Synthesis of (±)-Epibatidine and Its Analogues†

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A nonopiate analgesic, epibatidine (**1**), isolated from the skin of the Ecuadoran poison frog was synthesized in racemic form starting from tropinone. Distinctly different from the previously published approaches, this synthesis features the novel synthesis of the 7-azabicyclo[2.2.1]heptane ring system by contraction of the tropinone skeleton *via* Favorskii rearrangement. Five analogues of **1** were also prepared, and their analgesic activities were evaluated.

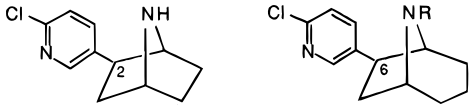
Introduction

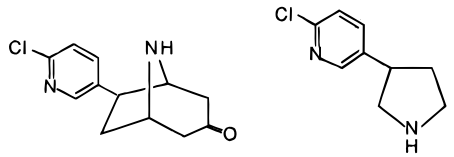
Epibatidine(**1**), which was isolated by Daly and his coworkers[1] in a trace amount from the skin of the Ecuadorian poison frog *Epipedobates tricolor* in 1992, represents a new class of alkaloid possessing a 7-azabicyclo[2.2.1]-heptane (7-azanorbornane) structure to which is attached, in an *exo*-orientation, a 2-chloro-5-pyridyl substituent. It was found to be at least 200 times more potent than morphine in bioassays of analgesic-like effects in mice, but its effects were not blocked by the opiate receptor antagonist naloxone.[1] Subsequent studies showed that epibatidine is an extremely potent agonist of the nicotinic acetylcholine receptor[2] that has been found to be involved in the mediation of several human disorders such as Alzheimer's and Parkinson's diseases.[3]

Interestingly, the (−)- and (+)-enantiomers of **1** are nearly equipotent in analgesic tests. This lack of stereospecificity suggests that epibatidine's chiral center is not critical for its interaction with the neuronal nicotinic receptor. The analgesic activity of **1** is blocked by the nicotinic antagonist mecamylamine. Epibatidine has little or no activity at a variety of other central receptors, including muscarinic, adrenergic, dopamine, serotonin, and GABA receptors. The discovery of **1** has rekindled an interest in nicotinic receptor-mediated analgesic effects.[2c]

Due to its unique structure, remarkable pharmacological activity, and scarcity in nature, epibatidine has been the subject of many biological[2,4] and synthetic studies.[5,6]

To date, more than 10 papers about the synthesis of epibatidine and its analogues have been published. Recently we too have been developing a synthetic approach to this target molecule.[7,8] In this paper, we describe the details of our synthesis of **1** and epibatidine analogues **11a**−**13**.





Results and Discussion

Total Synthesis of (±)-Epibatidine. Several approaches have been reported for the synthesis of **1** employing two different methodologies for the construction of the azabicyclic system: (1) Diels−Alder reaction of *N*-protected pyrroles with activated dienophiles[5] and (2) intramolecular nucleophilic ring closure of aminocyclohexane derivatives.[6] Our strategy is outlined in Scheme 1. In considering a synthetic route to epibatidine, we were led by other investigations in our laboratory to utilize the readily available tropinone (**4**) as a starting material. Retrosynthetic analysis of the target molecule suggested that the α,β-unsaturated ester **3** would be an advantageous precursor. Conjugate addition of a pyridyl anion to **3** followed by decarboxylation and deprotection would generate epibatidine. It was further

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(3) Javick, M. E. *Br. J. Addict.* **1991**, *86*, 571.

(4) (a) Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34. (b) Rupniak, N. M. J.; Patel, S.; Marwood, R.; Webb, J.; Traynor, J. R.; Elliott, J.; Freedman, S. B.; Fletcher S. R.; Hill, R. G. *Br. J. Pharmacol.* **1994**, *113*, 1487. (c) Sullivan, J. P.; Decker, M. W.; Brioni, J. D.; Donnelly-Roberts, D.; Anderson, D. J.; Bannon, A. W.; Kang, C. H.; Adams, P.; Piattoni-Kaplan, M.; Buckley, M. J.; Gopalakrishnan, M.; Williams, M.; Arneric, S. P. *J. Pharmcol. Exp. Ther.* **1994**, *271*, 624. (d) Bonhaus, D. W.; Bley, K. R.; Broka, C. A.; Fontana, D. J.; Leung, E.; Lewis, R.; Shieh, A.; Wong, E. H. F. *J. Pharmcol. Exp. Ther.* **1995**, *272*, 1199.

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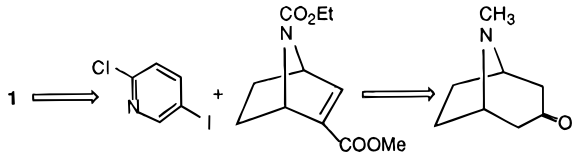
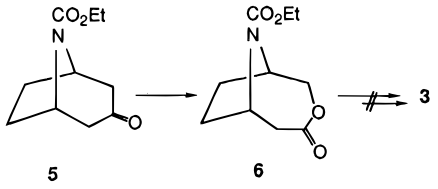
Scheme 1



Scheme 2

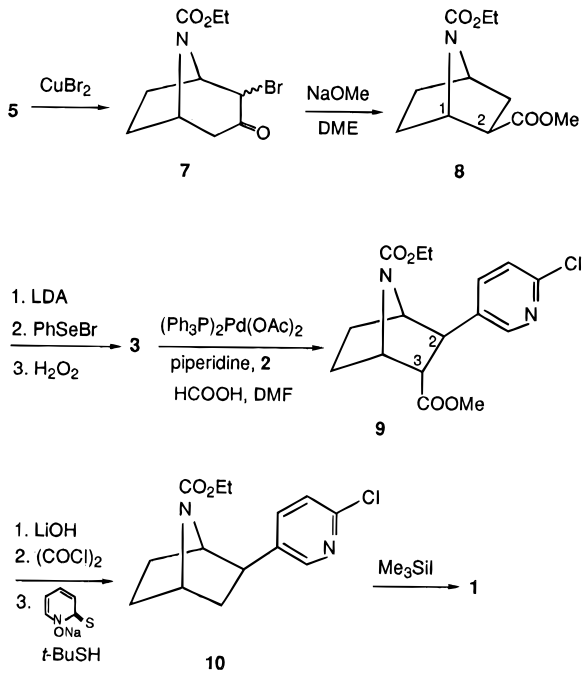


expected that the ester **3** could be obtained from **4** by contraction of its azabicyclo[3.2.1]octane ring. Thus, the key step in this approach would be the contraction of the tropane skeleton to the 7-azabicyclo[2.2.1]heptane ring system followed by the stereoselective introduction of a 2-chloropyridyl group.

