[3 + 2] Cycloaddition of Nonstabilized Azomethine Ylides. 7. Stereoselective Synthesis of Epibatidine and Analogues†,‡

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Epibatidine (**1**) is synthesized by employing a [3 + 2] cycloaddition strategy as a key step via nonstabilized azomethine ylide **10**, generated by one-electron oxidative double desilylation of *N*-benzyl-2,5-bis(trimethylsilyl)pyrrolidine (**12**). Cycloaddition of **10** with *trans*-ethyl-3-(6-chloro-3-pyridyl)-2-propenoate (**22a**) gives **26** in which the 6-chloro-3-pyridyl moiety is *endo*-oriented. Decarboxylation followed by debenzylation gives unnatural epimer **30** of **1**. The required cycloadduct **33**, in which 6-chloro-3-pyridyl moiety is *exo*-oriented, is obtained stereoselectively utilizing *cis*-ethyl-(6-chloro-3-pyridyl)-2-propenoate (**22b**) as dipolarophile. **30** is also converted to **1** by epimerization reaction using KO^{t}Bu. An alternative route involving conjugate addition of 6-chloro-3-iodo pyridine (**37**) to **36**, obtained by cycloaddition of **10** with ethyl propiolate, is also suggested for the stereoselective synthesis of **1**. A number of substituted epibatidines (**38**, **39**, **40**, **41**, and **42**) are synthesized through this strategy using appropriate dipolarophiles. Formal synthesis of the *N*-methyl homoepibatidine **48** and its epimer **46** is suggested from the cycloaddition of homologous azomethine ylide **44**, derived from **43**, with **22a** and **22b**, respectively.

Introduction

Epibatidine (**1**), a novel alkaloid possessing the 7-azabicyclo[2.2.1]heptane ring system with a 6-chloro-3-pyridyl substituent in *exo* orientation, isolated[1] by Daly et al. in 1992 from the skin extracts of Equadorian poison frogs, *Epipedobates tricolor*, has been shown to exhibit nonopiod analgesic activity 200−500 times more than that of morphine. Recent studies have also shown that **1** is an extremely potent agonist of the acetyl choline receptors[2−5] that has been found to be involved in the mediation of several human disorders such as Alzheimer and Parkinson diseases.[6] Epibatidine has also been shown to have little or no activity at a variety of other CNS receptors including muscarinic, adrenergic, dopamine, sertonine, and GABA receptors.[3] Therefore, renewed interest is emerging to screen **1** for other nicotine receptor mediated human disorders.[4]

Due to its intriguing pharmacological activity, interesting structural features, and scarcity in nature (less than 5 mg was isolated[1] from 750 frogs), epibatidine has been the subject of many biological[2−11] and synthetic studies.[12−19,21−29] Basically, the strategies adopted for the synthesis of this novel alkaloid, which are primarily

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† Dedicated to Prof. G. S. R. Subba Rao on the occasion of his 60th birthday.

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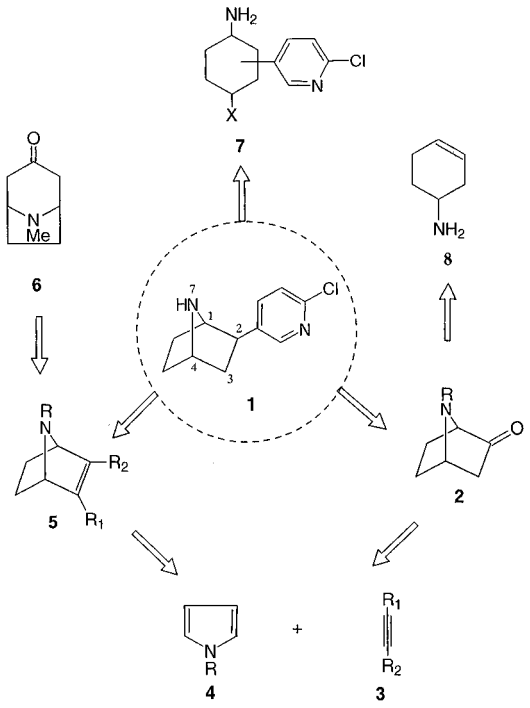
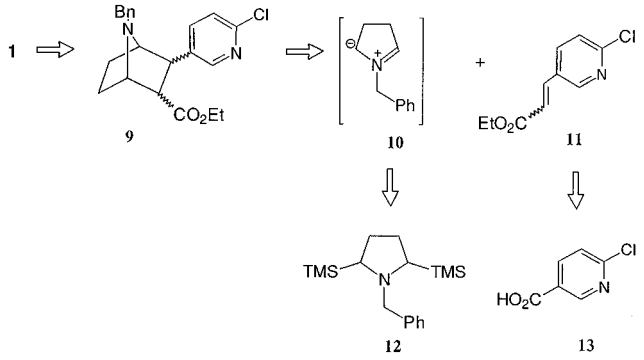
Scheme 1



R = CO_2Et or Boc or SO_2Ph ; R_1 = CO_2Et or SO_2Ph or H

R_2 = Br or H or  ; X = Br or OMs

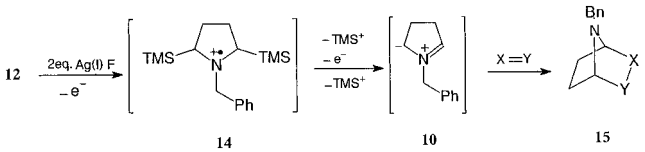
Scheme 2



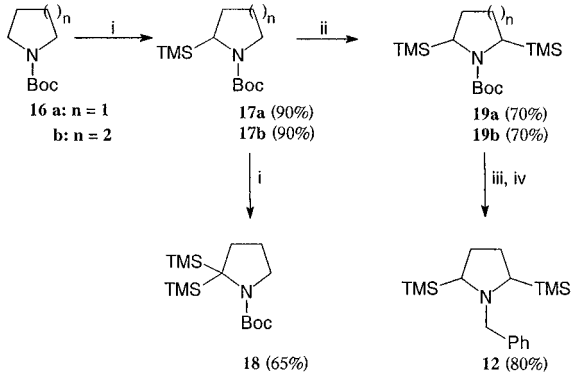
based on the construction of 7-azabicyclic heptane skeleton,[12] can be summarized in the retrosynthetic routes as depicted in Scheme 1.

The [4 + 2]-cycloaddition strategy, utilizing N-protected pyrroles **4** and activated dienophiles **3**, adopted for assembling the skeletons **2** or **5** and their further elaboration to **1** has involved many steps with overall poor yield.[13−18] Similarly, another well exploited methodology for the synthesis of **1** has employed intramolecular nucleophilic ring closure of 1,4-aminocyclohexane derivatives **7**, originally developed for the construction of 7-azanorbornane system,[19] and employs multiple steps even to reach the crucial *trans*-1,4-aminocyclohexanol derivatives.[20−27] More recently,[28] the elaboration of tropinone skeleton (**6**) into **1** via Favorskii rearrangement by Bai et al., although elegant, suffers from the poor

Scheme 3



Scheme 4[a]



[a] **Reagents and conditions:** (i) Ether, TMED, −78 °C, *s*-BuLi, 2 h, TMSCl; (ii) Ether, TMED, −45 °C, *s*-BuLi, −35 °C (15 min), −45 °C, TMSCl; (iii) DCM, TFA, rt, 4 h; (iv) BnCl, K_2CO_3, CH_3CN, Δ 4 h.

yield. Moreover, these strategies lack easy adaptability for the synthesis of epibatidine analogues. Harman et al.[29] have attempted the synthesis of **1** through the cycloaddition of pentaamine−osmium(II) $[(Os(NH_3)_5(\eta^2$-pyrrole)$]^{+2}$ $(OTf)_2$ complex; however, their effort remained unsuccessful owing to the lack of reactivity of the osmium complex toward pyridyl acrylates. To provide an efficient synthesis of **1** and its derivatives, we have developed a [3 + 2] cycloaddition based strategy utilizing nonstabilized azomethine ylide **10** as dipole and 6-chloro-3-vinyl pyridine derivatives **11** as dipolarophile (Scheme 2). Full details of our effort and success is delineated in this article.[30]

Results and Discussion

Background and Concept. While designing the synthesis of **1** through the retrosynthetic route as depicted in Scheme 2, we were guided by an earlier investigation from our group[31] on the construction of 7-azabicyclo[2.2.1]heptane skeleton (**15**) by the [3 + 2] cycloaddition of azomethine ylide **10** with electron deficient alkenes (Scheme 3). The generation of **10** involved sequential double desilylation from **12** by electron-transfer initiation using Ag(I)F as a one-electron oxidant. It was, thus, envisaged that the cycloaddition of **10** with **11** would produce **9** and that on decarboxylation followed by debenzylation would easily produce **1**.

