Enantiospecific Synthesis of Annulated Nicotine Analogues from D- and L-Glutamic Acid. Pyridotropanes

Sean C. Turner, Hongbin Zhai, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received October 14, 1999

The conformationally restricted nicotinoid 1-methyl-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine, pyrido-[3,4-*b*]tropane, has been prepared enantiospecifically from both D- and L-glutamic acid. The method involved coupling of pyroglutamic acid derivatives with *ortho*-lithiated 4-chloropyridine, followed by intramolecular imine formation and reduction to generate the D- and L-5-substituted proline esters. Chloro-iodo exchange and side chain extension gave the precursor for the [3.2.1] system. Construction of the 8-azabicyclo[3.2.1]octano-[2,3-*c*]pyridine framework was achieved by an intramolecular Heck reaction. Subsequent ozonolysis gave the ketone which was reduced to the carbinol or methylene, yielding the fused nicotine analogues.

Introduction

The alkaloid (−)-nicotine (**1**, Figure 1), present in tobacco at varying levels of 0.2−5%, activates nicotinic acetylcholine receptors (nAChR)[1] that are located at neuromuscular junctions and at cholinergic synapses of the central nervous system. Much of the interest in the medicinal chemistry of nAChRs stems from evidence following nicotine administration to humans, of the beneficial effects that have been observed with cognitive and attention deficits,[2] neuroprotection,[3] and Alzheimers disease.[4] Thus there is considerable current interest in the pharmacological effects of nicotinic analogues.[5]

We have recently reported[6] the synthesis of conformationally restricted analogues such as **2** which possess a pendant pyridine moiety. Fusing the pyridine ring as part of a tricyclic skeleton would further enhance the conformational restriction, and several related racemic examples have been reported.[7]

Our objective was to develop a synthetic route to the enantiomerically pure pyrido[3,4-*b*]tropane nicotine analogue **3** (Figure 1). Two routes were considered for the key cyclization step to construct the [3.2.1] bicyclic skeleton shown in Figure 2. The first route would employ an intramolecular cyclization via S_N2 displacement of halide by an enolate, **D** to **E**. In the second route, an intramolecular Heck cyclization would be conducted between an alkene and a 4-halopyridyl group, **B** to **C**. A particular challenge anticipated throughout was the difficulty of retaining the labile 4-halopyridyl group during the synthetic sequence.

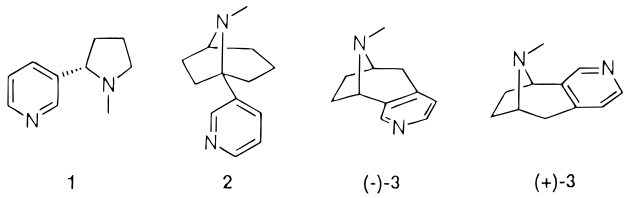


Figure 1.

Results and Discussion

Earlier work had demonstrated that a pyridyl moiety could be introduced at the γ-position of glutamic acid by addition of 3-pyridyllithium to *tert*-butyl-*N*-*tert*-butyloxycarbonylpyroglutamic acid **4a**,[6] specifically at the γ-carbonyl group. The lactam **4a** itself is readily prepared from D- or L-glutamic acid. To introduce the subsequently required activation at the 4-position of pyridine, a 4-halo group was selected. Although this functionality has not found widespread synthetic use, nucleophilic enolate displacement of the chloro group from 4-chloropyridine has been reported.[8] Also, it has been demonstrated that *ortho*-lithiation of 4-halopyridines using LDA occurs with high regioselectivity,[9] leading to the selection of 4-chloropyridine for these dual functions. Higher metalation yields are observed when Et_2O rather than THF is employed as the solvent.[10] The addition, therefore, was conducted using 3-lithio-4-chloropyridine generated regioselectively by *ortho*-lithiation of 4-chloropyridine using LDA in Et_2O at −78 °C (Scheme 1).

(1) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41.

(2) (a) Brioni, J. D.; Decker, M. W.; Sullivan, J. P.; Arneric, S. P. *Adv. Pharmacol.* **1997**, *37*, 1153. (b) Perry, E. K.; Morris, C. M.; Court, J. A.; Cheng, A.; Fairbairn, A. F.; McKeith, I. G.; Irving, D.; Brown, A.; Perry, R. H. *Neuroscience* **1995**, *64*, 385.

(3) Akaike, A.; Tamura, Y.; Yokota, T.; Shimohama, S.; Kimura, J. *Brain Res.* **1994**, *644*, 181.

(4) Decker, M. W.; Brioni, J. D. Neuronal Nicotinic Receptors: Potential Treatment of Alz-heimer's Disease with Novel Cholinergic Channel Modulators. In *Pharmacological Treatment of Alzheimer's Disease: Molecular and Neurobiological Foundations*; Brioni, J. D., Decker, M. W., Eds.; Wiley-Liss: New York, 1997; p 433.

(5) Holladay, M. W.; Cosford, N. D. P.; McDonald, I. A. Natural Products as a Source of Nicotinic Acetylcholine Receptor Modulators and Leads for Drug Discovery. In *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*; Arneric, S. P., Brioni, J. D., Eds.; Wiley-Liss: New York, 1999; Chapter 14.

(6) Xu, Y.-z.; Choi, J.; Calaza, M. I., Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069.

(7) (a) Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125. (b) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492. (c) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506. (d) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381.

(8) Smith, F. X.; Evans, G. G. *J. Heterocycl. Chem.* ***1976***, *13*, 1025.

(9) (a) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151. (b) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.

(10) Marsais, F.; Trécourt, F.; Bréant, P.; Quéguiner, G. *J. Heterocycl. Chem.* **1988**, *25*, 81.

10.1021/jo991609p CCC: $19.00
Published on Web 01/14/2000

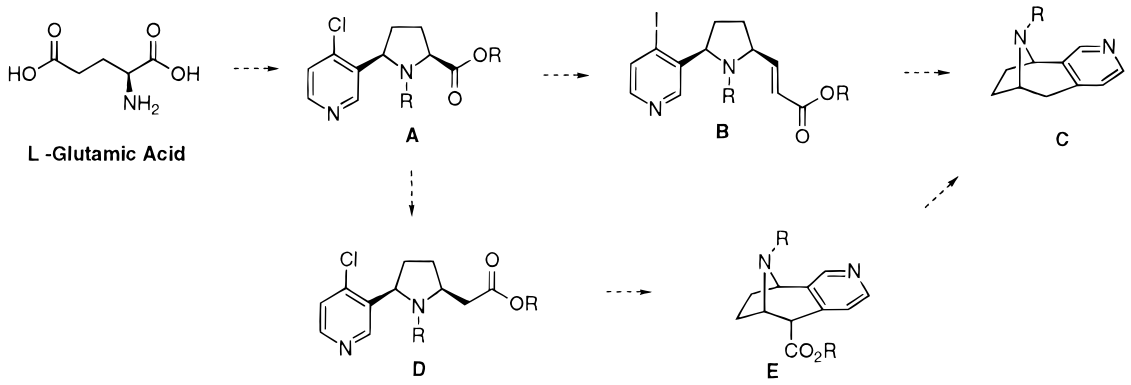
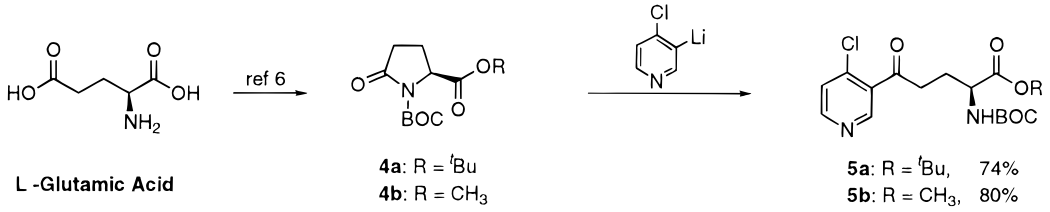
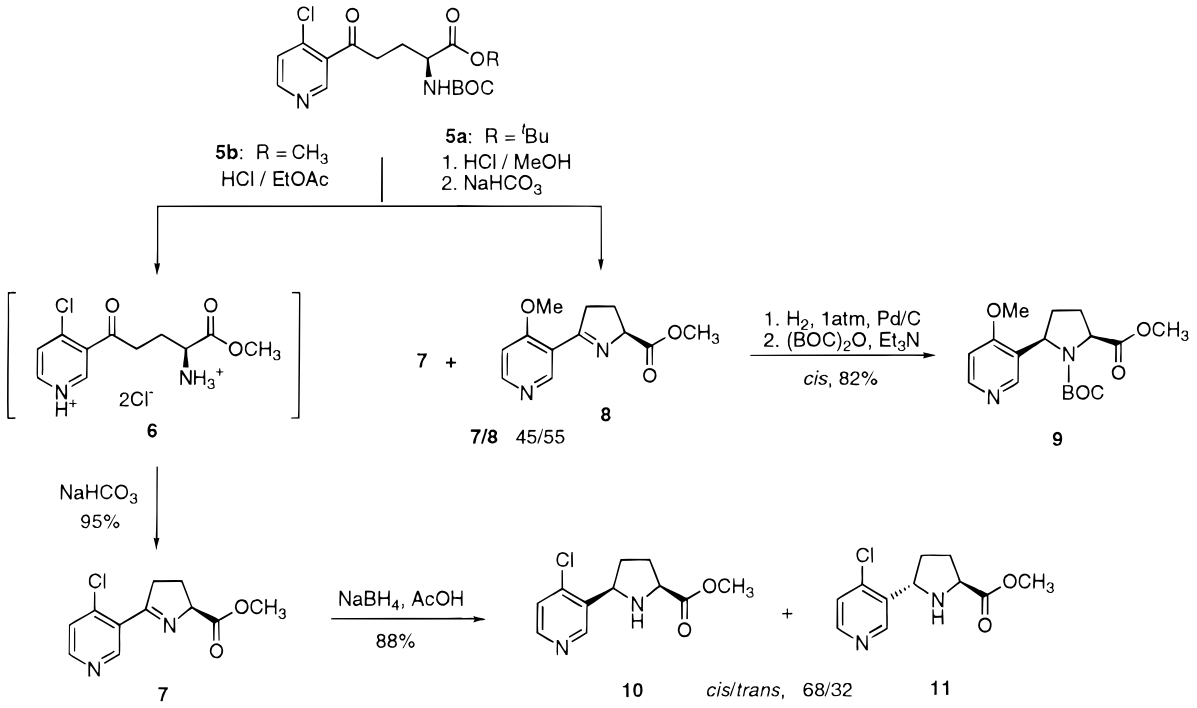


Figure 2. Proposed syntheses of the pyrido[3,4-*b*]tropane nicotine analogues.

Scheme 1. Synthesis of 4-Chloropyridinyl Ketones



Scheme 2. Synthesis of 5-Substituted Proline Derivatives



A range of different reaction temperatures and stoichiometries was examined. It was observed that when the reaction was allowed to reach rt overnight, the initial orange color changed to black and an intractable tar was obtained (possibly due to polymerization of the 4-chloropyridyl moiety). Favorable conditions were found giving a 74% yield of the pyridyl ketone **5a** using 150 mol % of *ortho*-lithiated 4-chloropyridine at −78 °C for 14 h.

