Conformationally Constrained Nicotines. 1-Pyridinyl-7-azabicyclo[2.2.1]heptane and 1-Pyridinyl-8-azabicyclo[3.2.1]octane Analogues

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Received January 25, 1999

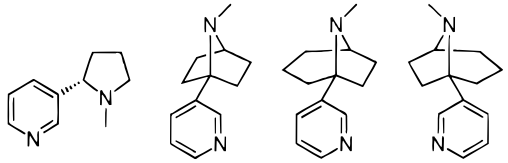
Conformationally constrained bicyclo analogues of natural (−)-nicotine and unnatural (+)-nicotine have been synthesized from D- and L-glutamic acid, respectively. Regioselective addition of 3-lithiopyridine to the γ-carbonyl of a protected glutamate was followed by intramolecular imine formation and stereospecific catalytic hydrogenation of the resultant pyrroline to give *cis*-5-pyridinylproline. A sequence of transformations to convert the ester to bromide was followed by the key intramolecular anionic cyclization at the benzylic position to form the 1-pyridinyl-7-azabicyclo[2.2.1]heptane analogue. Alternatively, homologation of the ester of *cis*-5-pyridinylproline and conversion to bromide allowed cyclization to the 1-pyridinyl-7-azabicyclo[3.2.1]octane analogues.

Introduction

Nicotinic acetylcholine receptors are a group of ion channel receptors[1] that play an important role in many biological processes related to a number of nervous system disorders. As ligands for the nicotinic acetylcholine receptor,[2,3] many groups of compounds have been isolated from natural sources or synthesized, of which (−)-nicotine (**1**, Chart 1) and its analogues represent an important class. In particular, nicotine analogues with rigid structures have become interesting targets stimulated by the isolation of the very active but highly toxic epibatidine[4] from the skin of a South American frog.

The targets in the work we are now reporting have been to synthesize nicotine analogues **2** and **3**, which possess azabicyclo ring systems with an apical nitrogen. The synthetic plan involves coupling of glutamic acid derivatives with 3-metalated pyridine, followed by cyclization to form proline **A**. By subsequent side-chain manipulation, **A** can afford bromide **B** or **C** (Figure 1). The key step then becomes generation of the carbanion at the benzylic position α to the pyridine followed by intramolecular cyclization to construct the bridged system. Depending on the number of carbons in the side chain of the bromide, either a [2.2.1]- or [3.2.1]azabicyclonicotine analogue will result. Although Beak's pioneering work has presented many examples of metalation and electrophilic substitution at the α-position of an amine derivative[5,6] (e.g., Boc-protected secondary amines), there were certain unexplored factors introduced by our system. Thus, there has been no report of application of this method to pyridines or to the deprotonation of a tertiary carbon α to the nitrogen. Also, after deprotonation, although an intramolecular cyclization seems to be preferred judging from the ring size, steric effects at the quaternary carbon in forming the bicyclo system might lead to competitive intermolecular reaction, including quaternization of the pyridine.

Chart 1



Results and Discussion

Synthesis of the Pyridinyl Ketone. Using a number of glutamic acid derivatives and 3-metallopyridines, a variety of conditions and combinations were examined for pyridinyl ketone formation. The first substrate was *N*-*tert*-butyloxycarbonyl-L-glutamic acid α-*tert*-butyl ester (**4**)[7] as its tetrahydrofuranyl ester.[8] In its reaction with the original Grignard reagent derived from 3-bromopyridine, a disappointing 30% yield of pyridinyl ketone **8** was obtained.

Since a quite satisfactory yield of the corresponding anisolyl ketone had resulted when the isoxazolidide **5** was treated with anisolyllithium,[7] this combination was applied to the preparation of the pyridinyl ketone. With 3-pyridinyllithium[9,10] and isoxazolidide **5**, an improved yield of 69% of ketone **8** was realized. Substitution of the 3-pyridinyl Grignard reagent led to a decreased yield of 50%.

The most convenient and efficacious process was found to be the coupling of 3-pyridinyllithium with the readily available *N*-Boc pyroglutamate esters[11] **6** and **7**. With *tert*-butyl ester **6**, a 73% yield of pyridinyl ketone **8** was realized, while methyl ester **7** gave the corresponding

(1) Galzi, J.-L., Changeux, J.-P. *Neuropharmacology* **1995**, *34*, 563.
(2) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, 465.
(3) McDonald, I. A.; Cosford, N.; Vemier, J.-M. *Ann. Rep. Med. Chem.* **1995**, *30*, 41.
(4) Spande, T. F.; Garraffo, M. W.; Edwards, M. W. H.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.
(5) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(6) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(7) Berrée, F.; Chang, K.; Cobas, A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 715.
(8) Mattson, M. N.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6071.
(9) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.
(10) Guthikonda, R. N.; Cams, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871.

10.1021/jo990130u CCC: $18.00
Published on Web 05/01/1999

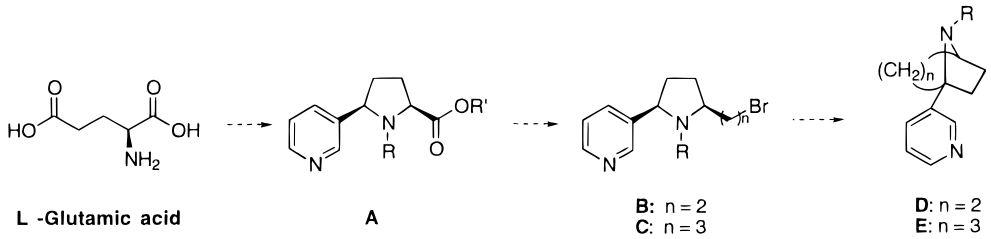
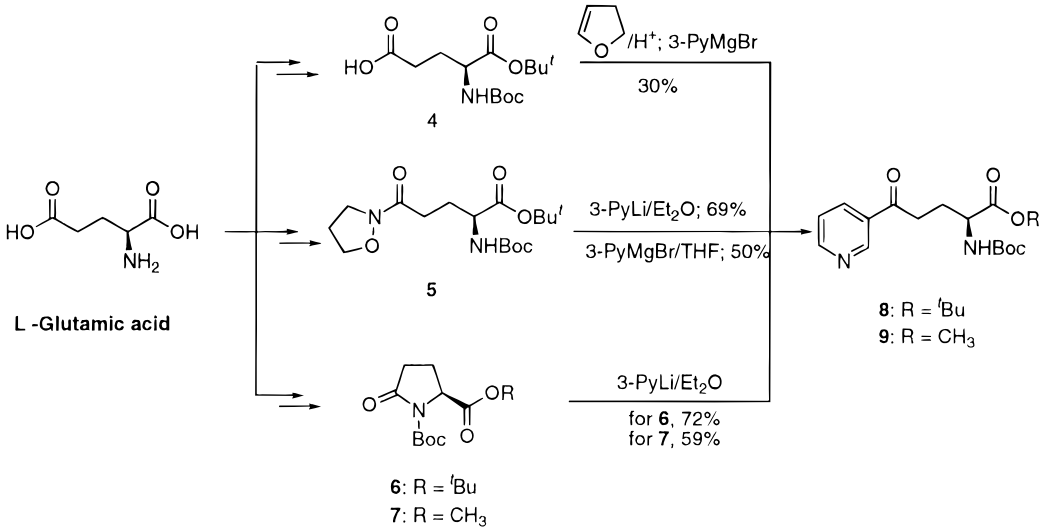


Figure 1. Proposed synthesis of the [2.2.1] and [3.2.1] azabicyclonicotine analogues.

Scheme 1. Synthesis of Pyridinyl Ketones



ketone **9** in 59% yield. These results are collated in Scheme 1.

Intramolecular Cyclization to the Proline Derivatives. Our initial intention was to selectively remove the *N*-Boc group without affecting the *tert*-butyl ester of **8**.[12] The free amine and the ketone functionalities thus could undergo intramolecular condensation to form the pyrroline under treatment with mild base, and subsequent reduction would produce the proline derivative. Removal of the *N*-Boc group, however, was not sufficiently selective and a partial removal of the *tert*-butyl ester was observed under various conditions. As a result, the plan was to remove both the *N*-Boc and *tert*-butyl ester groups under more strongly acidic conditions, then to re-esterify the acid. This was accomplished by treatment of **8** with saturated HCl in MeOH from which a 75% yield of keto-methyl ester **10** was obtained. A major side product was the ketal-methyl ester **11**, which could be easily hydrolyzed to ketone **10** at pH 1−2 with aqueous HCl. On the other hand, when methyl ester **9** was used, treatment with 3 M HCl in EtOAc afforded the single product **10**. After isolation using base, the pyrroline **12** was obtained in 87% yield. Catalytic hydrogenation of the imine gave the *cis*-proline derivative **13** as the sole product in 95% yield. In another experiment, with $NaCNBH_3$ as the reducing agent, a mixture of both diastereoisomers with a cis to trans ratio of 5/4 was isolated, as determined by ^1H NMR. These experiments are summarized in Scheme 2.

Side Chain Extension. With pyridinyl proline **13** in hand, the next task was to extend the carboxylate side chain at the 5-position. For this purpose, the nitrogen was protected as its Boc derivative and the methyl ester was hydrolyzed with LiOH to the acid **16**. A stepwise route utilizing the Arndt−Eistert synthesis[13,14] was applied to obtain the homologated ester **18**. In this sequence, a mixed anhydride intermediate[15] was superior to the acid chloride for diazoketone formation. Reduction of the ester with $Ca(BH_4)_2$ afforded both the desired alcohol **19** plus the borane complex of **19**. Use of a large amount of EtOH as solvent instead of a mixture of THF/EtOH[16] suppressed formation of this complex, which can also be broken up by refluxing in EtOH with 400 mol % of diethanolamine.

Our intention was to obtain bromide **21** directly from alcohol **19** using carbon tetrabromide and triphenylphosphine;[17] however, only poor yields of **21** were isolated. An alternative was to prepare the mesylate **20** and to use it directly in the alkylation step or convert it to bromide **21** as the alkylation reagent. All attempts at standard mesylate formation, requiring base, failed; elimination was the major product. A milder way to effect mesylation under essentially neutral conditions is to use the very active mesylating reagent 2-mesyl-5-methylimidazonium triflate.[18] When this reagent was used mesylate **20** was the sole product and treatment with LiBr in acetone afforded bromide **21** in 73% yield. A minor and

(11) (a) Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091. (b) Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; Navio, J. L. G.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317.

(12) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216.

(13) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(14) Arndt, F.; Eistert, B.; Partale, W. *Chem. Ber.* **1927**, *60*, 1364.