Synthesis of Azomethine Ylide Precursor 12. The preparation of precursor **12** employed sequential silylation of **16a**. The synthesis of *N*-Boc-2-(trimethylsilyl)-pyrrolidine (**17a**) essentially utilized the protocol reported by Beak et al.[32] (Scheme 4). Introduction of a second trimethylsilyl group at the 5-position of **17a** required careful silylation reaction. Silylation by repeating the sequence as described for **17a** gave predominantly **18** in

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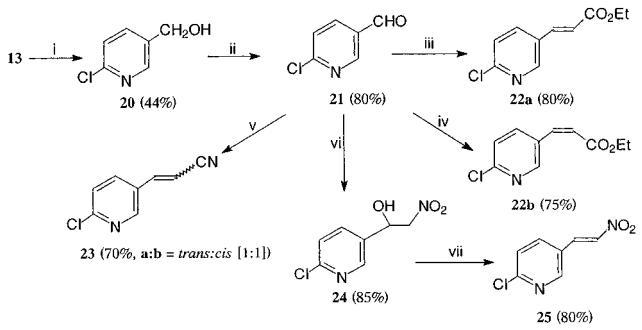
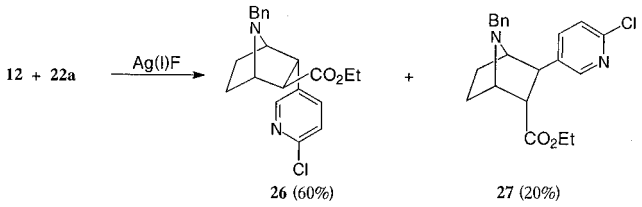
Scheme 5[a]



[a] **Reagents and conditions:** (i) THF, $LiAlH_4$; (ii) DCM, PCC, Celite, 3 h; (iii) Ph_3PCHCO_2Et, CH_3CN, Δ 3 h; (iv) THF, 18-crown-6: CH_3CN, $(CF_3CH_2O)_2P(O)CHCO_2Et$, KHMDS, −70 °C; (v) CH_3CN, Ph_3PCHCN, Δ 5 h; (vi) KF, CH_3NO_2, iPrOH; (vii) *p*-TsCl, Et_3N, DCM, 8 h.

Scheme 6

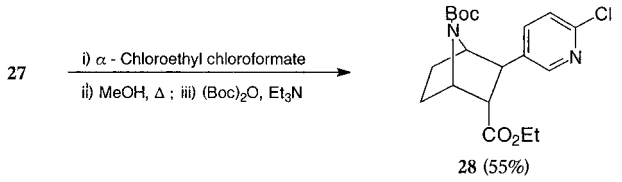


65% yield. However, **19a** could be obtained in 70% yield by carrying out the lithiation of **17a** in ether using *sec*-BuLi and tetramethylethylenediamine (TMEDA) initially at −45 °C and afterward warming the reaction mixture to −30 °C. After stirring the reaction mixture for 30 min, the temperature was lowered once again to −45 °C at which quenching with TMSCl gave **19a**. It was noticed that the use of THF as solvent gave mixtures of both **19a** and **18**. Conversion of **19a** to **12** was achieved by the deprotection of Boc moiety by stirring with trifluoroacetic acid at 0 °C followed by N-benzylation by refluxing the deprotected amine with benzyl chloride in acetonitrile in the presence of K_2CO_3.

Syntheses of Dipolarophiles 22, 23, and 25. Dipolarophiles **22a** and **22b** were prepared by the Wittig olefination of 6-chloro-3-pyridinecarboxaldehyde (**21**), obtained by simple chemical manipulations from commercially available 6-chloronicotinic acid (**13**) as shown in Scheme 5. Olefination of **21** using ethyl (triphenylphosphoranylidiene)acetate gave **22a** in 80% yield. However, **22b** was obtained by treating **21** with bis(2,2,2-trifluoroethyl) [(ethoxycarbonyl)methyl]phosphonate in the presence of 18-crown-6 (5 equiv) and KHMDS (1.1 equiv).[33] **23a** and **23b** were obtained as 1:1 mixture by the reaction of corresponding (cyanomethylene)triphenylphosphorane with **21** by following an identical reaction sequence as described for **22a**. **25** was prepared through the steps as shown in Scheme 5.

[3 + 2]-Cycloaddition and the Synthesis of 1. The cycloaddition reaction involved slow addition of **12** (1 equiv) to a stirring suspension of vacuum-dried Ag(I)F (2.0 equiv) and **22a** (1.2 equiv) in dry DCM (Scheme 6) at room temperature. The color of the reaction mixture gradually turned to dark brown, and the reaction was completed in 8−10 h with the formation of silver mirror on the walls of the flask. It may be mentioned that the reaction time could be shortened to 10−15 min using dry CH_3CN as solvent; however, cycloaddition yields are reduced due to the formation of polymeric materials. Filtration of the reaction mixture through a Celite pad and usual purification by silica gel column chromatography using hexane:ethyl acetate (9:2) as eluent gave cycloadducts **26** (60%) and **27** (20%). The exact ratio of these isomeric adducts was found to be 3:1 by HPLC [column: reverse phase C_{18} (bondapack 0.5 μm); MeOH: H_2O = 80:20] analysis. These cycloadducts were characterized by ^1H NMR, ^{13}C NMR, and mass spectral data.

Scheme 7



The stereochemistry of the major cycloadduct **26**, indicating the *endo*-orientation of 6-chloro-3-pyridyl group (H_{2exo}) and *exo*-orientation of carbethoxy group (H_{3endo}), was determined by detailed ^1H NMR decoupling and ^1H COSY experiments. For illustration, H_3 at δ 2.55 (d, J = 6.16 Hz) was found to couple only with H_2 at δ 3.95 (t, J = 4.55 Hz) and not with H_4 at δ 3.89 (dd, J = 0.87, 4.78 Hz). It is reported[1,34,35] that in the 7-azabicyclo-[2.2.1]heptane system no coupling is observed between bridgehead and adjacent *endo* hydrogens. Therefore, H_3 is assigned with *endo*-orientation. Similarly, *exo*-orientation for H_2 is suggested based on its coupling with H_1 (δ 3.60, dd, J = 0.87, 4.48 Hz). Based on the above results, thus, the relative stereochemistry between H_2 and H_3 in product **26** can be assigned trans.

In the ^1H NMR spectrum of the minor cycloadduct **27**, no coupling was observed between H_2 at δ 3.06 (d, J = 5.39 Hz) and bridgehead proton H_1 at δ 3.24 (d, J = 3.76 Hz) whereas H_3 coupled with H_2 and H_4 at δ 3.65 (t, J = 4.07, 4.43 Hz) indicating the *endo* orientation for H_2 and *exo* orientation for H_3. Confirmation of the stereochemical assignment of **27** was further ascertained by transforming **27** to the known carbamate **28** and comparing its spectral characteristics with those reported by Bai et al.[28] Conversion of **27** to **28** was easily achieved by following the simple reaction sequence as shown in Scheme 7.

Since the cycloaddition of **12** with trans-dipolarophile (**22a**) gave **26** as major adduct in which the 6-chloro-3-pyridyl moiety is *endo*-oriented, it was obvious that the decarboxylation and debenzylation from **26** would provide unnatural epimer (*endo*) of **1**. Thus, we decided to utilize **26** for the synthesis of the unnatural isomer of **1** as well. For this purpose, ester **26** was hydrolyzed by stirring in methanol:water (3:1) at 45 °C in the presence of LiOH, and the resulting crude acid was converted into corresponding acid chloride using oxalyl chloride in benzene at room temperature. Acid chloride was subjected to Barton's radical decarboxylation protocol[36] to afford decarboxylated product **29** in 55% yield.