An attempt to selectively remove the *N*-BOC protecting group, using 1 M HCl in EtOAc, failed due to partial removal of the *tert*-butyl ester.[11] Therefore, the simultaneous removal of both the *tert*-butyl ester and *N*-Boc protecting groups was affected with MeOH saturated with HCl. Subsequent treatment with aqueous $NaHCO_3$ caused intramolecular cyclization to the imine.[12] However, the product was found to be a mixture (45/55) of imines **7** and **8**, respectively (Scheme 2). The facility of formation of 4-methoxypyridyl imine **8** probably results from nucleophilic displacement of Cl by MeOH under the acid hydrolysis conditions, since protonation of the pyridyl nitrogen activates the 4-position toward nucleophilic attack.

To confirm the structure of **8**, which was highly polar

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

(12) Berrée, F.; Chang, K.; Cobas, A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 715.

and difficult to purify, the imine was reduced using catalytic hydrogenation (H_2, 10% Pd/C) and the resulting amine protected as its *N*-BOC derivative to give the crystalline *cis*-pyrrolidine derivative **9**, in which the 4-chloro had been replaced by methoxy. An attempt to reduce the proportion of unwanted 4-alkoxy ether by employing EtOH as the solvent failed to significantly change the ratio of products. Complete removal of both protecting groups in **5a** with 4 M aqueous HCl was successful; however, conditions for isolating the free imino acid (resulting from subsequent base-catalyzed ring closure) were not found.

The problem of the lack of orthogonality with respect to the *N*-BOC and *tert*-butyl ester was avoided by replacing the *tert*-butyl with a methyl ester in the initial organometallic addition. The methyl ester is readily prepared from pyroglutamic acid in 93% yield by reaction with thionyl chloride in MeOH, and subsequent conversion to the *N*-BOC derivative gives the protected pyroglutamate **4b** (Scheme 1). Using *ortho*-lithiated 4-chloropyridine (110 mol %), the ketone **5b** was obtained as the sole product in 80% yield. This product is unstable (polymerizing overnight at room temperature) and was used with minimal delay in the next step.

The ketone **5b** was treated with TFA in CH_2Cl_2 to remove the *N*-BOC group. After basic workup ($NaHCO_3$) the product, isolated in 95% yield, was found to be a mixture of 55% 4-chloro and 45% 4-trifluoroacetoxy products. However, when 1 M HCl in EtOAc[12] was used, *N*-BOC deprotection occurred in essentially quantitative yield to give the amine hydrochloride **6**. Isolation after treatment with $NaHCO_3$ gave the imine **7** in an overall yield of 95% (Scheme 2).

Our initial intention was to employ catalytic hydrogenation to reduce the imine functionality to give specifically the desired *cis*-proline. However, there was a question of selectivity between reduction of the imine and hydrogenolysis of the 4-chloropyridyl group. All attempts using Pd/C, $Pd(OH)_2$/C or $Pd/BaSO_4$ either gave no reaction or resulted in concomitant reduction of imine and dechlorination. Hydrogenation over PtO_2 resulted in a mixture of the desired *cis*-amine **10** together with dechlorinated amine.

We then turned our attention to chemical reduction procedures. DIBAL-H and L-Selectride reduced the ester functionality without reduction of the imine; 9-BBN gave no reaction, and $NaCNBH_3$ in AcOH[13] gave the amines **10/11** in a 58/42 ratio. Much of the product was isolated as a relatively nonpolar boron complex that was best cleaved by treatment with diethanolamine. An effective procedure involves heating the complex in EtOAc with diethanolamine as a biphasic mixture (60 °C, 14 h), followed by an aqueous wash to remove the diethanolamine−boron complex. A superior method employed $NaBH_4$ in AcOH/MeOH (1/4) at −40 °C[14] which successfully reduced imine **7** in 88% yield to a mixture of diastereomers **10** and **11** in a ratio of 68/32, respectively. Identical results were obtained when $NaBH(OAc)_3$[15] (thought to be the active reducing agent generated in situ from $NaBH_4$ in AcOH/MeOH) was used.

The resultant diastereomers were extremely difficult to separate by chromatography; however, treatment of the mixture with $ClCO_2Et$ and Et_3N gave the *cis*- and *trans*-carbamates which were separable by column chromatography. Alternatively, reaction of the amines with acetic anhydride and Et_3N gave the crystalline *cis*- and *trans*-*N*-acetyl derivatives **12** and **13** which were separable by either chromatography or recrystallization. Fortuitously, a more convenient separation resulted from treatment of the mixture with $(BOC)_2O$ and Et_3N which gave exclusively *N*-protection of the major diastereomer **14**. Facile separation by column chromatography then afforded a 60% yield of **14** and 32% recovery of the unreacted minor diastereomer *trans*-amine **11**. The recovered *trans*-amine can also be readily converted to its *N*-BOC derivative using $(BOC)_2O$ when the solvent is changed from THF to CH_3CN. A similar solvent-controlled *cis*−*trans* selectivity has been reported for 2,5-dialkylpyrrolidines.[16]

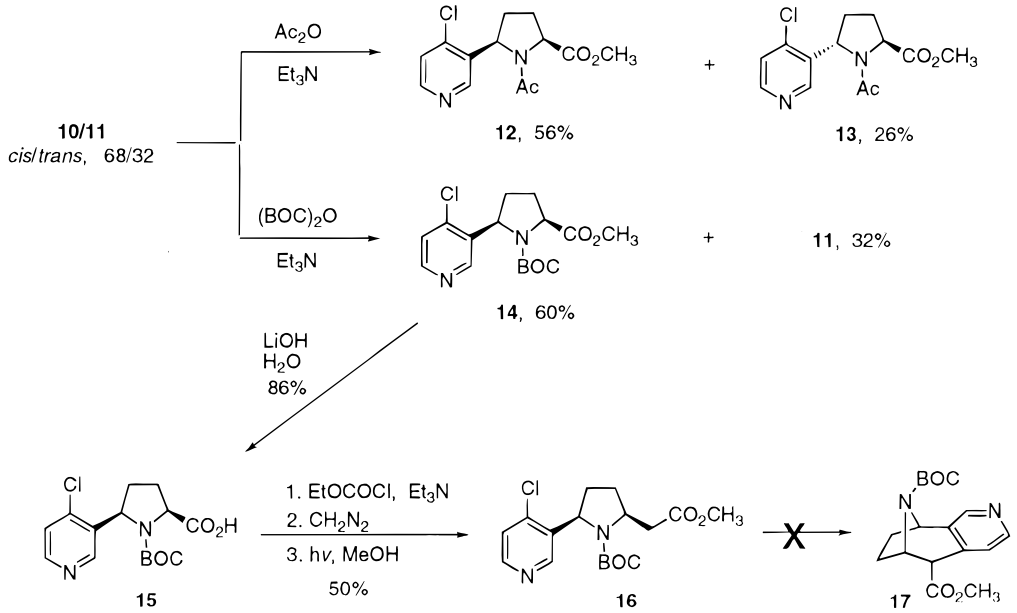
Following from our earlier work[6] we used the Arndt−Eistert method for 1-carbon homologation of the glutamate-derived α-carboxyl group. Accordingly the ester **14** was hydrolyzed to acid **15** by treatment with LiOH (Scheme 3). Acid **15** was reacted with ethyl chloroformate and Et_3N to form the mixed anhydride which was treated in situ with CH_2N_2 to give an essentially quantitative yield of the diazoketone. Although the anticipated Wolff rearrangement[17] to the homologated ester did take place upon treatment with Ag_2O or $PhCO_2Ag$, there was simultaneous removal of the chloro group. Irradiation (UV) of the diazoketone in MeOH for 36 h gave the homologated ester **16**; however, attempted intramolecular cyclization to tricycle **17** was unsuccessful. Only starting material and polymerization products were observed upon treatment with LDA or KHMDS in THF, which may be due to competition between the two possible sites of anion formation, α to the ester and α to the pyridine.[6]

We then turned to the second proposed approach. In this route, the *N*-bridged bicyclic targets were to be constructed by a Heck coupling reaction that typically takes place between an alkene and an aryl bromide or iodide. Considering the poor reactivity of the chloro substituent, it would be necessary to introduce either a 4-bromo- or 4-iodopyridyl functionality, more amenable to Pd-insertion in order to employ this methodology. Given the reported instability of *ortho*-lithiated 4-bromo- or 4-iodopyridine,[18] and their enhanced reactivity throughout the synthetic sequence, these substituents would need to be introduced at a late stage by exchange of the 4-chloro group. In addition to finding suitable conditions, an important question would be at which point in the synthesis to carry out the exchange reaction.

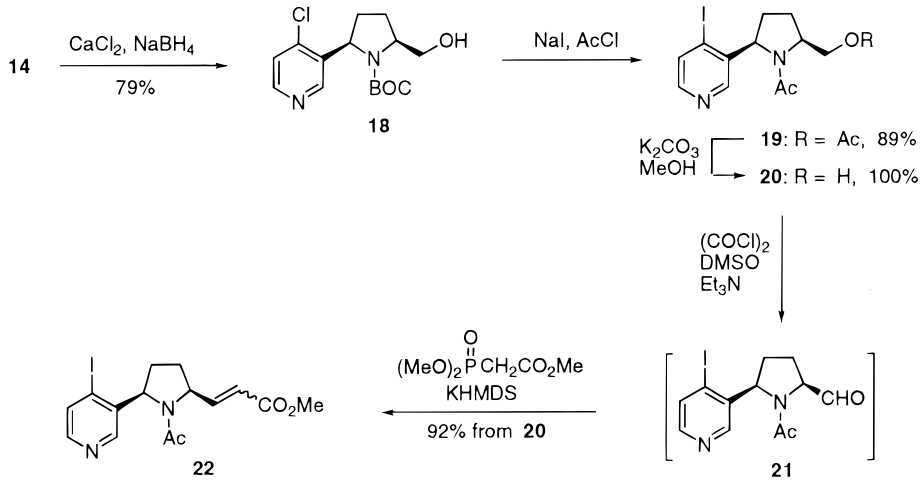
Using the key intermediate pyrrolidine **14**, a variety of methods were examined for exchange of iodo for the chloro substituent.[19] Quaternization in situ of the pyridine nitrogen with TMSI, $ClCO_2Et$, AcCl, and Ac_2O were compared using NaI or Bu_4NI as sources of iodide. Optimum conditions were found to be treatment with NaI and AcCl in CH_3CN (55 °C). Also, the 4-iodo group can be introduced earlier in the synthesis at the imine stage;

(13) Lane, C. F. *Synthesis* **1975**, 135.
(14) Bacos, D.; Celerier, J. P.; Marx, E.; Saliou, C.; Lhommet, G. *Tetrahedron Lett.* **1989**, *30*, 1081.
(15) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.
(16) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1988**, *53*, 5729.
(17) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(18) (a) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. (b) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.
(19) Corcoran, R. C.; Bang, S. H. *Tetrahedron Lett.* **1990**, *31*, 6757.