For the preparation of α,β-unsaturated ester **3**, two methods for contracting the tropinone ring by one carbon seemed possible. We first intended to convert *N*-carbethoxytropinone **(5)**, which could be obtained from **4** in one step,[9] to lactone **6** by Baeyer−Villiger oxidation. Subsequent hydrolysis of **6** followed by oxidation of the resulting alcohol to an aldehyde and final intramolecular aldol condensation should furnish **3** (Scheme 2). This approach, however, proved to be unsatisfactory because of the low yield of lactone **6**.[10] We then turned to the Favorskii reaction, which has been widely used for ring contraction in the synthesis of strained and monocyclic ring systems. This type of rearrangement, however, has been less studied in bicyclic systems, especially for substrates having halogen at a position other than a bridgehead.[11] To our knowledge, no precedents have been reported for any nonbridgehead-halogenated heterobicycloketones. Compound **5** was brominated with cupric bromide in a mixed solvent of $CHCl_3$ and EtOAc to give the monobromide **7**, which was subjected to rearrangement without separation of the two isomers. When **7** was treated with sodium methoxide in DME at 0 °C,[12] both isomers underwent Favorskii rearrangement to yield the expected ester **8** (56% overall yield from **5**) stereoselectively.[13] The key intermediate **3** was then easily obtained in 68% yield by α-selenation of **8** followed by selenoxide elimination (Scheme 3).

The structure of **8** was confirmed by infrared, mass, and ^{1}H NMR spectral analysis. In the IR spectrum an absorption band appeared at 1734 cm^{-1}, indicating the presence of the ester group; in the mass spectrum a molecular ion peak was found at *m/e* 227; and in the ^{1}H NMR spectrum all of the protons could be clearly assigned (see the Experimental Section). The stereochemisty of **8** was assigned on the basis of the lack of a

Scheme 3



coupling between H-1 and H-2 in the ^{1}H NMR spectrum, implying a dihedral angle close to 90°, which is consistent only with the *exo*-isomer.

With α,β-unsaturated ester **3** in hand, conjugate addition of a 5-pyridyl cuprate to **3** was investigated. However, it was unsuccessful under various conditions probably due to the low reactivity of the α,β-disubstituted unsaturated ester. We elected to use the reductive palladium-catalyzed coupling reaction.[14] Regan utilized this reaction as the key step in the total synthesis of epibatidine.[5b] However, when compound **3** and 2-chloro-5-iodopyridine (**2**)[15] were heated at 70 °C in DMF containing piperidine, formic acid, and 8 mol % of $(Ph_3P)_2$-$Pd(OAc)_2$, a complex mixture was obtained from which neither the product **9** nor the starting material **3** could be isolated. We assumed that the α,β-unsaturated ester **3** would undergo a *retro* Diels−Alder reaction and that the coupling reaction should be performed at lower temperature. Therefore, the reaction mixture of **3** and **2** was stirred at room temperature for 4 d with triethylamine as the base. To our delight, the coupling product **9** was formed stereoselectively in 56% yield. The *trans* relationship between H-2 and H-3 and the *exo*-orientation of the 2-chloropyridyl group of **9** were demonstrated on the basis of ^{1}H NMR coupling constants, which were in agreement with the reported values for the epibatidine ring system.[16]

Conversion of **9** to **1** was straightforward. Hydrolysis of **9** with LiOH followed by radical decarboxylation using Barton's method[17] gave **10** in 69% yield, and subsequent deprotection of **10** with iodotrimethylsilane led to epibatidine (**1**) in a yield of 83% after chromatography (Scheme 3). As detailed in the Experimental Section, the

(9) Montzka,T. A.; Matiskella, J. D.; Rartyka, R. A. *Tetrahedron Lett.* **1974**, *15*, 1325.
(10) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.
(11) Itooka, T.; Matoba, K.; Yamazaki, T.; Muraoka, O.; Momose, T. *Chem. Pharm. Bull.* **1986**, *34*, 2391.
(12) Chenier, P. J.; Kao, J. C. *J. Org. Chem.* **1976**, *41*, 3730.
(13) It would be a more direct procedure if α,α′-dihalotropinone could be rearranged to **3** in a single step. However, all attempts by means of Favorskii rearrangement on α,α′-dibromotropinone under various basic conditions to achieve the α,β-unsaturated ester **3** were unsuccessful.
(14) (a) Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G. J. *J. Organomet. Chem.* **1989**, *368*, 249. (b) Larock, R. C.; Johnson, P. L. *J. Chem. Soc., Chem. Commun.* **1989**, 1368.
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(16) Gonzalez, J.; Koontz, J. I.; Hodges, L. M.; Nilsson, K. R.; Neely, L. K.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 3405.
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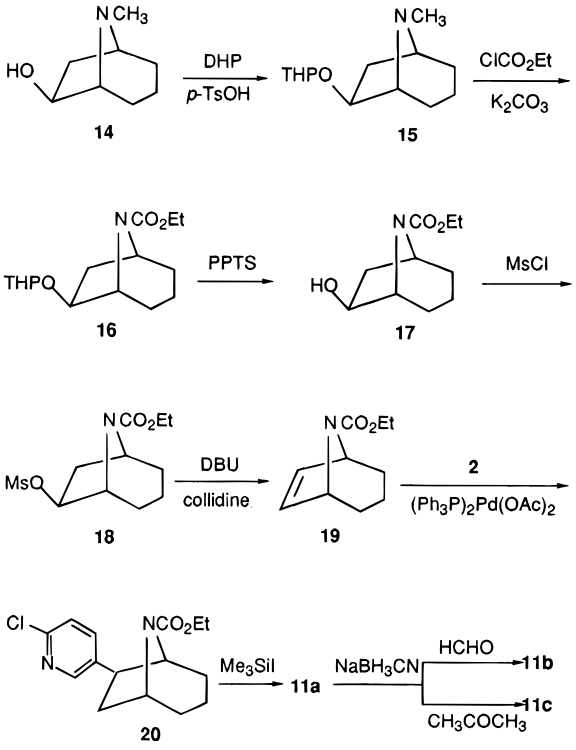
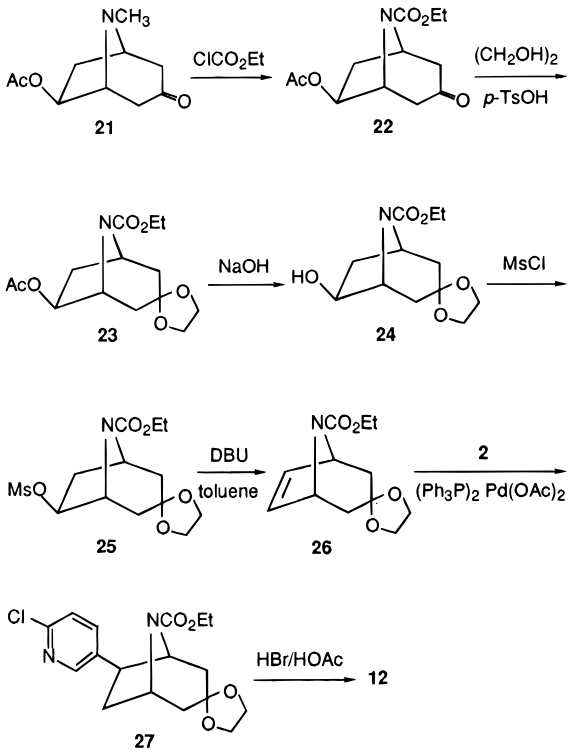
Scheme 4

