation on each of the
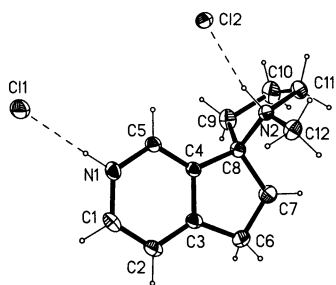
Figure 3. Thermal ellipsoid plot (20% ellipsoids) of crystalline (*R*)-(−)-**5b**·2HCl. Only one of the two independent molecules in the crystal structure is shown. Crystallographic atom numbering.

Table 1. Relative Affinities of Nicotine and Conformationally Constrained Analogues for the [^{3}H]Cytisine Binding Site

compd	K_i, [^{3}H]cytisine (nM)[a]	N^b
1 (nicotine)	0.94 ± 0.26	3
(+)-**3**	2.32 ± 0.36	3
(−)-**3**	1.89 ± 0.16	3
(*S*)-(+)-**4a**	962 ± 170	3
(*R*)-(−)-**4a**	1360 ± 180	3
(4a*S*)-(+)-**4b**	318 ± 34	3
(4a*R*)-(−)-**4b**	1040 ± 92	3
(*S*)-(+)-**5a**	53.1 ± 6.3	3
(*R*)-(−)-**5a**	533 ± 11	3
(*S*)-(+)-**5b**	4.79 ± 0.44	3
(*R*)-(−)-**5b**	148 ± 32	3

[a] All numbers are mean values $\pm$ SEM. Assay details are given in the Experimental Section. [b] Number of separate determinations.

enantiomers was easily accomplished following a modified Eschweiler−Clarke protocol to afford **5b**.[20]

The absolute configuration was determined in (−)-**5b** by X-ray diffraction analysis of its dihydrochloride (Figure 3) and found to be *R*. The *S* configuration was hence assigned to its enantiomer (+)-**5b**, and precursor molecules (+)-**5a** and (−)-**5a** were assigned their absolute configurations likewise.

Pharmacology

Each stereoisomer of compounds **3**−**5** (no binding data for compounds **3** have been previously published) was evaluated in an in vitro radioligand displacement assay and compared to nicotine, which was considered most appropriate for a first screening in order to determine binding ability of the ligands in central nervous system (CNS) tissue. In a procedure described by Pabreza et al.,[21] rat forebrain membrane was treated with the radioligand [^{3}H]cytisine that binds preferentially to the $\alpha 4\beta 2$ receptor.

The relative binding constants (K_i) of each compound for the [^{3}H]cytisine binding site are provided in Table 1. None of the tested substances was superior to nicotine; however, low nanomolar binding affinity was determined for (+)-**3** ($K_i = 2.32$ nM), (−)-**3** ($K_i = 1.89$ nM), and (+)-**5b** ($K_i = 4.79$ nM). It is evident that both enantiomers of **3**, which show the highest structural resemblance to nicotine, exhibit a binding profile most similar to the alkaloid. The conformational restriction accomplished by inserting a bridge in the pyrrolidine ring did not lead to significant enantioselectivity in this case, as both enantiomers show equally high affinity. The stereoisomers of bridged analogues **4a**,**b** did not achieve quite a similar profile; all four compounds bound in a low micromolar or submicromolar range, and no

remarkable enantioselectivity was observed. We conclude that either the extreme conformational constraint imposed on these molecules forced their molecular shapes in a disfavorable position, in which binding was impaired, or the high spatial demand that now characterized compounds **4** was not tolerated by the receptor. Spiro-annulated compounds **5a**,**b** exhibited much higher binding affinities. *nor*-Derivative (+)-**5a** bound at $K_i = 53.1$ nM with a 10-fold higher affinity than its enantiomer ($K_i = 533$ nM). Introduction of the *N*-methyl substituent resulted in a significant improvement, probably due to the gain of fortified receptor interaction: (+)-**5b** ($K_i = 4.79$ nM) appeared to be the most interesting ligand of this set as it not only bound in the low nanomolar range but also exhibited a 30-fold higher affinity than its enantiomer ($K_i = 148$ nM).

It can also be concluded from the data that with the exception of **3** all compounds featuring the *S* configuration show higher binding affinities than their *R* isomers, which indicates analogy with nicotine and suggests that the compounds bind in a nicotine-like manner. In the case of (+)-**5b**, not only a successful approach toward conformational restriction was found but also the beneficial effects of an *N*-methyl group present in the unbridged pyrrolidine ring were demonstrated. In compound (+)-**5b**, a conformation that comes close to the ideal conformation of a nicotinic ligand at the receptor may have been found, representing a rigid structure that provides nearly optimum locations of the active sites of the pharmacophore. These findings have the potential to give more insight to receptor−ligand interactions. Compound (+)-**5b** is a potential candidate for further investigation, such as peripheral binding and antinociceptive behavior, and may result in a new lead structure for the development of novel nAChR agonists and lead optimization, correspondingly.

Conclusion

Convenient synthetic routes to a set of novel nicotinic ligands with a focus on conformational constraint were established in the present study. The chemistry combined modern and traditional methods fit for multigram synthetic scales, including efficient optical resolution, and was supported by X-ray crystallography. The new compounds were evaluated in a preliminary radioligand displacement assay, and several substances showed low nanomolar binding affinities. The most promising candidate, compound (+)-**5b**, exhibited distinct enantioselectivity and is considered worthy of further investigation. The present structure−activity relationship study represents a valuable tool in our search for the development of improved nicotinic ligands.

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. TLC analyses were carried out on precoated silica gel plates (Merck 60 F$_{254}$), and signals were visualized with UV light. Flash chromatography refers to Fluka silica gel 60, 220−240 mesh. Melting points were recorded on a Kofler apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 200FS FT-NMR spectrometer. ^{1}H spectra are reported as parts per million downfield from Me$_4$Si with multiplicity, number of protons, and coupling constant(s) in Hertz indicated parenthetically. ^{13}C NMR spectral data are indicated as carbon units with the number of hydrogen atoms

attached. The following abbreviations are used to indicate spin multiplicities: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quin (quintet), or m (multiplet). Elemental analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry at Vienna University, Austria.

Ester Aminolysis. General Procedure. A mixture of the appropriate ester (**6a,b**) (1.00 mol), NH$_4$Cl (280 mmol), and pyrrolidine (2.00 mol) was refluxed for 4 h. After excess pyrrolidine was removed by distillation (first without reduced pressure, then at 300 mbar), the residue was cooled and taken up in Et$_2$O, and the precipitated salt was filtered off. The filtrate was concentrated, and the product was obtained by fractional distillation in a 25 cm Vigreux-column (0.5 mbar).