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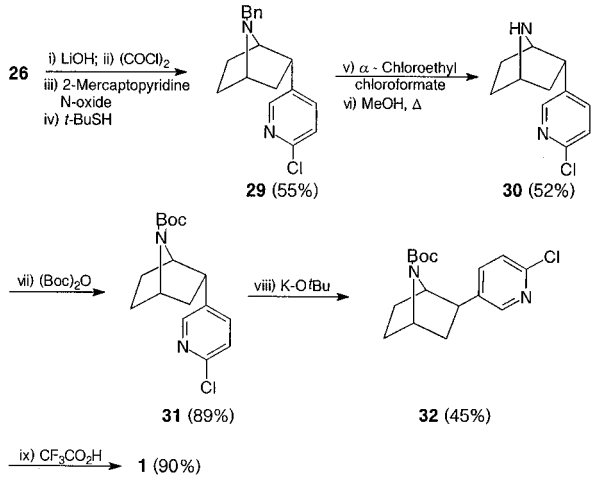
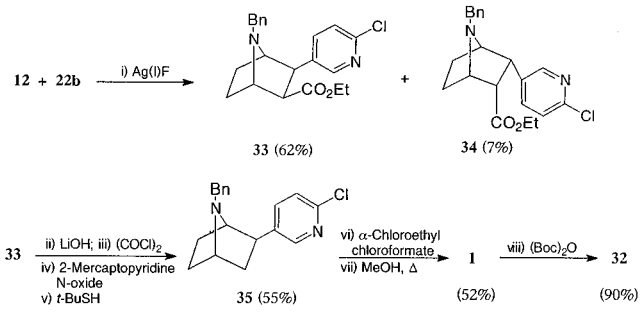
Scheme 8



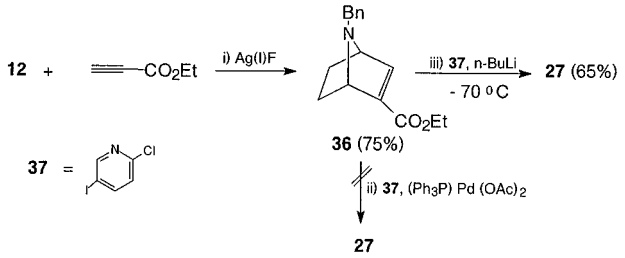
Scheme 9



N-Debenzylation of **29**, achieved by refluxing at first with α-chloroethyl chloroformate in 1,2-dichloroethane for 1.5 h followed by heating the crude salt in methanol[37] for 0.5 h, gave **30** in 52% yield. Due to the polar nature of **30**, its purification by chromatography was found difficult and therefore, it was purified and characterized as its *tert*-butyl carbamate derivative **31**. To synthesize **1** employing this reaction sequence, we also evaluated to utilize epimerized *exo*-isomer **32** (Scheme 8). However, poor yield (45%) of epimerization, performed by reacting **31** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, to **32** (^{1}H NMR and ^{13}C NMR were in complete agreement with the literature reports[16,17,23,29]) (Scheme 8) led us to seek an improved strategy.

Although, we could achieve the synthesis of **1** through the above route (Scheme 8), the poor yield of epimerization and multiple steps involved led us to envision the use of cis-dipolarophile **22b** for the cycloaddition reaction where *exo*-orientation of 6-chloro-3-pyridyl moiety was expected in the resultant cycloadduct. Keeping this logic in mind, cycloaddition of **12** with **22b**, utilizing exact experimental protocol as described above in Scheme 6, furnished cycloadducts **33** (62%) and **34** (7%) (Scheme 9). The *exo*-orientation of both 6-chloro-3-pyridyl and carbethoxy group in the adduct **33** was assigned by observing two sets of doublets at δ 2.9 (d, J = 10.12 Hz) and δ 3.1 (d, J = 10.13 Hz) corresponding to H_{3endo} and H_{2endo}, respectively, in the ^{1}H NMR spectrum. Both these protons (H_2 and H_3) did not couple with their respective bridgehead protons (H_1 and H_4) and thereby confirmed their *endo* orientations. Cycloadduct **33** was converted to **1** by following the identical reaction sequence as mentioned in Scheme 8. The spectral values of **1** were found in complete agreement with the values reported in the literature.[16,17,23,28]

Scheme 10



Alternative Approach For the Synthesis of 1. While pursuing the synthesis of **1** through the routes as described above, we also envisioned that **1** could be obtained by the introduction of 6-chloro-3-pyridyl moiety at appropriate position of **36**. It was expected on the basis of the addition stereochemistry known on the related norbornene substrate[38] that this reaction would be stereoselective toward the *exo* isomer. The crucial precursor **36** was visualized to be obtained through the cycloaddition of azomethine ylide **10** with ethyl propiolate. Toward this end, when the cycloaddition of **10** was performed by following the experimental protocol as described for **26**; utilizing **12** (1 equiv) and ethyl propiolate (1.2 equiv) in the presence of Ag(I)F (2 equiv) gave **36** in 75% yield (Scheme 10). Initially, we tried to introduce the 6-chloro-3-pyridyl group into **36** through the reductive palladium-catalyzed coupling (Heck reaction[39]) of 6-chloro-3-iodo pyridine (**37**); however, this was not successful. Therefore, we decided to solve this problem by carrying out conjugate addition of **37** via its lithio derivative onto **36**. Addition of **36** (0.97 mmol) to a stirring mixture of **37** (0.97 mmol) containing *n*-BuLi (0.97 mmol) in THF at −78 °C followed by workup and purification gave **27** in 65% yield. The characterization and assignment of stereochemistry of the product thus obtained was ascertained by comparing the spectral characteristics with the same product realized earlier through the reaction sequence delineated in Scheme 6. It may be mentioned that while our effort in this direction was in progress, a similar strategy for the synthesis of **1** was reported by Simpkins et al.[18]

Synthesis of Substituted Epibatidines. Due to the structural resemblance to nicotine, epibatidine and many of its derivatives and isomers have been found to exhibit a very high affinity, in the picomolar range, for [^{3}H] nicotine and [^{3}H] cystine binding sites in brain.[2] Therefore, there is growing interest in devising methodologies to synthesize various derivatives and structural analogues of **1**. To extend the scope of our methodology for this purpose, cycloadditions with different dipolarophiles having the 6-chloro-3-pyridyl group were studied. Cycloaddition of **10** with *trans*-3-(6-chloro-3-pyridyl)-2-propionitrile (**23a**) as well as *cis*-3-(6-chloro-3-pyridyl)-2-propionitrile (**23b**) gave corresponding cycloadducts **38** (45%) and **39** (18%), and **40** (55%) and **41** (13%), respectively. The stereochemistry of these cycloadducts, as shown in Scheme 11, was assigned on similar logic to that described for the corresponding ester derivatives (**26** and **27**, and **33** and **34**, respectively).

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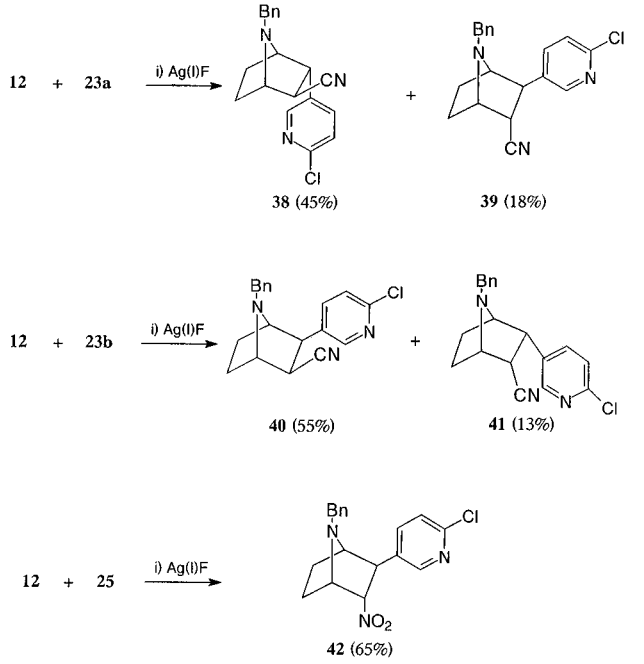
Scheme 11