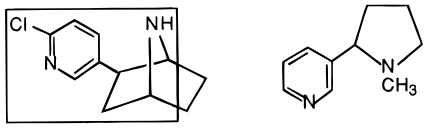


Scheme 5



^{1}H and ^{13}C NMR spectra of this compound are in good accordance with those described in the literature.

Synthesis of Epibatidine Analogues. All analogues of **1** reported so far have the same basic skeleton, the 7-azabicyclo[2.2.1]heptane ring system, as epibatidine itself. It is apparent that the chemical structure of epibatidine (**1**) has some structural resemblance to nicotine, and in fact, it exhibits a very high affinity, in the picomolar range, for [^{3}H]nicotine and [^{3}H]cytisine binding sites in the brain.[2] Analogues **11**−**13**, which have different skeletons from **1**, were thus designed and prepared.



1

nicotine

The synthesis of **11a**−**c** is summarized in Scheme 4. 6β-Tropanol (**14**), which could be easily obtained from the commercially available 6β-hydroxytropinone by Wolff Kischner reduction,[18] was used as the starting material. Because of the strongly basic nitrogen atom, the protection of the hydroxy group of **14** as the THP ether was accomplished using 1 equiv of *p*-toluenesulfonic acid. Demethylation of **15** by treatment with ethyl chloroformate[8] in the presence of K_2CO_3 afforded the carbamate **16** (90% overall yield from **14**). Deprotection of **16** with PPTS in ethanol yielded alcohol **17** (97%), which was mesylated to furnish **18** (93%). The elimination of mesylate **18** was accomplished by treatment with 1 equiv of DBU in refluxing collidine, yielding the olefin **19** (79%). Reductive coupling of compounds **19** and **2** was carried out in a manner similar to that mentioned above. The desired coupling product **20** was formed stereoselectively (75%). Finally, cleavage of the carbamate of **20** with iodotrimethylsilane gave homoepibatidine **11a** (93%). Compound **11a** was then further *N*-alkylated to produce **11b** and **11c** by reductive amination using sodium cyanoborohydride and formaldehyde or acetone, respectively.

The synthesis of **12** is summarized in Scheme 5. 6β-Acetoxytropinone (**21**) was demethylated and protected as the ketal **23**, which was hydrolyzed to give alcohol **24**. Compound **24** was mesylated to furnish mesylate **25**. Elimination was achieved by treatment of **25** with 8 equiv of DBU in toluene at reflux temperature. The overall yield of olefin **26** from acetate **21** via five steps is 51%. In a manner similar to that described above, the addition product **27** was obtained stereoselectively (70%). Finally, the protecting groups were removed in one step by treatment of **27** with hydrogen bromide in acetic acid for 60 h at room temperature, affording compound **12**.

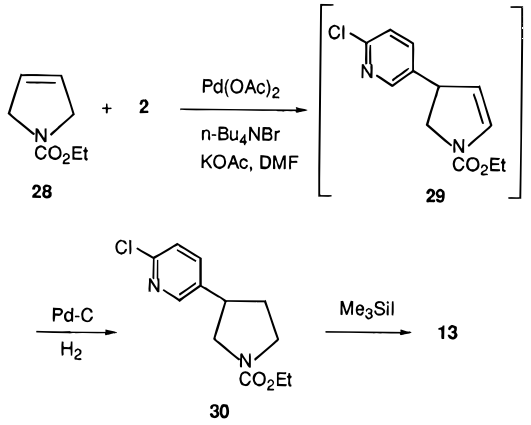
The stereochemistry of these compounds was confirmed by inspection of the ^{1}H NMR coupling constants of the protons involved. The dd peaks ($J_{6\alpha,7\alpha} = 9.0-9.5$ Hz and $J_{6\alpha,7\beta} = 4.4-5.5$ Hz) of H-6 in the homoepibatidine skeleton are diagnostic for *exo* substitution. In addition, because of the partial double bond character of the *N*-acyl bond, interconversion between the rotamers is very slow. As a result, we observed a series of doubled signals in the ^{1}H NMR spectra of many intermediates. This was also observed in the spectrum of *N*-acetylepibatidine during the original structure elucidation.[1]

The synthesis of desethyleneepibatidine **13** is outlined in Scheme 6. Although the synthesis of similar compounds via [3 + 2] cycloaddition between an azomethine ylide and an unsaturated ester was previously reported,[19] we prepared **13** by a more practical three-step reaction sequence. The synthesis started with the protected 3-pyrroline **28**, which was readily prepared from pyrrole

(18) Jones, J. B.; Pinder, A. R. *J. Chem. Soc.* **1959**, 615.

(19) (a) Johnson, G.; Drummond, J. T.; Boxer, P. A.; Bruns, R. F. *J. Med. Chem.* **1992**, *35*, 233. (b) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pham. Bull.* **1985**, *33*, 2762 and references cited therein.

Scheme 6



in two steps by reduction with zinc and protection of the amine as the carbamate.[20] Palladium-catalyzed allylic arylation[21] of **28** with **2** yielded the unstable cross-coupling product **29**, which was immediately hydrogenated, giving the pyrrolidine derivative **30** (62% overall yield). The carbethoxy group of **30** was removed with iodotrimethylsilane, giving desethyleneepibatidine **13**. In order to optimize the yield of **30**, different conditions were examined. Temperature was found to be critical. Reaction at higher temperature resulted in polymerization. Both tetrabutylammonium bromide and tetrabutylammonium chloride are effective to catalyze the addition, though the former is more efficient.