Scheme 3. Attempted Synthesis of Pyrido[3,4-*b*]tropane Analogue by Intramolecular Enolate Cyclization



Scheme 4. Synthesis of 1-Acetyl-2-(2-methoxycarbonylethenyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine



however, subsequent reduction of either the imine or the ester functionalities is not possible without simultaneous deiodination.

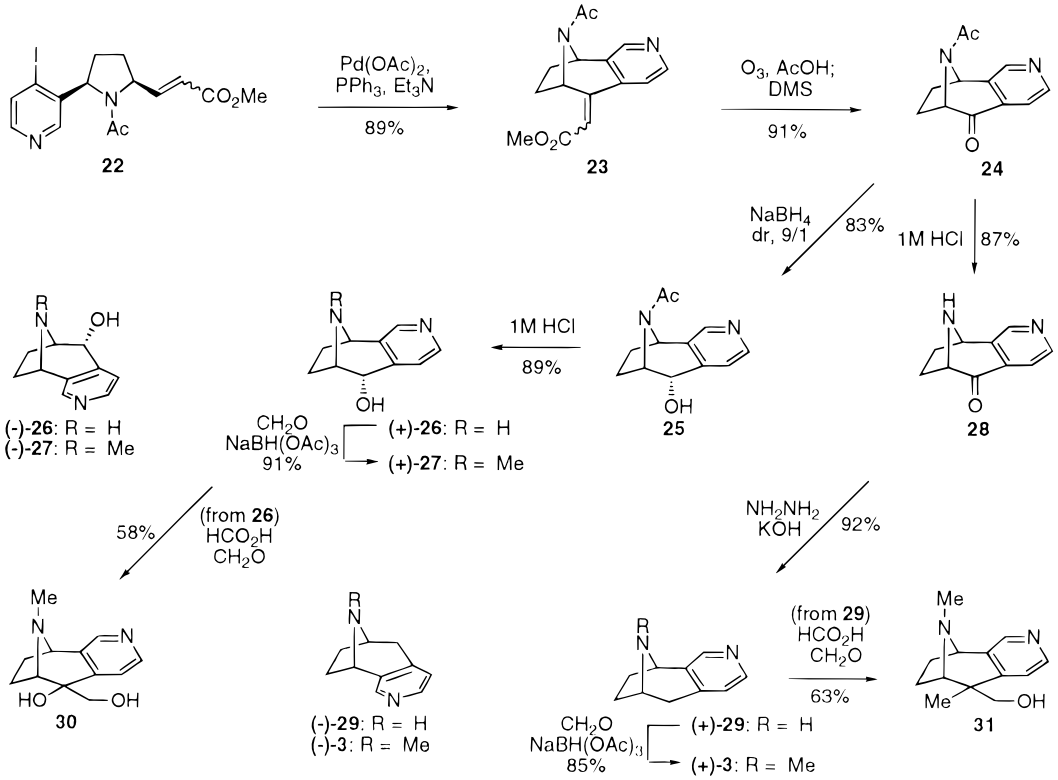
To avoid the problem of dehalogenation during reduction, the iodo group was introduced following reduction of the ester to alcohol. Mild reduction of the methyl ester of **14** using $Ca(BH_4)_2$ in THF/EtOH (4/1) gave the alcohol **18** in 68% yield (Scheme 4) by direct crystallization. An additional 11% of product can be obtained by the previously described technique of heating the crude alcohol with diethanolamine to liberate boron-complexed material. Application of the above conditions resulted in concomitant 4-chloro to 4-iodo exchange, *N*-BOC removal, and acetylation of the alcohol and amine functionalities to give **19** in 89% yield. Quantitative deacetylation to the alcohol **20** with K_2CO_3/MeOH[20] was followed by oxidation to aldehyde **21** using Moffatt−Swern oxidation. The aldehyde was used in situ to avoid compromising the stereochemical integrity at the α-position. Treatment with potassium trimethyl phosphonoacetate provided the olefin **22** in high yield as a mixture of *E* and *Z* isomers. A comparison reaction using (methoxycarbonylmethyl)-triphenylphosphonium bromide/Et_3N gave a similar yield, but the triphenylphosphine oxide generated proved difficult to separate from the product.

The alkene **22** was treated with $Pd(OAc)_2$ and Ph_3P in the presence of Et_3N for 5 h at 110 °C (Scheme 5). Intramolecular Heck coupling occurred giving cyclization to the [3.2.1] homotropane analogue **23** in 89% yield (Scheme 5). This proved to be a mixture of *E*/*Z* isomers in a 4/1 ratio. The alkene was oxidatively cleaved by treatment with ozone in the presence of AcOH. It was found that these conditions minimized the extent of pyridine *N*-oxide formation that occurs to around 10−20% under neutral conditions. Cleavage of the ozonide with Me_2S gave the ketone **24** in 91% yield. This ketone represents a key intermediate from which a wide variety of analogues may be derived.

Reduction of ketone of **24** with $NaBH_4$ in MeOH gave the alcohol **25** (83%) with high diastereoselectivity (>9:1). The *N*-acetyl group was removed by heating with 1 M HCl, giving the hydrochloride salt, and treatment with base and extraction gave the free amino alcohol **26**. The major isomer of this amino alcohol **26** is assigned

(20) Plattner, J. J.; Gless, R. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 8613.

Scheme 5. Synthesis of the (+) and (−) Pyrido[3,4-*b*]tropane Nicotine Analogues



the α-configuration for the hydroxyl group on the basis of the coupling patterns of the protons at C-4 (doublet) and C-5 (triplet). Thus the bridgehead proton at C-5 (triplet) is coupled with the *β*-protons at C-6 and C-4, indicating 4*R* stereochemistry.

Conversion of secondary amine **26** to the *N*-methyl analogue **27** was anticipated to be routine on treatment with formaldahyde and formic acid.[6] Surprisingly, the major product was the 4-hydroxymethyl *N*-methylated compound **30**. Additional reaction of formaldehyde at C-4 undoubtedly results from the enhanced acidity of the hydrogen at this position due to the pyridinium species generated in the acidic medium. A successful and simple method for *N*-methylation to **27** then was found in the reductive alkylation with formaldehyde and NaBH $(OAc)_3$.[21] These *N*-H and *N*-Me alcohols are in themselves interesting constrained nicotine analogues for prospective pharmacological evaluation. Tropanol derivatives bearing a hydroxy substituent at the same position are known to exhibit potent anticholinergic activity.[22]

Attempts were made to reduce the *N*-acetyl ketone **24** directly to the methylene derivative. Reaction with $LiAlH_4$ and $AlCl_3$ led to a complex mixture. Application of the Wolff−Kishner conditions (NH_2NH_2, triethylene glycol, 200 °C) led to some of the desired product together with products resulting from loss of the acetyl group. To eliminate this complication, the ketone was deacetylated with HCl to the free base **28** in high yield. Wolff−Kishner reaction now occurred cleanly to give the nornicotine analogue **29**. As previously attempted, *N*-methylation with formaldehyde and formic acid unexpectedly led to **31**, presumably via hydroxymethylation, dehydration, reduction, and a second hydroxymethylation at C-4. Alternatively, reductive alkylation with formaldehyde and $NaBH(OAc)_3$ gave nicotine analogue **3** in high yield.

Conclusions

We have developed an enantiospecific synthetic route to conformationally restricted annulated analogues of natural (−)-nicotine and unnatural (+)-nicotine from D- and L-glutamic acid, respectively. The route proceeds by preparing a *cis*-2,5-disubstituted pyrrolidine via regioselective addition of *ortho*-lithiated 4-chloropyridine to a pyroglutamate derivative. The 8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine framework is constructed by an intramolecular Heck cyclization. The functional versatility of key intermediates such as the *cis*-5-pyridinylproline ester **5** and the ketone, pyrido-homotropane **24**, should allow access to other nicotine analogues.

Experimental Section

Methods and Materials. Melting points were determined on an open capillary apparatus and are uncorrected. Column chromatography was performed using 230−400 mesh silica gel, and TLC analyses were performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (MCN Reagents), visualized with UV light (254 nm), followed by heating with ethanolic phosphomolybdic acid. ^{1}H- and ^{13}C-NMR spectra were recorded on an AM-400 (300 and 75 MHz) or AM-500 (500 and 125 MHz) instrument. These spectra were recorded, unless otherwise stated, in $CDCl_3$−tetramethylsilane (δ 0.0 for ^{1}H), $CDCl_3$ (δ 77.0 for ^{13}C), and CD_3OD (δ 49.0 for ^{13}C) as internal references. All chemical shifts were reported in δ ppm, and *J* values are in hertz. DEPT experiments were carried out with ^{13}C NMR acquisition, and the carbon multiplicities were listed as (0) quaternary, (1) methine, (2) methylene, and (3) methyl. THF and Et_2O were distilled from Na−benzophenone ketyl under

(21) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(22) Atkinson, E. R.; McRitchie, D. D.; Shoer, L. F.; Harris, L. S.; Archer, S.; Aceto, M. D.; Pearl, J.; Luduena, F. P. *J. Med. Chem.* **1977**, *20*, 1612.

nitrogen; Et_3N, DMF, CH_3CN, and CH_2Cl_2 were distilled from CaH_2 under argon; and MeOH was distilled from Mg. Acetyl chloride was distilled prior to use. Organic phases from liquid−liquid distributions were dried over Na_2SO_4. Elemental analyses and mass spectra were conducted by the Analytical Laboratory at the University of California at Berkeley.

***tert*-Butyl (2*S*)-2-(*N*-(*tert*-Butyloxycarbonyl)amino)-5-[3-(4-chloropyridinyl)]-5-oxopentanoate (5a).** A solution of LDA was prepared by the addition with stirring of *n*-BuLi (1.6 M solution in hexane, 42.6 mL, 68.1 mmol) to diisopropylamine (7.26 g, 71.7 mmol) in Et_2O (80 mL) at −78 °C over 5 min. The resulting pale yellow solution was stirred at −78 °C for 15 min. A solution of 4-chloropyridine in Et_2O was prepared by adding portionwise 4-chloropyridinium hydrochloride (11.4 g, 75.6 mmol) to a mixture of Et_2O (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). Care must be taken as vigorous effervescence takes place. The organic layer was separated, the aqueous layer was washed with Et_2O (10 mL), the combined extract was dried and added dropwise over 10 min to the LDA solution, and the resulting yellow slurry was stirred for 1 h, maintaining the internal temperature below −65 °C throughout to avoid pyridyne formation, which is characterized by the appearance of dark brown deposits. A solution of lactam **4a** (14.4 g, 50.4 mmol)[6] in Et_2O (15 mL) was then added over 5 min, and the resulting mixture was stirred at −78 °C for 14 h after which pH 7 phosphate buffer (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), the combined organic layer was dried and filtered, and the filtrate was evaporated. Chromatography (SiO_2, hexane/EtOAc, 9/1−2/3) of the residue afforded ketone **5a** (14.8 g, 74%) as a colorless oil. The product is susceptible to rapid polymerization and should be used either as the crude or rapidly after purification: $[\alpha]^{21}_D$ +12.2° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 1.41 and 1.47 (s, 18H), 1.95−2.05 (m, 1H), 2.20−2.33 (m, 1H), 2.97−3.15 (m, 2H), 4.25 (m, 1H), 5.11 (d, J = 8.1, 1H), 7.36 (d, J = 5.4, 1H), 8.55 (d, J = 5.4, 1H), 8.74 (s, 1H); ^{13}C NMR δ 27.4 (2), 28.2 (3), 28.5 (3), 39.4 (2), 53.5 (1), 80.1 (0), 82.5 (0), 125.6 (1), 134.5 (0), 141.5 (0), 150.4 (1), 152.4 (1), 155.8 (0), 171.6 (0), 199.8 (0).

