Enantiospecific Synthesis of Annulated Nicotine Analogues from D-Glutamic Acid. 7-Azabicyclo[2.2.1]heptano[2.3-*c*]pyridines

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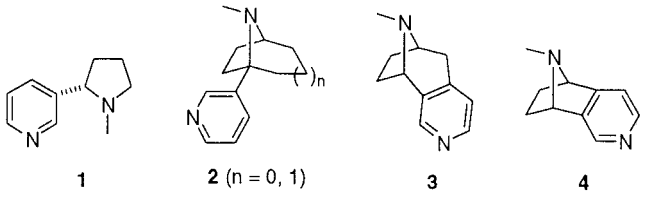
The conformationally restricted nicotinoid (1*S*,4*S*)-7-methyl-7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridine dihydrochloride has been prepared enantiospecifically from D-glutamic acid. The method involved a lithium *cis*-2,6-dimethylpiperidide-mediated intramolecular anionic cyclization of (2*S*,5*R*)-*N*-(*tert*-butyloxycarbonyl)-5-[3-(4-*N*-chloropyridinyl]proline methyl ester in tandem with a standard decarboxylation sequence. Reductive amination afforded the desired N-methylated [2.2.1]bicyclonicotinoid. Cyclization of the corresponding iodopyridinylproline methyl ester, obtained via ultrasound-facilitated chloro−iodo exchange, was also effected.

Introduction

Investigative studies in pharmacology and medicinal chemistry have spawned a virtual explosion of interest in the development of selective compounds that target nicotinic acetylcholine receptors (nAChRs), a family of ligand-gated ion channels widely distributed in the human brain.[1] The egregious consequences of (*S*)-(−)-nicotine **1** (Figure 1) have been well documented, but not until recently have the surprisingly beneficial effects of nicotine and nicotine analogues been established, including observations of favorable results with Alzheimer's disease (AD), anxiety, adult attention deficit hyperactivity disorder (ADHD), depression, Parkinson's disease, schizophrenia, Tourette's syndrome, and ulcerative colitis.[2,3]

Although the antinociceptive effects of nicotine have been known for some time,[4] a limitation of its therapeutic utility is the high doses required to achieve the desired effects, which are modest and of short duration. The discovery of (−)-epibatidine, however, has initiated a resurgence of interest in developing selective nAChRs for the treatment of chronic pain.[5]

Synthetic efforts toward novel compounds having the desired therapeutic indications have recently proliferated.[6] Modeling studies have suggested that the pyridine and pyrrolidine rings of nicotine are skewed and nearly perpendicular to one another[7] in low energy conformations; however, the exact conformation that induces ion-channel modulation is currently unknown.



1 **2** (n = 0, 1) **3** **4**

Figure 1. Nicotine and fused-ring analogues.

Pursuant to these synthetic and pharmacologic objectives, our laboratory has recently reported[8] the synthesis of the highly conformationally constrained nicotine analogues **2**, with a pendant pyridine ring, and the annulated pyridotropane **3**. We now report the synthesis of the bicyclo[2.2.1] analogue **4**.

To achieve the enantioselective synthesis of constrained nicotinoids **4**, we have proposed a route utilizing D-glutamic acid (Scheme 1). Paramount would be an intramolecular cyclization of enolate **6** to bicycle **7** proceeding via an S_NAr mechanism. Noncatalyzed additions of anionic carbon nucleophiles to halopyridines have precedent,[9] albeit most reported examples occur electrochemically[10] or require substantially activated pyridine systems.[11]

(1) (a) Paterson, D.; Nordberg, A. *Prog. Neurobiol.* **2000**, *61*, 75−111. (b) Clementi, F.; Fornasari, D.; Gotti, C. *Eur. J. Pharmacol.* **2000**, *393*, 3−10.

(2) (a) Levin, E. D.; Rezvani, A. H. *Eur. J. Pharmacol.* **2000**, *393*, 141−146. (b) Stolerman, I. P.; Mirza, N. R.; Hahn, B.; Shoaib, M. *Eur. J. Pharmacol.* **2000**, *393*, 147−154. (c) Quik, M.; Jeyarasasingam, G. *Eur. J. Pharmacol.* **2000**, *393*, 223−230. (d) Perry, E., et al. *Eur. J. Pharmacol.* **2000**, *393*, 215−222. (e) Leonard, S., et al. *Eur. J. Pharmacol.* **2000**, *393*, 237−242. (f) Newhouse, P. A.; Kelton, M. *Pharm. Acta Helv.* **2000**, *74*, 91−101. (g) Guslandi, M. *Br. J. Clin. Pharmacol.* **1999**, *48*, 481−484.

(3) Decker, M. W.; Aneric, S. P. *Neuronal Nicotinic Recept.* **1999**, 395−411.

(4) Davis, L.; Pollock, L. J.; Stone, T. T. *Surg. Gynecol. Obstet.* **1932**, *55*, 418.

(5) (a) Decker, M. W.; Meyer, M. D. *Biochem. Pharmacol.* **1999**, *58*, 917−923. (b) Elgen, R. M.; Hunter, J. C.; Dray, A. *Trends Pharm. Sci.* **1999**, *20*, 337−342. (c) Bannon, A. W., et al. *Science* **1998**, *279*, 77−81.