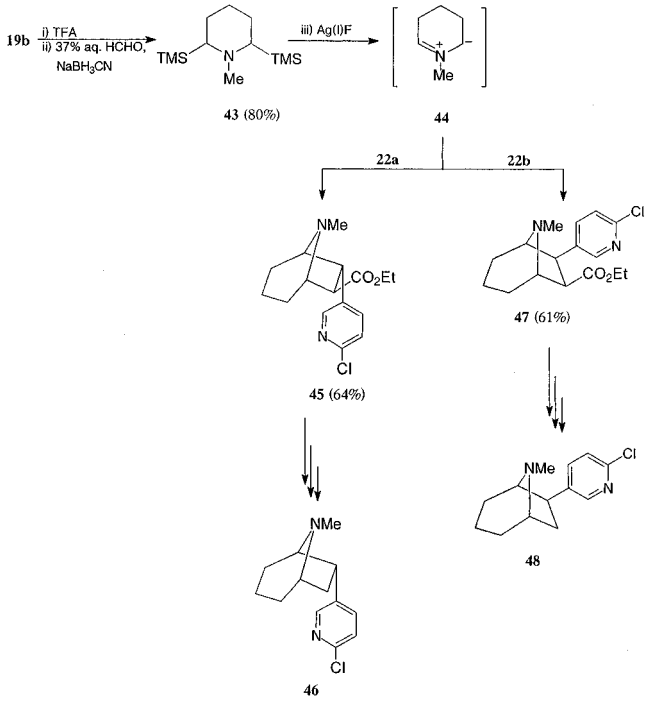
Cycloaddion of **10** with *trans*-2-(6-chloro-3-pyridyl)-1-nitro ethylene (**25**) gave adduct **42** (Scheme 11). The *exo*-orientation of the 6-chloro-3-pyridyl moiety in this compound was confirmed by observing a doublet for H_{2endo} at δ 3.45 (d, J = 5.36 Hz) and a multiplet for H_{3exo} at δ 4.75. The ^{1}H NMR decoupling experiments suggested that H_2 couples only with H_3 as observed in the case of **27**. The *exo*-selectivity for the 6-chloro-3-pyridyl moiety observed in the cycloaddition reaction using **25** as dipolarophile appears to be in contrast to the cycloaddition stereochemistries observed with dipolarophiles **22a** as well as **23a**. Although at present we do not have explanations for the reversal of stereochemistry in **42**, the difference in the orbital coefficients of nitro olefin from that of the ester may be considered for this observation.

Formal Synthesis of Homoepibatidine. Homoepibatidine and its *N*-methyl derivatives (**48**) have been reported to possess analgesic properties comparable to epibatidine.[11,28] The synthetic efforts devoted toward homoepibatidine have involved Heck-coupling of iodopyridyl derivative with 8-azabicyclo[3.2.1]oct-6-ene;[28,40] however, the yields of **48** were poor. In the general context of our strategy, as outlined in Scheme 12, cycloadditon of homologous azomethine ylide (**44**), derived from **43**, with **22b** was visualized to provide an easy synthetic route toward the synthesis of *N*-methylhomoepibatidine (**48**). The required precursor **43** for the generation of **44** was obtained from **19b** in 80% yield through the reaction sequence as described in Scheme 12. Usual cycloaddition of **43** (1 equiv) with **22b** (1.2 equiv) in the presence of Ag(I)F (2 equiv) afforded **47** in 61% yield (Scheme 12).

Adduct **47** was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data. Adduct **47** is expected to produce *N*-methylhomoepibatidine (**48**) upon simple chemical manipulations. Similarly, compound **45** required for the synthesis of corresponding *endo*-epimer **46** was obtained (64%) by the cycloaddition of **44** with **22a**.

(40) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, *37*, 3911.

Scheme 12



Conclusion

In conclusion, synthesis of **1** is accomplished in a stereoselective manner employing [3 + 2] cycloaddition of azomethine ylide, as a key step. Our approach has provided the scope for its application toward the synthesis of the various analogues of **1** and homoepibatidine.

Experimental Section

All the yields reported refer to isolated material but are not optimized. Temperatures above and below ambient temperature refer to bath temperature unless otherwise stated. Solvents and anhydrous liquid reagents were dried according to the established procedures by distillation under argon atmosphere from an appropriate drying agent. Chemicals and reagents were procured from Aldrich, Milwaukee, WI, and SD Fine Chemicals, India.

Analytical TLC was performed using precoated silica gel plates (0.25 mm). Column chromatography was performed using silica gel by standard chromatographic techniques. Product ratios were determined using HPLC analysis, performed on a liquid chromatograph using reverse phase (C_{18} bondapack 0.5 μm) column, eluting with MeOH:H_2O (80:20).

All nuclear magnetic resonance spectra were recorded on either 200 MHz NMR or 300 MHz NMR spectrometers. All chemical shifts are reported in parts per million downfield from TMS; coupling constants are given in hertz. Mass (*m/z*, relative intensity) spectra were recorded at a voltage of 70 eV.

***N*-Boc-2-(trimethylsilyl)pyrrolidine (17a).** A 40 mL solution of *N*-Boc pyrrolidine (**16a**) (6.84 g, 39.99 mmol) in dry ether, charged into a 250 mL flask equipped with a magnetic stirring bar and argon gas balloon, was cooled to −78 °C. TMEDA (5.57 g, 47.99 mmol) followed by s-BuLi (1.5 M solution in cyclohexane, 31.99 mL, 47.99 mmol) was introduced. The mixture was allowed to stir for 2 h at −78 °C. Chlorotrimethylsilane (5.21 g, 47.99 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and diluted with 15 mL of saturated aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined extracts were washed with water (80 mL), brine (80 mL) and dried over Na_2SO_4. The crude oily residue, obtained after the concentration, was purified by fractional distillation (bp 55 °C/0.5 mm) to give

17a as colorless oil (8.74 g, 90%). IR (neat) 1692, 1478, 1365, 1246, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 9H), 1.45 (s, 9H), 1.75−1.95 (m, 3H), 1.95−2.05 (m, 1H), 3.15−3.3 (m, 2H), 3.35−3.6 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −2.3, 27.8, 28.4, 46.7, 47.5, 78.0, 154.5; mass (*m*/*z*, relative intensity) 243 (M^+, 1), 186 (43), 172 (100), 142 (94).

An identical reaction procedure was adopted for the synthesis of *N*-Boc-2-(trimethylsilyl)piperidine (**17b**). Colorless oil. Yield (90%). IR (neat) 1688, 1415, 1159, 1098, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 9H), 1.43 (s, 9H), 1.55−1.75 (m, 6H), 2.15−2.30 (m, 2H), 3.60−3.75 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −1.0, 23.0, 25.7, 28.1, 45.0, 78.4, 154.5; mass (*m*/*z*, relative intesity) 257 (M^+, <1), 156 (84), 128 (54), 84 (75), 73 (100).

***N*-Boc-2,5-Bis(trimethylsilyl)pyrrolidine (19a).** A 250 mL two-neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of **17a** (4.86 g, 20 mmol) in 30 mL of ether and was cooled to − 45 °C. TMEDA (2.79 g, 24 mmol) followed by s-BuLi (1.5 M in cyclohexane, 15.92 mL, 24 mmol) were added to the flask dropwise while stirring. After 15 min of stirring at −45 °C, the temperature was raised to −30 °C. After 30 min, it was recooled to −45 °C and afterward chlorotrimethylsilane (2.6 g, 24 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, diluted with 10 mL of saturated aqueous NH_4Cl solution, and worked up as mentioned in the previous experiment, to get an oily residue which was purified by silica gel column chromatography (1:99/EtOAc:hexane) to give **19a** (4.41 g, 70%) as a pale yellow oil. Only a trace amount of **18** was isolated. IR (neat) 1684, 1406, 1365, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 18H), 1.45 (s, 9H), 1.75−2.00 (m, 4H), 3.00−3.10 (bs, 1H), 3.20−3.30 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −1.03, −0.50, 28.93, 29.0, 49.44, 50.0, 78.96, 154.82; mass (*m*/*z*, relative intensity) 315 (M^+, 1), 258 (83), 244 (41), 228 (45), 214 (71), 186 (33), 73 (100).

***N*-Boc-2,2-Bis(trimethylsilyl)pyrrolidine (18).** IR (neat) 1690, 1392, 1248, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.1 (s, 18H), 1.45 (s, 9H), 1.75 (m, 2H), 1.95 (t, J = 6.8 Hz, 2H), 3.35 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 0.18, 25.5, 28.8, 32.2, 46.5, 48.5, 78.1, 154.6; mass (*m*/*z*, relative intensity) 258 (72), 244 (70), 214 (37), 186 (36), 73 (100%).

***N*-Boc-2,6-Bis(trimethylsilyl)piperidine (19b).** Pale yellow oil. 75% yield. IR (neat) 1684, 1421, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 18H), 1.45 (s, 9H), 1.55−1.75 (m, 6H), 2.15 (m, 1H), 3.60−3.75 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.7, 0.1, 24.7, 26.2, 26.9, 28.7, 47.7, 48.5, 78.8, 155.8; mass (*m*/*z*, relative intensity) 272 (100), 258 (46), 242 (66), 228 (51), 200 (80), 156 (44), 73 (98).