Methyl (2*S*)-2-(*N*-(*tert*-butyloxycarbonyl)amino)-5-[3-(4-chloropyridinyl)]-5-oxopentanoate (5b) was prepared as described for **5a**, using 110 mol % of the 3-lithio-4-chloropyridine and pyroglutamate **4b** (9.00 g, 37.0 mmol). Ketone **5b** was obtained as a pale yellow oil (10.6 g, 80%). The crude product was used directly in the next reaction: ^{1}H NMR δ 1.39 (s, 9H), 1.97−2.07 (m, 1H), 2.25−2.38 (m, 1H), 2.97−3.17 (m, 2H), 3.74 (s, 3H), 4.37 (m, 1H), 5.13 (br s, 1H), 7.36 (d, J = 5.4, 1H), 8.55 (d, J = 5.4, 1H), 8.72 (s, 1H). HRMS (EI): calcd for $C_{16}H_{21}ClN_2O_5$ (M^+) 356.1121. Found 356.1217.

Methyl (2*R*)-2-(*N*-(*tert*-butyloxycarbonyl)amino)-5-[3-(4-chloropyridinyl)]-5-oxopentanoate ((2*R*)-5b), structure not shown, was prepared from the enantiomeric substrate in the same manner; ^{1}H NMR δ and chromatographic properties identical with (2*S*)**-5b**: $[\alpha]^{23}_D$ −12.0 (*c* 1.56, $CHCl_3$); ^{13}C NMR, (400 MHz) δ 26.82, 28.17, 38.96, 52.42, 52.60, 80.02, 125.27, 134.11, 141.19, 150.10, 152.14, 155.37, 172.60, 199.27. Anal. Calcd for $C_{16}H_{21}ClN_2O_5$: C, 53.9; H, 5.9; N, 7.9. Found: C, 53.8; H, 6.2; N, 8.1.

Methyl (2*S*)-2-Amino-5-[3-(4-chloropyridinyl)]-5-oxopentanoate Hydrochloride (6) and (2*S*)-2-[3-(4′-Chloropyridinyl)]-5-(methoxycarbonyl)-1-pyrroline (7). Ketone **5b** (2.75 g, 6.89 mmol) was dissolved in EtOAc (50 mL) [presaturated with HCl (g) and diluted to 1 M], stirred at room temperature for 4 h, and then evaporated to a red solid which was washed with EtOAc (40 mL × 3) and dried to give the amine hydrochloride salt **6** (1.92 g, 95%) as a buff solid: ^{1}H NMR (D_2O) δ 2.32 (m, 2H), 3.38 (m, 2H), 3.76 (s, 3H), 4.22 (t, J = 7.5, 1H), 8.21 (d, J = 5.4, 1H), 8.81 (d, J = 5.4, 1H), 9.11 (s, 1H). The crude salt was partitioned between EtOAc (40 mL) and saturated aqueous $NaHCO_3$ (30 mL), the aqueous layer was extracted with EtOAc (40 mL × 2), and the combined organic layer was dried, filtered, and evaporated to afford pyrroline **7** (1.56 g, 95%) as a red oil. The crude product was used directly in the next reaction. An analytical sample was prepared by chromatography [SiO_2; CH_2Cl_2/MeOH-Et_3N (4/1), 98/2−9/1]; $[\alpha]^{22}_D$ +79.1° (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 2.20−2.44 (m, 2H), 2.98−3.11 (m, 1H), 3.14−3.30 (m, 1H), 3.78 (s, 3H), 4.91 (dd, J = 8.7, 6.7, 1H), 7.33 (d, J = 5.4, 1H), 8.49 (d, J = 5.4, 1H), 8.74 (s, 1H); ^{13}C NMR δ 26.6 (2), 38.7 (2), 52.2 (3), 74.2 (1), 124.9 (1), 130.1 (0), 142.4 (0), 151.0 (1), 151.2 (1), 172.5 (0), 174.2 (0). Anal. Calcd for $C_{11}H_{11}N_2O_2Cl$; C, 55.5; H, 4.7; N, 11.8. Found: C, 55.6; H, 5.0; N, 11.9.

(2*R*)-2-[3-(4′-Chloropyridinyl)]-5-(methoxycarbonyl)-1-pyrroline ((2*R*)-7), structure not shown), was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{21}_D$ −80.0° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*)**-7**. The enantiomeric purity was established as >99% by chiral HPLC.

(2*S*)-2-[3-(4′-Methoxypyridinyl)]-5-(methoxycarbonyl)-1-pyrroline (8). Ketone **5a** (2.75 g, 6.89 mmol) was dissolved in MeOH (50 mL) [presaturated with HCl (g)] and stirred at room temperature for 4 h. The mixture was concentrated to a red oil which was dissolved in H_2O (10 mL) and partitioned between EtOAc (40 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (40 mL × 2), and the combined organic layer was dried, filtered, and evaporated. Chromatography (SiO_2, CH_2Cl_2/MeOH−Et_3N (4/1), 98/2−9/1) of the residue afforded imines **7** (0.62 g, 36%) and **8** (0.75 g, 44%) as yellow oils. For characterization of **7** see above. **8**: ^{1}H NMR δ 2.38−2.10 (m, 2H), 3.04−2.90 (m, 1H), 3.25−3.10 (m, 1H), 3.76 (s, 3H), 3.88 (s, 3H), 4.82 (dd, J = 8.6, 6.8, 1H), 6.82 (d, J = 5.8, 1H), 8.48 (d, J = 5.8, 1H), 8.86 (s, 1H); ^{13}C NMR δ 26.6, 38.6, 52.1, 55.4, 73.5, 106.5, 119.8, 151.0, 152.8, 163.9, 173.2, 174.2.

(2*R*,5*S*)-*N*-(*tert*-Butyloxycarbonyl)-5-[3-(4′-methoxypyridinyl)]proline Methyl Ester (9). Imine **8** (1.00 g, 4.27 mmol) was dissolved in MeOH (30 mL), Pd/C (10%, 100 mg) added, and the mixture was degassed and agitated under H_2 (1 atm.) for 16 h. After filtration twice through a short plug of Celite, the filtrate was evaporated to give amine as a yellow oil (0.97 g, 96%): NMR δ 1.88−2.02 (m, 1H), 2.10−2.40 (m, 3H), 3.80 (s, 3H), 3.99 (s, 3H), 4.24 (m, 1H), 4.63 (dd, J = 8.8, 6.2, 1H), 5.40 (br s, 1H), 6.93 (d, J = 6.0, 1H), 8.51 (d, J = 6.0, 1H), 8.76 (s, 1H); ^{13}C NMR δ 29.4, 31.0, 52.9, 56.1, 57.3, 59.4, 106.0, 146.7, 149.0, 173.3. The amine, di-*tert*-butyl dicarbonate (0.96 g, 4.42 mmol) and triethylamine (0.45 g, 4.42 mmol) were stirred in THF (30 mL) at room temperature for 14 h. Evaporation gave a residue which was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (50 mL × 2), the combined organic layer was dried and filtered, the filtrate was evaporated, and the residue was chromatographed (SiO_2; hexanes/EtOAc, 9/1, then CH_2Cl_2/MeOH/ Et_3N(4/1), 98/2−9/1) to afford **9** (1.20 g, 82% from **8**) as a colorless crystalline solid: mp 158 °C (EtOAc/hexane, 3/2); $[\alpha]^{22}_D$ +42.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR, rotamers, 3/2, δ 1.12 (s, minor, 3.6H), 1.17 (s, major, 5.4H), 1.73−2.08 (m, 2H), 2.14−2.35 (m, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 4.29 (t, J = 8.3, major, 0.6H), 4.43 (t, J = 5.2, minor, 0.4H), 5.08 (t, J = 5.2, minor, 0.4H), 5.23 (d, J = 5.7, major, 0.6H), 6.71 (d, J = 5.6, 1H), 8.37 (m, 1H), 8.87 (m, 1H); ^{13}C NMR, rotamers, δ 27.7, 28.0, 28.2, 28.8, 32.0, 32.8, 52.0, 57.9, 58.1, 60.0, 60.9, 67.7, 80.6, 81.0, 123.6, 124.1, 135.7, 136.8, 141.5, 141.6, 148.5, 148.8, 149.0, 149.2, 149.8, 153.5, 153.8, 172.9. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.2; N, 8.3. Found: C, 60.4; H, 7.1; N, 8.2.

(2*R*,5*S*)- and (2*S*,5*S*)-5-[3-(4′-Chloropyridinyl)]proline Methyl Esters ((2*R*,5*S*)**-10** and **(**2*S*,5*S*)**-11**). To a stirred solution of imine **7** (27.3 g, 0.114 mol) in glacial acetic acid/MeOH, 4/1 (400 mL) at −40 °C was added $NaBH_4$ (8.65 g, 0.23 mol) portionwise over 5 min. The solution was stirred for 4 h before quenching with pH 7 1 M phosphate buffer (200 mL), and stirring was continued for 10 min. The solution was concentrated to 50 mL and extracted with CH_2Cl_2 (3 × 400 mL), and the combined organic extract was dried, filtered, and evaporated to give an orange oil (24.2 g, 88%), shown by ^{1}H NMR spectroscopy to be a mixture of *cis* and *trans* diastereomers in the ratio 68/32. This product was used directly in the next reaction. The pure *cis* diastereomer can be isolated by chromatography on SiO_2 using 60% EtOAc/hexane as eluent; it is more readily obtained as its BOC derivative **14**

as described in the following procedure. Selected signals for *cis* diastereomer **10**: ^{1}H NMR δ 3.74 (s, 3H), 3.98 (m, 1H), 4.68 (t, J = 7.4, 1H), 7.16 (d, J = 5.3, 1H), 8.28 (d, J = 5.3, 1H), 8.97 (s, 1H).

(2*S*,5*R*)- and **(2*R*,5*R*)-5-[3-(4′-Chloropyridinyl)]proline methyl esters (**(2*S*,5*R*)-**10** and (2*R*,5*R*)-**11**), structures not shown, were prepared from the enantiomeric substrate in the same manner; spectral and chromatographic properties identical with those of (2*R*,5*S*)-**10** and (2*S*,5*S*)-**11**.