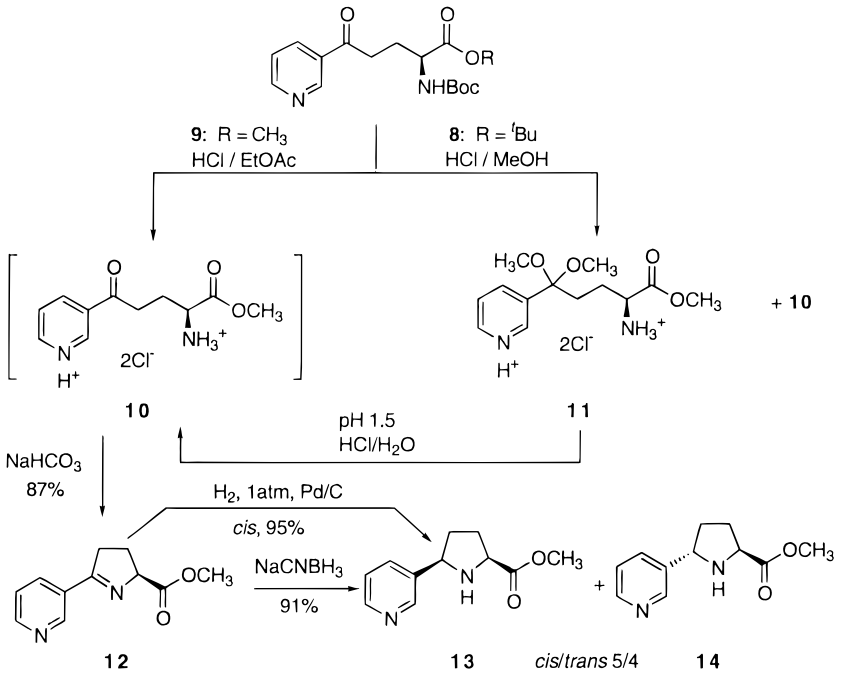
(15) Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217.

(16) Kang, M.; Park, J.; Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 5528.

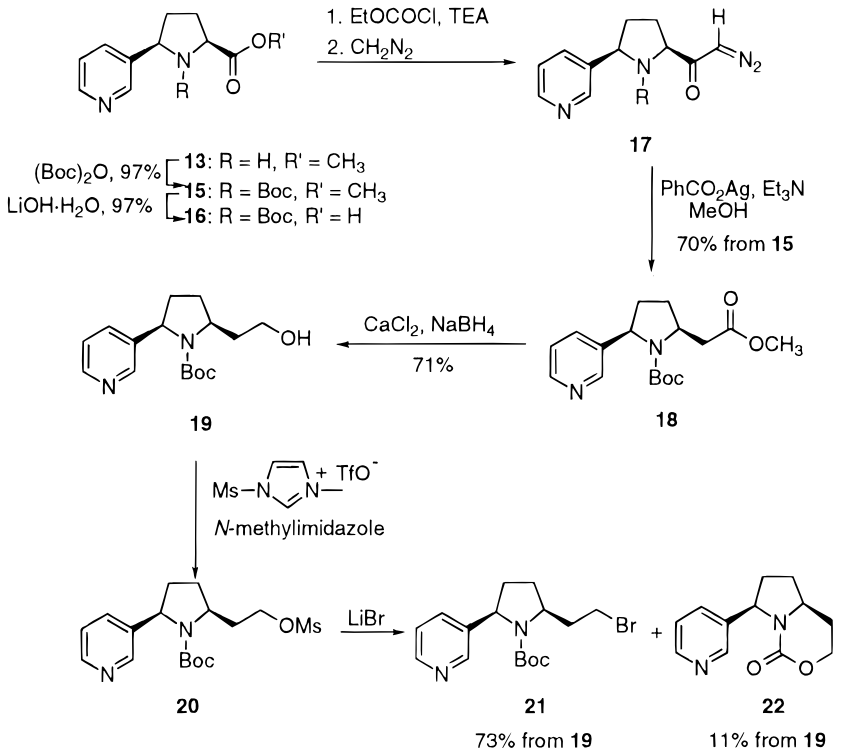
(17) Campell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313.

(18) O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 4775.

Scheme 2. Synthesis of 5-Substituted Proline Derivatives



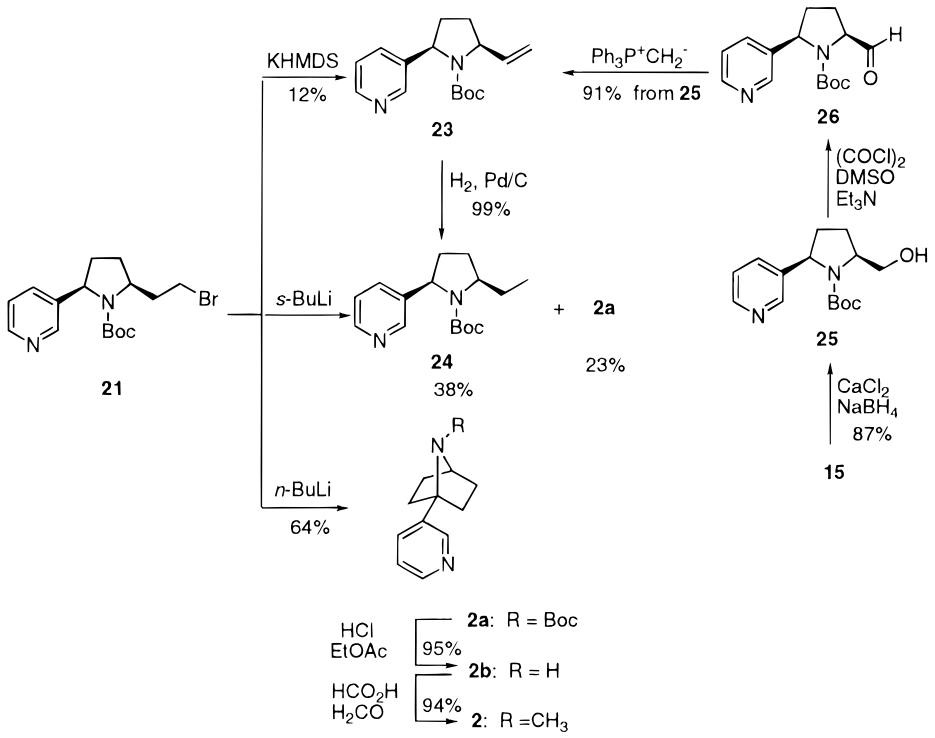
Scheme 3. Synthesis of 5-Pyridinyl-2-bromoethylpyrrolidine 21



unexpected product was cyclic carbamate **22**, resulting from attack at the carbonyl oxygen of the Boc group by the very active mesylated side chain during bromide formation. Bromide **21** was not stable, due to alkylation of the pyridine nitrogen by the side chain bromide. This is probably an intermolecular process since dilution with solvent significantly slows this process. These reactions are depicted in Scheme 3.

Construction of the Bicyclo [2.2.1] Ring System. Anion formation and closure of bromide **21** to the bicyclo [2.2.1] ring system was surprisingly sensitive to the specific base, as shown in Scheme 4. When KHMDS was used, a small amount of olefin **23** was isolated together with recovered starting material **21**. The structure of the olefin was confirmed by an alternative synthesis: methyl ester **15** was reduced with $Ca(BH_4)_2$, and the resulting alcohol **25** was oxidized to the aldehyde **26** and treated with methyltriphenylphosphonium bromide/*n*-Buli to afford the olefin **23**. When *s*-BuLi was used, two products were obtained, the desired [2.2.1] structure **2a** and **24**, in which the bromine had been replaced by hydrogen. The structure of **24** was established by catalytic hydrogenation (Pd/C) of olefin **23** to **24**. Apparently, under the reaction conditions, metal−halogen exchange and α-depro-

Scheme 4. Synthesis of the [2.2.1] Azabicyclo Nicotine Analogue



tonation are competitive processes, one leading to formation of the ethyl analogue **24** (after quenching and isolation) and the other yielding the desired bicyclo[2.2.1] product **2a**.

Although *n*-BuLi is known to add to the 1,2 double bond of pyridine,[19] the intramolecular cyclization of **21** to **2a** proceeded very rapidly at −78 °C, thus avoiding this potential addition. Under these conditions, metal−halogen exchange was not observed and **2a** was the only product, isolated in 55% yield. Treatment of **2a** with 3 M HCl in EtOAc removed the Boc group, and the amine **2b** was methylated (formic acid/formaldehyde)[20] to the target nicotine analogue **2**. Since **2** is a symmetric molecule it was unnecessary to carry out a parallel sequence from D-glutamic acid.

Construction of the Bicyclo [3.2.1] Ring System. From ester **15**, the intermediate needed for cyclization to the [3.2.1] system was constructed. Reduction of this ester and oxidation of the resulting alcohol **25** gave aldehyde **26**. Treatment with the sodium salt of trimethyl phosphono- acetate afforded olefin **27** as a mixture of the *E* and *Z* isomers (Scheme 5). This mixture of isomers was reduced to propionic ester **28**. Following the same procedure used for the formation of bromide **21**, ester **28** was reduced to the alcohol **29**, which was treated with the imidazolium mesylating reagent followed by LiBr to yield the desired bromide **31**.

Employing the same conditions used for formation of the [2.2.1] system, **31** was treated with *n*-BuLi at −78 °C in THF. Only a small amount of the desired [3.2.1] structure **3a** (<10%) was formed; the major products consisted of unidentified polar material. A possible explanation for this difference in behavior is that deprotonation at the α-carbon to the pyridine in **31** did occur but that the intramolecular cyclization to the [3.2.1] system is less favorable than formation of the [2.2.1] system, thus permitting intermolecular side reactions to occur. To reduce the extent of any competing intermolecular reactions, higher dilution conditions were applied. Bromide **31** was added to the solution of *n*-Buli in THF via a syringe pump over a period of 1 h. Indeed, an improved yield of 48% was obtained. When the same technique was applied to bromide **21**, the yield of the [2.2.1] system product **2a** was improved from 55% to 64%. Deprotection and methylation gave the final [3.2.1] azabicyclo (−)-**3** analogue. To obtain the enantiomer (+)-**3**, exactly the same sequence of reactions was applied to D-glutamic acid.