(6) (a) Barloco, D., et al. *J. Med. Chem.* **1998**, *41*, 674−681. (b) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1998**, *41*, 407−412.

(7) (a) Elmore, D. E.; Dougherty, D. A. *J. Org. Chem.* **2000**, *65*, 742−747. (b) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, 465−486.

(8) (a) Xu, Y.-z; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069−4078. (b) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861−870.

(9) Buschauer, A. *Arch. Pharm.* **1989**, *322*, 165−171.

(10) (a) Chahma, M.; Combellas, C.; Thiébault, A. *J. Org. Chem.* **1995**, *60*, 8015−8022. (b) Chahma, M.; Combellas, C.; Thiébault, A. *Synthesis* **1994**, 366−368.

(11) (a) Artamkina, G. A.; Kovalenko, S. V.; Beletskaya, I. P.; Reutov, O. A. *Zh. Org. Khim.* **1990**, *26*, 225−229. (b) Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Organomet. Chem.* **1987**, *325*, 13−23. (c) Banks, R. E.; Thomson, J. *J. Chem. Res., Synop.* **1985**, 33.

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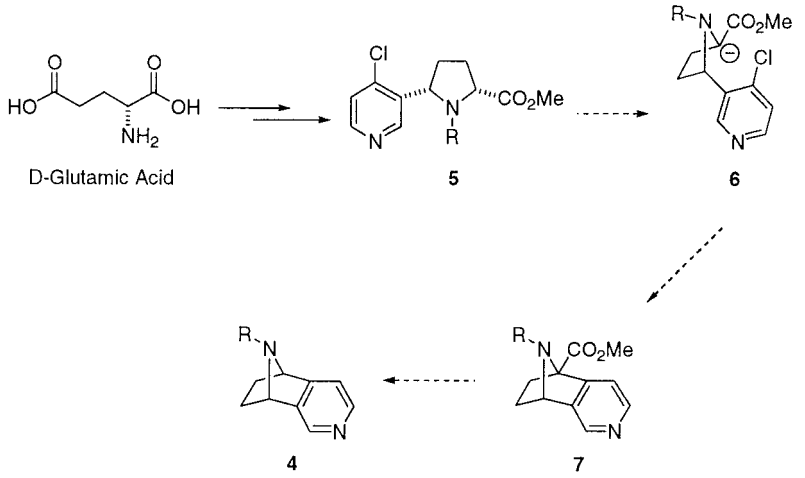
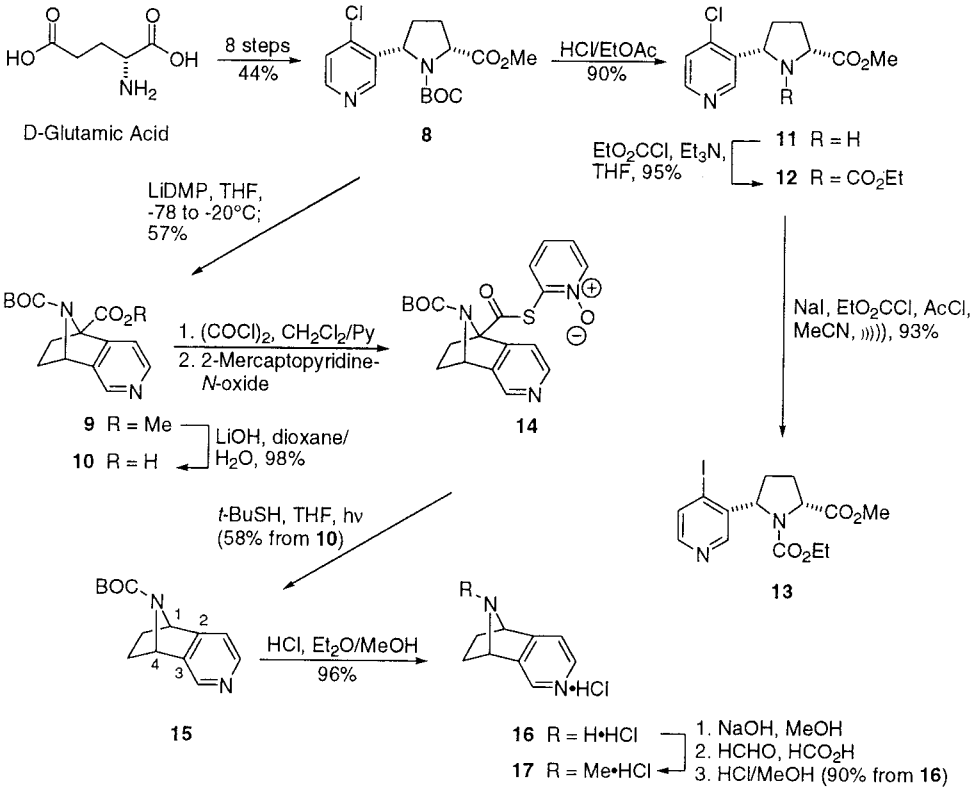
Scheme 1. Proposed Route to 7-Azabicyclo[2.2.1]heptano[2,3-*c*]pyridines