1-[4-(Methoxy)-1-oxobutyl]pyrrolidine (7a). The product was obtained as a colorless liquid (97%): *K*p 100 °C (0.5 mbar). ^{1}H NMR (CDCl$_3$): δ 3.50−3.36 (m, 6H), 3.30 (s, 3H), 2.33 (t, *J* = 8, 2H), 2.01−1.72 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 171.2 (C), 71.9 (CH$_2$), 58.4 (CH$_3$), 46.5 (CH$_2$), 45.5 (CH$_2$), 31.0 (CH$_2$), 26.0 (CH$_2$), 24.8 (CH$_2$), 24.3 (CH$_2$). Anal. (C$_9$H$_{17}$NO$_2$·0.17H$_2$O) C, H, N.

1-[5-(Methoxy)-1-oxopentyl]pyrrolidine (7b). The product was obtained as a colorless liquid (95%): *K*p 110 °C (0.5 mbar). ^{1}H NMR (CDCl$_3$): δ 3.52−3.32 (m, 6H), 3.30 (s, 3H), 2.29 (t, *J* = 8 Hz, 2H), 1.88 (quin, *J* = 8, 4H), 1.78−1.52 (m, 4H). ^{13}C NMR (CDCl$_3$): δ 171.7 (C), 72.3 (CH$_2$), 58.6 (CH$_3$), 46.7 (CH$_2$), 45.8 (CH$_2$), 35.2 (CH$_2$), 30.8 (CH$_2$), 27.3 (CH$_2$), 26.0 (CH$_2$), 24.3 (CH$_2$). Anal. (C$_{10}$H$_{19}$NO$_2$·0.22H$_2$O) C, H, N.

Iodomethylation. General Procedure. To a solution of diisopropylamine (502 mmol) in anhydrous THF (500 mL) was added *n*-BuLi (2.5 M solution in *n*-hexane; 502 mmol) at 0 °C and stirred for 1 h. The appropriate amide (**7a,b**) (502 mmol) in anhydrous THF (200 mL) was added dropwise at 0 °C and stirred for 2 h at 25 °C. The mixture was cooled to −80 °C, and bromochloromethane (502 mmol) was added at once. After it reached room temperature and was stirred for 2 h, the solution was partitioned between 2 N HCl (500 mL) and EtOAc (500 mL). The aqueous layer was extracted with 3 × 300 mL of EtOAc. The combined organic layers were dried (Na$_2$SO$_4$, activated charcoal), filtered, and evaporated. The crude product was dried thoroughly in vacuo and taken up in a solution of anhydrous NaI (468 mmol) in dry acetone (1 L). After it was refluxed for 48 h and the solvent was removed, the residue was diluted with 200 mL of Et$_2$O. Precipitated NaCl was filtered off, and the filtrate was evaporated. The crude product was purified by flash chromatography (1.5 kg of silica gel; EtOAc).

1-[2-(Iodomethyl)-4-(methoxy)-1-oxobutyl]pyrrolidine (8a). The product was obtained as a yellowish oil (36%): R_f = 0.3 (ethyl acetate). ^{1}H NMR (CDCl$_3$): δ 3.69−3.32 (m, 8H), 3.28 (s, 3H), 3.31−3.08 (m, 1H), 2.05−1.69 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 171.5 (C), 69.8 (CH$_2$), 58.3 (CH$_3$), 46.6 (CH$_2$), 45.6 (CH$_2$), 43.9 (CH), 33.9 (CH$_2$), 25.9 (CH$_2$), 24.3 (CH$_2$), 6.2 (CH$_2$). Anal. (C$_{10}$H$_{18}$INO$_2$) C, H, N.

1-[2-(Iodomethyl)-5-(methoxy)-1-oxopentyl]pyrrolidine (8b). The product was obtained as a red oil (49%): R_f = 0.5 (ethyl acetate). ^{1}H NMR (CDCl$_3$): δ 3.72−3.32 (m, 7H), 3.28 (s, 3H), 3.13 (dd, *J* = 17, 8, 1H), 3.06−2.88 (m, 1H), 2.02−1.78 (m, 4H), 1.78−1.43 (m, 4H). ^{13}C NMR (CDCl$_3$): δ 171.7 (C), 72.3 (CH$_2$), 58.6 (CH$_3$), 47.0 (CH), 46.7 (CH$_2$), 45.8 (CH$_2$), 30.8 (CH$_2$), 27.3 (CH$_2$), 26.0 (CH$_2$), 24.3 (CH$_2$), 6.1 (CH$_2$). Anal. (C$_{11}$H$_{20}$INO$_2$) C, H, N.

Pyridinium 1,4-Addition. General Procedure. Zinc powder (1.3 mmol) was suspended in a 50% solution of 1,2-dibromoethane (0.15 mmol) in anhydrous THF under nitrogen and briefly heated until gas began to evolve. This procedure was repeated twice, followed by addition of a few drops of chloro(trimethyl)silane. The mixture was stirred for 30 min at room temperature. Then, a 50% solution of the appropriate halide (**8a,b** or ethyl β-iodopropionate; 1 mmol) in anhydrous THF was carefully added. After it was stirred for 10 min and briefly heated to reflux temperature three times, the resulting suspension was allowed to stand for 1 h. Thoroughly dried LiCl

(0.9 mmol; predried at 120−130 °C in vacuo for at least 2 h) was mixed with CuCN (1 mmol), dissolved quickly in dry THF (20% solution), and cooled to −40 °C. The organozinc suspension was decanted quickly into a dropping funnel and added to the copper solution. After 5 min at 0 °C, the resulting mixture was cooled to −50 °C (flask 1). 3-Bromopyridine (0.75 mmol) in anhydrous THF (20% solution) was reacted with ethyl chloroformate (0.75 mmol) in anhydrous THF (20% solution) at 0 °C under nitrogen (flask 2). After 1 h, the contents of flask 2 were transferred into a dropping funnel and quickly added to flask 1 under vigorous stirring. The resulting mixture was allowed to reach room temperature. After 25% NH$_4$OH was added until a dark blue color prevailed, the obtained suspension was stirred for 1 h and filtered through Celite. After the solvent was removed, the residue was extracted with Et$_2$O (3×). The combined organic layers were washed with 2 N HCl and H$_2$O, dried (Na$_2$SO$_4$), filtered, and evaporated. The crude intermediate was dissolved in anhydrous xylene (20% solution), and elemental sulfur (1.3 mmol) was added. The mixture was refluxed for 72 h, cooled, poured on 2 N HCl, and washed with Et$_2$O. The aqueous layer was neutralized with NaHCO$_3$ and extracted 3× with Et$_2$O. The combined organic layers were dried (Na$_2$SO$_4$), filtered, and evaporated. The crude product was purified by flash chromatography (CH$_2$Cl$_2$/MeOH = 15:1). Yields are given referring to 3-bromopyridine as the starting material.