***N*-Benzyl-2,5-bis(trimethylsilyl)pyrrolidine (12).** A stirring solution of **19a** (3.15 g, 10 mmol) in 40 mL of dry CH_2Cl_2 was cooled to 0 °C and was treated with trifluroacetic acid (5.70 g, 50 mmol) dropwise. The mixture was allowed to warm to rt, and stirring was continued for an additional 4 h. The reaction mixture was recooled to 0 °C and basified with 20% aqueous NaOH solution (pH = 10). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give 1.93 g of crude amine which was utilized for the next step.

To a 40 mL solution of the crude amine (1.93 g, 8.97 mmol) in acetonitrile, were added K_2CO_3 (1.49 g, 10.8 mmol) and benzyl chloride (1.08 g, 8.55 mmol). The resultant suspension was refluxed for 5−6 h. Progress of the reaction was monitored by TLC. On completion of the reaction, the mixture was cooled and filtered, and the solvent was evaporated under vacuum. The crude yellow oil was purified by silica gel column chromatography, eluting with EtOAc:hexane (2:98), to obtain 2.44 g (80%) of **12** as a pale yellow oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.1 (s, 18H), 1.65−1.80 (m, 2H), 1.90−1.95 (m, 2H), 2.25−2.30 (m, 2H), 3.35 (d, J = 12.85 Hz, 1H), 3.8 (d, J = 12.87 Hz, 1H), 7.20−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −1.6, 26.8, 56.0, 60.1, 126.8, 128.1, 129.4, 141.7; mass (*m*/*z*, relative intensity) 305 (M^+, 3), 290 (17), 233 (100), 91 (90), 73 (54).

6-Chloro-3-pyridylcarbinol (20). A 250 mL flask, equipped with a magnetic stirring bar and argon gas balloon, containing a THF (50 mL) solution of 6-chloronicotinic acid (**13**) (5.12 g, 32.5 mmol) was cooled to 0 °C. A 1.0 M solution of lithium aluminum hydride (32.5 mL, 32.5 mmol) in THF was introduced to the flask while stirring. The stirring was allowed to continue for 3 h at 0 °C. The reaction mixture was quenched at 0 °C itself by the addition of NaF (5.46 g, 130 mmol) followed by H_2O (3.50 mL). The resulting slurry was washed with ethyl acetate (5 × 100 mL). The crude product obtained after concentration was purified by silica gel column chromatography (1:3/EtOAc:hexane) to afford 2.09 g (45%) of alcohol **20** as a white solid. Mp 40 °C. IR ($CHCl_3$) 3356, 1681, 1593, 1456, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.7 (bs, 1H), 4.75 (s, 2H), 7.3 (d, J = 8.2 Hz, 1H), 7.7 (dd, J = 2.1, 8.1 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.0, 124.0, 135.7, 137.8, 147.6, 149.7; mass (*m*/*z*, relative intensity) 142 (98), 114 (100), 78 (60).

6-Chloro-3-pyridinecarboxaldehyde (21). Compound **20** (2.09 g, 14.61 mmol) dissolved into CH_2Cl_2 (20 mL) was introduced to a stirring mixture of Celite (4.8 g) and pyridinium chlorochromate (4.72 g, 21.89 mmol) containing 40 mL of dry CH_2Cl_2 in one portion at 0 °C. The resulting black slurry was stirred for an additional 2 h at rt and finally diluted with dry ether (80 mL). The supernatant solution was decanted from the black residue and thoroughly washed with dry ether (2 × 50 mL). The combined washings were evaporated under vacuum, and the brown residue was purified by silica gel column chromatography (2:8/EtOAc:hexane) to afford 1.65 g (80%) of **21** as white solid. Mp 80 °C. IR ($CHCl_3$) 2870, 1746, 1587, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.5 (d, J = 8.2 Hz, 1H), 8.15 (dd, J = 2.4, 8.2 Hz, 1H), 8.9 (d, J = 2.4 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.9, 130.3, 137.9, 152.3, 156.8, 189.1; mass (*m*/*z*, relative intensity) 140 (100), 112 (27).

***trans*-Ethyl(6-Chloro-3-pyridyl)-2-propenoate (22a).** A solution of ethyl triphenylphosphoranylidine acetate (4.18 g, 12 mmol) dissolved in 30 mL of acetonitrile was added, while stirring, to a 20 mL acetonitrile solution containing **21** (1.69 g, 12 mmol). The reaction mixture was refluxed for 10 h. After the completion of the reaction, solvent was removed under vacuum to afford a solid compound which was purified by silica gel column chromatography using hexane:EtOAc (9:1) as eluent to give 2.03 g (80%) of **22a** as a white crystalline solid. Mp 81 °C. IR ($CHCl_3$) 1711, 1464, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.30 Hz, 3H), 4.25 (q, J = 7.30 Hz, 2H), 6.5 (d, J = 14.45 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 14.45 Hz, 1H), 7.8 (dd, J = 2.10, 8.42 Hz, 1H), 8.5 (d, J = 2.23 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 60.9, 121.3, 124.6, 129.3, 136.7, 139.3, 149.5, 152.7, 166.0; mass (*m*/*z*, relative intensity) 211 (M^+, 30), 183 (42), 166 (100), 138 (53).

***cis*-Ethyl(6-Chloro-3-pyridyl)-2-propenoate (22b).** 18-Crown-6 acetonitrile complex (10.83 g, 35.46 mmol) and bis(2,2,2-trifluoroethyl) [(ethoxycarbonyl)methyl]phosphonate (5.8 g, 15.60 mmol) dissolved in THF (400 mL) were charged into a two-neck flask equipped with a magnetic stirring bar and argon gas balloon. The contents were cooled to −78 °C. Potassium bis(trimethylsilyl)amide (1.0 M solution in THF, 15.60 mL, 15.60 mmol) was introduced into the flask while stirring. **21** (2.0 g, 14.13 mmol) dissolved in 10 mL of THF was later added to the reaction mixture, and the whole contents were allowed to stir for 30 min. Contents were poured into 120 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with ether (3 × 50 mL). Combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give crude oil which was purified by silica gel column chromatography (2:8/EtOAc:hexane) to afford 2.24 g (75%) of **22b** as pale yellow oil. IR (neat) 1721, 1636, 1555, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.12 Hz, 3H), 4.15 (q, J = 7.22 Hz, 2H), 6.1 (d, J = 12.49 Hz, 1H), 6.85 (d, J = 12.33 Hz, 1H), 7.30 (d, J = 8.30 Hz, 1H), 8.10 (dd, J = 2.44, 8.29 Hz, 1H), 8.45 (d, J = 2.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 60.6, 122.7, 123.4, 129.6, 138.2, 139.5, 150.7, 151.3, 165.3; mass (*m*/*z*, relative intensity) 211 (M^+, 28), 182 (42), 166 (100), 138 (53).

3-(6-Chloro-3-pyridyl)propionitriles (23a/23b). 23 was obtained in 1:1 ratio (**23a/23b**), in 70% yield, by the reaction

of (cyanomethylene)triphenylphosphorane (3.61 g, 12 mmol) and **21** (1.40 g, 10 mmol) by following the identical reaction procedure as described for **22a**.

23a: mp 168 °C. IR (Nujol) 2120, 1580, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.00 (d, J = 16.67 Hz, 1H), 7.40 (d, J = 16.67 Hz, 1H), 7.45 (d, J = 8.36 Hz, 1H), 7.45 (d, J = 8.36 Hz, 1H), 7.80 (dd, J = 2.55, 8.34 Hz, 1H), 8.50 (d, J = 2.49 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 98.6, 116.3, 123.5, 127.6, 135.4, 144.5, 148.0, 151.9; mass (*m*/*z*, relative intensity) 164 (M^+, 100), 137 (29), 129 (82), 102 (59).

23b: mp 97 °C. IR (Nujol) 2120, 1580, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.65 (d, J = 12.00 Hz, 1H), 7.10 (d, J = 12.00 Hz, 1H), 7.45 (d, J = 8.50 Hz, 1H), 8.40 (dd, J = 2.40, 8.49 Hz, 1H), 8.60 (d, J = 2.40 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 98.3, 116.2, 124.4, 128.2, 137.0, 143.5, 150.5, 153.1; mass (*m*/*z*, relative intensity) 164 (M^+, 100), 129 (82), 102 (59).