Scheme 2. Synthesis of [2.2.1] System and Transhalogenation Sequence



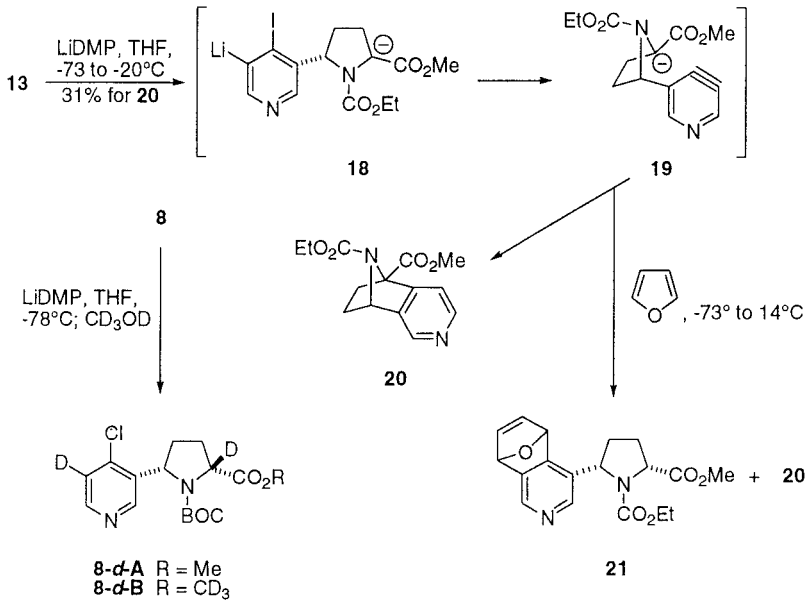
Results and Discussion

Previous reports[8] have detailed the synthesis of proline derivative **8** (Scheme 2) from glutamic acid. The synthetic sequence remains identical; however, the experimental details have been modified,[12] resulting in better, reproducible, and scalable yields. Thus, intermediate nicotine **8** became available in quantity in 44% yield from D-glutamic acid. The intramolecular alkylation, **8** to **9**, was exquisitely sensitive to every variable. A variety of amide bases bearing lithium and potassium counterions in nonpolar, ethereal, and dipolar aprotic solvents were used for the attempted conversion. Two modes of addition, adding a solution of substrate to the base and adding the base to the substrate, were employed as were a wide range of temperatures. The amides used included LDA, KHMDS, LiHMDS, tetramethylpiperidine (TMP), and *cis*-2,6-dimethylpiperidine (DMP). Temperature control from −78 °C to room temperature was examined, including a number of intermediate points for various times. From this exhaustive examination, the best conditions were found to be adding LiDMP to the substrate at −78 °C in THF and concluding the reaction at −20 °C. The result was a reproducible 57% yield of **9**. Evidence that the production of bicycle **9** was ineluctably accompanied by pyridyne formation will be discussed below.

Since the nature of the leaving group in an S_NAr reaction impacts directly on the outcome, it was of interest to explore the reactivity of an iodopyridine relative to a chloropyridine to determine if there was a leaving group effect. Known methods of pyridine transhalogenation were expected to be incompatible with the

(12) Modified experimental details for the synthesis of **8** from D-glutamic acid are available in the Supporting Information.

Scheme 3. Reactivity of Iodopyridine toward [2.2.1] Cyclization



N-tert-butyloxycarbonyl functionality of **8**; therefore, *N*-BOC deprotection of proline derivative **8** (Scheme 2) was effected in an overall 90% yield using HCl in anhydrous EtOAc, followed by isolation of the intermediate di-HCl salt and treatment with propylene oxide in CH_2Cl_2 as a hydrogen chloride scavenger. Amine **11** was subsequently protected in 95% yield as the ethyl carbamate **12** via treatment with EtO_2CCl and Et_3N. Reported strategies[13] for pyridine trans-halogenation of **12** to **13** using NaI/HI or NaI/AcCl were ineffective. The use of NaI and AcCl in anhydrous MeCN with moderate heat (45−50 °C) led predominantly to de-N-carbethoxylation and N-acylation plus decomposition products. Careful manipulation of the reaction parameters, however, resulted in very mild, high-yielding conditions for the trans-halogenation. Thus, submission of chloropyridine **12** to ultrasound-facilitated treatment with NaI and EtO_2CCl/AcCl (in a 10/1 ratio, precluding N-acylation) in anhydrous MeCN afforded iodopyridine **13** in a 93% yield and in a fraction of the time required by the less effective thermal process.

Exposure of iodopyridine **13** (Scheme 3) to the [2.2.1] cyclization conditions afforded bicycle **20** in a 31% yield, inferior to the yield from the chloride. The observation of pyridyne formation, to some degree, in all experiments performed with lithium amide bases raises questions as to the nature of the mechanism of the [2.2.1] cyclization. Interestingly, regioselective ortho-lithiation of halopyridines by LDA have been independently reported[14] as a means for the generation of pyridynes.

A Diels−Alder trapping reaction[14,15] was invoked to determine if the putative 3,4-pyridyne **19** was present during the cyclization events. Projecting that a pyridyne would form more quickly from an iodopyridine and at a lower temperature than from the corresponding chloropyridine,[14a] iodide **13** was chosen for the trapping episode. Furan (3300 mol %) was introduced into the reaction mixture at −73 °C after 2h. Stirring at −73 °C was continued while the reaction mixture was slowly warmed to +14 °C, where it was quenched with MeOH. Positive-ion mass spectrometry of the crude mixture under electrospray conditions detected the following molecular ions: $[M + H]^+$ for the [4 + 2] furan adduct **21** *m/z* 345.1; $[M + H]^+$ for the [2.2.1] product **20** *m/z* 277.2; and $[M + H]^+$ for the starting iodide **13** *m/z* 405.1. Prior studies involving the chloropyridine **24** had unambiguously verified that ortho-lithiation was occurring as established by MeOH-d_4 quench of a trial reaction at −78 °C, providing **8-*d*-A** and **8-*d*-B** wherein a >20% deuterium incorporation was observed ortho to the chloro group.