Conclusion

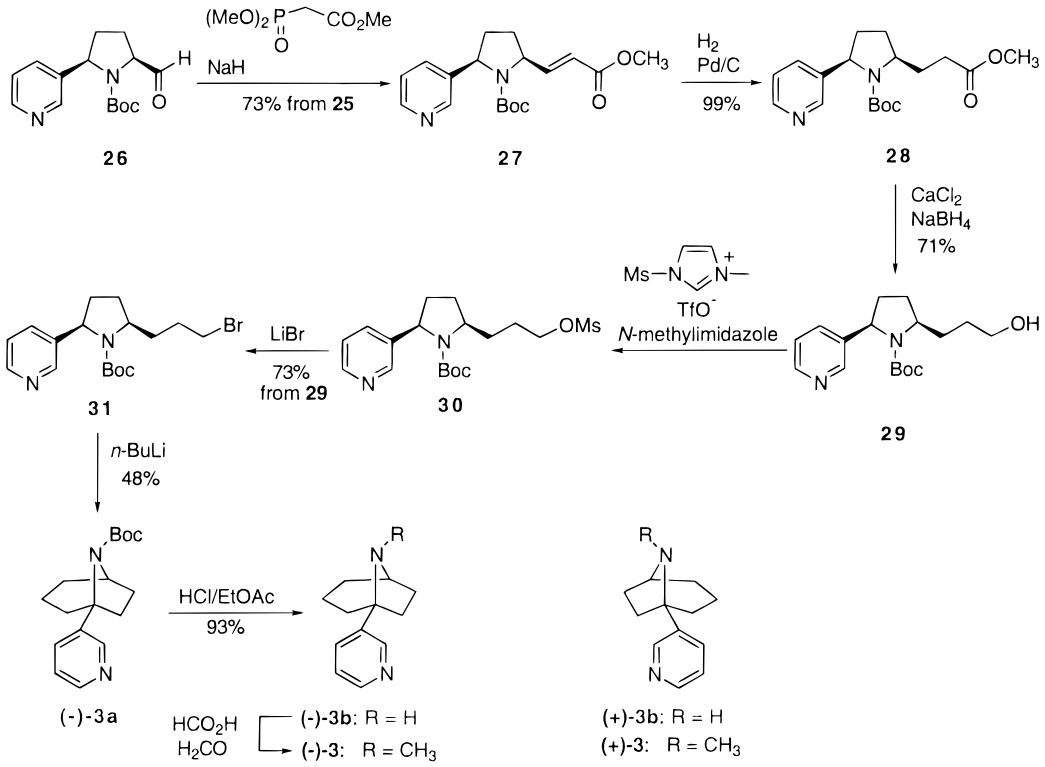
We report a process for the enantiospecific synthesis of nicotine analogues in which the pyrrolidine ring is conformationally constrained into an azabicyclo ring system. The specific systems prepared are the 1-(3-pyridinyl)-7-azabicyclo[2.2.1]heptanes and the 1-(3-pyridinyl)-8-azabicyclo[3.2.1] octanes. Enantiospecificity is achieved by basing the synthetic sequence on L- or D-glutamic acid to which the metallopyridine is attached. Conceivably, the method could be extrapolated to other substitution patterns and structural types.

Experimental Section

General Procedures. All melting points are uncorrected. ^{1}H NMR and ^{13}C spectra were recorded in $CDCl_3$ unless otherwise specified, and chemical shifts are reported in ppm from internal tetramethylsilane; ^{13}C chemical shifts are reported in ppm from $CDCl_3$ or CD_3OD, followed by multiplicity as determined from DEPT; *J* values are given in Hz. Reagents and solvents were dried and purified by distillation before use: CH_2Cl_2 from CaH_2; THF and Et_2O from Na; MeOH from Mg. Reactions were conducted under N_2 and organic extracts were dried over Na_2SO_4 prior to evaporation. Chromatography

(19) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485.
(20) Glenn, D. F.; Edwards, W. B., III. *J. Org. Chem.* **1978**, *43*, 2860.

Scheme 5. Synthesis of the (+)- and (−)-[3.2.1] azabicyclonicotine Analogues



26 **27** **28** **29** **30** **31** (-)-3a

was carried out on gravity-grade SiO_2. Elemental analyses were determined by Microanalytical Laboratory, University of California at Berkeley.

***tert*-Butyl (2*S*)-2-(*N*-(*tert*-Butyloxycarbonyl)amino)-5-oxo-5-(3-pyridinyl)pentanoate ((+)-8). Method A.** To a solution of 3-iodopyridine (123 mg, 0.6 mmol) in THF (5 mL) was added EtMgBr (0.72 mL of a 1.0 M THF solution, 0.72 mmol) at room temperature, and the mixture was stirred for 25 min. To a solution of *N*-(*tert*-butyloxycarbonyl)-L-glutamic acid α-*tert*-butyl ester (**4**, 152 mg, 0.5 mmol) in dichloromethane (2 mL) at −20 °C were added 2,3-dihydrofuran (38.5 mg, 0.55 mmol) and a solution of methanesulfonic acid in dichloromethane (5 μL, 0.5 M solution, 2.5 μmol). The mixture was allowed to warm to 0 °C over 4 h and then recooled to −20 °C, and to this mixture was added the 3-pyridinyl Grignard reagent dropwise over 5 min to yield a clear, colored solution. After 30 min at −20 °C, the mixture was very slowly warmed to room temperature over 18 h and then recooled to 0 °C and added dropwise to aqueous 1 M K_2CO_3. The mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic layer was dried, filtered, and evaporated to a residue that was chromatographed (CH_2Cl_2/EtOAc, 7/3) to afford **8** (55 mg, 30% yield) as a white solid: mp 89−90 °C; $[\alpha]^{22}_D$ +8.7 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 9H), 1.48 (s, 9H), 2.01−2.13 (m, 1H), 2.28−2.40 (m, 1H), 3.01−3.30 (m, 2H), 4.28 (m, 1H), 5.26 (d, *J* = 7.5, 1H), 7.43 (dd, *J* = 7.9, 4.8, 1H), 8.24 (dt, *J* = 7.9, 1.7, 1H), 8.79 (d, *J* = 4.8, 1H), 9.17 (s, 1H); ^{13}C NMR δ 27.0, 27.9, 28.1, 34.7, 53.3, 79.7, 82.1, 123.5, 131.9, 135.2, 149.4, 153.4, 155.4, 171.3, 197.7. Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.6; H, 7.7; N, 7.7. Found: C, 62.8; H, 7.8; N, 7.6.

Method B. 3-Bromopyridine (0.241 mL, 2.5 mmol) in ether (3.5 mL) was added dropwise to a solution of *n*-BuLi (1.56 mL of a 1.6 M solution in hexane, 2.5 mmol) in ether (10 mL) at −78 °C in 5 min. The resulting yellow slurry was stirred at −78 °C for 30 min, and a solution of *N*-(*tert*-butoxycarbonyl)-L-glutamic acid α-*tert*-butyl ester β-isoxazolidide (**5**, 354 mg, 1 mmol) in THF (5 mL) was added over 5 min. The resulting mixture was warmed to room temperature over 6 h, stirred at room temperature for 12 h, diluted with ether (30 mL), and quenched with H_2O (40 mL). The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layer was dried, filtered, and evaporated to a residue, which was chromatographed (SiO_2, CH_2Cl_2/EtOAc, 7/3), yielding a mixture of **8** and **5** (85/15, 293 mg); 69% yield of **8**.

Method C. To a solution of isoxazolidide **5** (177 mg, 0.5 mmol) in THF (2 mL) at room temperature was added the 3-pyridinyl Grignard reagent (0.72 mmol) dropwise over 5 min to yield a clear, colored solution (0.72 mmol) that was stirred for 9 h at room temperature. Aqueous K_2CO_3 was added, the mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic layer was dried, filtered, and evaporated. Chromatography (CH_2Cl_2/EtOAc, 7/3) of the residue afforded a mixture of **8** and **5** (63/37, 143 mg); 50% yield of **8**.

Method D. 3-Bromopyridine (7.23 mL, 74.7 mmol) in Et_2O (57 mL) was added dropwise to a solution of *n*-BuLi (1.6 M solution in hexane, 47 mL, 74.7 mmol) in Et_2O (167 mL) at −78 °C over 30 min. The resulting yellow slurry was stirred at −78 °C for 30 min, and a solution of *tert*-butyl *N*-(*tert*-butyloxycarbonyl)-L-pyroglutamate (**6**, 14.3 g, 50 mmol) in Et_2O/THF (70 mL, 1/1) was added over 10 min. The resulting mixture was stirred at −78 °C for 1 h, poured into H_2O (60 mL), and extracted with Et_2O (50 mL). The combined organic layer was dried, filtered, and evaporated, and the residue was chromatographed (CH_2Cl_2/EtOAc, 7/3) to afford **8** (13.1 g, 72%).

Methyl (2*S*)-2-(*N*-(*tert*-Butyloxycarbonyl)amino)-5-oxo-5-(3-pyridinyl)pentanoate ((+)-9). 3-Bromopyridine (7.23 mL, 74.7 mmol) in Et_2O (57 mL) was added dropwise to a solution of *n*-BuLi (1.6 M solution in hexane, 47 mL, 74.7 mmol) in Et_2O (167 mL) at −78 °C over 30 min. The resulting yellow slurry was stirred at −78 °C for 30 min, and a solution of methyl *N*-(*tert*-butyloxycarbonyl)-L-pyroglutamate (**7**, 16.4 g, 67.3 mmol) in THF/Et_2O (80 mL, 1/1) was added over 20 min. The resulting mixture was stirred at −78 °C for 1 h and then poured into H_2O (60 mL), the aqueous layer was extracted with Et_2O (50 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc, 7/3) to afford **9** (12.9 g, 59%) as a white solid: mp 90−92 °C; $[\alpha]^{22}_D$ +13.5 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 9H), 2.06 (m, 1H), 2.34 (m, 1H), 3.01−3.19 (m, 2H), 3.75 (s, 3H), 4.40 (m, 1H), 5.22 (d, *J* = 7.5, 1H), 7.41 (dd, *J* = 7.7, 4.9, 1H), 8.22 (dt, *J* = 7.7, 1.7, 1H), 8.77 (d, *J* = 4.9, 1H), 9.15 (d, *J* = 1.7, 1H); ^{13}C NMR δ 26.6, 28.1, 34.6, 52.3, 52.7, 80.0, 123.5,

131.8, 135.2, 149.4, 153.4, 155.3, 172.6, 197.5. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.9; N, 8.7. Found: C, 59.7; H, 6.9; N, 8.6.