2-(6-Chloro-3-pyridyl)-1-nitroethylene (25). A 10 mL *i*-PrOH solution of **21** (1.41 g, 10 mmol) was treated with KF (0.03 g, 0.5 mmol) and nitromethane (1.2 mL, 20 mmol). After stirring for 6 h at rt, solvent was evaporated to dryness, and the residue was purified by silica gel column chromatography, eluting with hexane:EtOAc (8:2), to obtain 2-hydroxy-2-(6-chloro-3-pyridyl)nitroethane (**24**) (1.63 g, 90%) as a thick dark yellow oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 4.6 (d, J = 4.36 Hz, 2H), 5.6 (dd, J = 9.72, 4.32 Hz, 1H), 7.3 (d, J = 8.40 Hz, 1H), 7.80 (dd, J = 2.6, 8.41 Hz, 1H), 8.40 (d, J = 8.35 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.9, 80.7, 124.7, 134.0, 137.3, 147.2, 151.2; mass (*m*/*z*, relative intensity) 202 (M^+, 4), 155 (82), 140 (100), 128 (20).

Compound **24** (1 g, 4.94 mmol) dissolved in 50 mL of dry DCM was cooled to 0 °C and was treated with pyridine (0.78 g, 9.89 mmol) followed by *p*-toluenesulfonyl chloride (1.035 g, 5.43 mmol). After the completion of the reaction, the reaction mixture was stirred at rt overnight. The mixture was successively washed with aqueous 1 M $NaHCO_3$ solution (2 × 25 mL), water, and brine and finally dried over Na_2SO_4. Evaporation of the solvent gave crude solid which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to get **25** (0.68 g, 75%) as a white solid, mp 139 °C. IR (Nujol) 1637, 1583, 1506, 1340, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45 (d, J = 8.30 Hz, 1H), 7.65 (d, J = 12.25 Hz, 1H), 7.85 (dd, J = 2.38, 8.30 Hz, 1H), 8.0 (d, J = 12.25 Hz, 1H), 8.55 (d, J = 2.38 Hz, 1H); mass (*m*/*z*, relative intensity) 184 (M^+, 41), 137 (91), 126 (19), 102 (100%), 75 (79%).

General Cycloaddition Procedure. Exemplified by the Reaction of 12 with 22a. A two-neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (1.58 g, 12.5 mmol) (dried previously under vaccum at 40 °C), dipolarophile **22a** (1.32 g, 6.26 mmol), and 40 mL of dry dichloromethane. Compound **12** (1.73 g, 5.69 mmol), dissolved in 30 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. The color of the reaction mixture gradually turned dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror, and the progress of the reaction mixture was periodically monitored by TLC. After stirring for 8−10 h, the reaction mixture was filtered through a small plug of Celite, and the solvent was evaporated to give a crude brown residue. Purification of the crude residue by silica gel column chromatography, eluting with hexane:EtOAc (9:1), afforded 0.42 g (20%) of **27**. Further elution with hexane:EtOAc (9:2) afforded 1.26 g (60%) of **26** as thick yellow oil.

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (26). IR (neat) 1728, 1462, 1142, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, J = 7.1 Hz, 3H), 1.35−1.45 (m, 2H), 1.60−1.80 (m, 1H), 1.95−2.05 (m, 1H), 2.55 (d, J = 6.16 Hz, 1H), 3.60 (dd, J = 0.87, 4.48 Hz, 1H), 3.61 (d, J = 13.71 Hz, 1H), 3.72 (d, J = 13.70 Hz, 1H), 3.89 (dd, J = 0.84, 4.78 Hz, 1H), 3.95 (t, J = 4.55 Hz, 1H), 4.20 (q, J = 7.21 Hz, 2H), 7.25−7.52 (m, 7H), 8.25 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.9, 27.2, 47.1, 51.3, 52.4, 60.7, 63.3, 63.9, 123.6, 126.7, 128.0, 134.7, 138.2, 139.4, 149.2, 173.1; mass (*m*/*z*, relative intensity) 370 (M^+, 3), 159 (100), 131 (26), 91 (81%).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (27). IR (neat) 1728, 1457, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, J = 7.05 Hz, 3H), 1.55 (dt, J = 2.32, 7.93 Hz, 2H), 2.0 (m, 2H), 2.85 (dt, J = 1.83, 5.07 Hz, 1H), 3.06 (d, J = 5.39 Hz, 1H), 3.24 (d, J = 3.76 Hz, 1H), 3.54 (s, 2H), 3.65 (t, J = 4.07, 4.43 Hz, 1H), 4.10 (q, J = 7.09 Hz, 2H), 7.20 (d, J = 8.35 Hz, 1H), 7.23−7.35 (m, 5H), 7.84 (dd, J = 2.47, 8.26, 1H), 8.42 (d, J = 2.41 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.8, 26.8, 47.4, 51.7, 57.5, 60.6, 66.1, 66.4, 123.6, 127.0, 128.2, 128.5, 137.9, 139.2, 140.2, 148.9, 172.0; mass (*m*/*z*, relative intensity) 370 (M^+, 20), 166 (72), 159 (100), 138 (30), 91 (90).

General Decarboxylation Procedure. Decarboxylation was achieved by following the Bartons procedure.[36] It is exemplified by taking **26** as an example. A solution of **26** (1.0 g, 2.7 mmol) in MeOH:H_2O (3:1, 20 mL) containing LiOH:H_2O (0.17 g, 4.04 mmol) was warmed to 45 °C with stirring. After 1.5 h, the mixture was cooled and washed with CH_2Cl_2 (3 × 20 mL). The aqueous layer was cooled to 0 °C, acidified with 6 N HCl to pH = 5, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate. Evaporation of the organic layer gave crude acid as a white solid. The resultant crude acid was dissolved in 30 mL of dry benzene and was transferred to a 50 mL flask equipped with argon gas balloon. Oxalyl chloride (1.18 mL, 13.52 mmol) and DMF (one drop) were added to the flask at rt and stirred for 2 h. Evaporation of the solvent under vacuum gave acid chloride as a brown solid. The crude acid chloride was dissolved in dry benzene (30 mL) and to the resultant solution were added DMAP (0.033 g, 0.26 mmol), *N*-hydroxy-2-mercaptopyridine (0.41 g, 3.24 mmol), and 1.2 mL pyridine, maintaining the argon atmosphere. The reaction mixture was stirred for 1.5−2 h at rt. The solid suspension was allowed to settle, and the supernatant solution was syringed out and added to a refluxing solution of *t*-BuSH (1.5 mL) in 40 mL of dry benzene. The mixture was refluxed for 2.5−3 h, cooled, washed with aqueous 1 N NaOH solution, water, and brine, and dried over Na_2SO_4. Concentration gave a brownish black residue which upon silica gel column chromatographic purification using EtOAc:hexane (2:8) as eluent afforded **29** (0.442 g, 55%) as a thick yellow oil. IR (neat) 1460, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30−1.40 (m, 2H), 1.45−1.60 (dd, J = 5.36, 17.92 Hz, 1H), 1.60−1.85 (m, 1H), 1.90−2.0 (m, 1H), 2.35 (m, 1H), 3.45 (t, J = 4.7 Hz, 2H), 3.55 (m, 1H), 3.70 (s, 2H), 7.25−7.50 (m, 7H), 8.25 (d, J = 2.51 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 28.3, 33.7, 42.7, 51.7, 60.2, 63.9, 123.5, 126.8, 128.2, 128.3, 136.1, 138.3, 139.6, 148.9, 149.5; mass (*m*/*z*, relative intensity) 298 (M^+, 9), 159 (70), 91 (100), 83 (36).

General Debenzylation Procedure. Exemplified by the conversion of 29 to 30. α-Chloroethyl chloroformate (0.18 g, 1.26 mmol) was added at rt to a 20 mL solution of **29** (0.3 g, 0.99 mmol) in dry 1,2-dichloroethane. The reaction mixture was refluxed for 2 h, cooled, and concentrated under vacuum. The residue was dissolved in 15 mL of methanol and further refluxed for 3 h. The reaction mixture was evaporated to dryness, and the solid residue was dissolved in chloroform (20 mL) and basified with aqueous 1 N NaOH solution to pH = 8. The chloroform layer was separated, and the aqueous layer was further extracted with (2 × 10 mL) chloroform. Combined extracts were dried over anhydrous $CaCl_2$ and concentrated to give brown oily residue. Column chromatographic purification eluting with hexane:EtOAc (8:2) gave 0.025 g of unreacted **29**. Further elution using (9:0.5:0.1/$CHCl_3$:MeOH:NH_4OH) as eluent gave **30** (0.107 g, 52%).