Elaboration to nicotine analogues **16** and **17** (Scheme 2) proceeded by methyl ester hydrolysis of **9** to carboxylic acid **10** in 98% yield with aqueous LiOH in dioxane. Using a previously established protocol for reductive radical decarboxylation[16] of the quaternary C-1 carboxy group, the acid chloride of **10** (prepared via treatment with oxalyl chloride in a pyridine-buffered medium) was condensed with 2-mercaptopyridine *N*-oxide providing the thioester **14**. Completion of the sequence by irradiating **14** with two 100 W incandescent lamps in the presence of *t*-BuSH afforded bicycle **15** in an overall 58% yield from **10**.

Removal of the *N*-Boc protecting group of **15** was effected with HCl in EtOAc, affording the crystalline di-HCl salt **16**. Treatment of **16** with NaOH in MeOH released the corresponding free base, which was submitted to reductive amination to provide the desired N-methylated bicycle **17** in a 90% yield over three steps. Interestingly, the room-temperature ^1H and ^{13}C NMR spectra of **17** in MeOH-d_4 exhibit an unexpected doubling of resonances, indicating the presence of two species. This effect is not observed in the ^1H NMR spectrum of the

(13) (a) Corcoran, R. C.; Bang, S. H. *Tetrahedron Lett.* **1990**, *31*, 6757−6758. (b) Newkome, G. R.; Moorfield, C. N.; Sabbaghian, B. *J. Org. Chem.* **1986**, *51*, 953−954. (c) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 626−633. (d) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 4764−4768.

(14) (a) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151−169. (b) Marsais, F.; Trécourt, F.; Bréant, P.; Quéginer, G. *J. Heterocycl. Chem.* **1988**, *25*, 81−87.

(15) (a) Connon, S. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245−1249. (b) Walters, M. A.; Shay, J. J. *Synth. Commun.* **1997**, *27*, 3573−3579. (c) Walters, M. A.; Shay, J. J. *Tetrahedron Lett.* **1995**, *36*, 7575−7578. (d) Tsukazaki, M.; Snieckus, V. *Heterocycles* **1992**, *33*, 533−536.

(16) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313−6325; Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479−5486.

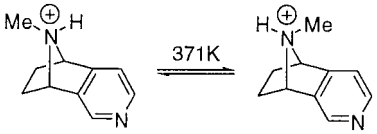


Figure 2. Equilibrium between the two protonated quarternary *N*-methyl diastereomers.

corresponding free base of **17**. Comparable results are obtained in DMSO-d_6 at ambient temperature. When the ^{1}H NMR sample is heated to 98 °C, however, a single species is observed as indicated by coalescence of the resonances. Upon cooling to room temperature, the sample returns to its unchanged ambient temperature ^{1}H NMR spectrum. These results suggest an equilibrium (Figure 2) of two protonated quaternary *N*-methyl diastereomers wherein the chiral nitrogen is stable to pyramidal inversion due to the high barrier of energy required for interconversion.

Conclusion

A method for the enantiospecific synthesis of 7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridines **16** and **17** from D-glutamic acid has been developed. These compounds represent the most rigid of the conformationally constrained nicotine analogues reported, involving the introduction only of a carbon−carbon single bond between C-4 and C-5′ of (−)-nicotine. The key reaction, a lithium amide promoted anionic cyclization of chloropyridine **8**, is highly dependent upon stoichiometry and steric effects of the base used. Pyridyne formation has been detected during the course of the reaction, although the degree to which a pyridyne intermediate serves a role in the transformation is currently unknown. The rigidity of this bicyclo system is clearly demonstrated by the appearance at room temperature of diastereomeric, protonated, quaternary *N*-methyl species in the ^{1}H NMR that coalesce at 98 °C.

Experimental Section

Methods and Materials. Melting points were determined on an open capillary apparatus and are uncorrected. Column chromatography was completed under positive pressure (N_2) using 230−400 mesh silica gel or 50−200 mesh neutral alumina. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica gel 60 F_{254} 0.2 mm plates and visualized with UV light (254 nm) followed by heating with commercial ethanolic phosphomolybdic acid. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$−tetramethylsilane (δ 0.0 for ^{1}H), $CDCl_3$ (δ 77.0 for ^{13}C), CD_3OD (δ 3.30 for ^{1}H), and CD_3OD (δ 49.0 for ^{13}C) as internal references. DEPT experiments were performed with ^{13}C NMR acquisition, and the carbon multiplicities were listed as (0) quaternary, (1) methine, (2) methylene, and (3) methyl. The following solvents and reagents were distilled under a blanket of dry nitrogen: THF, Et_2O, and furan were distilled from Na-benzophenone ketyl; CH_2Cl_2, diisopropylamine, *cis*-dimethylpiperidine, and Et_3N were distilled from CaH_2; MeCN was distilled first from P_2O_5 and then from CaH_2; MeOH was distilled from Mg; HOAc was distilled from anhydrous $CuSO_4$; and EtOAc was distilled from anhydrous $CaCl_2$. Organic phases from liquid−liquid distribution were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Elemental analyses and mass spectra were conducted by the Analytical Laboratory at the University of California, Berkeley.