1-[2-[(3-Bromo-4-pyridyl)methyl]-4-methoxy-1-oxobutyl]pyrrolidine (9a). The product was obtained as a yellow oil (52%): R_f = 0.5 (CH$_2$Cl$_2$/MeOH = 15:1). ^{1}H NMR (CDCl$_3$): δ 8.60 (s, 1H), 8.29 (d, *J* = 6, 1H), 7.12 (d, *J* = 6, 1H), 3.43−3.02 (m, 7H), 3.22 (s, 3H), 3.02−2.74 (m, 2H), 2.05−1.49 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 172.1 (C), 151.5 (CH), 147.9 (C), 147.8 (CH), 126.2 (CH), 122.8 (C), 69.9 (CH$_2$), 58.3 (CH$_3$), 46.2 (CH$_2$), 45.3 (CH$_2$), 39.5 (CH), 38.2 (CH$_2$), 32.6 (CH$_2$), 25.7 (CH$_2$), 24.0 (CH$_2$). Anal. (C$_{15}$H$_{21}$BrN$_2$O$_2$) C, H, N.

1-[2-[(3-Bromo-4-pyridyl)methyl]-4-methoxy-1-oxopentyl]pyrrolidine (9b). The product was obtained as a yellow oil (62%): R_f = 0.5 (CH$_2$Cl$_2$/MeOH = 15:1). ^{1}H NMR (CDCl$_3$): δ 8.62 (s, 1H), 8.33 (d, *J* = 6, 1H), 7.13 (d, *J* = 6, 1H), 3.50−3.30 (m, 7H), 3.28 (s, 3H), 3.00−2.79 (m, 2H), 1.98−1.42 (m, 8H). ^{13}C NMR (CDCl$_3$): δ 172.3 (C), 151.6 (CH), 148.2 (C), 147.9 (CH), 126.4 (CH), 122.9 (C), 72.4 (CH$_2$), 58.5 (CH$_3$), 46.4 (CH$_2$), 45.6 (CH$_2$), 42.7 (CH), 38.4 (CH$_2$), 29.5 (CH$_2$), 27.4 (CH$_2$), 25.8 (CH$_2$), 24.1 (CH$_2$). Anal. (C$_{16}$H$_{23}$BrN$_2$O$_2$) C, H, N.

3-(3-Bromo-4-pyridyl)propionic Acid Ethyl Ester (13). The product was obtained as a yellow oil (49%): *K*p 102−105 °C (0.1 mbar); R_f = 0.25 (petroleum ether/EtOAc = 4:1). ^{1}H NMR (CDCl$_3$): δ 8.63 (s, 1H), 8.39 (d, *J* = 6, 1H), 7.18 (d, *J* = 6, 1H), 4.10 (q, *J* = 7.1, 2H), 3.02 (t, *J* = 7.5, 2H), 2.63 (t, *J* = 7.5, 2H), 1.21 (t, *J* = 7.1, 3H). ^{13}C NMR (CDCl$_3$): δ 171.8 (C), 151.8 (CH), 148.6 (C), 148.2 (CH), 125.1 (CH), 122.9 (C), 60.7 (CH$_2$), 32.7 (CH$_2$), 30.4 (CH$_2$), 14.1 (CH$_3$). Anal. (C$_{10}$H$_{12}$BrNO$_2$) C, H, N.

5,6-Dihydro-6-[2-(methoxy)ethyl]-7*H*-2-pyrindin-7-one (10a). To a solution of *n*-BuLi (2.5 M in *n*-hexane; 64 mL; 159 mmol) in anhydrous toluene (500 mL), **9a** (49.2 g; 144 mmol) in anhydrous toluene (500 mL) was added dropwise at −90 °C. The mixture was stirred for 30 min, with the temperature allowed to rise to −50 °C. After it was cooled to −90 °C, a second portion of *n*-BuLi (2.5 M in *n*-hexane; 64 mL; 159 mmol) was added to the mixture, followed by another 30 min of stirring. The cold solution was poured on 2 N HCl (13 mL) and ice (100 g). After the organic layer was separated, the aqueous phase was washed with EtOAc (5 × 200 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and evaporated. The crude product was purified by flash chromatography (1 kg of silica gel; EtOAc) to give 21.5 g (78%) of a yellow oil: R_f = 0.3 (EtOAc). ^{1}H NMR (CDCl$_3$): δ 8.88 (s, 1H), 8.64 (d, *J* = 6, 1H), 7.38 (d, *J* = 6, 1H), 3.50 (t, *J* = 8, 2H), 3.32 (dd, *J* = 17, 6, 1H), 3.23 (s, 3H), 2.89 (dd, *J* = 17, 9, 1H), 2.80−2.67 (m, 1H), 2.25−2.08 (m, 1H), 1.78−1.58 (m, 1H). ^{13}C NMR (CDCl$_3$): δ 206.8 (C), 161.4 (C), 153.4 (CH), 146.3 (CH), 132.2 (C), 121.7 (CH), 70.3 (CH$_2$), 58.4 (CH$_3$), 44.5 (CH), 32.7 (CH$_2$), 30.6 (CH$_2$). Anal. (C$_{11}$H$_{13}$NO$_2$·0.09H$_2$O) C, H, N.

5,6-Dihydro-6-[3-(methoxy)propyl]-7H-2-pyrindin-7-one (10b). To a solution of **9b** (77.0 g; 217 mmol) in anhydrous THF (1.4 L), *n*-BuLi (2.5 M in *n*-hexane; 87.0 mL; 217 mmol) was added at −78 °C. The mixture was stirred for 30 min, allowing the temperature to rise to −60 °C. The cold solution was quenched with 2 N HCl (500 mL). After the organic solvent was separated, the aqueous phase was washed with EtOAc (2 × 200 mL), neutralized with NaHCO$_3$, and extracted with Et$_2$O (5 × 300 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and evaporated. The crude product was purified by flash chromatography (500 g of silica gel; CH$_2$Cl$_2$/MeOH = 15:1) to give 30.3 g (68%) of a yellow oil: R_f = 0.4 (EtOAc). ^{1}H NMR (CDCl$_3$): δ 8.98 (s, 1H), 8.70 (d, J = 6, 1H), 7.42 (d, J = 6, 1H), 3.41 (t, J = 8, 2H), 3.38 (dd, J = 17, 9, 1H), 3.31 (s, 3H), 2.87 (dd, J = 17, 6, 1H), 2.78−2.63 (m, 1H), 2.08−1.90 (m, 1H), 1.79−1.48 (m, 3H). ^{13}C NMR (CDCl$_3$): δ 207.0 (C), 161.6 (C), 153.5 (CH), 146.5 (CH), 132.5 (C), 121.9 (CH), 72.3 (CH$_2$), 58.5 (CH$_3$), 46.9 (CH), 32.7 (CH$_2$), 27.9 (CH$_2$), 27.2 (CH$_2$). Anal. (C$_{12}$H$_{15}$NO$_2$·0.15H$_2$O) C, H, N.