Biological Evaluation. The analogues were evaluated for analgesic activity using the hot plate assay and compared with (±)-epibatidine. At a dose of 10 μg/kg, (±)-epibatidine caused significant analgesia upon ip in mice. Compound **11a**, with a LD_{50} of about 1 mg/kg in mice, caused a marked analgesic effect at a dose of 40 μg/kg comparable to that elicited by 10 μg/kg of racemic epibatidine. While **11b** showed analgesic activity similar to that of **11a**, **11c** was less potent and imparted analgesia at a higher dose (190 μg/kg). The analogues **12** and **13** showed no activity at a dose of up to 4 mg/kg. The order of analgesic potency is **1** > **11a** ≈ **11b** > **11c** >> **12** and **13**, which indicates that the bridge ring and *N*-substituents are crucial to analgesic activity. We also noted that the analgesia elicited by compound **11a** was completely abolished by treatment with the nicotinic receptor antagonist mecamylamine (2 mg/kg, 7 min afterwards). This result suggests the possible involvement of nicotinic receptors.

Conclusions

Many approaches to the total synthesis of epibatidine have appeared in recent years. However, this novel and efficient route is distinctly different from the others in the generation of 7-azabicyclo[2.2.1]heptane from tropinone. The use of a Favorskii rearrangement for ring contraction has the potential of general utility for preparing 7-azabicyclo[2.2.1]heptane derivatives. The preparation and analgesic activity of homoepibatidines and desethyleneepibatidine are reported. The results should prove valuable for structure−activity relationship studies of epibatidine.

(20) Kawaguchi, M.; Hayashi, O.; Kanamoto, M.; Hamada, M.; Yamamoto, Y.; Oda, J. *Agric. Biol. Chem.* **1987**, *51*, 435.
(21) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.

Experimental Section

General Procedures. All air- or moisture-sensitive reactions were performed in flame-dried glassware under N_2 atmosphere. Solvents were distilled from appropriate drying agents under nitrogen atmosphere when necessary. Melting points were not corrected. NMR spectra were recorded at 400 MHz from $CDCl_3$ solutions. Chemical shifts are reported in δ relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. IR spectra were obtained as films or potassium bromide pellets. Mass spectra were determined at an ionizing voltage of 70 eV by electron impact. Anhydrous sodium sulfate was used as drying agent. Elemental analyses were performed by the Analytic Department of the Institute.

7-Carbethoxy-2-carbomethoxy-7-azabicyclo[2.2.1]-heptane (8). Powdered cupric bromide (99%, 4.60 g, 20.6 mmol) was added portionwise to a refluxing solution of *N*-carbethoxytropinone (**5**) (2.02 g, 10.3 mmol) in $CHCl_3$ (20 mL) and EtOAc (20 mL) for 20 min with a constant stream of nitrogen bubbled through the solution. When the addition was complete, the solution was heated for 30 min until the green color and dark solid disappeared. The reaction mixture was cooled to rt and filtered, and the filtrate was evaporated. The residue was dissolved in EtOAc, and the solution was washed with water, 5% $NaHCO_3$, and brine successively. The organic layer was dried over Na_2SO_4 and evaporated to give the bromide **7** as an oil, which was used for the next reaction directly.

The foregoing crude product **7** was dissolved in DME (15 mL), and the solution was added dropwise at 0 °C to a well-stirred suspension of NaOMe (1.67 g, 30.9 mmol) in DME (35 mL). The mixture was stirred at rt for 30 min. The resulting solution was neutralized with glacial AcOH, and then dry Et_2O (50 mL) was added to precipitate NaOAc. The filtrate was evaporated and the residue chromatographed on silica, eluting with petroleum ether:EtOAc (8:1). The Favorskii rearrangement product **8** (1.32 g, 56% overall yield from **5**) was isolated as a colorless oil: IR 1734, 1715 cm^{-1}; MS (*m*/*z*) 227 (M^+), 198, 168, 154, 140; ^{1}H NMR δ 4.52 (1H, m), 4.33 (1H, br s), 4.06 (2H, q, J = 7.0 Hz), 3.70 (3H, s), 2.55 (1H, dd, J = 8.5, 4.9 Hz), 2.22 (1H, m), 1.77 (2H, m), 1.60 (1H, dd, J = 12.2, 9.0 Hz), 1.42 (2H, m), 1.19 (3H, t, J = 7.1 Hz); HRMS calcd for $C_{11}H_{17}NO_4$ 227.1157, found 227.1163.

7-Carbethoxy-2-carbomethoxy-7-azabicyclo[2.2.1]-heptane-2-ene (3). To a solution of dry diisopropylamine (0.96 mL, 6.9 mmol) in THF (25 mL) at −30 °C was added *n*-BuLi (4.30 mL of 1.6 M, 6.9 mmol) dropwise. Ester **8** (1.20 g, 5.3 mmol) in THF (5 mL) was then added dropwise at −78 °C to the foregoing solution. After the mixture was stirred for 20 min, a solution of PhSeBr (1.50 g, 6.3 mmol) in THF (3 mL) was added in one portion. The reaction mixture was warmed to 0 °C and partitioned between 0.5 N HCl (50 mL) and ether (50 mL). The organic layer was separated and the aqueous phase reextracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL). H_2O_2 (30%, 2 mL) was added slowly below 25 °C. After being stirred for 15 min, the reaction mixture was washed with 5% $NaHCO_3$ and brine. The residual oil was chromatographed on silica, eluting with petroleum ether:EtOAc (8:1) to afford α,β-unsaturated ester **3** (0.81 g, 68%) as a colorless oil: IR 3070, 1740, 1721, 1608 cm^{-1}; MS (*m*/*z*) 197 ($M^+ - C_2H_4$), 122, 94; ^{1}H NMR δ 6.98 (1H, br s), 5.00 (1H, d, J = 2.3 Hz), 4.83 (1H, br s), 4.04 (2H, q, J = 7.1 Hz), 3.72 (3H, s), 1.80−2.04 (4H, m), 1.19 (3H, t, J = 7.1 Hz).

7-Carbethoxy-2β-(2-chloro-5-pyridinyl)-3α-carbomethoxy-7-azabicyclo[2.2.1]heptane (9). To a stirred solution of **3** (350 mg, 1.59 mmol), 2-chloro-5-iodopyridine (**2**) (950 mg, 3.97 mmol), triethylamine (550 mg, 5.44 mmol), and $Ph(OAc)_2(PPh_3)_2$ (125 mg, 0.16 mmol) in DMF (5 mL) was added HCOOH (0.17 mL, 4.4 mmol) all at once. The mixture was stirred at rt for 4 d. EtOAc (15 mL) and water (5 mL) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica (petroleum

ether:EtOAc 6:1) gave **9** (304 mg, 56%) as a colorless oil: IR 2956, 1735, 1708, 1461, 1292, 1183, 1105 cm^{-1}; MS (*m/z*) 338/340 (M^+), 307/309, 199, 141; ^1H NMR δ 8.30 (1H, d, J = 2.5 Hz), 7.62 (1H, dd, J = 8.3, 2.5 Hz), 7.24 (1H, d, J = 8.3 Hz), 4.64 (1H, m), 4.30 (1H, br s), 4.12 (2H, q, J = 7.1 Hz), 3.71 (3H, s), 3.29 (1H, d, J = 5.4 Hz), 2.99 (1H, dd, J = 5.4, 5.0 Hz), 1,40−1.95 (4H, m), 1.23 (3H, t, J = 7.1 Hz); HRMS calcd for $C_{16}H_{19}{}^{37}ClN_2O_4$ and $C_{16}H_{19}{}^{35}ClN_2O_4$ 340.1004 and 338.1034, found 340.1008 and 338.1014.