(2*S*,5*R*)-*N*-(*tert*-Butyloxycarbonyl)-5-[3-(4′chloropyridinyl)]proline methyl ester (8) was prepared by the sequence reported.[8] A number of changes have been made, however, particularly in larger scale reactions, that have led to easier isolations and better yields (eight steps, 44% yield from D-glutamic acid). These improvements are delineated in detail in the Supporting Information.

(1*R*,4*S*)-7-*tert*-Butyloxycarbonyl-1-methoxycarbonyl-7-azabicyclo[2.2.1heptano[2,3-*c*]pyridine (9). It is critical that the THF for this experiment be distilled from LAH just prior to use to obtain reproducible results. To a solution of *cis*-2,6-dimethylpiperidine (1.66 mL, 12.3 mmol) in THF (1.75 mL) at −20 °C was added *n*-BuLi (2.35 M in hexanes, 5.20 mL, 12.2 mmol). The LiDMP solution was stirred for an additional 1 h at −20 °C and then cannula transferred over 15 min to a solution of chloropyridine **8** (2.033 g, 5.965 mmol) in THF (174 mL) at −78 °C. The burgundy reaction mixture was stirred for an additional 2 h at −78 °C, at which point it was immersed into a −65 °C bath and warmed to −20 °C (turning brown between −38 and −35 °C) at a rate of 0.36 °C/min. To the reaction mixture was added MeOH (5.0 mL) followed by 1 M pH 8 phosphate buffer (50 mL). Dilution with CH_2Cl_2 (150 mL) permitted clean separation of the aqueous phase, which was further extracted with CH_2Cl_2 (3 × 200 mL). The combined extract was dried, filtered, and evaporated to a yellow oil that on chromatography (SiO_2, elution with 40% EtOAc/hexanes + 1% Et_3N) provided bicycle **9** (1.04 g, 57%) as a pale yellow oil: $[\alpha]^{25}_D$ −49.3° (*c* 0.036, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.37−1.45 (m, 1H), 1.59−1.63 (m, 1H), 2.29−2.43 (m, 1H), 2.51−2.60 (m, 1H), 3.94 (s, 3H), 5.28 (d, J = 4.5, 1H), 8.60 (d, J = 4.8, 1H), 8.52 (d, J = 5.1, 1H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$), δ 26.8 (2), 27.8 (3), 31.0 (2), 52.4 (3), 61.4 (1), 71.9 (0), 81.8 (0), 115.9 (1), 139.7(0), 140.4 (1), 148.7 (1), 151.7 (0), 155.7 (0), 168.9 (0); MS (+)-FAB $[M + H]^+$ *m*/*z* 305. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 62.8; H, 7.0; N, 8.8.

(1*R*,4*S*)-7-*tert*-Butyloxycarbonyl-7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridine-1-carboxylic Acid (10). To a solution of methyl ester **9** (2.32 g, 7.61 mmol) in dioxane (38.0 mL) was added $LiOH\cdot H_2O$ (958 mg, 22.6 mmol) followed by water (38.0 mL). The reaction mixture was stirred for 12 h, whereupon the pH was adjusted to 6 by the addition of glacial acetic acid (871 μL, 15.2 mmol) followed by pH 4 buffer, evaporated to approximately 40 mL, and extracted with 20% IPA/$CHCl_3$ (15 × 100 mL). The organic extract was dried, filtered, and evaporated. Submission of the crude material to chromatography (SiO_2, gradient elution with 0−20% MeOH−CH_2Cl_2) afforded **9** (2.17 g, 98%) as an off-white solid: $[\alpha]^{25}_D$ −36.3° (*c* 0.029, $CDCl_3$); mp >230 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 1H), 1.68 (ddd, J = 12.7, 8.8, 4.1, 1H), 2.44 (ddd, J = 14.8, 11.3, 3.9, 1H), 2.71 (ddd, J = 14.5, 10.7, 3.6, 1H), 5.36 (d, J = 4.4, 1H), 7.95 (d, J = 5.0, 1H), 8.64 (d, J = 5.4, 1H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6 (2), 27.8 (3), 31.6 (2), 61.4 (1), 72.7 (0), 82.2 (0), 117.5 (1), 137.9 (1), 141.2 (0), 146.5 (1), 155.2 (0), 156.0 (0), 171.0 (0). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.3; N, 9.6. Found: C, 61.9; H, 6.3; N, 9.6.