Cyanomethylation. General Procedure. To a 5% solution of diisopropylamine (1 mmol) in anhydrous THF, *n*-BuLi (2.5 M solution in *n*-hexane; 1 mmol) was added at −30 °C and stirred for 30 min. A 10% solution of the appropriate pyrindinone (**10a,b**, 1 mmol) in anhydrous THF was added dropwise at −20 °C and stirred for 1 h at 0 °C. The mixture was cooled to −90 °C, and a 20% solution of iodoacetonitrile (1 mmol) in anhydrous THF was added quickly. After it was stirred for 1 h at room temperature, the mixture was extracted with 2 N HCl. The aqueous phase was washed with EtOAc, neutralized with Na$_2$CO$_3$, and extracted 3× with EtOAc. The combined organic layers were dried (Na$_2$SO$_4$), filtered, and evaporated. The crude product was purified by flash chromatography (EtOAc).

6,7-Dihydro-6-(2-methoxyethyl)-7-oxo-5H-2-pyrindine-6-acetonitrile (11a). The product was obtained as a yellow oil (78%): R_f = 0.3 (EtOAc). ^{1}H NMR (CDCl$_3$): δ 8.92 (s, 1H), 8.70 (d, J = 6, 1H), 7.42 (d, J = 6, 1H), 3.32−3.12 (m, 2H), 3.28 (t, J = 8, 2H), 2.97 (s, 3H), 2.72−2.58 (m, 1H), 2.12−1.80 (m, 2H). ^{13}C NMR (CDCl$_3$): δ 204.7 (C), 159.3 (C), 154.1 (CH), 146.7 (CH), 131.0 (C), 121.6 (CH), 116.8 (C), 67.9 (CH$_2$), 58.2 (CH$_3$), 48.8 (CH), 37.2 (CH$_2$), 36.2 (CH$_2$), 25.2 (CH$_2$). Anal. (C$_{13}$H$_{14}$N$_2$O$_2$·0.14H$_2$O) C, H, N.

6,7-Dihydro-6-(3-methoxypropyl)-7-oxo-5H-2-pyrindine-6-acetonitrile (11b). The product was obtained as a yellow oil (78%): R_f = 0.4 (EtOAc). ^{1}H NMR (CDCl$_3$): δ 9.03 (s, 1H), 8.75 (d, J = 6, 1H), 7.48 (d, J = 6, 1H), 3.32−3.18 (m, 4H), 3.20 (t, J = 8, 2H), 2.70−2.57 (m, 2H), 1.82−1.78 (m, 2H), 1.53−1.22 (m, 2H). ^{13}C NMR (CDCl$_3$): δ 205.1 (C), 159.7 (C), 154.8 (CH), 147.0 (CH), 131.1 (C), 121.8 (CH), 116.8 (C), 71.7 (CH$_2$), 58.4 (CH$_3$), 49.7 (CH), 37.4 (CH$_2$), 33.8 (CH$_2$), 24.9 (CH$_2$), 24.3 (CH$_2$). Anal. (C$_{14}$H$_{16}$N$_2$O$_2$·0.05H$_2$O) C, H, N.

Reductive Amination of Ketones. General Procedure. The appropriate nitrile (**11a,b**, 10 mmol) was dissolved in anhydrous MeOH (10 mL), treated with activated charcoal, and filtered. Activated Raney cobalt (3 equiv of weight) was added to the filtrate. The mixture was transferred into a Parr hydrogenator and shaken for 12 h at 50 °C (90 psi H$_2$). The procedure was repeated with another equivalent of weight of Raney cobalt. After the reaction was completed (by TLC), the catalyst was filtered through Celite. The solvent was removed in vacuo, and the residue was purified by flash chromatography (MeOH/NH$_4$OH = 50:1). The product was dissolved in CH$_2$Cl$_2$, dried (Na$_2$SO$_4$), filtered, and concentrated.

[3aα,8bβ]-1,2,3,3a,4,8b-Hexahydro-3a-[(2-methoxy)ethyl]pyrrolo[3′,2′:4,5]cyclopenta[1,2-c]pyridine (12a). The product was obtained as a yellow oil (55%): R_f = 0.4 (MeOH/NH$_4$OH = 50:1). ^{1}H NMR (CDCl$_3$): δ 8.52 (s, 1H), 8.41 (d, J = 6, 1H), 7.09 (d, J = 6, 1H), 4.47 (s, 1H), 3.49 (t, J = 8, 2H), 3.29 (s, 3H), 3.15−2.98 (m, 1H), 3.05−2.90 (m, 2H), 2.79−2.63 (m, 1H), 2.30 (bs, 1H), 2.00−1.63 (m, 4H). ^{13}C NMR (CDCl$_3$): δ 152.0 (C), 148.5 (CH), 147.3 (CH), 141.0 (C), 120.3 (CH), 72.5 (CH), 70.3 (CH$_2$), 58.6 (CH$_3$), 52.7 (C), 46.6 (CH$_2$), 43.6 (CH$_2$), 40.4 (CH$_2$), 39.2 (CH$_2$). Anal. (C$_{13}$H$_{18}$N$_2$O·0.05H$_2$O) C, H, N.

[3aα,8bβ]-1,2,3,3a,4,8b-Hexahydro-3a-[(3-methoxy)propyl]pyrrolo[3′,2′:4,5]cyclopenta[1,2-c]-pyridine (12b). The product was obtained as a yellow oil (41%): R_f = 0.4 (MeOH/NH$_4$OH = 50:1). ^{1}H NMR (CDCl$_3$): δ 8.40 (s, 1H), 8.38 (d, J = 6, 1H), 7.06 (d, J = 6, 1H), 4.38 (s, 1H), 3.38 (t, J = 8, 2H), 3.31 (s, 3H), 3.13−2.98 (m, 1H), 3.00−2.87 (m, 2H), 2.78−2.64 (m, 1H), 2.34 (bs, 1H), 1.77−1.53 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 152.2 (C), 148.3 (CH), 147.1 (CH), 140.4 (C), 119.8 (CH), 72.8 (CH), 72.2 (CH$_2$), 58.4 (CH$_3$), 53.7 (C), 46.6 (CH$_2$), 43.3 (CH$_2$), 40.4 (CH$_2$), 36.4 (CH$_2$), 25.9 (CH$_2$). Anal. (C$_{14}$H$_{20}$N$_2$O·0.06H$_2$O) C, H, N.

Ether Cleavage and Cyclization. General Procedure. A solution of the appropriate pyrrolidine (**12a,b**, 10 mmol) in 62% HBr (10 mL) was refluxed in a glass autoclave for 4 h. After water (1 mL) and Na$_2$CO$_3$ (pH 8−9) were added, the mixture was refluxed for 2 h and concentrated in vacuo. The residue was triturated 5× with hot EtOAc, and the combined, decanted organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The crude product was purified by flash chromatography (MeOH) and crystallized from Et$_2$O.