7-Carbethoxy-2β-(2-chloro-5-pyridinyl)-3α-carbomethoxy-7-azabicyclo[2.2.1]heptane (10). A solution of ester **9** (293 mg, 0.87 mmol) in methanol−water (3 mL and 2 mL) containing $LiOH\cdot H_2O$ (37 mg, 0.87 mmol) was stirred at 45 °C for 1 h and then cooled and washed with CH_2Cl_2. The aqueous layer was cooled to 0 °C, acidified to pH 1 with 6 N HCl, and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated to give the hydrolyzed product as a foaming solid. The crude acid in benzene (6 mL) was treated with oxalyl chloride (0.52 mL) and DMF (1 drop) at rt for 2 h. The mixture was evaporated to dryness and dissolved in benzene (6 mL). This solution was added dropwise to a stirred suspension of *N*-hydroxypyridine-2-thione−Na salt (156 mg, 1.04 mmol), DMAP (11 mg, 0.09 mmol), *tert*-butyl mercaptan (0.85 mL), and benzene (18 mL) at reflux under nitrogen . After 3 h, the mixture was cooled to rt, thoroughly washed with water, filtered on Celite, and evaporated to dryness. The residue was chromatographed on silica, eluting with petroleum ether:EtOAc (6:1). The decarboxylated product **10** (170 mg, 69% overall yield from **9**) was separated as a colorless oil: IR 2957, 1704, 1459, 1313, 1103 cm^{-1}; MS (*m/z*) 280/282 (M^+), 205, 199, 141; ^1H NMR δ 8.22 (1H, d, J = 2.3 Hz), 7.60 (1H, dd, J = 8.3, 2.3 Hz), 7.23 (1H, d, J = 8.3 Hz), 4.42 (1H, m), 4.19 (1H, br s), 4.08 (2H, q, J = 7.1 Hz), 2.87 (1H, dd, J = 8.5, 5.2 Hz), 2.00 (1H, dd, J = 11.9, 9.1 Hz), 1.5−1.9 (3H, m), 1.21 (3H, t, J = 7.1 Hz); HRMS calcd for $C_{14}H_{17}{}^{37}ClN_2O_2$ and $C_{14}H_{17}{}^{35}ClN_2O_2$ 282.0949 and 280.0979, found 282.0961 and 280.0978.

2β-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane ((±) Epibatidine, 1). A solution of carbamate **10** (76 mg, 0.27 mmol) and iodotrimethylsilane (46 μL, 0.32 mmol) in $CHCl_3$ (2 mL) was heated at reflux for 4 h under nitrogen. When the reaction was complete, methanol (1.0 mL) was added, and the volatile components were removed under reduced pressure. The residue was dissolved in 1 N NaOH (2 mL), and the base generated was extracted with $CHCl_3$. The chloroform layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica, eluting with CH_2Cl_2:MeOH:NH_3 (97:3:1) to give the racemic epibatidine (**1**) (47 mg, 83%) as a colorless solid: mp 50−51 °C (lit.[5a] mp 50−51 °C); MS (*m/z*) 208/210 (M^+), 179/181, 140/142, 69; ^1H NMR δ 8.26 (1H, d, J = 2.4 Hz), 7.77 (1H, dd, J = 8.3, 2.4 Hz), 7.23 (1H, d, J = 8.3 Hz), 3.83 (1H, m), 3.59 (1H, br s), 2.79 (1H, dd, J = 8.8, 5.3 Hz), 1.92 (1H, dd, J = 12.2, 9.1 Hz), 1.4−1.8 (5H, m); ^{13}C NMR δ 149.1, 148.8, 140.0, 137.6, 124.0, 62.7, 55.7, 44.3, 39.8, 30.9, 29.4; HRMS calcd for $C_{11}H_{13}{}^{37}ClN_2$ and $C_{11}H_{13}{}^{35}ClN_2$ 210.0737 and 208.0767, found 210.0718 and 208.0786.

8-Carbethoxy-6β-[(tetrahydropyranyl)oxy]-8-azabicyclo[3.2.1]octane (16). *p*-Toluenesulfonic acid monohydrate (13.2 g, 69.4 mmol) was added portionwise over 30 min to a stirred solution of 6-hydroxytropane (**14**) (9.70 g, 68.8 mmol) and DHP (17.0 mL, 187 mmol) in CH_2Cl_2 (280 mL) at 0 °C. After being stirred at rt for 5 h, the reaction mixture was washed with saturated $NaHCO_3$ and water and dried over Na_2SO_4. Evaporation of the solvent gave the THP ether **15** as a colorless oil.

A suspension of the foregoing crude THP ether **15**, anhydrous K_2CO_3 (40.0 g, 289 mmol), ethyl chloroformate (22.0 mL, 228 mmol), and $CHCl_3$ (480 mL) was heated at reflux for 2 h. The reaction mixture was cooled to rt and filtered. The filtrate was then evaporated and the residue chromatographed directly on silica eluting with petroleum ether:EtOAc (5:1 to 1:1). The demethylated product **16** (17.6 g, 90% overall yield from **14**) was separated as a colorless oil: IR 2940, 1738, 1700 cm^{-1}; MS (*m/z*) 283 (M^+), 198, 154; ^1H NMR δ 4.89 (1H, br s), 3.98−4.59 (5H, m), 3.77 (1H, m), 3.52 (1H, m), 1.4−2.2 (14H, m), 1.21 (3H, t, J = 7.0 Hz). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.46; H, 9.19; N, 4.88.