(1*S*,4*S*)-7-*tert*-Butyloxycarbonyl-7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridine (15). To a solution of carboxylic acid **10** (30.0 mg, 0.103 mmol) in 1/1 CH_2Cl_2/pyridine (2.0 mL) at −15 °C was added $(COCl)_2$ (9.9 μL, 0.114 mmol). The reaction mixture was slowly warmed to 0 °C, at which point the cold bath was removed and stirring was continued for 2.5 h at room temperature. The solution of acid chloride was treated with 2-mercaptopyridine *N*-oxide (14.4 mg, 0.114 mmol) and then stirred for an additional 2 h at room temperature. Evaporation *in vacuo* was followed by trituration of the residue with THF (10 mL), filtration, and addition of *tert*-butylthiol (1 mL). The solution was then immersed in a bath at room temperature and irradiated with two 100 W incandescent lamps for 3 h. Evaporation of the volatiles *in vacuo* was followed by partitioning of the residue between saturated $NaHCO_3$ (10 mL) and EtOAc (25 mL). The aqueous phase was further extracted with EtOAc (2 × 25 mL), and the combined organic phase was dried, filtered, and evaporated. Submission of the crude material to chromatography (SiO_2, elution with 80% EtOAc−hexanes + 1% Et_3N) afforded **15** (14.8 mg, 58%) as a colorless solid: mp 68.8−69.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.37 (m, 2H), 1.39 (s, 9H), 2.14−2.20 (m, 2H), 5.14 (br d, J = 3.0, 1H), 5.20 (br d, J = 3.0, 1H), 7.23 (d, J = 4.8, 1H), 8.45 (d, J = 4.8, 1H), 8.51 (s,

1H); ^{13}C NMR ($CDCl_3$) δ 25.73 (2), 26.4 (2), 28.1 (3), 59.1 (1), 60.6 (1), 80.5 (0), 115.0 (1), 140.1 (1), 140.5 (0), 148.3 (1), 153.4 (0), 155.0 (0). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.3; H, 7.4; N, 11.4. Found: C, 68.2; H, 7.4; N. 11.1.

(1*S*,4*S*)-7-Azabicyclo[2.2.1]heptano[2,3-*c*]pyridine Dihydrochloride (16). To a solution of carbamate **15** (103 mg, 0.418 mmol) in MeOH (3.0 mL) was added dropwise 1 M ethereal HCl (3.0 mL, 3.0 mmol). The homogeneous solution was stirred for 18 h, whereupon it had become heterogeneous. All volatiles were removed *in vacuo*, and the residual solid material was triturated at 60 °C with MeOH (1.0 mL) and MeCN (9.0 mL). The mixture was cooled to room temperature, filtered under a blanket of dry nitrogen, washed with MeCN (10.0 mL), and dried under high vacuum at 55 °C to afford 88 mg (96%) of a white solid: $[\alpha]^{25}_D$ −5.9 (*c* 0.028, (CD_3OD); mp 223.5−224.6 °C; ^{1}H NMR (CD_3OD) δ 1.66−1.85 (2H, m), 2.54−2.62 (m, 2H), 5.66 (d, J = 4.2, 1H), 5.67 (d, J = 3.6, 1H), 8.28 (d, J = 5.7, 1H), 8.98 (d, J = 5.7, 1H), 9.06 (s, 1H); ^{13}C NMR (CD_3OD) δ 23.2 (2), 23.8 (2), 61.3 (1), 62.9 (1), 121.9 (1), 136.5 (1), 140.4 (0), 145.1 (1), 159.6 (0); MS (+)-FAB $[M + H]^+$ *m*/*z* 147 (free base). Anal. Calcd for $C_9H_{10}N_2$·2HCl: C, 49.3; H, 5.5; N, 12.8. Found: C, 49.1; H, 5.7; N, 12.7.

(1*S*,4*S*)-7-Methyl-7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridine Dihydrochloride (17). Dihydrochloride **16** (156 mg, 0.714 mmol) was treated with 0.514 M NaOH (4.7 mL, 2.4 mmol) in MeOH and evaporated to dryness. To the residue was added 37% aqueous HCHO (3.0 mL, 38 mmol) and HCO_2H (2.0 mL, 53 mmol). The resultant mixture was stirred at 95 °C for 18 h, cooled to room temperature, evaporated to dryness, and partitioned between 1 M NaOH (20 mL) and 20% IPA/CH_2Cl_2 (25 mL). The aqueous phase was saturated with solid KCl and then further extracted with 20% IPA/CH_2Cl_2 (5 × 25 mL). The combined extracts were dried, evaporated, and then submitted to flash chromatography (SiO_2, elution with 5% MeOH [saturated with NH_3]/CH_2Cl_2).