Methyl (2*R*)-2-(*N*-(*tert*-butyloxycarbonyl)amino)-5-oxo-5(3-pyridinyl)pentanoate ((−)-9, structure not shown) was prepared from the corresponding D-pyroglutamate: mp 91−93 °C; $[\alpha]^{22}_D$ −14.1 (*c* 1, $CHCl_3$); spectral and chromatographic properties identical with those of **(+)-9**.

Methyl (2*S*)-Amino-5-oxo-5-(3-pyridinyl)pentanoate Dihydrochloride (10), (2*S*)-2-(3-Pyridinyl)-5-methoxycarbonyl-1-pyrroline (12), and (2*S*)-*cis*-5-(3-Pyridinyl)proline Methyl Ester ((+)-13). To pyridinyl ketone (+)-**9** (2.65 g, 8.24 mmol) was added slowly, while stirring, HCl in EtOAc (3 M, 30 mL) at room temperature. The mixture was stirred overnight while precipitate formed; concentration under reduced pressure gave crude dihydrochloride **10** as a pale yellow solid: ^{1}H NMR δ 2.25−2.50 (m, 2H), 3.41 (q, J = 6.6, 2H), 3.79 (s, 3H), 4.26 (t, J = 6.9, 1H), 8.22 (t, J = 7.0, 1H), 8.98 (d, J = 4.2, 1H), 9.09 (d, J = 8.2, 1H), 9.33 (s, 1H). The crude **10** was dissolved in H_2O (20 mL) and shaken with EtOAc (100 mL) and saturated $NaHCO_3$ in H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 × 60 mL), and the combined organic layer was dried, filtered, and evaporated to afford crude pyrroline **12** (1.46 g, 87%) as a yellow oil: ^{1}H NMR δ 2.15−2.40 (m, 2H), 2.85−3.05 (m, 1H), 3.08−3.20 (m, 1H), 3.74 (s, 3H), 4.89 (dd, J = 8.7, 6.6, 1H), 7.31 (dd, J = 7.9, 4.8, 1H), 8.19 (dt, J = 7.9, 1.8, 1H), 8.62 (dd, J = 4.8, 1.6, 1H), 8.97 (d, J = 2.0, 1H); ^{13}C NMR δ 26.1 (CH_2), 35.2 (CH_2), 52.2 (CH_3), 74.5 (CH), 123.3 (CH), 129.4 (C), 135.0 (CH), 149.2 (CH), 151.7 (CH), 172.9 (C), 173.8 (C). Pyrroline **12** (1.2 g, 5.88 mmol) in IPA (15 mL) was treated with H_2 at 1 atm in the presence of 10% Pd/C (0.12 g, 10% w/w) at room temperature overnight. The resulting mixture was filtered and evaporated to give **13** (1.2 g, 95%) as a colorless oil. This crude product was suitable for further reactions. An analytic sample was obtained by chromatography (CH_2Cl_2/MeOH saturated with NH_3, 95/5): $[\alpha]^{22}_D$ +34.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.58−1.71 (m, 1H), 2.01−2.25 (m, 3H), 2.41 (bs, 1H), 3.70 (s, 3H), 3.90 (dd, J = 8.2, 4.9, 1H), 4.19 (dd, J = 9.0, 6.0, 1H), 7.20 (dd, J = 7.8, 4.8, 1H), 7.80 (dt, J = 7.8, 1.8, 1H), 8.43 (dd, J = 4.8, 2.5, 1H), 8.54 (d, J = 2.0, 1H); ^{13}C NMR δ 30.0 (CH_2), 34.0 (CH_2), 51.9 (CH_3), 59.7 (CH), 60.6 (CH), 123.3 (CH), 134.1 (CH), 138.9 (C), 148.4 (CH), 148.6 (CH), 175.1 (C). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.7; H, 6.9; N, 13.5.

(2*R*)-*cis*-5-(3-Pyridinyl)proline methyl ester ((−)-**13**, structure not shown) was prepared from the corresponding pyridinyl ketone (−)-**9**: $[\alpha]_D$22−35.0 (*c* 1.3, $CHCl_3$); spectral and chromatographic properties identical with those of (+)-**13**.

Methyl (2*S*)−(*N*-(*tert*-Butyloxycarbonyl)amino)-5,5-dimethoxy-5-(3-pyridinyl)pentanoate (11). Pyridinyl ketone **8** (0.3 g, 0.824 mmol) was treated with saturated HCl in MeOH (10 mL) at room temperature for 4 h. The mixture was evaporated, and the residue was dissolved in H_2O (5 mL) and distributed between EtOAc (20 mL) and saturated $NaHCO_3$ in H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH saturated with NH_3, 97/3) to afford first **12** (126 mg, 75%) then **11** (38 mg, 18%) both as colorless oils. For **11**: ^{1}H NMR δ 1.05−1.45 (m, 2H), 1.92−2.15 (m, 2H), 3.14 (s, 3H), 3.15 (s,3H), 3.63 (s, 3H), 7.27 (dd, J = 7.9, 4.8, 1H), 7.73 (dt, J = 7.9, 2.0, 1H), 8.53 (dd, J = 4.8, 1.7, 1H), 8.67 (d, J = 2.2, 1H); ^{13}C NMR δ 28.5, 33.1, 48.6, 51.8, 53.9, 102.2, 122.9, 134.6, 135.8, 148.7, 149.0, 175.9. Treatment of **11** with aqueous HCl at pH 1.5 for 2 h, concentration of the mixture, and partition between saturated $NaHCO_3$ in H_2O and EtOAc as above, led to complete conversion to **12**.

(2*S*)-*trans*-5-(3-Pyridinyl)proline Methyl Ester (14). Pyrroline **12** (300 mg, 1.47 mmol) in MeOH/Acetate buffer (25 mL, 1/1, v/v) was treated with $NaCNBH_3$ (110 mg, 1.76 mmol) at room temperature overnight. The mixture was poured into saturated $NaHCO_3$ in H_2O (25 mL) and extracted with $CHCl_3$/IPA (3/1, v/v, 3 × 30 mL). The combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH saturated with NH_3, 95/5) to afford first **14** (121 mg, 40%) and then **13** (153 mg, 51%), both as colorless oils. For **14**: ^{1}H NMR δ 1.60−1.80 (m, 1H), 1.90−2.05 (m, 1H), 2.05−2.28 (m, 1H), 2.30−2.38 (m, 1H), 2.64 (br, 1H), 3.75 (s, 3H), 4.03 (dd, J = 8.4, 5.7, 1H), 4.39 (t, J = 7.2, 1H), 7.23 (dd, J = 7.8, 4.7, 1H), 7.80 (dt, J = 7.8, 1.7, 1H), 8.47 (dd, J = 4.7, 1.4, 1H), 8.59 (d, J = 1.9, 1H); ^{13}C NMR δ 29.7 (CH_2), 34.6 (CH_2), 52.2 (CH_3), 59.2 (CH), 59.4 (CH), 123.3 (CH), 134.1 (CH), 139.8 (C), 148.4 (CH), 148.5 (CH), 176.2 (C). Anal. Calcd for $C_{11}H_{14}N_2O_2 \cdot {}^1/_4H_2O$: C, 62.7; H, 6.9; N, 13.3. Found: C,62.9; H,7.1; N, 13.3.

(2*S*)-*cis*-1-(*tert*-Butyloxycarbonyl)-5-(3-pyridinyl)proline Methyl Ester ((+)−15). Proline (+)-**13** (3.4 g, 16.5 mmol) in THF (160 mL) at room temperature was treated with Et_3N (2.5 g, 24.8 mmol) followed by $(BOC)_2O$ (4.32 mg, 19.8 mmol). The mixture was stirred at room temperature for 1 h and evaporated, and the residue was distributed between EtOAc (100 mL) and saturated $NaHCO_3$ in H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), the combined organic layer was dried, filtered, and evaporated, and the residue was chromatographed (CH_2Cl_2/EtOAc, 4/6) to afford **15** (4.9 g, 97%) as a colorless oil: $[\alpha]^{22}_D$ +27.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (298 K, rotamer ratio, 60/40, *denotes minor rotamer) δ 1.16 (s, 5.4H), 1.41* (s, 3.6H), 1.90−2.18 (m, 2H), 2.20−2.30 (m, 1H), 2.32−2.42 (m, 1H), 3.82 (s, 3H), 4.39* (t, J = 8.4, 0.4H), 4.51−4.58 (m, 0.6H), 4.78 (t, J = 7.4, 0.6H), 4.98−5.03* (m, 0.4H), 7.20−7.40 (m, 1H), 8.01* (d, J = 7.7, 0.4H), 8.15 (d, J = 7.7, 0.6H), 8.50 (br, 1H), 8.60 (bs, 0.6H), 8.69* (bs, 0.4H); ^{1}H NMR (C_6D_6, 298 K, rotamer ratio 70/30) δ 1.09 (s, 6.3H), 1.32* (s, 2.7H), 1.40−1.60 (m, 4H), 3.30 (s, 2.1H), 3.34* (s, 0.9H), 4.15* (br, 0.3H), 4.28 (br, 0.7H), 4.41 (br, 0.7H), 4.72* (br, 0.3H), 6.75−6.85 (m, 1H), 8.00* (bd, J = 7.8, 0.3H), 8.21 (d, J = 7.8, 0.7H), 8.42 (br, 1H), 8.70 (bs, 0.7H), 8.84* (bs, 0.3H); ^{1}H NMR (C_6D_6, 343 K) δ 1.20 (s, 9H), 1.45−1.58 (m, 4H), 3.38 (s, 3H), 4.33 (br, 1H), 4.53 (br, 1H), 6.86 (dd, J = 7.8, 4.7, 1H), 7.97 (d, J = 7.8, 1H), 8.41 (dd, J = 4.7, 1.6, 1H), 8.73 (s, 1H); ^{13}C NMR very complex because of rotamers. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.4; H, 7.1; N, 9.2.

(2*R*)-*cis*-1-(*tert*-Butyloxycarbonyl)-5-(3-pyridinyl)proline methyl ester ((−)-**15**, structure not shown) was prepared from the corresponding proline (−)-**13**: $[\alpha]^{22}_D$ −27.3 (*c* 1.1, $CHCl_3$); spectral and chromatographic properties identical with those of (+)-**15**.