***N*-(*tert*-Butyloxycarbonyl)-(2*R*,5*S*)-5-[3-(4′-chloropyridinyl)]proline Methyl Ester (14) and (2*S*,5*S*)-2-[3-(4′-Chloropyridinyl)]proline Methyl Ester (11).** The mixture of amines **10** and **11** (22.0 g, 91.5 mmol) and Et_3N (12.4 mL, 89.3 mmol) were stirred in THF (200 mL) at room temperature, di-*tert*-butyl dicarbonate (15.7 g, 71.8 mmol) in THF (50 mL) was added over 30 min, and stirring was continued for 15 h. The solution was evaporated, and the residue was partitioned between EtOAc (500 mL) and saturated aqueous $NaHCO_3$ (300 mL). The aqueous layer was extracted with EtOAc (300 mL × 2), and the organic layers were combined, dried, filtered, and evaporated. Chromatography of the residue, using EtOAc/hexanes, 3/2-EtOAc/MeOH, 9/1, as eluent, afforded the *N*-BOC amine **14** as colorless crystals (18.7 g, 60%) and the unreacted *trans*-diastereomer **11** as a colorless oil (7.0 g, 32%). For **14**: $[\alpha]^{20}_D$ +23.0° (*c* 1.0, $CHCl_3$); mp 95−96 °C (hexane); ^{1}H NMR, 1/1 rotamers, δ 1.15 (s, 4.5H), 1.38 (s, 4.5H), 1.82−2.10 (m, 2H), 2.18−2.28 (m, 1H), 2.36−2.50 (m, 1H), 3.79 (s, 3H), 4.35 (t, J = 7.8, 0.5H), 4.49 (dd, J = 7.9, 5.2, 0.5H), 5.16 (t, J = 7.0, 0.5H), 5.27 (m, 0.5H), 7.24 (m, 1H), 8.36 (m, 1H), 9.11 (s, 0.5H), 9.17 (s, 0.5H); ^{13}C NMR, rotamers, δ 27.7 (3), 28.0 (3), 28.2 (3), 28.8 (2), 32.0 (2), 32.8 (2), 52.0 (3), 57.9 (1), 58.1 (1), 60.0 (1), 60.9 (1), 67.7 (1), 80.6 (0), 81.0 (0), 123.6 (1), 124.1 (1), 135.7 (0), 136.8 (0), 141.5 (0), 141.6 (0), 148.5 (1), 148.8 (1), 149.0 (1), 149.2 (1), 149.8 (1), 153.5 (0), 153.8 (0), 172.9 (0). Anal. Calcd for $C_{16}H_{21}N_2O_4Cl$: C, 56.4; H, 6.2; N, 8.2. Found: C, 56.1; H, 6.0; N, 8.2. For **11**: $[\alpha]^{20}_D$ −110 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.44−1.55 (m, 1H), 1.84−1.95 (m, 1H), 2.11−2.28 (m, 2H), 2.59 (br s, 1H), 3.64 (s, 3H), 3.95 (dd, J = 8.0, 5.1, 1H), 4.64 (t, J = 7.1, 1H), 7.12 (d, J = 5.3, 1H), 8.24 (d, J = 5.3, 1H), 8.76 (s, 1H); ^{13}C NMR δ 29.4, 32.4, 52.2, 56.7, 59.5, 123.9, 137.8, 142.4, 148.6, 149.4, 176.0. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.9; H, 5.4; N, 11.6. Found: C, 55.2; H, 5.8; N, 11.3.

(2*S*,5*R*)-*N*-(*tert*-Butyloxycarbonyl)-5-[3-(4′-chloropyridinyl)]proline Methyl Ester ((2*S*,5*R*) -14), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −22.8° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*R*,5*S*)-**14**.

(2*R*,5*S*)-1-Acetyl-5-[3-(4′-chloropyridinyl)]proline Methyl Ester (12) and (2*S*,5*S*)-1-Acetyl-5-[3-(4′-chloropyridinyl)]proline Methyl Ester (13). The crude mixture of amines **10** and **11** (3.00 g, 12.5 mmol), acetic anhydride (1.53 g, 15.0 mmol), and Et_3N (1.52 g, 15.0 mmol) were stirred in THF (50 mL) at room temperature followed by evaporation of the solvent and partitioning of the residue between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (50 mL × 2), and the organic layers were combined, dried, filtered, and evaporated. Chromatography of the residue, using EtOAc then EtOAc/MeOH, 9/1, as eluent, afforded both the *cis*-*N*-acetyl ester **12** (2.04 g, 56%) and *trans*-*N*-acetyl ester **13** (0.96 g, 26%) as colorless crystals. For **12**: mp 148−149 °C (EtOAc);$[\alpha]^{19}_D$ −22.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR, rotamers, 3/1, δ 1.83 (s, major, 2.25H), 1.85−2.10 (m, 2.75H), 2.12−2.60 (m, 2H), 3.80 (s, major, 2.25H), 3.82 (s, minor, 0.75H), 4.54 (m, 1H), 5.30 (d, J = 7.9, major, 0.75), 5.39 (t, J = 7.1, minor, 0.25H), 7.24 (d, J = 5.2, minor, 0.25H), 7.31 (d, J = 5.2, major, 0.75H), 8.34 (d, J = 5.2, minor, 0.25H), 8.47 (d, J = 5.2, major, 0.75H), 8.88 (s, minor, 0.25H), 9.32 (s, major, 0.75H); ^{13}C NMR, rotamers, 22.1, 22.5, 27.3, 29.9, 31.6, 33.7, 52.3, 52.8, 58.5, 58.7, 60.6, 61.3, 79.6, 124.1, 124.3, 135.2, 135.3, 141.7, 148.7, 148.8, 149.8, 149.9, 156.0, 170.1, 170.3, 172.2, 172.3. Anal. Calcd for $C_{13}H_{15}N_2O_3$ Cl: C, 55.2; H, 5.3; N, 9.9. Found: C, 55.3; H, 5.4; N, 9.8. For **13**: mp 135 °C (EtOAc); $[\alpha]^{19}_D$ −105° (*c* 1.0, $CHCl_3$); ^{1}H NMR, rotamers, 4/1, δ 1.84 (s, major, 2.4H), 1.75−1.90 (m, 1H), 1.95−2.01 (m, major, 0.8H), δ 2.00 (s, minor, 0.6H), 2.08−2.22 (m, 1H), 2.24−2.50 (m, minor, 0.4H), 2.58−2.70 (m, major, 0.8H), 3.73 (s, major, 2.4H), 3.78 (s, minor, 0.6H), 4.69 (d, J = 8.4, minor, 0.2H), 4.75 (d, J = 9.1, major, 0.8H), 5.45 (d, J = 8.4, major, 0.8H), 5.56 (d, J = 8.4, minor, 0.2H), 7.26 (d, J = 5.3, minor, 0.2H), 7.33 (d, J = 5.2, major, 0.8H), 8.17 (s, minor, 0.2H), 8.31 (s, major, 0.8H), 8.32 (d, J = 5.2, minor, 0.2H), 8.44 (d, J = 5.2, major, 0.8H); ^{13}C NMR δ 22.5, 26.4, 32.3, 52.7, 58.7, 60.1, 125.2, 135.8, 142.2, 148.0, 150.3, 170.3, 172.6. Anal. Calcd for $C_{13}H_{15}N_2O_3Cl$: C, 55.2; H, 5.3; N, 9.9. Found: C, 55.3; H, 5.5; N, 9.6.

(2*R*,5*R*)-1-Acetyl-5-[3-(4′-chloropyridinyl)]proline methyl ester ((2*R*,5*R*)-13), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ +101° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*,5*S*)-**13**.

(2*S*,5*R*)-*N*-(*tert*-Butyloxycarbonyl)-2-[3-(4′-chloropyridinyl)]proline (15). Methyl ester **14** (340 mg, 1.00 mmol) and LiOH (168 mg, 4.00 mmol) were stirred in MeOH/H_2O (3/1, 10 mL) at room temperature for 5 h. The solution was poured into aqueous H_3PO_4 solution (0.1 M, 30 mL) and extracted with CH_2Cl_2/IPA (3/1, 30 mLx3), the combined extract was dried and filtered, and the filtrate was evaporated to afford **15** (280 mg, 86%) as a white foam: ^{1}H NMR, rotamers, 3/1, δ 1.18 (s, minor, 2.25H), 1.37 (s, major, 6.75H), 1.84−1.96 (m, 1H), 2.04−2.14 (m, 1H), 2.22−2.40 (m, 1H), 2.41−2.53 (m, 1H), 4.38 (t, J = 7.4, major, 0.75H), 4.57 (m, minor, 0.25H), 5.23 (m, minor, 0.25H), 5.35 (m, major, 0.75H), 7.41 (d, J = 5.4, minor, 0.25H), 7.44 (d, J = 5.5, major, 0.75H), 8.50 (m, 1H), 9.49 (s, minor, 0.25H), 9.54 (s, major, 0.75H); ^{13}C NMR, rotamers, δ 28.0 (3), 28.1 (3), 28.8 (2), 31.9 (2), 33.2 (2), 57.4 (1), 58.3 (1), 61.0 (1), 61.8 (1), 80.7 (0), 81.3 (0), 124.8 (1), 125.5 (1), 138.2 (0), 145.6 (0), 147.1 (0), 153.9 (0), 175.6 (0). HRMS (EI) calcd for $C_{15}H_{20}N_2O_4Cl$ (M^+ + 1) 327.1112. Found: 327.1106.

(2*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-2-(methoxycarbonylmethyl)-5-(3-pyridinyl)pyrrolidine (16). The proline **15** (280 mg, 0.86 mmol) in THF (4 mL) at −15 °C was treated with Et_3N (119 μL, 0.86 mmol) followed by ethyl chloroformate (81 μL, 0.86 mmol), and the mixture was stirred at −15 °C for 15 min, warmed to 0 °C before excess CH_2N_2 (0.5 M in Et_2O, 4 mL, 2.0 mmol) was added, stirred for 5 h, and then warmed to room temperature slowly. The resulting mixture was flushed with N_2 until the bright yellow color disappeared and evaporated, and the residue was partitioned between EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (20 mL × 2), and the combined organic extract was dried, filtered, and evaporated to afford crude diazoketone (270 mg, 90%) as a pale yellow oil which was used directly. Crude diazoketone (100 mg, 0.28 mmol) in MeOH (4 mL) was irradiated with UV light, the reaction mixture was evaporated, and the residue was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (10 mL × 2), and the combined organic extract was dried, filtered, and evaporated to afford **16** (51 mg, 50% from **15**) as a colorless oil: ^{1}H NMR δ 1.08−1.55 (9H), 1.70−1.90 (m, 2H), 2.12−2.26 (m, 1H), 2.40−2.60 (m, 2H), 3.12 (m, 1H), 3.69 (s, 3H), 4.40 (m, 1H), 5.10 (m, 1H), 7.27 (d, J = 5.4, 1H), 8.32 (d, J = 5.4, 1H), 8.50 (m, 1H).

