Total Synthesis and Determination of the Absolute Configuration of Epibatidine

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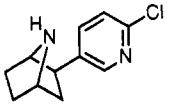
Received October 8, 1993•

The synthesis of (+)- and (−)-epibatidine (*exo*-2-(2-chloropyridin-5-yl)-7-azabicyclo[2.2.1]heptane) *via* reaction of 5-lithio-2-chloropyridine with (+)- and (−)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one is described. The absolute configuration of the natural product is shown to be 1*R*,2*R*,4*S*.

In 1992 Daly *et al.* described the isolation and structural elucidation of the alkaloid epibatidine (1) obtained from the Ecuadoran poison frog, *Epipedobates tricolor*.[1] Epibatidine represents a new class of alkaloid containing a 7-azabicyclo[2.2.1]heptane structure to which is attached, in an *exo*-orientation, a 5-(2-chloropyridinyl) substituent. The compound displays remarkable analgesic properties. It is 200–500 times more potent than morphine in eliciting a Straub tail test and in causing hot plate analgesia and appears to operate *via* a non-opioid mechanism since naloxone, a general opioid antagonist, does not reverse the analgesic effects.[1] In view of these findings there has been considerable interest in the total synthesis of epibatidine.



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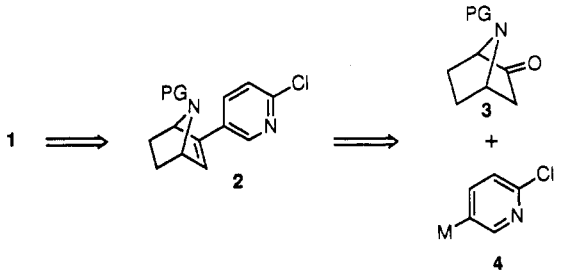
Broka first reported the preparation of racemic material *via* a multistep procedure, thus confirming the structure of the natural product.[2] Shen *et al.* subsequently reported preparation of the racemate *via* a Diels–Alder approach and resolution of the di-*p*-toluoyl tartrate salt to afford the (+)- and (−)-enantiomers.[3] We have previously communicated[4] our concomitant synthesis of the (+)- and (−)-epibatidine hydrogen oxalate salts *via* reaction of 5-lithio-2-chloropyridine with (+)- and (−)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one and have described how the (+)-enantiomer was found to correspond to the natural product.[5] More recently an alternative racemic synthesis has been described by Regan *et al.*,[6] and E. J. Corey[7] has reported on the preparation of (+)- and (−)-epibatidine. We now wish to describe our synthetic efforts in more detail, in particular to describe an unexpected synthesis

Scheme 1



of the 7-azabicyclo[2.2.1]heptane ring system. We also wish to report the absolute stereochemistry of the natural product.

Results and Discussion

In considering synthetic approaches to epibatidine we elected to synthesize a suitably protected 7-azabicyclo-[2.2.1]heptan-2-one derivative **3** and investigate condensation reactions with a metallopyridine species **4** to construct the carbon framework (Scheme 1). It was envisaged that functionalization and elimination of the resulting hydroxyl group would provide a suitably protected 7-azabicyclo[2.2.1]hept-2-ene derivative **2** as a valuable precursor. Hydrogenation was projected to give a mixture of *exo*- and *endo*-derivatives which, it was proposed, could be converted to the desired, more thermodynamically stable *exo*-product by equilibration. In this way we would be following similar work carried out in these laboratories for the construction of (1-azanorbornyl)pyrazine derivatives of interest as muscarinic agonists.[8] In addition, an efficient preparation of *endo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol had been previously reported.[9] Our synthetic efforts thus began with the attempted preparation of *endo*-7-benzyl-7-azabicyclo-[2.2.1]heptan-2-ol (**9**).

Alkylation of *N*-[(trifluoroacetyl)amino]cyclohex-3-ene[10] (**5**) in DMF at 70 °C with benzyl bromide, in the presence of cesium carbonate, afforded the benzylated derivative **6** in 66% yield (Scheme 2). Treatment with *m*-CPBA in dichloromethane at room temperature for 4 h afforded a 2.4:1 *cis*:*trans* mixture of epoxides **7** in 74%

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• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

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(2) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251–4.