(±)-1,3a-Ethano-1,2,3,3a,4,8b-hexahydropyrrolo[3′,2′:4,5]cyclopenta[1,2-c]-pyridine (4a). The product was obtained as colorless crystals (60%): mp 104−107 °C; R_f = 0.3 (MeOH/NH$_4$OH = 50:1). ^{1}H NMR (CDCl$_3$): δ 8.52 (s, 1H), 8.40 (d, J = 6, 1H), 7.15 (d, J = 6, 1H), 3.93 (s, 1H), 3.57−3.30 (m, 1H), 3.08−2.63 (m, 3H), 2.98−2.80 (m, 2H), 1.82−1.61 (m, 1H), 1.51−1.38 (m, 1H), 1.38−1.20 (m, 1H), 1.19−1.00 (m, 1H). ^{13}C NMR (CDCl$_3$): δ 158.3 (C), 148.7 (CH), 145.6 (CH), 135.0 (C), 122.2 (CH), 82.6 (CH), 61.8 (CH$_2$), 57.9 (CH$_2$), 55.0 (C), 35.2 (CH$_2$), 34.1 (CH$_2$), 32.1 (CH$_2$). Anal. (C$_{12}$H$_{14}$N$_2$·0.03H$_2$O) C, H, N.

(±)-[4aα,9bβ]-2H-1,4a-Ethano-3,4,5,9b-tetrahydro-1H-cyclopenta[2,1-b:3,4-c′]dipyridine (4b). The product was obtained as colorless crystals (46%): mp 84−86 °C; R_f = 0.3 (MeOH/NH$_4$OH = 50:1). ^{1}H NMR (CDCl$_3$): δ 8.52 (s, 1H), 8.42 (d, J = 6, 1H), 7.13 (d, J = 6, 1H), 3.95 (s, 1H), 3.12−2.65 (m, 6H), 2.08−1.60 (m, 4H), 1.60−1.38 (m, 1H), 1.34−1.09 (m, 1H). ^{13}C NMR (CDCl$_3$): δ 151.9 (C), 148.5 (CH), 145.6 (CH), 138.4 (C), 121.2 (CH), 78.9 (CH), 56.1 (CH$_2$), 52.2 (CH$_2$), 51.1 (C), 40.3 (CH$_2$), 36.2 (CH$_2$), 35.0 (CH$_2$), 19.4 (CH$_2$). Anal. (C$_{13}$H$_{16}$N$_2$·0.49H$_2$O) C, H, N.

Optical Resolution of 4a. Step 1: A solution of (+)-O,O'-di-*p*-toluoyltartaric (0.5 mmol) in anhydrous EtOH (1 mL) was added to (±)-**4a** (1 mmol) in anhydrous EtOH. The solution was stored at −20 °C until precipitation of the chiral salt was completed. The product was obtained by filtration, washed with EtOH, and dried in vacuo. **Step 2:** The crude product was recrystallized 2× from EtOH. The optically resolved material (ee > 95%) was free-based with 0.1 N NaOH, extracted with CHCl$_3$, dried (Na$_2$SO$_4$), and concentrated to give crystalline (−)-**4a**. **Step 3:** The mother liquor from step 1 was free-based and worked up in the same manner and submitted to derivatization with (−)-O,O'-di-*p*-toluoyltartaric acid, as described above, to afford (+)-**4a** (ee > 95%).

Optical Resolution of 4b. Step 1: A solution of (+)-O,O'-di-*p*-toluoyltartaric acid (0.5 mmol) in anhydrous EtOH (1 mL) was added to (±)-**4b** (1 mmol) in anhydrous EtOH. The solution was stored at −20 °C until precipitation of the chiral salt was completed. The product was obtained by filtration, washed with EtOH, and dried in vacuo. **Step 2:** The crude product was recrystallized 2× from MeOH. The optically resolved material (de > 95%) was free-based with 0.1 N NaOH, extracted with CHCl$_3$, dried (Na$_2$SO$_4$), and concentrated to give an amorphous solid that was dissolved in 8 N methanolic HCl and concentrated in vacuo. Treatment with methanolic HCl in this manner was repeated twice, and (−)-**4b**·2HCl precipitated from the methanolic solution upon storage at −20 °C for 3 days. **Step 3:** The mother liquor from step 1 was free-based and worked up in the same manner and submitted to derivatization with (−)-O,O'-di-*p*-toluoyltartaric acid, as described above, to afford (+)-**4b**·2HCl (de > 95%).

(R)-(−)-1,3a-Ethano-1,2,3,3a,4,8b-hexahydropyrrolo[3′,2′:4,5]cyclopenta[1,2-c]-pyridine (4a). The product was obtained as colorless crystals (20%): [α]$_D^{20}$ −51.2° (*c* 1, MeOH).

Anal. ($C_{12}H_{14}N_2 \cdot 0.04H_2O$) C, H, N. All other analytical data were identical with those of ($\pm$)-**4a**.

(*S*)-(+)-1,3a-Ethano-1,2,3,3a,4,8b-hexahydropyrrolo-[3′,2′:4,5]cyclopenta[1,2-*c*]-pyridine (4a). The product was obtained as colorless crystals (23%): $[\alpha]_D^{20}$ +50.7° (*c* 1, MeOH). Anal. ($C_{12}H_{14}N_2 \cdot 0.12H_2O$) C, H, N. All other analytical data were identical with those of ($\pm$)-**4a**.

[4a*R*-(4aα,9bβ)]-(−)-2*H*-1,4a-Ethano-3,4,5,9b-tetrahydro-1*H*-cyclopenta[2,1-*b*:3,4-*c*′]dipyridine, Dihydrochloride (4b). The product was obtained as colorless, hygroscopic crystals (18%): mp not measurable; $[\alpha]_D^{20}$ −44.6° (*c* 1, MeOH). ^{1}H NMR (D_2O): δ 8.82 (s, 1H), 8.73 (d, *J* = 6, 1H), 8.09 (d, *J* = 6, 1H), 4.91 (s, 1H), 3.70–3.20 (m, 6H), 2.38–1.97 (m, 5H), 1.72–1.51 (m, 1H). ^{13}C NMR (D_2O): δ 166.7 (C), 144.1 (CH), 139.1 (CH), 137.3 (C), 127.2 (CH), 76.7 (CH), 56.5 (CH_2), 54.2 (CH_2), 52.5 (C), 42.4 (CH_2), 33.6 (CH_2), 33.0 (CH_2), 18.6 (CH_2). Anal. ($C_{13}H_{18}Cl_2N_2 \cdot 0.35H_2O$) C, H, N.

[4a*S*-(4aα,9bβ)]-(+)-2*H*-1,4a-Ethano-3,4,5,9b-tetrahydro-1*H*-cyclopenta[2,1-*b*:3,4-*c*′]dipyridine, Dihydrochloride (4b). The product was obtained as colorless, hygroscopic crystals (27%): $[\alpha]_D^{20}$ +44.3° (*c* 1, MeOH). Anal. ($C_{13}H_{18}Cl_2N_2 \cdot 0.37H_2O$) C, H, N. All other analytical data were identical with those of (−)-**4b**.