(2*S*)-*cis*-1-(*tert*-Butyloxycarbonyl)-2-(hydroxymethyl)-5-[3-(4′-chloropyridinyl)]pyrrolidine (18). To a solution of ester **14** (12.0 g, 35.2 mmol) in THF/EtOH (240/360 mL) at 0 °C was added $CaCl_2$ (7.80 g, 70.4 mmol) followed by $NaBH_4$ (5.40 g, 0.143 mol). The mixture was stirred for 18 h while it warmed to room temperature, K_2CO_3 (2M, 200 mL) was added, and it was distributed between EtOAc (500 mL) and saturated aqueous $NaHCO_3$ (200 mL). The aqueous layer was extracted with EtOAc (500 mL × 2), and the combined layer was dried, filtered, and evaporated. To the residue dissolved in EtOAc (50 mL) was added diethanolamine (7.40 g, 70.4 mmol), the biphasic mixture was heated to 60 °C for 16 h, and the cooled mixture was diluted with EtOAc (200 mL), washed with H_2O (50 mL × 2), dried, and filtered. The filtrate was evaporated, and the residue was chromatographed (SiO_2, EtOAc/hexanes,

3/2) to afford alcohol **18** (8.70 g, 79%) as colorless crystals: $[\alpha]^{20}_D$ −5.7° (*c* 1.0, $CHCl_3$); mp 84−86 °C (hexane/EtOAc, 9/1); ^{1}H NMR, rotamers, δ 1.15 (br, 9H), 1.74 (br m, 2H), 2.04 (m, 1H), 2.40 (br m, 1H), 3.85 (m, 2H), 4.12 (br, 1H), 4.65 (br, 1H), 5.18 (m, 1H), 7.25 (d, J = 5.5, 1H), 8.38 (br, 1H), 8.60 (s, 1H); ^{13}C NMR δ 26.2 (2), 27.0 (2), 27.9 (3), 28.3 (3), 31.8 (2), 32.3 (2), 58.0 (1), 58.7 (1), 60.8 (1), 62.0 (1), 65.2 (2), 80.5 (0), 80.8 (0), 124.5 (1), 138.1 (0), 142.0 (0), 147.2 (1), 148.3 (1), 154.8 (0). Anal. Calcd for $C_{15}H_{21}N_2O_3Cl$: C, 57.6; H, 6.8; N, 9.0. Found: C, 57.5; H, 6.9; N, 9.0.

(2*R*)-*cis*-1-(*tert*-Butyloxycarbonyl)-2-(hydroxymethyl)-5-[3-(4′-chloropyridyl)]pyrrolidine ((2*R*)-18), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ +7.2° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*)-**18**.

(2*S*,5*R*)-1-Acetyl-2-(acetoxymethyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine (19). To a solution of alcohol **18** (3.70 g, 11.8 mmol) in CH_3CN (100 mL) was added NaI (32.0 g, 0.213 mol) followed by acetyl chloride (6.50 g, 82.3 mmol), and the mixture was heated to 55 °C under N_2 and stirred for 40 h. The reaction mixture was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was distributed between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layer was washed with $Na_2S_2O_3$ (1 M, 50 mL), dried, filtered, and evaporated. Chromatography of the residue, using EtOAc/hexanes, 3/2−EtOAc/MeOH, 9/1, as eluent, gave **19** (4.07 g, 89%) as colorless crystals: mp 110−112 °C (Et_2O); $[\alpha]^{21}_D$ −27.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR, rotamers, 7/3, δ 1.60−2.20 (m, 3H), 1.74 (s, major, 2.1H), 1.82−1.92 (m, 1H), 1.95−2.15 (m, 2H), 2.07 (s, minor, 0.9H), 2.53 (m, major, 0.7H), 2.71 (m, minor, 0.3H), 4.17 (m, minor, 0.3H), 4.28 (m, major, 0.7H), 4.40 (m, minor, 0.6H), 4.50 (m, major, 1.4H), 5.00 (t, J = 6.7, major, 0.7H), 5.07 (t, J = 8.8, minor, 0.3H), 7.70 (d, J = 5.0, minor, 0.3H), 7.76 (d, major, J 5.1, 0.7H), 7.98 (d, J = 5.0, minor, 0.3H), 8.10 (d, major, J = 5.1, 0.7H), 8.18 (s, minor, 0.3H), 8.61 (s, major, 0.7H); ^{13}C NMR δ 21.3 (3), 23.4 (3), 26.6 (2), 33.9 (2), 58.6 (1), 64.8 (1), 66.4 (2), 109.2 (0), 134.9 (1), 141.2 (0), 148.0 (1), 149.4 (1), 171.1 (0), 171.9 (0). HRMS (EI) calcd for $C_{14}H_{18}N_2O_3I$ (M^+ + 1) 389.0362. Found: 389.0370.

(2*R*,5*R*)-1-Acetyl-2-(acetoxymethyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine ((2*R*,5*R*)-19), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ +26.4° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*,5*S*)-**19**.

(2*S*,5*R*)-1-Acetyl-2-(hydroxymethyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine (20). The acetylated alcohol **19** (8.20 g, 21.1 mmol) was stirred in MeOH (60 mL) with K_2CO_3 (3.00 g, 21.7 mmol) at room temperature for 45 min, the solvent was evaporated in vacuo, and the residue was extracted with CH_2Cl_2 (3 × 60 mL). The combined extract was dried, filtered, and evaporated to give alcohol **20** as a colorless oil (7.30 g, 100%) which was used directly for the next reaction: $[\alpha]^{21}_D$ −26.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR rotamers, 9/1, δ 1.62−1.72 (m, 1H), 1.81 (s, 3H), 1.78−1.88 (m, 1H), 1.97−2.10 (m, 1H), 2.38−2.50 (m, 1H), 3.85 (m, 2H), 4.30 (m, 1H), 5.06 (dd, J = 8.3, 3.7, 1H), 5.19 (br s, 1H), 7.78 (d, J = 5.1, 1H), 8.10 (d, J = 5.1, 1H), 8.44 (s, 1H); ^{13}C NMR δ 26.2 (3), 27.5 (2), 32.8 (2), 63.7 (1), 65.8 (1), 66.9 (2), 109.1 (0), 134.8 (1), 140.3 (0), 147.4 (1), 149.2 (1), 173.1 (0).

(2*R*,5*S*)-1-Acetyl-2-(hydroxymethyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine ((2*R*,5*S*)-20), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ +27.4° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*,5*R*)-**20**. Anal. Calcd for $C_{12}H_{15}IN_2O_2$: C, 41.6; H, 4.4; N, 8.1. Found: C, 42.0; H, 4.2; N, 7.8.

(2*S*,5*R*)-1-Acetyl-2-(2-(methoxycarbonyl)ethenyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine (22). To a solution of oxalyl chloride (1.66 g, 1.15 mL) in dry CH_2Cl_2 (25 mL) at −78 °C was added DMSO (1.87 mL), the cloudy mixture was stirred for 15 min, and a solution of alcohol **20** (2.30 g, 6.65 mmol) in dry CH_2Cl_2 (25 mL) was added over 10 min. The mixture was stirred for 1 h, triethylamine (5.5 mL) was added dropwise over 5 min, and the mixture was stirred for an additional 1 h and then poured into brine (30 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried, and evaporated to afford aldehyde **21** (2.30 g) as a pale yellow oil: ^{1}H NMR, rotamers, 9/1, δ 1.82 (s, 3H), 1.82−2.06 (m, 2H), 2.09−2.22 (m, 1H), 2.48−2.60 (m, 1H), 4.61 (d, J = 8.0, 1H), 5.11 (dd, J = 8.1, 3.4, 1H), 7.80 (d, J = 5.1, 1H), 8.14 (d, J = 5.1, 1H), 8.73 (s, 1H), 9.82 (s, 1H); ^{13}C NMR δ 22.2 (3), 24.0 (3), 27.5 (2), 34.1 (2), 46.0, 65.3 (1), 66.7 (1), 109.1 (0), 134.8 (1), 139.8 (0), 147.7 (1), 149.5 (1), 156.0 (0), 170.9 (0), 198.0 (0).

Aldehyde **21** (2.30 g) was dissolved in CH_2Cl_2 (10 mL) and added to a preformed mixture of the sodium salt of trimethyl phosphonoacetate [prepared by the addition of NaH (324 mg, 13.5 mmol) to a solution of trimethyl phosphonoacetate (2.83 g, 13.5 mmol) in THF (150 mL) at 0 °C, followed by stirring for 30 min, and then cooling to −78 °C] over 30 min, followed by stirring at −78 °C for 1 h. The reaction mixture was then slowly warmed to −55 °C over 2 h, saturated aqueous K_2HPO_4 (10 mL) was added, and, after stirring for 15 min, the solution was poured into saturated aqueous $NaHCO_3$ (50 mL) and distributed between CH_2Cl_2 (300 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (200 mL × 2), and the combined organic layer was washed with brine (50 mL), dried, filtered, and evaporated. Chromatography of the residue, using EtOAc as eluent, afforded α,β-unsaturated ester **22** as colorless crystals (2.68 g, 92% from **20**): mp 125 °C (dec); $[\alpha]^{21}_D$ −8.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR, rotamers, 6/4, δ 1.68 (s, major, 1.8H), 1.96 (s, minor, 1.2H), 1.70−1.90 (m, 2H), 2.02−2.22 (m, 1H), 2.32−2.48 (m, 1H), 3.62 (s, minor, 1.2H), 3.67 (s, major, 1.8H), 4.51 (m, minor, 0.4H), 4.72 (m, major, 0.6H), 4.97 (m, major, 0.6H), 5.07 (t, J = 7.1, minor, 0.4H), 5.97 (t, J = 16.1, 1H), 6.97 (dt, J = 16.1, 6.4, 1H), 7.64 (d, J = 5.0, minor, 0.4H), 7.70 (d, J = 5.1, major, 0.6H), 7.91 (d, J = 5.0, minor, 0.4H), 8.01 (d, J = 5.1, major, 0.6H), 8.17 (s, minor, 0.4H), 8.29 (s, major, 0.6H); ^{13}C NMR, rotamers, δ 22.8, 22.9, 28.7, 31.4, 32.4, 33.4, 33.7, 51.5, 51.8, 52.6, 53.1, 53.1, 53.5, 59.7, 61.0, 65.4, 66.0, 122.1, 122.8, 134.6, 134.7, 140.0, 146.4, 146.8, 146.9, 147.3, 148.3, 149.2, 166.0, 166.4, 171.0, 171.2. Anal. Calcd for $C_{15}H_{17}IN_2O_3$: C, 45.0; H, 4.3; N, 7.0. Found: C, 45.0; H, 4.5; N, 6.9.

(2*R*,5*S*)-1-Acetyl-2-(2-(methoxycarbonyl)ethenyl)-5-[3-(4′-iodopyridinyl)]pyrrolidine (2*R*,5*S*-22), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ +8.6° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (2*S*,5*R*)-**22**.