(2*S*)-*cis*-1-(*tert*-Butyloxycarbonyl)-5-(3-pyridinyl)proline (16), (2*S*,5*R*)-1-(*tert*-Butyloxy-carbonyl)-2-(1-diazomethylcarbonyl)-5-(3-pyridinyl)pyrrolidine (17), and (2*S*,5*R*)-1-(*tert*-Butyl-oxycarbonyl)-2-(methoxycarbonylmethyl)-5-(3-pyridinyl)pyrrolidine (18). To methyl ester **15** (3.0 g, 9.8 mmol) in MeOH/H_2O (3/1, v/v, 100 mL) at room temperature was added LiOH·H_2O (1.65 g, 39.2 mmol). The solution was stirred at room temperature for 5 h, poured into aqueous H_3PO_4 solution (0.1 M, 150 mL), and extracted with $CHCl_3$/IPA (3/1, v/v, 3 × 150 mL). The combined organic layer was dried, filtered, and evaporated to afford acid **16** (2.8 g, 97%) as a white solid that is suitable for the next reaction without further purification: ^{1}H NMR (298 K, rotamer ratio 60/40) δ 1.14 (s, 9H), 1.36 (s, 9H), 1.80−2.40 (m, 4H), 4.39 (t, J = 7.4, 0.6H), 4.56* (dd, J = 7.0, 5.0, 0.4H), 4.81* (t, J = 7.5, 0.4H), 5.04 (dd, J = 7.5, 4.2, 0.6H), 7.38* (m, 0.4H), 8.42 (dd, J = 7.8, 5.3, 0.6H), 7.82 (d, J = 7.8, 0.6H), 7.86* (d, J = 7.7, 0.4H), 8.59 (br, 1H), 9.19* (bs, 0.4H), 9.22 (bs, 0.6H). To acid **16** (0.93 g, 3.17 mmol) in THF (15 mL) at −15 °C was added Et_3N (440 μL, 3.17 mmol) followed by ethyl chloroformate (300 μL, 3.17 mmol). The mixture was stirred at −15 °C for 15 min then warmed to 0 °C followed by addition of excess CH_2N_2 (0.5 M in Et_2O, 20 mL, 10.0 mmol). The reaction mixture stayed bright yellow and was stirred for 5 h, warmed to room temperature slowly, and stirred vigorously until the bright yellow color disappeared. The mixture was evaporated, and the residue was distributed between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was

extracted with EtOAc (2 × 25 mL), and the combined organic layer was dried, filtered, and evaporated, affording crude diazo ketone **17** (0.95 g) as a pale yellow oil that is suitable for the next reaction without further purification: ^{1}H NMR (298 K, rotamers) δ 1.00−1.50 (br, 9H), 1.90−2.40 (m, 4H), 4.45 (br, 1H), 4.60−5.10 (br, 1H), 5.35−5.75 (br, 1H), 7.29 (dd, J = 7.8, 4.7, 1H), 8.02 (bd, J = 7.8, 1H), 8.49 (dd, J = 4.7, 2.0, 1H), 8.55 (br, 1H); ^{1}H NMR (323 K) δ 1.27 (s, 9H), 1.95−2.05 (m, 2H), 2.20−2.40 (m, 2H), 4.84 (br, 1H), 4.80 (br, 1H), 5.58 (bs, 1H), 7.27 (dd, J = 7.9, 4.7, 1H), 7.96 (d, J = 7.9, 1H), 8.50 (d, J = 4.7, 1H), 8.58 (s, 1H). To diazoketone **17** (0.95 g, 3 mmol) in MeOH (12 mL) at −25 °C was added a solution of $PhCO_2$-Ag (80 mg, 0.33 mmol) in Et_3N (880 mg, 8.7 mmol) with the exclusion of light. The mixture was warmed to 0 °C over 3 h and was stirred overnight while it warmed to room temperature. The reaction mixture was evaporated, the residue was distributed between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layer was dried and filtered. The filtrate was evaporated and the residue chromatographed (CH_2Cl_2/EtOAc, 4/6) to afford homologous ester **18** (700 mg, 70% from **15**) as a colorless oil: ^{1}H NMR (298 K, rotamers) δ 1.00−1.60 (br, 9H), 1.70−1.95 (m, 2H), 1.90−2.18 (m, 2H), 2.08−2.25 (m, 1H), 2.25−2.41 (m, 1H), 2.48 (dd, J = 14.8, 9.5, 1H), 3.08 (br, 1H), 3.90 (s, 3H), 4.40 (br, 1H), 4.65−5.00 (br, 1H), 7.27 (br, 1H), 7.56 (bd, J = 7.8, 1H), 8.50 (br, 2H); ^{1}H NMR (C_6D_6, 298 K, rotamers) δ 1.14 (br, 9H), 1.10−1.40 (m, 2H), 1.60−1.80 (m, 2H), 2.26 (dd, J = 14.8, 9.3, 1H), 3.02 (br, 1H), 3.36 (s, 3H), 4.28 (br, 1H), 4.41 (br, 1H), 6.82 (dd, J = 4.9, 6.7, 1H), 7.29 (dt, J = 7.9, 1.8, 1H), 8.45 (d, J = 4.7, 1H), 9.11 (br, 1H); ^{1}H NMR (C_6D_6, 329 K) δ 1.21 (s, 9H), 1.35.1.50 (m, 2H), 1.60−1.80 (m, 2H), 2.30 (dd, J = 14.7, 9.2, 1H), 3.03 (dd, J = 14.7, 4.4, 1H), 3.39 (s, 3H), 4.35 (br, 1H), 4.50 (br, 1H), 6.84 (dd, J = 7.8, 4.8, 1H), 7.31 (d, J = 7.8, 1H), 8.43 (d, J = 4.8, 1H), 8.57 (s, 1H); ^{13}C NMR (C_6D_6, 298 K, rotamers) δ 28.2, 30.2 (br), 33.8 (br), 40.1 (br), 51.2, 56.2, 60.8, 79.5, 123.2, 132.6, 140.0 (br), 148.6, 148.7, 154.3, 171.3; ^{13}C NMR (C_6D_6, 328 K) δ 28.2 (CH_3), 30.2 (CH_2), 33.8 (CH_2), 40.1 (CH_2), 51.0 (CH_3), 56.3 (CH), 60.9 (CH), 79.5 (C), 123.0 (CH), 132.7 (CH), 140.0 (C), 148.5 (CH), 148.7 (CH), 154.4 (C), 171.2 (C). Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.7; H, 7.5; N, 8.7; Found: C, 63.6; H, 7.5; N, 8.7.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(2-hydroxyethyl)-5-(3-pyridinyl)pyrrolidine (19). To a solution of ester **18** (2.0 g, 6.25 mmol) in EtOH (200 mL) at 0 °C was added $CaCl_2$ (1.47 g, 12.5 mmol) followed by $NaBH_4$ (950 mg, 25 mmol). The mixture was stirred overnight while it warmed to room temperature, and then aqueous K_2CO_3 (2M, 50 mL) was added and the mixture was evaporated. The residue was distributed between EtOAc (100 mL) and H_2O (50 mL), the aqueous layer was extracted with EtOAc (2 × 40 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 2/8) to afford alcohol **19** (1.3 g, 71%) as a colorless oil: $[\alpha]^{22}_D$ +39.6 (*c* 1, $CHCl_3$); ^{1}H NMR (298 K, rotamer ratio, 60/40) δ 1.22 (bs, 5.4H), 1.25* (bs, 3.6H), 1.60−2.00 (m, 4H), 2.00−2.20 (m, 1H), 2.25−2.40 (m, 1H), 3.80 (bm, 2H), 4.19 (br, 0.6H), 4.38 (br, 0.6H), 4.49* (br, 0.4H), 4.55−4.67* (br, 0.4H), 4.71 (bt, J = 7.6, 0.6H), 4.86* (bt, J = 7.1, 0.4H), 7.25 (br, 1H), 7.51 (d, J = 7.9, 0.6H), 7.61* (d, J = 7.9, 0.4H), 8.50 (br, 2H); ^{1}H NMR (C_6D_6, 298 K, rotamers) δ 1.07 (bs, 9H), 1.20−1.70 (bm, 4H), 3.60−3.85 (br, 2H), 4.21 (br, 2H), 4.66 (br, 1H), 6.75 (dd, J = 7.9, 4.7, 1H), 7.13 (br, 1H), 8.42 (bd, J = 4.7, 1H), 8.51 (br, 1H); ^{1}H NMR (C_6D_6, 329 K) δ 1.22 (s, 9H), 1.25−1.38 (m, 1H), 1.40−1.72 (m, 4H), 1.75−1.83 (m, 1H), 3.70−3.90 (m, 2H), 3.80−4.20 (br, 1H), 4.28 (bq, J = 7.0, 1H), 4.45 (dt, J = 7.4, 1H), 6.89 (bd, J = 7.9, 4.7, 1H), 7.31 (d, J = 7.9, 1H), 8.51 (d, J = 4.7, 1H), 8.63 (s, 1H); ^{13}C NMR (C_6D_6, 298 K) δ 28.0 (CH_3), 30.0 (CH_2), 34.8 (CH_2), 39.2 (CH_2), 55.9 (CH), 59.2 (CH_2), 61.3 (CH), 80.1 (C), 123.2 (CH), 132.6 (CH), 140.1 (C), 148.6 (CH), 148.8 (CH), 156.3 (C); ^{13}C NMR (C_6D_6, 329 K) δ 27.7, 30.4, 34.2, 39.1, 55.9, 59.1, 61.0, 79.7, 122.7, 132.2, 139.7, 148.2, 148.4, 155.7. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.7; H, 8.3; N, 9.6. Found: C, 65.5; H, 8.2; N, 9.6.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(2-methylsulfonyloxyethyl)-5-(3-pyridinyl)pyrrolidine (20), (2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(2-bromoethyl)-5-(3-pyridinyl)pyrrolidine (21), and Cyclic Carbamate 22. To a solution 1-methanesulfonylimidazolide (180 mg, 1.2 mmol) in THF (12 mL) at 0 °C was added methyl triflate (127 μL, 1.2 mmol) dropwise, the mixture was stirred at 0 °C for 30 min, and then a mixture of alcohol **19** (300 mg, 1.03 mmol) and 1-methylimidazole (84 μL, 1.03 mmol) in THF (3 mL) was added dropwise at 0 °C. After addition, the ice bath was removed, the mixture was stirred overnight and evaporated, and the residue was dissolved in EtOAc (10 mL) and washed with H_2O (5 mL). The organic layer was dried and evaporated to afford crude mesylate **20** (containing a small amount of 1-mesylimidazolide): ^{1}H NMR (298 K, rotamers) δ 1.00−1.50 (br, 9H), 1.75-(br, 1H), 1.80−2.00 (m, 2H), 2.13 (m, 1H), 2.27−2.44 (m, 2H), 3.00 (s, 3H), 4.12 (bs, 1H), 4.37 (bs, 2H), 4.60−4.80 (br, 1H), 7.25 (br, 1H), 7.55 (bd, J = 7.9, 1H), 8.51 (bs, 2H). Crude mesylate **20** was dissolved in acetone (12 mL), LiBr (358 mg, 4.12 mmol) was added, and the mixture was heated under reflux for about 1 h, with monitoring by TLC. After evaporation, the residue was distributed between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 10), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 4/6) to afford bromide **21** (260 mg, 73%) as a colorless oil; elution with EtOAc gave cyclic carbamate **22** (23 mg, 11% yield) as a white solid with a broad (60−80 °C) mp. For bromide **21**: ^{1}H NMR (298 K, rotamers) δ 1.00−1.60 (br, 9H), 1.65−1.79 (br, 1H), 1.80−1.95 (m, 1H), 1.91−2.20 (m, 2H), 2.28−2.40 (m, 1H), 2.43−2.60 (br, 1H), 3.37−3.60 (m, 2H), 4.10−4.20 (m, 1H), 4.60−5.00 (br, 1H), 7.27 (dd, J = 7.9, 4.9, 1H), 7.52 (dt, J = 7.9, 1.8, 1H), 8.51 (bs, 2H); ^{1}H NMR (C_6D_6, 298 K, rotamers) δ 0.90−1.80 (br, 14H), 2.20−2.40 (br, 1H), 2.95−3.25 (br, 2H), 3.89 (br, 1H), 4.20−4.80 (br, 1H), 6.74 (dd, J = 7.8, 4.6, 1H), 7.15 (overlap with solvent, 1H), 8.47 (d, J = 4.6, 1H), 8.59 (br, 1H); ^{1}H NMR (C_6D_6, 333 K) δ 1.05−1.20 (m, 1H), 1.24 (s, 9H), 1.15−1.28 (m, 2H), 1.60−1.80 (m, 2H), 2.38 (p, J = 6.9, 1H), 3.10−3.29 (m, 2H), 3.91 (m, 1H), 4.50 (dt, J = 7.4, 1H), 6.79 (dd, J = 7.7, 4.6, 1H), 7.21 (bd, J = 7.7, 1H), 8.44 (d, J = 4.6, 1H), 8.58 (s, 1H); ^{13}C NMR (C_6D_6, 298 K) δ 28.3 (CH_3), 29.8 (CH_2), 30.0 (CH_2), 33.8 (CH_2), 39.6 (CH_2), 58.4 (CH), 60.9 (CH), 79.7 (C), 123.0 (CH), 132.7 (CH), 139.7 (C), 148.6 (CH), 148.7 (CH), 154.9 (C). For cyclic carbamate **22**: ^{1}H NMR δ 1.70−1.86 (m, 2H), 1.93−2.04 (m, 1H), 2.12 (m, 1H), 2.20−2.40 (m, 2H), 3.75 (ddt, J = 3.0, 5.1, 11.1, 1H), 4.28 (ddd, J = 3.3, 11.3, 12.8, 1H), 4.51 (ddd, J = 1.4, 5.1, 11.3), 5.05 (d, J = 8.9, 1H), 7.24 (dd, J = 4.9, 7.9, 1H), 7.46 (dt, J = 1.9, 7.9, 1H), 8.48 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_2), 29.9 (CH_2), 32.6 (CH_2), 57.4 (CH), 59.4 (CH), 67.4 (CH_2), 123.2 (CH), 133.1 (CH), 138.1 (C), 147.3 (CH), 148.3 (CH), 155.7 (C). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. Found: C, 66.1; H, 6.5; N, 12.7.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-vinyl-5-(3-pyridinyl)pyrrolidine (23). Methyltriphenylphosphonium bromide (2.64 g, 7.38 mmol) was suspended in 30 mL of THF, and with stirrring at 25 °C, a solution of n-BuLi (2.5 M in hexane, 2.95 mL, 7.38 mmol) was added dropwise over 15 min and the mixture was stirred for 3 h at 25 °C. An aliquot of this suspension (1.0 mL, 0.22 mmol) was placed in another flask, to it a solution of aldehyde **26** (0.18 mmol) in THF was added dropwise at 0 °C, and the resulting mixture stirred overnight. To the mixture, after being stirred overnight, was added pH 7 phosphate buffer (1 mL) followed by evaporation. The residue was distributed between EtOAc (10 mL) and H_2O (5 mL), the organic layer was dried, filtered, and evaporated, and the residue was chromatographed (CH_2Cl_2/EtOAc 4/6) to afford vinyl pyrrolidine **23** (46 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ +52.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (298 K, rotamers) δ 1.00−1.60 (br, 9H), 1.85−1.95 (m, 2H), 2.09 (m, 1H), 2.28 (m, 1H), 4.20−4.50 (br, 1H), 4.60−4.95 (br, 1H), 5.17 (bd, 1H), 5.26 (bd, 1H), 5.95 (br, 2H), 7.22 (dd, J = 7.9, 4.9, 1H), 7.56 (dt, J = 7.9, 1.8,