3-Bromo-4-[2-(4,5-dihydro-3H-pyrrol-2-yl)ethyl]pyridine (15). A solution of freshly distilled *N*-vinyl-2-pyrrolidinone (18.2 g, 164 mmol) and **13** (40.0 g, 155 mmol) in anhydrous THF (300 mL) was added to a suspension of NaH (4.30 g, 179 mmol) in anhydrous THF (300 mL) in a N_2 atmosphere. The mixture was refluxed for 1 h and poured on a saturated NH_4Cl solution (300 mL). After THF was removed in vacuo, the aqueous mixture was extracted with Et_2O (3 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude intermediate (**14**) was not further purified but taken up in 8 N HCl (650 mL) and refluxed for 12 h. The mixture was cooled with an ice bath, alkalified with 50% NaOH until pH 10, and extracted with CH_2Cl_2 (4 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by flash chromatography (450 g of silica gel; CH_2Cl_2/acetone = 2:1) to give 16.3 g (42%) of a yellow oil: R_f = 0.35 (CH_2Cl_2/acetone = 2:1). ^{1}H NMR ($CDCl_3$): δ 8.65 (s, 1H), 8.39 (d, *J* = 6, 1H), 7.19 (d, *J* = 6, 1H), 3.90–3.78 (m, 2H), 3.12–3.01 (m, 2H), 2.63 (t, *J* = 8, 2H), 2.50 (t, *J* = 8, 2H), 2.00–1.83 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 176.1 (C), 151.7 (CH), 149.5 (C), 148.1 (CH), 124.9 (CH), 122.8 (C), 60.7 (CH_2), 37.5 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 22.3 (CH_2). Anal. ($C_{11}H_{13}BrN_2$) C, H, N.

(±)-1,2,3,4,10,11-Hexahydrospiro[7*H*-2-pyrindine-7,2′-2*H*-pyrrole] (5a). *n*-BuLi (2.5 M solution in *n*-hexane, 97.5 mmol) was added to **15** (24.5 g, 96.8 mmol) in anhydrous toluene (350 mL) at −78 °C under a N_2 atmosphere. After it was stirred for 30 min, the mixture was poured on 2 N NaOH (400 mL) and extracted with Et_2O (5 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by flash chromatography (400 g of silica gel; MeOH) to give 7.44 g (44%) of a yellow oil: R_f = 0.3 (MeOH). ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 1H), 8.38 (d, *J* = 6, 1H), 7.11 (d, *J* = 6, 1H), 3.26–2.99 (m, 2H), 2.99–2.70 (m, 2H), 2.23–1.89 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 152.5 (C), 148.2 (CH), 145.3 (C), 144.4 (CH), 120.0 (CH), 71.6 (C), 46.5 (CH_2), 41.0 (CH_2), 38.2 (CH_2), 29.9 (CH_2), 25.9 (CH_2). Anal. ($C_{11}H_{16}Cl_2N_2$) C, H, N.

Optical Resolution of 5a. Step 1: A solution of (±)-**5a** (3.30 g, 18.9 mmol) in EtOH (20 mL) was treated with (−)-*O,O*′-di-*p*-toluoyltartaric acid (7.31 g, 18.9 mmol). The resulting solution was diluted with acetone (10 mL) and H_2O (7 mL) and stored at −20 °C until precipitation of the chiral salt was completed. The product was obtained by filtration, washed with hot MeOH, and dried in vacuo. Step 2: The residue was free-based with 0.1 N NaOH, extracted with Et_2O, dried (Na_2SO_4), and concentrated to give partially resolved material (ee = 70%) that underwent the same procedure twice with equimolar amounts of (−)-*O,O*′-di-*p*-toluoyltartaric acid, to furnish optically resolved (−)-**5a** (ee > 95%) that was dissolved in 8 N methanolic HCl and concentrated in vacuo. Treatment

with methanolic HCl in this manner was repeated twice, and (−)-**5a**·2HCl precipitated from acetone/EtOH upon storage at −20 °C for 3 days. Step 3: The combined mother liquors from step 1 were free-based and worked up in the same manner and submitted to derivatization with (−)-*O,O*′-di-*p*-toluoyltartaric acid, as described above, to afford (+)-**5a**·2HCl (ee > 95%).

(*R*)-(−)-1,2,3,4,10,11-Hexahydrospiro[7*H*-2-pyrindine-7,2′-2*H*-pyrrole]dihydrochloride (5a). The product was obtained as colorless, hygroscopic crystals (26%): mp not measurable; $[\alpha]_D^{20}$ −23.1° (*c* 1, MeOH). ^{1}H NMR (D_2O): δ 8.94 (s, 1H), 8.77 (d, *J* = 6, 1H), 8.10 (d, *J* = 6, 1H), 3.71–3.52 (m, 2H), 3.52–3.36 (m, 2H), 2.84–2.26 (m, 6H). ^{13}C NMR (D_2O): δ 169.4 (C), 144.2 (CH), 142.1 (C), 139.5 (CH), 126.6 (CH), 76.6 (C), 47.2 (CH_2), 38.1 (CH_2), 37.9 (CH_2), 33.3 (CH_2), 24.8 (CH_2). Anal. ($C_{11}H_{16}Cl_2N_2 \cdot 0.3H_2O$) C, H, N.

(*S*)-(+)-1,2,3,4,10,11-Hexahydrospiro[7*H*-2-pyrindine-7,2′-2*H*-pyrrole]dihydrochloride (5a). The product was obtained as colorless, hygroscopic crystals (22%): mp not measurable; $[\alpha]_D^{20}$ +24.0° (*c* 1, MeOH). Anal. ($C_{11}H_{16}Cl_2N_2$) C, H, N. All other analytical data were identical with those of (−)-**5a**·2HCl.

N-Methylation. General Procedure. A solution of the appropriate pyrrolidine ((+)-**5a** or (−)-**5a**) (650 mg, 3.73 mmol) and 35% aqueous formaldehyde (3.1 mL, 36.1 mmol) in anhydrous CH_3CN (30 mL) was treated with $NaBH_3CN$ (540 mg, 8.58 mmol) and stirred for 30 min at room temperature. The mixture was quenched with 2 N HCl until pH 1. The resulting slurry was washed with CH_2Cl_2 (2 × 50 mL), alkalified with 6 N NaOH (pH 10), and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give a solid (R_f = 0.5/MeOH) that was dissolved in 8 N methanolic HCl and concentrated in vacuo. Treatment with methanolic HCl in this manner was repeated twice, and the product was precipitated from acetone/EtOH upon storage at −20 °C for 3 days.