***endo*-2-(6-Chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane (30).** ^1H NMR ($CDCl_3$, 200 MHz) δ 1.4−1.5 (m, 6H), 2.25 (m, 1H), 3.55 (m, 1H), 3.9 (bs, 2H), 7.3 (d, J = 8.30 Hz, 1H), 7.5 (dd, J = 8.28, 2.47 Hz, 1H), 8.24 (d, J = 2.45 Hz, 1H).

***endo*-*N*-Boc-Epibatidine (31).** To a stirring solution of **30** (0.10 g, 0.48 mmol) in 15 mL of THF was added $(Boc)_2O$ (0.126 g, 0.576 mmol) followed by triethylamine (0.06 g, 0.576 mmol) under argon atmosphere. The resulting mixture was stirred for 6−8 h and concentrated, and the residue was purified by silica gel column chromatography, eluting with hexane:EtOAc (9:1), to afford 0.132 g (89%) of **31**. IR (neat)

1693, 1582, 1460, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37−1.45 (m, 2H), 1.5 (s, 9H), 1.55−1.65 (dd, J = 5.6, 12.39 Hz, 2H), 1.85−1.95 (m, 1H), 2.30 (m, 1H), 3.45 (m, 1H), 4.30 (bs, 2H), 7.30 (d, J = 8.67 Hz, 1H), 7.50 (dd, J = 2.63, 8.69 Hz, 1H), 8.26 (d, J = 2.46 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 28.1, 30.0, 34.2, 43.4, 57.1, 60.1, 79.8, 123.7, 134.6, 138.3, 149.3, 155.3; mass (*m*/*z*, relative intensity) 308 (M^+, 2), 208 (37), 140 (72), 126 (11), 69 (51), 57 (100).

Epimerization of 31 to 32. A mixture containing **31** (0.10 g, 0.32 mmol) and *t*-BuOK (0.182 g, 1.62 mmol) in *tert*-butyl alcohol (5 mL) was refluxed for 40 h under argon atmosphere. Removal of the solvent and the purification of the residue by silica gel column chromatogrphy gave 0.045 g (45%) of **32** along with unreacted **31** (0.03 g). IR ($CHCl_3$) 1693, 1582, 1460, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 1.55−1.65 (m, 2H), 1.75−1.85 (m, 3H), 1.95 (dd, J = 8.93, 12.3 Hz, 1H), 2.87 (dd, J = 5.04, 8.93 Hz, 1H), 4.16 (bs, 1H), 4.38 (bs, 1H), 7.25 (d, J = 8.35 Hz, 1H), 7.65 (dd, J = 2.42, 8.32 Hz, 1H), 8.25 (d, J = 2.46 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 28.6, 29.5, 40.2, 44.7, 55.9, 61.8, 79.8, 124.0, 137.1, 139.9, 148.5, 155.1; mass (*m*/*z*, relative intensity) 308 (M^+, 3), 208 (37), 140 (72), 69 (51), 57 (100).

Epibatidine (1). Trifluoroacetic acid (0.1 mL, 1.16 mmol) was added to a stirring solution of **32** (0.045 g, 0.15 mmol) in DCM (5 mL) at 0 °C under argon atmosphere. Contents were further stirred for additional 4 h at room temperature. The reaction mixture was basified with saturated aqueous Na_2CO_3 solution. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with $CHCl_3$:MeOH:NH_4OH (98:2:1), to give **1** (0.028 g, 90%) as a thick pale yellow paste. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.5−1.65 (m, 5H), 1.91 (dd, J = 12.1, 8.8 Hz, 1H), 2.77 (dd, J = 8.6, 4.8 Hz, 1H), 3.57 (bs, 1H), 3.8 (bs, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.75 (dd, J = 8.3, 2.5 Hz, 1H), 8.26 (d, J = 2.6 Hz, 1H).

7-(*tert*-Butoxycarbonyl)-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (28). Yellow viscous oil. Yield 55%. IR (neat) 1727, 1708, 1460, 1227, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.21 Hz, 3H), 1.42 (s, 9H), 1.50−1.55 (m, 1H), 1.55−1.70 (m, 1H), 1.70−1.95 (m, 2H), 3.0 (t, J = 4.89 Hz, 1H), 3.30 (d, J = 5.46 Hz, 1H), 4.2 (q, J = 7.31 Hz, 2H), 4.30 (bs, 1H), 4.60 (bs, 1H), 7.25 (d, J = 8.44 Hz, 1H), 7.65 (dd, J = 2.43, 8.27 Hz, 1H), 8.30 (d, J = 2.44 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 24.5, 28.0, 29.3, 47.0, 56.8, 58.1, 61.0, 62.3, 80.2, 124.0, 137.0, 138.4, 148.4, 154.57, 170.9; mass (*m*/*z*, relative intensity) 380 (M^+, 3), 280 (25), 212 (60), 142 (10), 69 (100).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (33). Yellow viscous oil. Yield 62%. IR ($CHCl_3$) 1731, 1455, 1215, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.8 (t, J = 6.95 Hz, 3H), 1.60−1.45 (m, 2H), 2.1−2.2 (m, 2H), 2.90 (d, J = 10.12 Hz, 1H), 3.1 (d, J = 10.13 Hz, 1H), 3.25 (d, J = 4.03 Hz, 1H), 3.73−3.5 (m, 4H), 3.75 (m, 1H), 7.20 (d, J = 8.38 Hz, 1H), 7.45−7.25 (m, 4H), 7.5 (m, 1H), 8.05 (dd, J = 8.35 Hz, 1H), 8.35 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 25.3, 26.2, 49.1, 51.4, 54.8, 59.5, 59.7, 65.3, 122.9, 126.6, 127.9, 128.2, 136.7, 138.5, 139.0, 149.0, 170.6; mass (*m*/*z*, relative intensity) 370 (M^+, 8), 159 (100), 130 (15), 91 (87), 68 (18).

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (34). Yellow viscous oil. Yield 7%. IR ($CHCl_3$) 1720, 1216, 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (t, J = 7.1 Hz, 3H), 1.60−1.80 (m, 2H), 1.85−2.0 (m, 1H), 2.10−2.20 (m, 1H), 3.45 (m, 2H), 3.60 (t, J = 4.45 Hz, 1H), 3.75 (s, 2H), 3.80 (m, 1H), 3.80−4.06 (m, 2H), 7.25−7.42 (m, 7H), 8.10 (d, J = 2.19 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 21.3, 22.7, 29.4, 44.6, 47.9, 51.1, 60.0, 62.2, 64.5, 122.9, 126.9, 128.2, 133.5, 138.7, 139.1, 149.0, 150.0, 171.6; mass (*m*/*z*, relative intensity) 370 (M^+, 3.5), 159 (100), 131 (13.5), 91 (89).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]-heptane (35). Yellow viscous oil. Yield 55%. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60−1.80 (m, 2H), 1.85−2.00 (m, 2H), 2.10−2.20 (m, 1H), 3.15 (d, J = 4.03 Hz, 1H), 3.45 (m, 2H), 3.65 (d, J = 16.8 Hz, 2H), 4.15 (m, 1H), 7.25−7.42 (m, 7H), 8.10 (dd, J = 2.19, 8.0 Hz, 1H), 8.40 (d, J = 2.30 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.3, 26.9, 29.1, 51.5, 54.4, 63.7, 66.6, 79.9, 123.3, 127.8, 128.2, 137.4, 148.2.

7-Benzyl-2-carbethoxy-7-azabicyclo[2.2.1]hept-2-ene (36). Compound **36** was prepared by the reaction of **12** (0.50 g, 1.64 mmol) with ethyl propiolate (0.178 g, 1.8 mmol) using Ag(I)F (0.458 g, 3.6 mmol) in DCM (30 mL) in an identical manner as described for compound **26**. The crude residue was purified by silica gel column chromatography eluting with EtOAc:hexane (1.5:8.5), to obtain 0.29 g (75%) of **36** as a pale yellow oil. IR (neat) 1714, 1606, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (d, J = 10.20 Hz, 2H), 1.30 (t, J = 7.10 Hz, 3H), 1.98 (dd, J = 3.0 Hz, 10.45 Hz, 2H), 3.42 (s, 2H), 3.89 (bs, 1H), 4.10 (d, J = 2.49 Hz, 1H), 4.25 (q, J = 7.15 Hz, 2H), 6.95 (d, J = 2.1 Hz, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 23.5, 51.8, 60.1, 64.0, 65.1, 126.7, 127.1, 128.1, 128.5, 128.7, 139.1, 142.9, 164.5; mass (*m*/*z*, relative intensity) 257 (M^+, 2), 228 (80), 183 (68), 91 (100).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (27). To a stirring solution of **37** (0.233 g, 0.97 mmol) into a mixture of ether (8 mL) and THF (4 mL) at −70 °C was introduced *n*-BuLi (1.6 M in hexane, 0.61 mL, 0.97 mmol) dropwise. The mixture was stirred at −70 °C for 20 min before a solution of **36** (0.25 g, 0.97 mmol) dissolved in ether (4 mL) was introduced. The reaction mixture was allowed to stir additionally for 2 h at −70 °C before warming to −50 °C. After stirring for 30 min at −50 °C, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was warmed to rt. The aqueous phase was extracted with EtOAc (15 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography eluting with hexane:EtOAc (8.5:1.5) to give **27** (0.215 g, 60%).