The free base was submitted to high vacuum to remove all traces of NH_3, dissolved in EtOH (2.5 mL), and treated dropwise with 1.0 M ethereal HCl (5.0 mL, 5 mmol) while stirring vigorously. The mixture was further diluted with ether (20 mL) and stirred for 18 h. Filtration of the suspension under nitrogen followed by drying at 65 °C under high vacuum afforded 151 mg (90%) of an off-white solid: $[\alpha]^{25}_D$ −4.57° (*c* 0.033, CD_3OD); mp 199.8−200.4 °C; ^{1}H NMR (CD_3OD) 2/1, quaternary diastereomers, δ 1.71−1.88 (m, 2H), 2.66 (s, 2H), 2.68−2.73 (m, 2H), 2.99 (s, 1H), 5.52 (d, J = 3.9, 0.35H) (d, J = 3.6, 0.35H), 5.61 (d, J = 4.2, 0.65H), 5.63 (d, J = 3.9, 0.65H), 8.28 (d, J = 5.7, 0.35H), 8.32 (d, J = 5.7, 0.65), 8.99 (d, J = 5.7, 0.35H), 9.04 (d, J = 6.0, 0.65H), 9.07 (s, 0.35H), 9.08 (s, 0.65); ^{1}H NMR (DMSO-d_6, 98.4 °C) δ 1.46−1.59 (m, 2H), 2.49 (s, 3H), 2.54−2.56 (m, 2H), 5.21 (d, J = 3.9, 1H), 5.25 (d, J = 3.8, 1H), 7.70 (d, J = 5.03, 1H), 8.71 (d, J = 5.0, 1H), 8,76 (s, 1H); ^{13}C NMR (CD_3OD), 2/1, quaternary distereomers, δ 20.9 (2), 21.5 (2), 23.6 (2), 24.2 (2), 34.3 (3), 34.5 (3) 67.4 (1), 68.7 (1), 69.0 (1), 70.2 (1), 122.0 (1), 136.7 (1), 138.1 (1), 138.4 (0), 140.5 (0), 145.2 (1), 145.6 (1), 157.6 (0), 159.5 (0); upon cooling to room temperature, the sample showed an unchanged ambient temperature ^{1}H NMR spectrum. MS (+)-FAB $[M + H]^+$ *m*/*z* 161 (free base). Anal. Calcd for $C_{10}H_{12}N_2$·2HCl: C, 51.5; H, 6.1; N, 12.0. Found: C, 51.2; H, 6.2; N, 11.6.

The free base of **17** has the following spectrum: ^{1}H NMR (CD_3OD) δ 1.23 (m, 2H), 2.03 (br, s, 3H), 2.18 (m, 2H), 4.28 (d, 1H, J = 3.4), 4.33 (d, 1H, J = 2.8), 7.41 (d, 1H, J = 4.8), 8.39 (d, 1H, J = 4.9), 8.44 (s, 1H).

(2*R*,5*S*)-*N*-Ethoxycarbonyl-5-[3-(4-*N*-chloropyridinyl)]-proline Methyl Ester (12). To a solution of pyrrolidine **11** (222 mg, 0.92 mmol) and Et_3N (390 μL, 2.8 mmol) in THF (9.2 mL) at 0 °C was added $ClCO_2Et$ (93 μL, 0.97 mmol), leading to the formation of a white precipitate. The reaction mixture was warmed to room temperature over 3 h, at which point all volatiles were evaporated and the residue was partitioned between EtOAc (30 mL) and $NaHCO_3$ (30 mL). The aqueous phase was further extracted with EtOAc (2 × 30 mL), and the combined organic phase was dried, filtered, and evaporated. Chromatography (SiO_2, elution with 40%, EtOAc/hexanes + 1% Et_3N) of the crude material afforded the ethyl carbamate **12** (273 mg, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$), 1:1 rotamers, δ 1.00 (t, J = 7.5, 1.5H), 1.23 (t, J = 7.5, 1.5H), 1.89−1.99 (m, 1H), 2.02−2.14 (m, 1H), 2.24−2.36 (m, 1H), 2.42−2.56 (m, 1H), 3.83 (s, 3H), 3.96−4.22 (m, 2H), 4.46−4.58 (m, 1H), 5.24−5.37 (m, 1H), 7.28 (d, J = 5.4, 1H), 8.42 (br d, J = 4.8, 1H), 9.13 (s, 0.5H), 9.17 (s, 0.5H); ^{13}C NMR ($CDCl_3$) δ 14.2 (3), 14.4 (3), 28.3 (2), 29.0 (2), 32.1 (2), 33.1 (2), 52.4 (3), 58.0 (1), 58.5 (1), 60.5 (1), 60.7 (1), 61.7 (2), 61.8 (2), 123.8 (1), 124.1 (1), 315.5 (0), 136.1 (0), 141.5 (0), 141.8 (0), 184.9 (1), 149.0 (1), 149.3 (1), 149.7 (1), 145.5 (0), 155.0 (0), 172.6 (0), 172.7 (0). Anal. Calcd for $C_{14}H_{17}ClN_2O_4$: C, 53.8; H, 5.5; N, 9.0. Found: C, 53.4; H, 5.6; N, 8.7.