(*R*)-(−)-1,2,3,4,10,11-1-Hexahydro-1-methylspiro[7*H*-2-pyrindine-7,2′-2*H*-pyrrole]dihydrochloride (5b). The product was obtained as colorless, hygroscopic crystals (78%): mp not measurable; $[\alpha]_D^{20}$ −39.9° (*c* 1, MeOH). ^{1}H NMR (D_2O): δ 8.93 (s, 1H), 8.74 (d, *J* = 6, 1H), 8.04 (d, *J* = 6, 1H), 3.92–3.23 (m, 4H), 2.88–2.21 (m, 6H), 2.68 (s, 3H). ^{13}C NMR (D_2O): δ 170.4 (C), 144.7 (CH), 140.5 (CH), 139.4 (C), 126.9 (CH), 81.6 (C), 56.1 (CH_3), 38.1 (CH_2), 36.5 (CH_2), 36.2 (CH_2), 33.8 (CH_2), 22.1 (CH_2). Anal. ($C_{12}H_{18}Cl_2N_2$) C, H, N.

(*S*)-(+)-1,2,3,4,10,11-1-Hexahydro-1-methylspiro[7*H*-2-pyrindine-7,2′-2*H*-pyrrole]dihydrochloride (5b). The product was obtained as colorless, hygroscopic crystals (82%): mp not measurable; $[\alpha]_D^{20}$ +39.8° (*c* 1, MeOH). Anal. ($C_{12}H_{18}Cl_2N_2$) C, H, N. All other analytical data were identical with those of (−)-**5b**·2HCl.

X-ray Structure Determinations. X-ray data collection was carried out with a Bruker SMART CCD area detector diffractometer and graphite monochromatized Mo Kα radiation, λ(Mo − Kα) = 0.71073 Å. For each crystal, four sets of frames were measured, which covered complete spheres of the reciprocal space (4 × 606 frames, ω-scans, $\Delta\omega$ = 0.3°). Corrections for absorption was with program SADABS, structure solution was with direct methods and the program SHELXS97, and structure refinement on F^2 was with the program SHELXL97.[22] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors and rided on the C atoms to which they were bonded or, if N- or O-bound, were refined in *x,y,z* without restraints.

Compound 16 [[(2*R*,3*R*)-(−)-*O,O*′-Di-*p*-toluoyltartrate of (*R*)-(−)-4a]. Crystal data: $C_{32}H_{32}N_2O_8$, M_r = 572.60, colorless prism (0.24 mm × 0.20 mm × 0.18 mm) from ethanol, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 12.277(5) Å, *b* = 15.126(5) Å, *c* = 15.957(5) Å, *V* = 2963.2(18) Å^3, *Z* = 4, D_x = 1.283 Mg/m^3, μ = 0.093 mm^{-1}, *T* = 295(2) K. A total of 29 164 reflections with θ < 25.0° measured and merged to 5177 unique reflections, R_{int} = 0.074. The final refinement varied 388 parameters and converged at $R1 = \sum ||F_o| - |F_c||/\sum|F_o| = 0.080$, $wR2 = [\sum(w(F_o^2 - F_c^2)^2)/\sum(w(F_o^2)^2)]^{1/2} = 0.097$, and $S =$

1.10 for the 5177 unique reflections; $R1 = 0.056$ for the 4078 observed data $[I > 2\sigma(I)]$.

Compound 17 [(2S,3S)-(+)-O,O′-Di-p-toluoyltartrate of (4aS)-(+)-4b]. Crystal data: $C_{33}H_{34}N_2O_8$, $M_r = 586.62$, colorless prism of poor quality and low scattering power (0.32 mm × 0.24 mm × 0.24 mm) from ethanol, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 12.369(8)$ Å, $b = 15.446(8)$ Å, $c = 15.711(8)$ Å, $V = 3002(3)$ Å³, $Z = 4$, $D_x = 1.298$ mg/m⁻³, $\mu = 0.093$ mm⁻¹, $T = 295(2)$ K. A total of 23 123 reflections with $\theta < 22.5°$ measured and merged to 3871 unique reflections, $R_{int} = 0.122$. The final refinement varied 397 parameters and converged at $R1 = 0.085$, $wR2 = 0.141$, and $S = 1.18$ for the 3871 unique reflections; $R1 = 0.069$ for the 3273 observed data $[I > 2\sigma(I)]$.

(R)-(−)-5b·2HCl. Crystal data: $C_{12}H_{18}Cl_2N_2$, $M_r = 586.62$, colorless block (0.65 mm × 0.4 mm × 0.4 mm) from ethanol, monoclinic, space group $P2_1$ (no. 4), $a = 11.225(3)$ Å, $b = 10.221(4)$ Å, $c = 11.617(4)$ Å, $V = 1330.6(8)$ Å³, $Z = 4$ (two independent molecules per asymmetric unit), $D_x = 1.304$ mg/m⁻³, $\mu = 0.464$ mm⁻¹, $T = 295(2)$ K. A total of 19 244 reflections with $\theta < 30°$ measured and merged to 7549 unique reflections, $R_{int} = 0.019$. The final refinement varied $3\beta2$ parameters and converged at $R1 = 0.041$, $wR2 = 0.093$, and $S = 1.07$ for the 7549 unique reflections; $R1 = 0.037$ for the 6940 observed data $[I > 2\sigma(I)]$.

Compounds **16** and **17** form an enantiomeric pair of almost identical structures, which differ only by one ring CH_2 group but not in the basic spatial arrangement, orientation, and mutual hydrogen bonding of their constituents. In each compound, the nonaromatic N atom is protonated and donates a hydrogen bond to a COO⁻ oxygen atom whereas the second active hydrogen atom remains part of a toluoyltartaric acid COOH group and forms a hydrogen bond to the pyridine nitrogen as the acceptor. In the structure of (R)-(−)-**5b**·2HCl, the two active hydrogen atoms are bonded to both N atoms of the **5b** molecule and form hydrogen bonds to the Cl⁻ anions as acceptors. Further details on all structures are given in the Supporting Information.

Radioligand Assay. [³H]Cytisine binding to the $\alpha4\beta2$ subtype in rat brain membranes was determined using a modification of the method described by Pabreza et al.[21] Membrane-enriched fractions from rat brain minus cerebellum (ABS Inc., Wilmington, DE) were slowly thawed at 4 °C, washed, and resuspended in 30 volumes of BSS-Tris buffer (120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 2 mM MgCl₂, and 50 mM Tris-Cl, pH 7.4, 4 °C). Seven log-dilution concentrations of test compounds (10⁻⁵ to 10⁻¹¹ M) containing 100−200 μg of protein and 0.75 nM [³H] cytisine (30 Ci/mmol; Perkin-Elmer-NEN, Boston, MA) were incubated in a final volume of 500 μL for 75 min at 4 °C in duplicate. Nonspecific binding was determined in the presence of 10 μM (−)-nicotine. Incubations were terminated by vacuum filtration through Whatman GF/C filters that were prewet with 0.5% polyethylenimine. Bound radioactivity was collected on Millipore MultiScreen harvest plates FB using a Packard cell harvester, and radioactivity was determined using a Packard TopCount Microplate beta counter. IC_{50} values were determined by nonlinear regression in Microsoft Excel. K_i values were calculated from the IC_{50} values using the Cheng−Prusoff equation, where $K_i = IC_{50}/1 + [ligand]/K_D$. Average K_i values were derived from a minimum of three separate determinations (N).