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo[2.2.1]heptane (38). Yellow oil. Yield 45%. IR ($CHCl_3$) 2221, 1462, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40−1.52 (m, 2H), 1.70−1.90 (m, 1H), 1.95−2.12 (m, 1H), 2.65 (d, J = 5.94 Hz, 1H), 3.65 (t, J = 4.15 Hz, 1H), 3.75 (m, 4H), 7.5−7.25 (m, 7H), 8.25 (d, J = 2.46 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 27.2, 36.6, 49.9, 51.2, 63.5, 64.4, 121.4, 124.0, 127.1, 128.1, 128.3, 132.2, 137.9, 138.5, 148.7, 150.1; mass (*m*/*z*, relative intensity) 323 (M^+, <1), 159 (34), 140 (55), 126 (54), 105 (39), 91 (100), 83 (55).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo[2.2.1]heptane (39). Viscous yellow oil. Yield 18%. IR ($CHCl_3$) 2400, 1461, 1217, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55−1.70 (m, 1H), 2.00−2.15 (m, 3H), 2.85 (dd, J = 4.76, 9.73 Hz, 2H), 3.30 (s, 1H), 3.55 (s, 2H), 3.65 (s, 1H), 7.25−7.45 (m, 6H), 7.58 (dd, J = 2.45, 8.24 Hz, 1H), 8.45 (d, J = 2.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0, 26.8, 41.4, 51.2, 51.7, 61.59, 65.7, 119.9, 124.0, 127.3, 128.4, 128.5, 137.5, 138.4, 148.5, 150.2.

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*exo*-cyano-7-azabicyclo[2.2.1]heptane (40). Viscous oil. Yield 55%. IR (Nujol) 2400, 1461, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55−1.75 (m, 2H), 2.05−2.15 (m, 2H), 3.0 (s, 2H), 3.38 (d, J = 4.17 Hz, 1H), 3.67 (s, 2H), 3.8 (d, J = 4.08 Hz, 1H), 7.25−7.50 (m, 6H), 8.05 (dd, J = 2.45, 8.30 Hz, 1H), 8.26 (d, J = 2.45 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 24.0, 34.9, 44.7, 51.5, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 130.9, 138.4, 139.4, 150.4, 150.5; mass (*m*/*z*, relative intensity) 323 (M^+, <1), 159 (61), 131 (25), 91 (100).

7-Benzyl-2-*endo*-(6-chloro-3-pyridyl)-3-*endo*-cyano-7-azabicyclo[2.2.1]heptane (41). Yellow oil. Yield 13%. IR ($CHCl_3$) 2400, 1522, 1463, 1217, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.80−1.95 (m, 2H), 2.05−2.15 (m, 2H), 3.55 (m, 2H), 3.75 (m, 4H), 7.3−7.45 (m, 6H), 7.47 (dd, J = 2.45, 8.23 Hz, 1H), 8.26 (d, J = 2.44 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 24.0, 34.9, 44.7, 51.4, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 128.8, 130.9, 138.4, 139.4, 150.4, 150.5; mass (*m*/*z*, relative intensity) 323 (M^+, 1), 189 (26), 159 (73), 91 (100).

7-Benzyl-2-*exo*-(6-chloro-3-pyridyl)-3-*endo*-nitro-7-azabicyclo[2.2.1]heptane (42). Viscous oil. Yield 65%. IR

($CHCl_3$) 1550, 1470, 1230, 1120, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60−1.75 (m, 2H), 2.0−2.2 (m, 2H), 3.35 (d, J = 4.5 Hz, 1H), 3.45 (d, J = 5.36 Hz, 1H), 3.63 (s, 2H), 4.02 (m, 1H), 4.75 (m, 1H), 7.28 (d, J = 8.45 Hz, 1H), 7.35−7.45 (m, 5H), 7.78 (dd, J = 2.45, 8.3 Hz, 1H), 8.5 (d, J = 2.46 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) gd 20.3, 26.5, 48.4, 51.8, 62.8, 66.9, 93.0, 124.0, 127.5, 128.5, 128.6, 137.2, 137.9, 138.1, 148.9, 150.1; mass (*m*/*z*, relative intensity) 221 (6), 191 (14), 140 (9), 83 (100).

***N*-Methyl-2,6-bis(trimethylsilyl)piperidine (43). 19b** (4 g, 12.1 mmol) was deprotected using trifluoroacetic acid (9.70 g, 85.1 mmol) in an identical fashion as described for **19a**. To a stirring solution of crude amine (2.54 g, 11.09 mmol) in CH_3CN (120 mL) were added a 37% aqueous solution of HCHO (4 mL) and $NaBH_3CN$ (0.836 g, 13.30 mmol). The reaction mixture was stirred for an additional 15 min. Neutralization of the reaction mixture by adding glacial acetic acid followed by basification by the slow addition of concentrated NH_4OH and extraction with hexane (3 × 50 mL) followed by concentration and purification of the residue by silica gel column chromatography, eluting with EtOAc:hexane (3:97), gave **43** (2.15 g, 80% yield) as a colorless viscous liquid. ^1H NMR ($CDCl_3$, 200 MHz) gd 0.06 (s, 18H), 1.52−1.67 (m, 6H), 2.2−2.3 (m, 2H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.2, 20.7, 24.3, 42.4, 54.1; mass (*m*/*z*, relative intensity) 243 (M^+, <1), 170 (100).

8-Methyl-2-*endo*-(6-chloro-3-pyridyl)-3-*exo*-carbethoxy-8-azabicyclo[3.2.1]octane (45). Yellow oil. Yield 64%. IR (neat) 1724, 1582, 1241, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.21 Hz, 3H), 1.50−1.75 (m, 3H), 1.85−2.05 (m, 3H), 2.52 (s, 3H), 3.17 (m, 2H), 3.55 (m, 1H), 3.65 (d, J = 6.65 Hz, 1H), 4.2 (q, J = 7.2 Hz, 2H), 7.27 (d, J = 8.24 Hz, 1H), 7.88 (dd, J = 2.73, 8.25 Hz, 1H), 8.42 (d, J = 2.75 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.1, 16.7, 19.5, 23.2, 34.6, 45.9, 57.1, 60.5, 62.0, 66.1, 123.9, 137.2, 142.2, 148.4, 149.1, 171.9; mass (*m*/*z*, relative intensity) 308 (M^+, 3), 166 (10), 97 (100), 83 (72).

8-Methyl-2-*exo*-(6-choro-3-pyridyl)-3-*exo*-carbethoxy-8-azabicyclo[3.2.1]octane (47). Viscous liquid. Yield 61%. IR ($CHCl_3$) 1728, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80 (t, J = 7.21 Hz, 3H), 1.10−1.22 (m, 2H), 1.62−1.75 (m, 2H), 1.92−2.05 (m, 2H), 2.58 (s, 3H), 3.08 (m, 1H), 3.25 (d, J = 10.2 Hz, 1H), 3.42 (m, 2H), 3.68 (m, 2H), 7.12 (d, J = 3.37 Hz, 1H), 7.92 (dd, J = 2.76, 8.34 Hz, 1H), 8.24 (d, J = 2.78 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.4, 17.4, 20.5, 21.2, 32.6, 47.7, 53.5, 59.5, 60.0, 66.2, 123.5, 138.1, 138.5, 149.2, 149.7, 171.8; mass (*m*/*z*, relative intensity) 308 (M^+, 16), 235 (37), 194 (18), 97 (100), 82 (14).

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Supporting Information Available: Copies of NMR spectra of new compounds (59 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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