1H), 8.42 (dd, $J = 4.7, 1.4$, 1H), 8.54 (d, $J = 1.9$, 1H); ^{1}H NMR (328 K) δ 1.27 (s, 9H), 1.75−1.95 (m, 2H), 2.07 (m, 1H), 2.27 (m, 1H), 4.45 (bs, 1H), 4.81 (bt, $J = 6.8$, 1H), 5.14 (d, $J = 10.3$, 1H), 5.23 (d, $J = 17.1$, 1H), 5.94 (m, 1H), 7.17 (dd, $J = 7.9$, 4.9, 1H), 7.53 (dt, $J = 7.9, 1.8$, 1H), 8.42 (d, $J = 4.7$, 1H), 8.51 (s, 1H); ^{13}C NMR (328 K) δ 28.2, 30.4, 34.0, 60.7, 60.8, 79.8, 115.1, 122.9, 133.3, 139.1, 139.4, 148.0, 148.2, 154.6. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.0; H, 8.1; N, 10.2. Found: C, 70.0; H, 8.1; N, 10.1.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-ethyl-5-(3-pyridinyl)pyrrolidine (24). Vinyl pyrrolidine **23** (20 mg, 0.073 mmol) in IPA (1 mL) was treated with H_2 at 1 atm in the presence of 10% Pd/C (2 mg, 10% w/w) at room temperature overnight. The resulting mixture was filtered and evaporated to give ethyl pyrrolidine **24** (20 g, 99%) as a colorless oil: $[\alpha]^{22}_D$ +40.5 (*c* 1, $CHCl_3$); ^{1}H NMR (298 K, rotamers) δ 0.95 (t, $J = 7.4$, 3H), 1.00−1.60 (bm, 10H), 1.69 (br, 1H), 1.81 (m, 1H), 1.98 (m, 2H), 2.29 (m, 1H), 3.86 (br, 1H), 4.69 (br, 1H), 7.20 (dd, $J = 7.9, 4.9$, 1H), 7.51 (dt, $J = 7.9, 1.8$, 1H), 8.44 (d, $J = 4.7$, 1H), 8.48 (s, 1H); ^{1}H NMR (328 K) δ 0.96 (t, $J = 7.4$, 3H), 1.28 (s, 9H), 1.46 (m, 1H), 1.69 (m, 1H), 1.85 (m, 1H), 1.98 (m, 2H), 2.29 (m, 1H), 3.89 (m, 1H), 4.78 (t, $J = 7.4$,1H), 7.19 (dd, $J = 7.9, 4.9$, 1H), 7.52 (dt, $J = 7.9, 1.8$, 1H), 8.44 (d, $J = 4.7$, 1H), 8.50 (d, $J = 1.8$, 1H); ^{13}C NMR (328 K) δ 11.0, 28.3, 28.5, 29.3, 34.1, 60.7, 60.8, 79.6, 123.0, 133.1, 140.1, 148.0, 148.1, 155.0. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.5; H, 8.7; N, 10.1. Found: C, 69.1; H, 8.7; N, 10.1.

7-(*tert*-Butyloxycarbonyl)-1-(3-pyridinyl)-7-azabicyclo-[2.2.1]heptane (2a). To a solution of bromide **21** (90 mg, 0.25 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 0.55 mL) dropwise. The mixture was stirred at −78 °C for 30 min, and then pH 7 buffer (10 mL) was added. The mixture was allowed to warm to room temperature and extracted with EtOAc (2 × 20 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (hexanes/EtOAc, 1/1) to afford **2a** (45 mg, 64%) as a white solid: mp 83−85 °C; ^{1}H NMR δ 1.13 (s, 9H), 1.58 (tm, $J = 11.5$, 2H), 1.85−2.10 (m, 6H), 4.49 (t, $J = 4.4$, 1H), 7.26 (overlap with solvent, 1H), 7.71 (d, $J = 8.0$, 1H), 8.48 (br, 1H), 8.64 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7 (CH_3), 29.3 (CH_2), 37.4 (CH_2), 59.8 (CH), 68.4 (C), 79.7 (C), 122.8 (CH), 134.5 (CH), 138.3 (C), 147.3 (CH), 148.0 (CH), 156.8 (C). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.0; H, 8.1; N, 10.2. Found: C, 69.8; H, 8.2; N, 9.9.

1-(3-Pyridinyl)-7-azabicyclo[2.2.1]heptane (2b). To **2a** (39 mg, 0.14 mmol) was added a solution of HCl in EtOAc (3 M, 2 mL), the resulting solution was stirred at room temperature for 1 h and then evaporated. The residue was distributed between saturated aqueous Na_2CO_3 (10 mL) and EtOAc (2 × 10 mL), the combined organic layer was dried and filtered, and the filtrate was evaporated to afford **2b** (24 mg, 95%) as a colorless oil: ^{1}H NMR δ 1.70−2.10 (m, 8H), 3.15 (br, 1H), 3.82 (t, $J = 4.7$, 1H), 7.26 (dd, $J = 7.9, 4.8$, 1H), 7.79 (dt, $J = 7.9, 1.7$, 1H), 8.50 (dd, $J = 4.8, 1.6$, 1H), 8.71 (d, $J = 1.6$, 1H); ^{13}C NMR ($CDCl_3$) δ 31.8 (CH2), 37.3 (CH2), 57.0 (CH), 67.5 (C),123.0 (CH), 133.4 (CH), 139.3 (C), 147.5 (CH), 147.9 (CH). The hydrogen fumarate of **2b** was formed by mixing **2b** (20 mg, 0.115 mmol) in CH_2Cl_2 (2 mL) with fumaric acid (15 mg, 0.129 mmol) in MeOH (2.47 mL) and evaporating the solution to an amorphous white solid (35 mg, 99%): ^{1}H NMR (CD_3OD) δ 1.99 (tm, $J = 11.5$, 2H), 2.05−2.30 (m, 4H), 2.38 (tm, $J = 11.5$, 2H), 4.38 (t, $J = 4.7$, 1H), 6.67 (s, 2H), 7.54 (dd, $J = 8.0, 4.7$, 1H), 7.98 (d, $J = 8.0$, 1H), 8.59 (br, 1H), 8.68 (bs, 1H); ^{13}C NMR (CD_3OD) δ 29.3 (CH2), 35.3 (CH2), 60.8 (CH), 73.0 (C),-125.5 (CH), 134.8 (C), 135.8 (CH), 136.1 (CH), 147.4 (CH),-150.4 (CH), 171.0 (C). Anal. Calcd. for $C_{11}H_{14}N_2 \cdot 1.1C_4H_4O_4$: C, 61.3; H, 6.1; N, 9.3. Found: C, 61.1; H, 6.4; N, 9.2.