Supporting Information Available: Tables of X-ray structural data, including data collection parameters, positional and thermal parameters, and bond distances and angles for compounds **16**, **17**, and (R)-(−)-**5b**·2HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Schmitt, J. D.; Bencherif, M. Chapter 5: Targeting Nicotinic Acetylcholine Receptors: Advances in Molecular Design and Therapies. *Ann. Rep. Med. Chem.* **2000**, *35*, 41−45.

(2) Meyer, M. D.; Decker, M. W.; Rueter, L. E.; Anderson, D. J.; Dart, M. J.; Kim, K. H.; Sullivan, J. P.; Williams, M. The Identification of Novel Structural Compound Classes Exhibiting High Affinity for Neuronal Nicotinic Acetylcholine Receptors and Analgesic Efficacy in Preclinical Models of Pain. *Eur. J. Pharmacol.* **2000**, *393*, 171−177.

(3) Levin, E. D.; Simon, B. B. Nicotinic Acetylcholine Involvement in Cognitive Function in Animals. *Psychopharmacology* **1998**, *138*, 217−230.

(4) Williams, M.; Arneric, S. P. Beyond the Tobacco Debate: Dissecting Out the Therapeutic Potential of Nicotine. *Exp. Opin. Invest. Drugs* **1996**, *5*, 1035−1045.

(5) For a comprising review on nicotinic agonists, see Tonder, J. E.; Olesen, P. H. Agonists at the $\alpha4\beta2$ Nicotinic Acetylcholine Receptors: Structure−Activity Relationships and Molecular Modelling. *Curr. Med. Chem.* **2001**, *8*, 651−674.

(6) Spande, T. F.; Garaffo, H. M.; Edwards, M. W.; Yeh, H. J.; Pannell, L.; Daly, J. W. Epibatidine: a Novel (Chloropyridyl)-azabicycloheptane with Potent Analgesic Activity from an Ecuadoran Poison Frog. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478.

(7) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. Synthesis, Optical Resolution, Absolute Configuration, and Preliminary Pharmacology of (+)- and (−)-cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1H-pyrrolo[3,2-h]isoquinoline, a Structural Analogue of Nicotine. *J. Med. Chem.* **1993**, *36*, 3381−3385.

(8) For an excellent review on conformationally restricted analogues of nicotine, see Glennon, R. A.; Dukat, M. Nicotine Receptor Ligands. *Med. Chem. Res.* **1996**, 465−486.

(9) Holladay, M. W.; Lebold, S. A.; Lin, N.-H. Structure−Activity Relationships of Nicotinic Acetylcholine Receptor Agonists as Potential Treatments for Dementia. *Drug Dev. Res.* **1995**, *35*, 191−213.

(10) Martin, B. R. In *The Receptors*; Conn, P. M., Ed.; Academic Press: New York, 1986; pp 393−415.

(11) Damaj, M. I.; Glassco, W.; Marks, M. J.; Slobe, B.; James, J. R.; May, E. L.; Rosecrans, J. A.; Collins, A. C.; Martin, B. R. Pharmacological Investigation of (+)- and (−)-cis-2,3,3a,4,5,9b-Hexahydro-1H-pyrrolo[3,2-h]isoquinoline, a Bridged-Nicotine Analogue. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 1425−1434.

(12) Tonder, J. E.; Olesen, P. H.; Hansen, J. B.; Begtrup, M.; Petterson, I. An Improved Nicotinic Pharmacophore and a Stereoselective CoMFA-Model for Nicotinic Agonists Acting at the Central Nicotinic Acetylcholine Receptors Labeled by [³H]-N-Methylcarbamylcholine. *J. Comput. Mol. Des.* **2001**, *15*, 247−258.

(13) Ullrich, T.; Binder, D.; Pyerin, M. Asymmetric Synthesis of (+)- and (−)-7-(3-Pyridyl)-1-azabicyclo[2.2.1]heptane as Conformationally Restricted Analogues of Nicotine. *Tetrahedron Lett.* **2002**, *43*, 177−179.

(14) King, S. A. Ortho ester-Dependent Alcoholysis of Lactones. Facile Preparation of 4-Alkoxybutanoates and 5-Alkoxypentanoates. *J. Org. Chem.* **1994**, *59*, 2253−2256.

(15) Gassman, P. G.; Proehl, G. S. [3.1.1]Propellane. *J. Am. Chem. Soc.* **1980**, *102*, 6863−6864.

(16) (a) Shing, T. L.; Shia, W. L.; Shiao, M. J.; Chau, T. Y. Regio- and Chemoselective addition of Mixed Copper, Zinc Benzylic Organometallics to Functionalized Pyridinium Salts: a Facile Synthesis of Functionalized 4-Benzylpyridines. *Synthesis* **1991**, 849−850. (b) Shiao, M. J.; Liu, K. J.; Lin, L. G. Facile Synthesis of 4-Arylpyridines with an Electron-Withdrawing Group on the Benzene Ring. *Synlett* **1992**, 655−656. (c) Shiao, M. J.; Chia, W. L.; Peng, C. J.; Shen, C. C. Facile Synthesis of Two Pyridine Alkaloids via Functionalized 3,4-Dialkylpyridines. *J. Org. Chem.* **1993**, *58*, 3162−3164.

(17) Chadwell, A. J.; Smith, H. A. Raney Cobalt Catalyst. *J. Phys. Chem.* **1956**, *60*, 1339−1340.

(18) Ravard, A.; Crooks, P. A. Chiral Purity Determination of Tobacco Alkaloids and Nicotine-like Compounds by 1H NMR Spectroscopy in the Presence of 1,1′-Binaphthyl-2,2′-diylphosphoric acid. *Chirality* **1996**, *8*, 295−299.

(19) Haslego, M.; Maryanoff, C. A.; Scott, L.; Sorgi, K. A Practical Preparation of 1-2-Substituted and 1-2,3-Disubstituted Pyrrolines. *Heterocycles* **1993**, *35*, 643−647.

(20) Chavdarian, C. G.; Seemann, J. I.; Wooten, J. B. Bridged Nicotines. Synthesis of cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1H-pyrrolo[2,3-f]quinoline. *J. Org. Chem.* **1983**, *48*, 492−494.

(21) Pabreza, L. A.; Dhawan, S.; Kellar, K. J. [³H]Cytisine Binding to Nicotinic Cholinergic Receptors in Brain. *Mol. Pharmacol.* **1991**, *39*, 9−12.

(22) (a) Sheldrick, G. M. *SADABS*: Program for Absorption Correction, University of Göttingen, Germany, 1996. (b) Sheldrick, G. M. *SHELXS97*: Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1997. (c) Sheldrick, G. M. *SHELXL97*: Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.