8-Carbethoxy-6β-hydroxy-8-azabicyclo[3.2.1]octane (17). A solution of THP ether **16** (17.0 g, 60.1 mmol) and PPTS (3.30 g, 13.1 mmol) in anhydrous ethanol (600 mL) was heated at 55−60 °C for 5 h. The solvent was removed under reduced pressure and the residue chromatographed directly on silica eluting with petroleum ether:EtOAc (3:1). The alcohol **17** (11.6 g, 97%) was obtained as a colorless oil: IR 3430, 2928, 1682 cm^{-1}; MS (*m/z*) 199 (M^+), 155, 82; ^1H NMR δ 4.31 (1H, br s), 4.22 (1H, dd, J = 7.2, 2.0 Hz), 4.06 (2H, q, J = 7.1 Hz), 3.95 (1H, br s), 2.93 (1H, br s), 2.19 (1H, dd, J = 13.8, 7.2 Hz), 1.83 (1H, m), 1.3−1.7 (6H, m), 1.20 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.01; H, 8.72; N, 7.03.

8-Carbethoxy-6β-[(methylsulfonyl)oxy]-8-azabicyclo-[3.2.1]octane (18). Mesyl chloride (3.80 mL, 48.8 mmol) was added dropwise to a solution of alcohol **17** (6.03 g, 30.3 mmol) in pyridine (75 mL) at 0 °C. The reaction mixture was stirred for 24 h at rt. Water (120 mL) was added, and the mixture was extracted with $CHCl_3$. The extract was successively washed with 0.5 N HCl, saturated $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated. Chromatography of the residue on silica (petroleum ether:EtOAc 3:2) gave the mesylate **18** (7.77 g, 93%) as white crystals: mp 54−55 °C; IR 2940, 1702, 1360 cm^{-1}; MS (*m/z*) 277 (M^+), 232, 198, 154; ^1H NMR δ 5.10 (1H, dd, J = 6.1, 3.9 Hz), 4.32−4.47 (2H, m), 4.12 (2H, q, J = 7.1 Hz), 3.00 (3H, s), 2.22 (1H, m), 1.4−1.8 (7H, m), 1.24 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{11}H_{19}NO_5S$: C, 47.64; H, 6.91; N, 5.05. Found: C, 47.30; H, 6.95; N, 4.89.

8-Carbethoxy-8-azabicyclo[3.2.1]oct-6-ene (19). A solution of mesylate **18** (3.23 g, 11.7 mmol) and DBU (1.80 mL, 12.0 mmol) in collidine (60 mL) was refluxed for 8 h under nitrogen. The reaction mixture was cooled to rt, poured into cold water (100 mL), and extracted with $CHCl_3$. The combined organic phases were successively washed with 0.5 N HCl, saturated $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica, eluting with petroleum ether:EtOAc (8:1) to afford the olefin **19** (1.69 g, 79%) as a colorless oil: IR 3070, 2942, 1700 cm^{-1}; MS (*m/z*) 181 (M^+), 232, 152, 108, 80; ^1H NMR δ 6.01, 5.99 (2H, 2 br s), 4.51, 4.44 (2H, 2 br s), 4.11 (2H, q, J = 7.1 Hz), 1.3−1.8 (6H, m), 1.21 (3H, t, J = 7.1 Hz); HRMS calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1096.

8-Carbethoxy-6β-(2-chloro-5-pyridinyl)-8-azabicyclo-[3.2.1]octane (20). Piperidine (0.83 g, 9.8 mmol) and $Pd(OAc)_2$-$(PPh_3)_2$ (0.17 g, 0.22 mmol) were added to a stirred solution of the olefin **19** (0.50 g, 2.8 mmol) and **2** (1.67 g, 7.0 mmol) in DMF (5 mL). The mixture was purged with nitrogen, and HCOOH (0.28 mL, 7.4 mmol) was added all at once. The mixture was stirred at 70 °C for 5 h followed by addition of EtOAc (15 mL) and water (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica (petroleum ether:EtOAc 10:1) gave **20** (0.61 g, 75%) as a colorless oil: IR 2970, 1690, 1450, 1103 cm^{-1}; MS (*m/z*) 294/296 (M^+), 155; ^1H NMR δ 8.22 (1H, d, J = 2.3 Hz), 7.46 (1H, dd, J = 8.3 Hz, 2.3 Hz), 7.23 (1H, d, J = 8.3 Hz), 4.04−4.47 (4H, m), 3.18 (1H, m), 2.29, 2.26 (1H, 2 dd, J = 12.7, 9.6 Hz), 1.5−1.9 (7H, m), 1.27, 1.20 (3H, 2t, J = 7.1 Hz); HRMS calcd for $C_{15}H_{19}{}^{37}ClN_2O_2$ and $C_{15}H_{19}{}^{35}ClN_2O_2$ 296.1106 and 294.1135, found 296.1091 and 294.1135.

6β-(2-Chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane ((±) Homoepibatidine, 11a). In the same manner as described for the preparation of **1**, **20** (670 mg, 2.28 mmol) was treated with iodotrimethylsilane (0.45 mL, 3.16 mmol) to afford homoepibatidine (**11a**) (472 mg, 93%) as a white solid: mp 65−66 °C; MS (*m/z*) 222/224 (M^+), 193/195, 83; ^1H NMR δ 8.20 (1H, d, J = 2.2 Hz), 7.66 (1H, dd, J = 8.2, 2.2 Hz), 7.15 (1H, d, J = 8.2 Hz), 3.61 (1H, t, J = 3.2 Hz), 3.24 (1H, br s), 3.06 (1H, dd, J = 9.2, 5.0 Hz), 2.15 (1H, dd, J = 13.2, 9.2 Hz), 1.5−1.9 (7H, m); ^{13}C NMR δ 148.8, 148.2, 142.6, 137.1, 124.1, 62.7, 55.7, 44.3, 39.4, 33.4, 32.8, 17.7; HRMS calcd for $C_{12}H_{15}{}^{37}ClN_2$ and $C_{12}H_{15}{}^{35}ClN_2$ 224.0894 and 222.0924, found 224.0876 and 222.0905.

6β-(2-Chloro-5-pyridinyl)-8-methyl-8-azabicyclo[3.2.1]-octane (11b). To a solution of compound **11a** (35 mg, 0.16 mmol) and formaldehyde (37% solution in water, 0.1 mL) in CH_3CN (2 mL) was added sodium cyanoborohydride (22 mg, 0.33 mmol). After being stirred at rt for 5 h, the mixture was treated with K_2CO_3 and extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated. Purification of the residue by PTLC (MeOH:$CHCl_3$ 1:6) afforded **11b** (33 mg, 87%) as a colorless syrup: MS (*m*/*z*) 236/238 (M^+), 193/195, 97; ^{1}H NMR δ 8.26 (1H, d, J = 2.3 Hz), 7.78 (1H, dd, J = 8.3, 2.3 Hz), 7.15 (1H, d, J = 8.3 Hz), 3.29 (1H, t, J = 3.2 Hz), 3.10 (1H, dd, J = 9.4, 4.9 Hz), 3.02 (1H, br s), 2.46 (3H, s), 2.18 (1H, dd, J = 12.7, 9.4 Hz), 1.5−2.0 (7H, m); ^{13}C NMR δ 148.6, 148.3, 143.1, 137.3, 123.9, 66.1, 59.4, 44.2, 39.1, 34.3, 23.4, 22.9, 17.2; HRMS calcd for $C_{13}H_{17}{}^{37}ClN_2$ and $C_{13}H_{17}{}^{35}ClN_2$ 238.1051 and 236.1080, found 238.1031 and 236.1107.