(1*R*,5*S*)-8-Acetyl-4-((methoxycarbonyl)methylidene)-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine (23). To a solution of α,β-unsaturated ester **22** (500 mg, 1.25 mmol) in 10 mL of dry DMF were added $Pd(OAc)_2$ (10 mg, 0.044 mmol), Ph_3P (20 mg, 0.076 mmol), and Et_3N (150 mg, 1.48 mmol). The flask was flushed with N_2, sealed, and heated to 110 °C for 5 h; the characteristic formation of a Pd mirror in the reaction flask was observed. The reaction mixture was allowed to cool, quenched with saturated aqueous $NaHCO_3$ (5 mL), and distributed between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layer was washed with brine, dried, filtered, and evaporated to a crystalline solid. Chromatography of the residue, using EtOAc/hexanes, 3/2, then EtOAc/MeOH, 9/1, as eluent, afforded bicyclic α,β-unsaturated ester **23** as colorless crystals (303 mg, 89%): $[\alpha]^{20}_D$ +206° (*c* 1.0, $CHCl_3$); mp 195−196 °C (hexane/EtOAc, 3/2);^{1}H NMR, *E*/*Z* isomers or rotamers, 4/1, δ 1.52−1.82 (m, 2H), 1.86 (s, minor, 0.6H), 1.90 (s, major, 2.4H), 2.10−2.22 (m, 1H), 2.26−2.52 (m, 1H), 3.64 (s, minor, 0.6H), 3.68 (s, major, 2.4H), 4.90 (d, J = 6.0, minor, 0.2H), 5.43 (d, J = 6.6, major, 0.8H), 6.30 (d, J = 8.0, major, 0.8H), 6.40 (s, 1H), 6.41 (d, J = 7.4, minor, 0.2H), 7.38 (d, J = 5.4, major, 0.8H), 7.42 (d, J = 5.3, minor, 0.2H), 8.36 (d, J = 5.4, major, 0.8H), 8.40 (d, J = 5.3, minor, 0.2H), 8.42 (s, 1H); ^{13}C NMR, *E*/*Z* isomers or rotamers, δ 14.1, 21.3, 29.4, 31.6, 51.8, 53.3, 54.7, 112.4, 117.8, 136.6, 137.4, 147.8, 149.0, 151.3, 166.2, 167.5. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.1; H, 5.9; N, 10.3. Found: C, 65.9; H, 6.2; N, 10.3.

(1*S*,5*R*)-8-Acetyl-4-((methoxycarbonyl)methylidene)-8-azabicyclo[3.2.1]octano[2,3-*c*]-pyridine ((1*S*,5*R*)-23), struc-

ture not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −219° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,5*S*)-**23**.

(1*R*,5*S*)-8-Acetyl-4-oxo-8-azabicyclo[3.2.1]octano[2,3-*c*]-pyridine (24). A solution of α,β-unsaturated ester **23** (500 mg, 1.84 mmol) and acetic acid (132 mg, 2.20 mmol) in dry CH_2Cl_2 (20 mL) was stirred at −78 °C as ozone was passed through the solution for 20 min which was then purged for 15 min with O_2. A solution of dimethyl sulfide (171 mg, 2.75 mmol) in dry CH_2Cl_2 (5 mL) was added, the mixture was allowed to reach rt over 14 h, and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried, filtered, and evaporated to give the ketone **24** (360 mg, 91%) as a colorless oil which was used directly for the next reaction: $[\alpha]^{20}_D$ +44.0° (*c* 1.0, $CHCl_3$; ^{1}H NMR, rotamers, 2/1, δ 1.68−1.94 (m, 2H), 2.00 (s, 2H), 2.02 (s, 1H), 2.25−2.70 (m, 2H), 4.71 (d, *J* = 8.5, 0.67H), 5.17 (m, 0.67H), 5.71 (d, *J* = 6.6, 0.67H), 7.73 (d, *J* = 4.9, 0.67H), 7.77 (d, *J* = 4.9, 0.33H), 8.71 (m, 1H), 8.75 (s, 1H); ^{13}C NMR, rotamers, δ 21.9, 22.3, 23.6, 25.5, 30.0, 32.0, 54.0, 57.7, 62.2, 65.1, 120.5, 120.9, 135.3, 146.4, 147.8, 150.2, 150.8, 168.0, 193.1.

(1*S*,5*R*)-8-Acetyl-4-oxo-8-azabicyclo[3.2.1]octano[2,3-*c*]-pyridine ((1*S*,5*R*)-24), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −45.2° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,5*S*)-**24**. Anal. Calcd for C_{12} H_{12} N_2O_2: C, 66.7; H, 5.6; N, 13.0. Found: C, 66.3; H, 5.7; N, 12.7.

(1*R*,4*R*,5*S*)-8-Acetyl-4-hydroxy-8-azabicyclo[3.2.1]-octano[2,3-*c*]pyridine (25). To a solution of ketone **24** (250 mg, 1.16 mmol) in MeOH (15 mL) at −20 °C was added $NaBH_4$ (60 mg, 1.58 mmol) in portions over 10 min, and then the mixture was allowed to reach 0 °C and, after 2 h, was evaporated. The residue was dissolved in 1 M HCl and evaporated again, and the residue was partitioned between aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with $CHCl_3$/IPA 3/1 (20 mL × 4), and the combined organic layer was dried, filtered, and evaporated to give alcohol **25** as colorless crystals (210 mg, 83%) which were recrystallized from EtOAc before use in the next reaction: $[\alpha]^{20}_D$ +22.6° (*c* 1.0, $CHCl_3$); mp 174−176 °C (EtOAc); ^{1}H NMR, rotamers, 3/1, 1.70−1.92 (m, 1H), 2.07 (s, major, 2.25H), 2.10 (s, minor, 0.75H), 1.95−2.20 (m, 3H), 4.38 (m, minor, 0.25H), 4.90 (m, major, 0.75H), 4.87 (d, *J* = 5.4, major, 0.75H), 5.07 (d, *J* = 5.1, minor, 0.25H), 5.16 (d, *J* = 5.0, major, 0.75H), 5.47 (d, *J* = 5.3, minor, 0.25H), 7.44 (d, *J* = 5.1, minor, 0.25H), 7.50 (d, *J* = 5.0, major, 0.75H), 8.28, 8.32 (s, major, 0.75H), 8.32 (s, minor, 0.25H), 8.41 (d, *J* = 5.1, minor, 0.25H), 8.46 (d, *J* = 5.0, major, 0.75H); ^{13}C NMR, rotamers, 20.1, 21.9, 33.4, 35.2, 52.1, 55.9, 57.4, 59.3, 68.5, 123.6, 144.4, 149.5, 156.0, 168.0. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. Found: C, 65.9; H, 6.5; N, 12.9.

(1*S*,4*S*,5*R*)-8-Acetyl-4-hydroxy-8-azabicyclo[3.2.1]octano-[2,3-*c*]pyridine ((1*S*,4*S*,5*R*)-25), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −21.4° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,4*R*,5*S*)-**25**.

(1*R*,4*R*,5*S*)-4-Hydroxy-8-azabicyclo[3.2.1]octano[2,3-*c*]-pyridine (26). A solution of *N*-acetyl alcohol **25** (240 mg, 1.10 mmol) in 1 M HCl (10 mL) was heated at 90 °C for 12 h. The solution was allowed to cool and evaporated to give the hydrochloride salt of **26** as an amorphous solid (215 mg, 91%): ^{1}H NMR (D_2O) δ 2.08−2.14 (m, 1H), 2.20−2.30 (m, 2H), 2.34−2.49 (m, 1H), 4.43 (m, 1H), 5.21 (d, *J* = 6.1, 1H), 5.49 (d, *J* = 4.9, 1H), 8.19 (d, *J* = 6.2, 1H), 8.75 (s, 1H).

The HCl salt of **26** (200 mg, 0.94 mmol) was partitioned between IPA/$CHCl_3$ (1/3, 20 mL) and 1 M KOH (10 mL), the aqueous layer was washed with IPA/$CHCl_3$ (1/3, 50 mL × 2), and the combined organic layer was dried, filtered, and evaporated to give the free amino alcohol **26** as a colorless oil (160 mg, 97%) which was used directly for the next reaction: ^{1}H NMR 1.85−1.93 (m, 2H), 1.98−2.12 (m, 2H), 3.80 (t, *J* = 6.3, 1H), 4.29 (d, *J* = 5.3, 1H), 5.05 (d, *J* = 5.0, 1H), 7.38 (d, *J* = 5.0, 1H), 8.22 (s, 1H), 8.41 (d, *J* = 5.0, 1H); ^{13}C NMR δ 21.5 (2), 35.8 (2), 56.2 (1), 59.2 (1), 70.7 (1), 122.8 (1), 137.4 (0), 145.0 (1), 146.2 (1), 148.4 (0). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.1; H, 6.9; N, 15.9. Found: C, 67.8; H, 7.0; N, 15.8.

(1*S*,4*S*,5*R*)-4-Hydroxy-8-azabicyclo[3.2.1] octano[2,3-*c*]-pyridine ((1*S*,4*S*,5*R*)-26), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −55.5° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,4*R*,5*S*)-**26**.

(1*R*,4*R*,5*S*)-4-Hydroxy-8-methyl-8-azabicyclo[3.2.1]-octano[2,3-*c*]pyridine (27). To a mixture of alcohol **26** (22.5 mg, 0.13 mmol) and formaldehyde (37%, 84 mg, 1.03 mmol) in dichloroethane (5.5 mL) was added sodium triacetoxyborohydride (108 mg, 0.51 mmol), and the mixture was stirred under nitrogen at room temperature for 2 h. Aqueous 1 M NaOH (5 mL) was added, the mixture was extracted with IPA/$CHCl_3$ (1/3, 10 mL × 3), and the combined organic extract was dried, filtered, and evaporated. The residue was chromatographed (SiO_2, MeOH saturated with NH_3/CH_2Cl_2, 1/10) to give 22 mg (91%) of the *N*-methyl alcohol **27** as a colorless oil: ^{1}H NMR δ 1.65−1.71 (m, 1H), 1.97−2.04 (m, 2H), 2.29−2.39 (m, 1H), 2.46 (s, 3H), 3.44 (t, *J* = 5.5, 1H), 3.94 (d, *J* = 5.9, 1H), 5.12 (d, *J* = 5.2, 1H), 7.40 (d, *J* = 5.0, 1H), 8.22 (s, 1H), 8.42 (d, *J* = 5.0, 1H); ^{13}C NMR δ 19.6, 31.5, 39.9, 62.6, 65.7, 69.7, 122.5, 137.0, 145.4, 145.5, 148.4. HRMS (EI) Calcd for $C_{11}H_{14}N_2O$ 190.1106. Found: 190.1106. A small amount of **27** was treated with excess 2 M HCl, and the water was removed under reduced pressure. The residue was recrystallized from MeOH/EtOAc to give the HCl salt of **27** as colorless crystals: mp 208−209 °C. Anal. Calcd for $C_{11}H_{14}N_2O$·HCl: C, 58.3; H, 6.7; N, 12.4. Found: C, 57.9; H, 6.7; N, 12.1.