7-Methyl-1-(3-pyridinyl)-7-azabicyclo[2.2.1]heptane (2). A mixture of **2b** (50 mg) in H_2O (0.5 mL), formic acid (0.25 mL), and formaldehyde (0.25 mL) was heated at reflux for 14 h. The solution was evaporated, the residue was partitioned between EtOAc (10 mL) and 2 M K_2CO_3 (10 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried, filtered, and evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH saturated with NH_3, 97/3) to afford **2** (51 mg, 94%) as a colorless oil: ^{1}H NMR δ 1.30−2.80 (br, 11H, with s at 2.04, 3H), 3.46 (t, $J = 4.3$, 1H), 7.28 (dd, $J = 7.9, 4.8$, 1H), 7.78 (dt, $J = 7.9, 1.7$, 1H), 8.50 (d, $J = 4.8$, 1H), 8.62 (s,1H); ^{13}C NMR (two CH_2 obscured by pyramidyl inversion) δ 32.3, 63.2, 70.1, 123.4, 135.2, 137.7, 148.2, 149.0. Anal. Calcd for $C_{11}H_{14}N_2 \cdot 0.5H_2O$: C, 73.1; H, 8.7; N, 14.2. Found: C, 73.2; H, 8.7; N, 13.9.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-hydroxymethyl-5-(3-pyridinyl)pyrrolidine ((+)-25). To a solution of (+)-**15** (400 mg, 1.3 mmol) in EtOH (40 mL) at 0 °C was added $CaCl_2$ (433 mg, 3.9 mmol) followed by $NaBH_4$ (296 mg, 7.8 mmol). The mixture was stirred overnight as it warmed to room temperature. Aqueous K_2CO_3 (2 M, 5 mL) was added, the mixture was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL), the aqueous layer was extracted with EtOAc (2 × 40 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (EtOAc) to afford **25** (315 mg, 87%) as a white solid: mp 75−78 °C; $[\alpha]^{22}_D$ +17.4 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.20 (bs, 9H), 1.69 (br, 1H), 1.87 (m, 1H), 2.07 (m, 1H), 2.34 (m, 1H), 3.80 (m, 2H), 4.18 (br, 1H), 4.55 (br, 1H), 4.83 (bt, 1H), 7.6 (m, 1H), 7.39 (d, $J = 4.8$, 1H), 8.52 (m, 2H); ^{1}H NMR (C_6D_6, 298 K, rotamers) δ 1.07 (bs, 9H), 1.20−1.70 (bm, 4H), 3.60−3.85 (br, 2H), 4.21 (br, 2H), 4.66 (br, 1H), 6.75 (dd, $J = 7.9, 4.7$, 1H), 7.13 (br, 1H), 8.42 (bd, $J = 4.7$, 1H), 8.51 (br, 1H); ^{1}H NMR (C_6D_6, 329 K) δ 1.22 (s, 9H), 1.25−1.38 (m, 1H), 1.40−1.72 (m, 4H), 1.75−1.83 (m, 1H), 3.70−3.90 (m, 2H), 3.80−4.20 (br, 1H), 4.28 (bq, $J = 7.0$, 1H), 4.45 (dt, $J = 7.4$, 1H), 6.89 (bd, $J = 7.9, 4.7$, 1H), 7.31 (d, $J = 7.9$, 1H), 8.51 (d, $J = 4.7$, 1H), 8.63 (s, 1H); ^{13}C NMR (C_6D_6, 328 K) δ 27.2, 28.1, 34.1, 61.2, 61.6, 65.9, 80.0, 123.1, 132.9, 140.1, 148.4, 148.7, 156.0. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.7; H, 8.0; N, 10.1. Found: C, 65.0; H, 8.0; N, 10.4.

(2*R*,5*S*)-1-(*tert*-Butyloxycarbonyl)-2-hydroxymethyl-5-(3-pyridinyl)pyrrolidine ((−)-25, structure not shown) was prepared from (−)-**15** in the same way: $[\alpha]^{22}_D$ −17.0 (*c* 1, $CHCl_3$); spectral and chromatographic properties identical with those of **(+)-25**.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-formyl-5-(3-pyridinyl)pyrrolidine (26) and (2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(2-methoxycarbonylvinyl)-5-(3-pyridinyl)pyrrolidine (27). To a solution of oxalyl chloride (0.75 g, 5.9 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DMSO (0.84 mL, 11.8 mmol), the mixture was stirred for 15 min, a solution of **25** (0.82 g, 2.95 mmol) in CH_2Cl_2 (10 mL) was added over 10 min, the mixture was stirred for 1 h, and triethylamine (2.5 mL, 17.7 mmol) was added dropwise over 5 min. The mixture was stirred for an additional 1 h and poured into H_2O (30 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried, filtered, and evaporated to afford crude aldehyde **26**: ^{1}H NMR (298 K, rotamers) δ 1.00−1.50 (br, 9H), 1.70−2.45 (bm, 4H), 4.26 (br, 0.5H), 4.46 (br, 0.5H), 4.78 (br, 0.5H), 5.02 (br, 0.5H), 7.26 (br, 1H),7.60−7.80 (br, 1H),8.40−8.70 (br, 2H). To a suspension of NaH (85 mg, 3.54 mmol) in THF (40 mL) at 0 °C was added a solution of trimethyl phosphonoacetate (0.57 mL, 3.54 mmol) dropwise, the resulting mixture was stirred at 0 °C for 30 min, and the crude **26** in THF (40 mL) was added via cannula. The resulting solution was stirred for another 30 min, pH 7 phosphate buffer (5 mL) was added, the mixture was concentrated to about 20 mL, and the residue was partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL), and the combined organic phase was dried and evaporated, leaving a residue that was chromatographed (EtOAc/hexanes, 6/4) to give the unsaturated ester **27** (0.73 g, 73% from **25**) as a mixture of cis and trans isomers: ^{1}H NMR (298 K) δ 1.10−1.51 (br, 9H major, 9H minor), 1.68 (br, 1H minor), 1.86 (m, 2H major, 1H minor), 2.13 (m, 1H major), 2.30 (m, 1H major, 2H minor), 3.67 (s, 3H minor), 3.71 (s, 3H major), 4.30−4.70 (br, 1H major), 4.70−5.10 (br, 1H major, 1H minor), 5.43 (bq, $J = 7.2$, 1H minor), 5.80 (bd, $J = 11.1$, 1H minor), 6.00 (br, 1H major), 6.23−6.57 (br, 1H minor), 6.95 (br, 1H

major), 7.22 (m, 1H major, 1H minor), 7.53 (m, 1H major, 1H minor), 8.45 (m, 1H major, 1H minor), 8.49 (s, 1H major), 8.51 (s, 1H minor); ^{1}H NMR (328 K) δ 1.27 (s, 9H major), 1.28 (s, 9H minor), 1.68 (m, 1H minor), 1.90 (m, 2H major, 1H minor), 2.15 (m, 1H major), 2.31 (m, 1H major, 2H minor), 3.69 (s, 3H minor), 3.72 (s, 3H major), 4.55 (br, 1H major), 4.85 (br, 1H major), 4.96 (br, 1H minor), 5.44 (bq, J = 7.2, 1H minor), 5.80 (dd, J = 11.5, 1.2, 1H minor), 6.00 (d, J = 15.7, 1H major), 6.37 (bt, J = 9.6, 1H minor), 6.96 (dd, J = 15.7, 6.5, 1H major), 7.21 (m, 1H major, 1H minor), 7.53 (m, 1H major, 1H minor), 8.44 (d, J = 4.7, 1H major, 1H minor), 8.51 (s, 1H major), 8.53 (s, 1H minor); ^{13}C NMR (328 K) δ 28.1 × 2, 30.4, 30.5, 33.6, 33.9, 51.0, 51.4, 57.4, 59.5, 60.4, 60.8, 80.2, 80.4, 118.5, 121.5, 123.1, 123.2, 133.2, 138.8, 139.1, 147.8, 148.1 × 2, 148.2 × 2, 152.2, 154.6, 154.8, 166.1, 166.5. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.0; H, 7.3; N, 8.4. Found: C, 64.7; H, 7.5; N, 8.2.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(2-β-methoxycarbonylethyl)-5-(3-pyridinyl)pyrrolidine (28). Unsaturated ester **27** (1.0 g, 3.0 mmol) in MeOH (10 mL) was treated with H_2 at 1 atm in the presence of 10% Pd/C (100 mg, 10% w/w) at room temperature for 4 h. The resulting mixture was filtered through Celite and evaporated to give **28** (1.0 g, 99%) as a colorless oil: ^{1}H NMR (298 K, rotamers) δ 1.00−1.50 (br, 9H), 1.65 (m, 1H), 1.70−1.92 (m, 2H), 2.00 (m, 1H), 2.13−2.37 (m, 2H), 2.41 (br, 1H), 3.64 (s, 3H), 3.97 (br, 1H), 4.60−5.20 (br, 1H), 7.21 (dd, J = 7.8, 4.7, 1H), 7.51 (d, J = 7.8, 1H), 8.43 (d, J = 4.8, 1H), 8.45 (s, 1H); ^{1}H NMR (328 K) δ 1.26 (s, 9H), 1.68 (m, 1H), 1.80 (m, 1H), 1.88 (m, 1H), 2.07 (m, 1H), 2.15−2.35 (m, 2H), 2.41 (t, J = 7.8, 2H), 3.65 (s, 3H), 4.00 (m, 1H), 4.77 (t, J = 7.6, 1H), 7.19 (dd, J = 7.8, 4.8, 1H), 7.52 (dt, J = 7.8, 1.8, 1H), 8.43 (d, J = 4.8, 1H), 8.48 (d, J = 1.8, 1H); ^{13}C NMR (328 K) δ 28.2, 29.8, 31.0, 31.5, 33.9, 51.3, 58.6, 60.8, 79.9, 123.1, 133.1, 139.6, 147.9, 148.0, 154.9, 173.4.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(3-hydroxypropyl)-5-(3-pyridinyl)pyrrolidine ((+)-29). To a solution of ester **28** (1 g, 3 mmol) in EtOH (30 mL) at 0 °C was added $CaCl_2$ (1 g, 9 mmol) followed by $NaBH_4$ (0.68 g, 18 mmol). The mixture was stirred overnight as it warmed to room temperature, aqueous K_2CO_3 (2 M, 20 mL) was added, and the mixture was evaporated. The residue was partitioned between EtOAc (100 mL) and H_2O (50 mL), the aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (EtOAc) to afford alcohol **29** (0.65 g, 71%) as a colorless oil: $[\alpha]^{22}_D$ +16.5 (*c* 1, $CHCl_3$); ^{1}H NMR (298 K) δ 1.18−1.45 (br s, 9H), 1.45−1.76 (m, 4H), 1.87 (m, 1H), 2.00 (m, 2H), 2.26 (m, 1H), 2.40−3.50 (br, 1H), 3.67 (bs, 2H), 3.98 (br, 1H), 4.69 (br, 1H), 7.19 (dd, J = 7.8, 4.8, 1H), 7.51 (dt, J = 7.8, 1.8, 1H), 8.41 (d, J = 4.8, 1H), 8.45 (d, J = 1.8, 1H); ^{1}H NMR (328 K) δ 1.23 (s, 9H), 1.48−1.72 (m, 4H), 1.87 (m, 1H), 2.01 (m, 2H), 2.28 (m, 1H), 2.66 (br, 1H), 3.69 (bs, 2H), 4.02 (br, 1H), 4.74 (dt, J = 7.2, 1H), 7.18 (dd, J = 7.9, 4.7, 1H), 7.51 (d, J = 7.9, 1.8, 1H), 8.42 (dd, J = 4.7, 1.8, 1H), 8.47 (d, J = 1.8, 1H); ^{13}C NMR (328 K) δ 28.2, 29.7, 29.8, 32.1, 34.1, 58.9, 60.7, 62.4, 79.7, 123.1, 133.1, 140.0, 147.9, 154.9. Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.6; H, 8.6; N, 9.1. Found: C, 66.4; H, 8.8; N, 9.0.