6β-(2-Chloro-5-pyridinyl)-8-isopropyl-8-azabicyclo[3.2.1]-octane (11c). In the same manner as described above, a solution of compound **11a** (39 mg, 0.18 mmol), acetone (0.1 mL), and sodium cyanoborohydride (24 mg, 0.36 mmol) in CH_3CN (3 mL) was stirred at rt for 12 h to furnish **11c** (37 mg, 78%) as a colorless syrup: MS (*m*/*z*) 264/266 (M^+), 249/251, 179/181, 125, 83; ^{1}H NMR δ 8.34 (1H, d, J = 2.3 Hz), 7.90 (1H, dd, J = 8.3, 2.3 Hz), 7.19 (1H, d, J = 8.3 Hz), 3.56 (1H, br s), 3.16−3.21 (2H, m), 3.04 (1H, dd, J = 9.4, 4.4 Hz), 2.20 (1H, dd, J = 12.8, 9.5 Hz), 1.5−1.9 (7H, m), 1.01 (1H, d, J = 6.5 Hz), 0.97 (1H, d, J = 6.5 Hz); ^{13}C NMR δ 148.6, 148.4, 143.2, 137.5, 123.9, 66.0, 54.7, 43.8, 43.3, 39.9, 30.9, 22.4, 22.1, 17.1, 14.1; HRMS calcd for $C_{15}H_{21}{}^{37}ClN_2$ and $C_{15}H_{21}{}^{35}ClN_2$ 266.1364 and 264.1393, found 266.1361 and 264.1410.

6β-Acetoxy-8-carbethoxy-8-azabicyclo[3.2.1]octan-3-one (22). A solution of 6β-acetoxytropinone (**21**) (11.9 g, 60.4 mmol) and ethyl chloroformate (17.6 mL, 182 mmol) in benzene (400 mL) was heated at reflux for 20 h. Then, additional ethyl chloroformate (5.9 mL, 61 mmol) was added, and reflux was continued for 10 h. The solvent was removed under reduced pressure and the residue chromatographed directly on silica eluting with petroleum ether:ether (2:1). The title product **22** (13.8 g, 90%) was separated as a colorless oil: IR 1734, 1718, 1705 cm^{-1}; MS (*m*/*z*) 255(M^+), 195, 168, 80, 69; ^{1}H NMR δ 4.92 (1H, dd, J = 5.2, 4.9 Hz), 4.43−4.67 (2H, m), 4.19 (2H, q, J = 7.0 Hz), 1.7−2.8 (9H, m), 1.27 (3H, t, J = 7.0 Hz). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.39; H, 6.82; N, 5.22.

6β-Acetoxy-8-carbethoxy-3-(ethylenedioxy)-8-azabicyclo[3.2.1]octane (23). A solution of ketone **22** (13.7 g, 54.0 mmol) in benzene (150 mL) containing ethylene glycol (3.20 mL, 57.7 mmol) and *p*-toluenesulfonic acid monohydrate (1.03g, 5.40 mmol) was heated at reflux for 12 h using a Dean−Stark trap. The reaction mixture was cooled to rt and successively washed with saturated $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica (petroleum ether:ether 3:1) to give the ketal **23** (14.8 g, 92%) as a colorless oil: IR 1734, 1701 cm^{-1}; MS (*m*/*z*) 299(M^+), 270, 239, 99; ^{1}H NMR δ 5.32 (1H, dd, J = 7.3, 2.4 Hz), 4.09−4.43 (4H, m), 3.78−3.95 (4H, m), 2.60 (1H, m), 1.6−2.2 (8H, m), 1.25, 1.20 (3H, 2 t, J = 7.1 Hz). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.20; H, 7.17; N, 4.64.

8-Carbethoxy-3-(ethylenedioxy)-6β-hydroxy-8-azabicyclo[3.2.1]octane (24). A solution of ester **23** (14.1 g, 47.2 mmol) in methanol (300 mL) was treated with 3 N NaOH (600 mL) at rt for 6 h. The reaction mixture was extracted with $CHCl_3$, and the combined organic layers were washed with water and dried (Na_2SO_4). Removal of the solvent gave the alcohol **24** (11.6g, 96%) as a colorless oil which solidified on standing. Recrystallization from EtOAc:petroleum ether (1:1) afforded **24** as white crystals: mp 99−100 °C; IR 3377, 1662 cm^{-1}; MS (*m*/*z*) 257 (M^+), 213, 149, 99; ^{1}H NMR δ 4.51 (1H, d, J = 6.9 Hz), 4.38 (1H, br s), 4.13 (1H, br s), 4.12 (2H, q, J = 7.1 Hz), 3.78−3.94 (4H, m), 2.63 (1H, dd, J = 13.5, 7.0 Hz), 1.6−2.1 (5H, m), 1.24 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.90; H, 7.53; N, 5.27.

8-Carbethoxy-3-(ethylenedioxy)-6β-[(methylsulfonyl)-oxy]-8-azabicyclo[3.2.1]octane (25). Mesyl chloride (2.23 mL, 28.6 mmol) was added dropwise to a stirred solution of alcohol **24** (6.19 g, 24.1 mmol) and triethylamine (5.30 mL, 38.4 mmol) in CH_2Cl_2 (180 mL) at 0 °C. After 1 h, the mixture was diluted with CH_2Cl_2, washed with water, cold 5% HCl, water, and brine successively and dried over Na_2SO_4. Evaporation of the solvent followed by recrystallization of the residual solid from ether gave the mesylate **25** (8.30g, 97%) as white crystals: mp 106−107 °C; IR 1687, 1338, 1115 cm^{-1}; MS (*m*/*z*) 335 (M^+), 256, 161; ^{1}H NMR δ 5.39 (1H, d, J = 6.3 Hz), 4.37−4.52 (2H, m), 4.14 (2H, q, J = 7.1 Hz), 3.80−3.97 (4H, m), 3.00 (3H, s), 2.71 (1H, m), 1.7−2.2 (5H, m), 1.24 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{13}H_{21}NO_7S$: C, 46.56; H, 6.31; N, 4.18. Found: C, 46.52; H, 6.41; N, 4.01.