(2*R*,5*S*)-*N*-Ethoxycarbonyl-5-[3-(4-*N*-iodopyridinyl)]-proline Methyl Ester (13). To a mixture of chloropyridine **12** (1.06 g, 3.39 mmol) and NaI (10.16 g, 67.8 mmol) in anhydrous MeCN (34 mL) at room temperature was added consecutively $ClCO_2Et$ (3.24 mL, 33.9 mmol) and AcCl (241 μL, 3.39 mmol). The rust-colored mixture was sonicated for 12 h, during which time the bath temperature had reached 39 °C. The yellow reaction mixture was then cooled to 0 °C and, with magnetic stirring, was treated consecutively with concentrated NH_4OH (3.0 mL, 44.1 mmol) and 1 M pH 8 phosphate buffer (50 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phase was partitioned with 2 M $Na_2S_2O_3$ (100 mL), the aqueous phase was extracted with CH_2Cl_2 (60 mL), and the combined extract was dried, filtered, and evaporated. Chromatography (SiO_2, gradient elution, 40−60% EtOAc−hexanes + 1% Et_3N) afforded the iodopyridine **13** (1.26 g, 93%) as a light tan oil: ^{1}H NMR ($CDCl_3$) 1/1 rotamers, δ 0.99 (t, J = 6.9, 1.5H), 1.22 (t, J = 6.9, 1.5H), 1.83−1.95 (m, 1H), 2.05−2.16 (m, 1H), 2.23−2.36 (m, 1H), 2.43−2.57 (m, 1H), 3.84 (s, 3H), 3.99 (q, J = 7.0, 1.0H), 4.12 (q, J = 7.0, 1.0H), 4.46−4.57 (m, 1H), 5.01−5.13 (m, 1H), 7.74 (d, J = 5.1, 1H), 8.08 (br d, J = 4.8, 1H), 9.01 (s, 0.5H), 9.05 (s, 0.5H); ^{13}C NMR ($CDCl_3$) δ 14.1 (3), 14.4 (3), 28.1 (2), 32.4 (2), 33.4 (2), 52.3 (3), 60.8 (1), 60.9 (1),61.6 (2), 61.7 (2), 64.9 (1), 65.2 (1), 108.7 (0), 108.9 (0), 133.8 (0), 134.0 (0), 140.1 (1), 140.8 (0), 148.1 (1), 148.2 (1), 148.3 (1), 148.6 (1), 154.4 (0), 154.9 (0), 172.5 (0), 172.6 (0). Anal. Calcd for $C_{14}H_{17}IN_2O_4$: C, 41.6; H, 4.2; N, 6.9. Found: C, 41.8; H, 4.3; N, 6.8.

(1*R*,4*S*)-7-*N*-Ethoxycarbonyl-1-methoxycarbonyl-7-azabicyclo[2.2.1]heptano[2,3-*c*]pyridine (20). To a solution of *cis*-2,6-dimethylpiperidine (687 μL, 5.1 mmol) in THF (7.06 mL) at −20 °C was added *n*-BuLi (2.22 M in hexanes, 2.25 mL, 5.0 mmol). The LiDMP solution was stirred an additional 1 h at −20 °C, and then an aliquot (3.30 mL, 1.65 mmol) was added over 13 min to a solution of iodopyridine **13** (303 mg, 0.750 mmol) in THF (24.3 mL) at −72 °C. The pale reddish orange reaction mixture was stirred an additional 2 h at −72 °C, and was then warmed to −20 °C at a rate of 0.7 °C/min. The reaction was quenched with MeOH (0.5 mL) followed by 1 M pH 8 buffer (10 mL) and then partitioned between CH_2Cl_2 (75 mL) and 1 M $Na_2S_2O_3$ (10 mL), further extracting the aqueous phase with CH_2Cl_2 (3 × 50 mL). The combined extract was dried, filtered, and evaporated to a brown oil, which was chromatographed (SiO_2, elution with 60% EtOAc/hexanes + 1% Et_3N) to provide bicycle **20** (65 mg, 31%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.1, 3H), 1.42 (ddd, J = 12.6, 9.0, 3.7, 1H), 1.62 (ddd, J = 12.8, 8.9, 3.9, 1H), 2.34−2.45 (m, 1H), 2.58 (ddd, J = 14.2, 10.6, 3.6, 1H), 3.81 (s, 3H), 4.02 (q, J = 7.1, 2H), 5.35 (d, J = 4.5, 1H), 7.63 (d, J = 5.1, 1H), 8.53 (d, J = 5.1, 1H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (3), 27.0 (2), 31.1 (2), 52.5 (1), 61.1 (1), 62.1 (2), 71.7 (0), 116.1 (1), 139.5 (0), 140.4 (1), 148.8 (1), 151.5 (0), 156.4 (0), 168.6 (0); MS (+)-FAB $[M + H]^+$ *m*/*z* 277. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.9; H, 5.8; N, 10.1. Found: C, 60.6; H, 6.0; N. 10.0.

(2*R*,5*S*)-*N*-Ethoxycarbonyl-5-[3-(oxabicyclo[2.2.1]-hepteno[4N,5N-*c*]pyridinyl)]proline Methyl Ester (21). To a solution of iodopyridine **13** (343 mg, 0.848 mmol) in THF (25 mL) at −73 °C was added over 15 min 0.50 M LiDMP (3.56 mL, 1.78 mmol) in THF. The resultant orange red solution was stirred 3 h at −72 °C and then treated with freshly distilled furan (2.05 mL, 28.2 mmol). The reaction mixture was

warmed to 14 °C over 18 h, treated with MeOH (2 mL), and partitioned between pH 8 buffer (25 mL) and CH_2Cl_2 (75 mL). The aqueous phase was further extracted with CH_2Cl_2 (3 × 75 mL), dried over Na_2SO_4, and then concentrated to a viscous orange-brown oil. The highly labile oxabicyclopyridine **21** was not isolated, but instead submitted to (+)-ES MS (capillary, 4.16 kV; HV lens, 0.57 kV; cone, 76 V) on a VG Quattro triple quadrupole Instrument. The following molecular ions were detected: $[M + H]^+$ for **21** *m*/*z* 345.1 (8% of base peak); $[M + H]^+$ for **20** *m*/*z* 277.2 (36% of base peak); $[M + H]^+$ for **13** *m*/*z* 405.1 (20% of base peak).

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Supporting Information Available: Detailed experimental procedures for the conversion of D-glutamic acid to (2*S*,5*R*)-*N*-(*tert*-butyloxycarbonyl)-5-[3-(4′-chloropyridinyl)]proline methyl ester (**8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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