(1*S*,4*S*,5*R*)-4-Hydroxy-8-methyl-8-azabicyclo[3.2.1]-octano[2,3-*c*]pyridine (27) was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{21}_D$ −56.0 (*c* 0.99, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,4*R*,5*S*)-**27**.

(1*R*,5*S*)-4-Oxo-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine (28). The *N*-acetyl ketone **24** (300 mg, 1.39 mmol) was converted to the hydrochloride salt of **28** (264 mg, 90%) and then to the free base amino ketone by the procedure described for the conversion of **25** to **26**. Hydrochloride: ^{1}H NMR (D_2O) δ 2.00−2.14 (m, 2H), 2.34−2.42 (m, 2H), 4.31 (d, *J* = 7.3, 1H), 5.28 (d, *J* = 5.5, 1H), 8.31 (d, *J* = 5.5, 1H), 8.84 (d, *J* = 5.5, 1H), 8.87 (s, 1H); ^{13}C NMR (D_2O) δ 20.6, 31.1, 56.7, 63.4, 93.2, 125.9, 134.0, 140.6, 143.8, 154.9. Free base amino ketone **28** (200 mg, 97%): mp 68−69 °C;$[\alpha]^{19}_D$ +75.9° (*c* 0.5, $CHCl_3$); ^{1}H NMR 1.68−1.75 (m, 1H), 1.77−1.85 (m, 1H), 2.15−2.50 (m, 3H), 4.12 (d, *J* = 8.0, 1H), 4.53 (d, *J* = 6.1, 1H), 7.72 (d, *J* = 4.9, 1H), 8.63 (s, 1H), 8.67 (d, *J* = 4.9, 1H); ^{13}C NMR 24.2 (2), 31.1 (2), 55.7 (1), 64.5 (1), 119.7 (1), 134.7 (0), 142.6 (1), 146.9 (1), 149.7 (0), 197.4 (0). HRMS (EI) Calcd for $C_{10}H_{10}N_2O$ (M^+) 174.0793. Found: 174.0792.

(1*S*,5*R*)-4-Oxo-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine ((1*S*,5*R*)-28), structure not shown, was prepared from the enantiomeric substrate in the same manner; $[\alpha]^{19}_D$ −74.4° (*c* 0.5, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,5*S*)-**28**.

(1*R*,5*S*)-8-Azabicyclo[3.2.1]octano[2,3-*c*]pyridine (29). A solution of ketone **28** (83 mg, 0.48 mmol), hydrazine (65 mg, 85%), and KOH (55 mg, 0.96 mmol) in triethylene glycol (1 mL) was heated at 100 °C for 14 h. The solution was then heated to 200 °C for a further 30 min, allowed to cool to room temperature, and partitioned between $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was washed with CH_2Cl_2 (20 mL × 2), and the combined organic extract was dried, filtered, and evaporated. The residue was dissolved in 1 M HCl (2 mL) and evaporated. The solid was washed with EtOAc (5 mL × 2) and dried in vacuo to give the hydrochloride salt of **29** (86 mg, 92%): mp 59−60 °C. Anal. Calcd for $C_{10}H_{12}N_2$·HCl; C, 61.1; H, 6.7; N, 14.2. Found: C, 61.1; H, 6.9; N, 14.2. By the previously described procedure, the salt was converted to the free base nornicotine analogue **29** as a yellow oil (68 mg, 97%): ^{1}H NMR δ 1.52−1.62 (m, 1H), 1.85−1.94 (m, 1H), 2.06−2.18 (m, 2H), 2.54 (d, *J* = 15.5, 1H), 3.11 (dd, *J* = 15.5, 5.0, 1H), 3.87 (m, 1H), 4.27 (d, *J* = 5.6, 1H), 6.96 (d, *J* = 5.0, 1H),

8.22 (s, 1H), 8.29 (d, $J = 5.0$, 1H); ^{13}C NMR δ 29.1(2), 36.2(2), 37.0(2), 52.9(1), 55.5(1), 124.6(1), 137.5(0), 142.0(1), 146.1(1), 148.0(1).

(1*S*,5*R*)-8-Azabicyclo[3.2.1]octano[2,3-*c*]pyridine ((1*S*,5*R*)-29), structure not shown, was prepared from the enantiomeric substrate in the same manner; spectral and chromatographic properties identical with (1*R*,5*S*)-**29**; $[\alpha]^{21}_D$ −12.5 (*c* 0.43, $CHCl_3$).

(1*R*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine (3). To a mixture of **29** (72.7 mg, 0.45 mmol) and formaldehyde (37%, 336 mg, 4.14 mmol) in dichloroethane (8 mL) was added sodium triacetoxyborohydride (434 mg, 2.05 mmol), and the mixture was stirred under nitrogen at room temperature for 3 h. Aqueous 1 M NaOH (5 mL) was added, the mixture was extracted with IPA/$CHCl_3$ (1/3, 10 mL × 3), and the combin·d organic extract was dried, filtered, and evaporated. The residue was chromatographed (SiO_2, MeOH saturated with NH_3/CH_2Cl_2 (1/25)) to give 67 mg (85%) of the nicotine analogue **3** as a colorless oil: ^{1}H NMR δ 1.53−1.64 (m, 1H), 1.76−1.82 (m, 1H), 2.20−2.36 (m, 2H), 2.37 (s, 3H), 2.41 (d, $J = 17.8$, 1H), 3.19 (dd, $J = 17.8$, 4.9, 1H), 3.48 (dd, $J = 6.4$, 5.4, 1H), 3.93 (d, $J = 5.9$, 1H), 6.99 (d, $J = 5.0$, 1H), 8.23 (s, 1H), 8.34 (d, $J = 5.0$, 1H); ^{13}C NMR δ 29.0, 33.0, 34.5, 36.7, 57.8, 61.1, 123.9, 136.4, 142.0, 147.1, 147.6. HRMS (EI) calcd for $C_{11}H_{14}N_2(M^+)$ 174,1157. Found 174.1159. By the previously described procedure the HCl salt of **3** was obtained as colorless crystals: mp 257−259 °C. Anal. Calcd for $C_{11}H_{14}N_2{\cdot}2HCl{\cdot}H_2O$: C, 49.8; H, 6.8; N, 10.6. Found: C, 50.3; H, 6.5; N, 10.8.

(1*S*,5*R*)-8-Methyl-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine ((1*S*,5*R*)-3), structure not shown, was prepared from the enantiomeric substrate in the same manner; spectral and chromatographic properties identical with (1*R*,5*S*)-**3**: $[\alpha]^{21}_D$ −77.3 (*c* 1.12, $CHCl_3$). HRMS (EI) calcd for $C_{11}H_{14}N_2$ (M^+) 174.1157. Found: 174.1157.

(1*R*,5*S*)-4-Hydroxy-4-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine ((1*R*,5*S*)-30). A solution of **26** (141 mg, 0.80 mmol), formaldehyde (37%, 819 mg, 10.1 mmol), and formic acid (922 mg, 20.0 mmol) in water (2 mL) was heated under nitrogen at 100 °C for 14 h and allowed to cool to room temperature. Aqueous 2 M K_2CO_3 (25 mL) was added and the mixture extracted with IPA/$CHCl_3$ (1/3, 30 mL × 3). The combined organic extract was dried, filtered, and evaporated, and the residue was chromatographed (SiO_2, Et_3N/MeOH saturated with $NH_3/CHCl_3$/EtOAc(6/20/100/100)) to give 102.5 mg, 58% yield, of **30**: ^{1}H NMR (CD_3OD) δ 1.60−1.65 (m, 1H), 2.00−2.17 (m, 2H), 2.34−2.41 (m, 1H), 2.42 (s, 3H), 3.48 (d, $J = 6.9$, 1H), 3.70 (d, $J = 10.4$, 1H), 3.77 (d, $J = 10.3$, 1H), 4.14 (d, $J = 6.1$, 1H), 7.51 (d, $J = 5.2$, 1H), 8.23 (s, 1H), 8.38 (d, $J = 5.0$, 1H); ^{13}C NMR (CD_3OD) δ 20.7, 31.0, 41.5, 64.7, 70.2, 71.7, 75.9, 124.0, 140.3, 145.5, 148.7, 148.8. By the previously described procedure the HCl salt of **30** was obtained as colorless crystals: mp 226−227 °C. Anal. Calcd for $C_{12}H_{16}N_2O_2{\cdot}HCl$: C, 56.1; H, 6.7; N, 10.9. Found: C, 55.8; H, 6.6; N, 10.6.

(1*S*,5*R*)-4-Hydroxy-4-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]octano[2,3-*c*]pyridine ((1*S*,5*R*)-30), structure not shown, was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{21}_D$ −76.7 (*c* 0.45, MeOH); spectral and chromatographic properties identical with (1*R*,5*S*)-**30**.

(1*R*,5*S*-4,8-Dimethyl-4-(hydroxymethyl)-8-azabicyclo-[3.2.1]octano[2,3-*c*]pyridine ((1*R*,5*S*)-31). A solution of **29** (90 mg, 0.56 mmol), formaldehyde (37%, 574 mg, 7.07 mmol), and formic acid (646 mg, 14.0 mmol) in water (1.5 mL) was refluxed under nitrogen for 3 d and allowed to cool to room temperature. Aqueous 1 M NaOH (20 mL) was added and the mixture extracted with IPA/$CHCl_3$ (1/3, 30 mLx 3). The combined organic extract was dried, filtered, and evaporated, and the residue was chromatographed (SiO_2, MeOH saturated with NH_3/CH_2Cl_2 (6.5/100)) to give 74 mg (63%) of **31**: ^{1}H NMR δ 1.13 (s, 3H), 1.67−1.78 (m, 2H), 2.02−2.10 (m, 1H), 2.27−2.40 (m, 1H), 2.41 (s, 3H), 3.24 (d, $J = 7.7$, 1H), 3.60 (d, $J = 10.2$, 1H), 3.84 (d, $J = 10.2$, 1H), 4.02 (d, $J = 6.1$, 1H), 7.16 (d, $J = 5.2$, 1H), 8.24 (s, 1H), 8.44 (d, $J = 5.2$, 1H); ^{13}C NMR δ 20.2, 21.8, 30.4, 40.4, 43.5, 63.3, 72.0, 76.0, 121.3, 138.0, 145.6, 147.8, 148.9. HRMS (EI) calcd for $C_{13}H_{18}N_2O$ (M^+) 218.1419. Found 218.1421.

(1*S*,5*R*-4,8-Dimethyl-4-(hydroxymethyl)-8-azabicyclo-[3.2.1]octano[2,3-*c*]pyridine ((1*S*,5*R*)-31), structure not shown, was prepared from the enantiomeric substrate in the same manner: $[\alpha]^{21}_D$ −118.3 (*c* 0.93, $CHCl_3$); spectral and chromatographic properties identical with (1*R*,5*S*)**-31**.

JO991609P