(2*R*,5*S*)-1-(*tert*-Butyloxycarbonyl)-2-(3-hydroxypropyl)-5-(3-pyridinyl)pyrrolidine (**(−)-29**, structure not shown) was prepared in the same manner from ester **(−)-28**: $[\alpha]^{22}_D$ −17.0 (*c* 1.2, $CHCl_3$); spectral and chromatographic properties identical with **(+)-29**.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(3-methylsulfonyloxypropyl)-5-(3-pyridinyl)pyrrolidine (30) and (2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(3-bromopropyl)-5-(3-pyridinyl)pyrrolidine (31). To a solution of 1-methansulfonylimidazolide (180 mg, 1.2 mmol) in THF (12 mL) at 0 °C was added methyl triflate (127 μL, 1.2 mmol) dropwise, and the mixture was stirred at 0 °C for 30 min followed by the dropwise addition at 0 °C of a mixture of **29** (315 mg, 1.03 mmol) and 1-methylimidazole (84 μL, 1.03 mmol) in THF (3 mL). After the addition, the ice bath was removed, the mixture was stirred overnight and then evaporated, and the residue was partitioned between EtOAc (2 × 20 mL) and H_2O (20 mL). The organic layer was dried, filtered, and evaporated to afford crude mesylate **30** containing a small amount of mesylimidazolide: ^{1}H NMR (298 K, rotamers) δ 1.00−2.40 (m, 17H), 2.98 (s, 3H), 3.95 (bs, 1H), 4.28 (bs, 2H), 4.75 (br, 1H), 7.20 (br, 1H), 7.49 (bd, J = 7.9, 1H), 8.48 (bs, 2H). Crude **30** was dissolved in acetone (12 mL), LiBr (358 mg, 4.12 mmol) was added, and the mixture was refluxed for 1 h. Evaporation left a residue that was partitioned between EtOAc (10 mL) and H_2O (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc, 4/6) to afford bromide **31** (270 mg, 73%) as a colorless oil: ^{1}H NMR (298 K, rotamers) δ 1.00−1.50 (br, 9H), 1.55−1.78 (br, 2H), 1.85−2.10 (m, 5H), 2.20−2.28 (m, 1H), 3.44 (m, 2H), 4.02 (br, 1H), 4.60−5.00 (br, 1H), 7.27 (dd, J = 7.9, 4.7, 1H), 7.57 (d, J = 7.9, 1H), 8.47 (d, J = 4.7, 1H), 8.57 (s, 1H); ^{1}H NMR (323 K) δ 1.28 (bs, 9H), 1.55−1.78 (m, 2H), 1.85−2.10 (m, 5H), 2.20−2.28 (m, 1H), 3.44 (m, 2H), 4.02 (br, 1H), 4.79 (bt, 1H), 7.23 (dd, J = 7.9, 4.7, 1H), 7.54 (d, J = 7.9, 1H), 8.47 (d, J = 4.7, 1H), 8.54 (s, 1H); ^{13}C NMR (328 K) δ 28.2, 30.1, 30.3, 33.3, 34.0, 34.5, 58.4, 61.8, 79.9, 123.1, 133.2, 139.6, 147.8, 147.9, 154.8. Bromide **31** is unstable and was used immediately after a short period of drying under vacuum.

8-*tert*-Butyloxycarbonyl-1-(3-pyridinyl)-8-azabicyclo-[3.2.1]octane ((−)-3a). To a solution of *n*-BuLi (0.21 mmol, 1.6 M in hexane, 0.13 mL) in THF (15 mL) at −78 °C was added bromide **31** (27 mg, 0.083 mmol) in THF (2 mL) slowly (syringe pump) over 1 h. The mixture was stirred at −78 °C for 30 min, and then pH 7 phosphate buffer (20 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed (hexanes/EtOAc, 1/1) to afford **3a** (10 mg, 48%) as a white solid: mp 104−106 °C; $[\alpha]^{22}_D$ −46.1 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.50−2.40 (m, 10H), 3.49 (s, 3H), 4,47 (bs, 1H), 7.22 (dd, J = 7.8, 4.8, 1H), 7.63 (d, J = 7.8, 1H), 8.43 (bs, 1H), 8.60 (s, 1H); ^{13}C NMR δ 17.6, 26.7, 27.9, 29.0, 30.9, 41.9, 57.8, 63.7, 79.4, 122.7, 132.9, 141.9, 147.0, 154.4. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.8; H, 8.4; N, 9.7. Found: C, 70.4; H, 8.8; N, 9.7.

8-(*tert*-Butoxycarbonyl)-1-(3-pyridinyl)-8-azabicyclo-[3.2.1]octane ((+)-3a) was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{22}_D$ +45.8 (*c* 0.93, $CHCl_3$); spectral and chromatographic properties identical with those of (−)-**3a**.

1-(3-Pyridinyl)-8-azabicyclo[3.2.1]octane ((−)-3b). To **3a** (39 mg, 0.14 mmol) was added HCl in EtOAc (3 M, 2 mL), and the resulting mixture was stirred at room temperature for 30 min. After evaporation, the residue was partitioned between saturated aqueous Na_2CO_3 (10 mL) and EtOAc (2 × 10 mL). The combined organic layer was dried, filtered, and evaporated to afford (−)-**3b** (23 mg, 93%) as a colorless oil: $[\alpha]^{22}_D$ −7.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.50−2.10 (m, 10H), 2.20−2.32 (m, 1H), 3.72 (m, 1H), 7.24 (dd, J = 7.9, 4.8, 1H), 7.73 (dt, J = 7.9, 1.7, 1H), 8.46 (dd, J = 4.8, 1.6, 1H), 8.65 (d, J = 1.6, 1H); ^{13}C NMR δ 18.7, 30.1, 31.6, 35.8, 41.1, 55.5, 64.1, 123.1, 132.8, 143.7, 146.3, 147.6. Anal. Calcd for $C_{12}H_{16}N_2 \cdot {}^1/_4H_2O$: C, 74.8; H, 8.6; N, 14.5. Found: C, 75.1; H, 8.8; N, 14.7.

1-(3-Pyridinyl)-8-azabicyclo[3.2.1]octane ((+)-3b) was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{22}_D$ +6.8 (*c* 0.96, $CHCl_3$); spectral and chromatographic properties identical with those of (−)-**3b**.

7-Methyl-1-(3-pyridinyl)-8-azabicyclo[3.2.1]octane ((−)-3). A mixture of (−)-**3b** (50 mg) in H_2O (0.5 mL), formic acid (0.25 mL), and formaldehyde (0.25 mL) was heated at reflux for 14 h and then evaporated, and the residue was partitioned between EtOAc (5 mL) and 2 M K_2CO_3 (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic layer was dried and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH saturated with NH_3, 97/3) to afford (−)-**3** (48 mg, 90%) as a colorless oil: $[\alpha]^{22}_D$ −10.9

(*c* 1, $CHCl_3$); ^1H NMR δ 1.20−1.35 (m, 1H), 1.55−2.20 (m, 13H, with singlet at 2.10), 3.39 (m, 1H), 7.24 (dd, J = 7.9, 4.8, 1H), 7.75 (dt, J = 7.9, 1.7, 1H), 8.45 (dd, J = 4.8, 1.6, 1H), 8.65 (d, J = 1.6, 1H); ^{13}C NMR (328 K) δ 18.3, 26.4, 27.3, 33.0, 34.2, 35.4, 61.9, 66.0, 123.0, 134.5, 141.8, 147.7, 148.7. Anal. Calcd. for $C_{13}H_{18}N_2 \cdot {}^1/_4H_2O$: C, 75.5; H, 9.0; N, 13.6. Found: C, 75.6; H, 9.0; N, 13.8.

7-Methyl-1-(3-pyridinyl)-8-azabicyclo[3.2.1]octane ((+)-3) was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{22}_D$ +11.2 (*c* 1.3, $CHCl_3$); spectral and chromatographic properties identical with those of (−)-**3**.

Acknowledgment. J. Choi thanks the Korea Science and Engineering Foundation for partial fellowship support. M.I.C. is grateful to the Xunta de Galicia for an internship.

JO990130U