8-Carbethoxy-3-(ethylenedioxy)-8-azabicyclo[3.2.1]oct-6-ene (26). A solution of mesylate **25** (1.50 g, 4.47 mmol) and DBU (5.40 mL, 36.0 mmol) in toluene (30 mL) was refluxed for 56 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The solution was washed with 1 N HCl, saturated $NaHCO_3$, and water and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue on silica, eluting with petroleum ether:ether (3:1), gave the olefin **26** (0.72g, 67%) as a colorless oil which solidified on refrigeration: mp 47−48 °C; IR 2998, 1697, 1433, 1302, 1107 cm^{-1}; MS (*m*/*z*) 239, 152, 80; ^{1}H NMR δ 6.14, 6.11 (2H, 2 br s), 4.63, 4.58 (2H, 2 br s), 4.13 (2H, q, J = 7.0 Hz), 3.74−3.88 (4H, m), 2.05−2.17 (2H, m), 1.79 (1H, d, J = 13.7 Hz), 1.23 (3H, t, J = 7.0 Hz). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.18; H, 7.23; N, 5.80.

8-Carbethoxy-6β-(2-chloro-5-pyridinyl)-3-(ethylenedioxy)-8-azabicyclo[3.2.1]octane (27). Reductive coupling reaction between olefin **26** (1.96g, 8.20 mmol) and **2** (4.80 g, 20.0 mmol) was carried out as descibed for the preparation of **20**. The crude product was purified by chromatography (petroleum ether:EtOAc 4:1) to give the coupling product **27** (2.03g, 70%) as white crystals: mp 108−109 °C; IR 2983, 1701, 1454, 1319, 1107 cm^{-1}; MS (*m*/*z*) 352/354 (M^+), 149, 99; ^{1}H NMR δ 8.19 (1H, d, J = 2.2 Hz), 7.50 (1H, dd, J = 8.2, 2.2 Hz), 7.22 (1H, d, J = 8.2 Hz), 3.65−4.50 (6H, m), 3.64 (1H, dd, J = 9.1, 4.5 Hz), 2.66 (1H, 2 dd, J = 13.2, 9.1 Hz), 1.7−2.2 (5H, m), 1.21, 1.27 (3H, 2 t, J = 7.1 Hz). Anal. Calcd for $C_{17}H_{21}ClN_2O_4$: C, 57.87; H, 6.00; N, 7.94. Found: C, 57.91; H, 6.08; N, 7.96.

6β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octan-3-one (12). Carbamate **27** (826 mg, 2.35 mmol) was treated with hydrogen bromide in acetic acid (1 mL) for 60 h at rt. Water was added, and the pH of the mixture was adjusted to 10 with 40% NaOH. The base generated was extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on silica (MeOH:CH_2Cl_2 1:20) yielded **12** (464 mg, 84%) as white crystals: mp 124−126 °C; MS (*m*/*z*) 236/238 (M^+), 193/195, 140, 97; ^{1}H NMR δ 8.20 (1H, d, J = 2.4 Hz), 7.62 (1H, dd, J = 8.4, 2.4 Hz), 7.19 (1H, d, J = 8.4 Hz), 4.02 (1H, t, J = 5.3 Hz), 3.68 (1H, t, J = 2.9 Hz), 3.02 (1H, dd, J = 9.1, 5.4 Hz), 2.38−2.54 (4H, m), 2.19 (1H, dd, J = 13.5, 9.2 Hz), 1.88 (1H, m); ^{13}C NMR δ 208.3, 149.3, 148.0, 140.9, 137.0, 124.2, 62.6, 55.6, 51.6, 51.0, 45.0, 40.3; HRMS calcd for $C_{12}H_{13}{}^{37}ClN_2O$ and $C_{12}H_{13}{}^{35}ClN_2O$ 238.0687 and 236.0717, found 238.0720 and 236.0717.

2-Chloro-5-(1-carbethoxy-3-pyrrolidinyl)pyridine (30). A solution of 1-carbethoxy-3-pyrroline (**28**) (736 mg, 5.22 mmol), **2** (500 mg, 2.09 mmol), palladium acetate (20 mg, 0.089 mmol), KOAc (530 mg, 5.40 mmol), and tetrabutylammonium bromide (680 mg, 2.09 mmol) in DMF (6 mL) was stirred at 40 °C for 4 d. Then EtOAc (15 mL) and water (5 mL) were added, the organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on silica (petroleum ether:EtOAc 20:1 to 8:1) gave the product **29** as a colorless gum. This substance is unstable and decomposes rapidly at rt. It should be converted into **30** as soon as possible. Thus, a solution of the foregoing product **29** was hydrogenated with 10% Pd−C (260 mg) at 12 °C for 16 h. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica, eluting with petroleum ether:EtOAc (4:1), to give the title

product **30** (328 mg, 62% overall yield from **2**) as a colorless oil: IR 2968, 1701, 1459, 1107 cm^{-1}; MS (*m*/*z*) 254/256 (M^+), 225/227, 149, 115; ^1H NMR δ 8.25 (1H, d, J = 2.4 Hz), 7.49 (1H, dd, J = 8.2, 2.4 Hz), 7.24 (1H, d, J = 8.2 Hz), 4.13 (2H, q, J = 6.9 Hz), 4.84 (1H, m), 3.63 (1H, m), 3.25−3.47 (2H, m), 2.30 (1H, br s), 1.95 (1H, m); HRMS calcd for $C_{12}H_{15}{}^{37}ClN_2O_2$ and $C_{12}H_{15}{}^{35}ClN_2O_2$ 256.0793 and 254.0822, found 256.0780 and 254.0825.

2-Chloro-5-(3-pyrrolidinyl)pyridine (13). Using the same procedure as described for the preparation of **1**, carbamate **30** (37 mg, 0.15 mmol) was treated with iodotrimethylsilane (26 μL, 0.18 mmol) to afford desethyleneepibatidine **13** (25 mg, 94%) as a white solid: mp 63−64 °C; MS (*m*/*z*) 182/184 (M^+), 140/142; ^1H NMR δ 8.22 (1H, d, J = 2.4 Hz), 7.52 (1H, dd, J = 8.4, 2.4 Hz), 7.23 (1H, d, J = 8.4 Hz), 5.70 (1H, br s), 2.83−3.39 (5H, m), 2.25 (1H, m), 1.80 (1H, m); ^{13}C NMR δ 149.5, 148.6, 137.6, 137.3, 124.1, 53.6, 46.5, 41.8, 34.0; HRMS calcd for $C_9H_{11}{}^{37}ClN_2$ and $C_9H_{11}{}^{35}ClN_2$ 184.0581 and 182.0611, found 184.0578 and 182.0601.

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