(3) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477–80.

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(5) Watt, A. P.; O'Connor, D.; Verrier, H. *J. Liq. Chromatogr.*, in press. See supplementary material for experimental details.

(6) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493–6.

(7) Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600–2.

(8) Street, L. J.; Baker, R.; Book, T.; Reeve, A. J.; Saunders, J.; Willson, T.; Marwood, R. S.; Patel, S.; Freedman, S. B. *J. Med. Chem.* **1992**, *35*, 295–305.

(9) Pfister, J. R.; Wymann, W. E.; Weissberg, R. M.; Strasberg, A. M. *J. Pharm. Sci.* **1985**, *74*, 208–10.

(10) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38–40.

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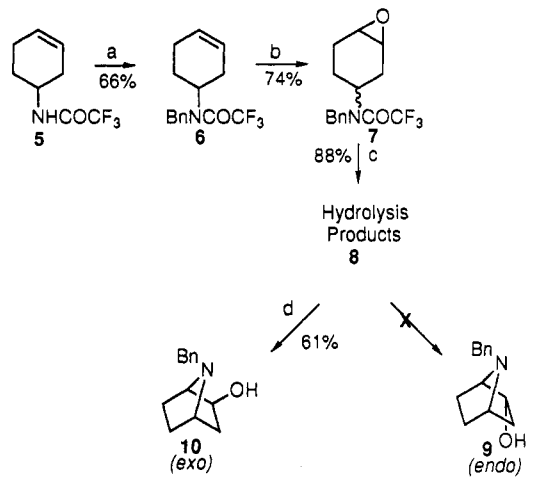
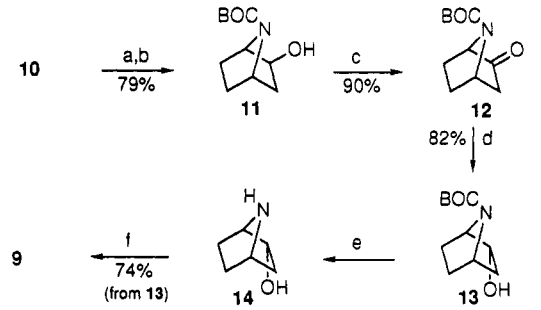
Scheme 2[a]



[a] Reagents: (a) BnBr, Cs_2CO_3, DMF, 70 °C, 40 h; (b) *m*-CPBA, CH_2Cl_2, 0 → 20 °C, 4 h; (c) K_2CO_3, MeOH, 3 days; (d) 1-Methyl-2-pyrrolidinone, 180 °C, 16 h.

Scheme 3[a]



[a] Reagents: (a) $Pd(OH)_2$, EtOH, HCl, 40 °C, H_2 (40 psi); (b) $(BOC)_2O$, dioxane, 1 N NaOH, 18 h; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, Et_3N; (d) L-Selectride, THF, −55 → 0 °C; (e) TFA, CH_2Cl_2, 3 h; (f) BnBr, K_2CO_3, DMF, 60 °C, 3 h.

yield. Mild base hydrolysis using potassium carbonate in methanol for 3 days then afforded a 2.5:1 inseparable mixture **8** which was initially considered to be the corresponding benzylamines. In accordance with the conditions of Pfister *et al.*[9] this mixture was heated in *N*-methyl-2-pyrrolidinone at 180 °C for 16 h and cyclized product was obtained in 61% yield. Remarkably, however, upon close inspection of high-resolution ^{1}H COSY NMR spectra, the product was found to be *exo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**10**) rather than the expected *endo*-alcohol **9**. In order to confirm this the *endo*-alcohol was synthesized independently in the following manner (Scheme 3). The *N*-benzyl group of **10** was removed by hydrogenolysis (40 psi H_2) using Pearlman's catalyst. *N*-BOC protection was then carried out using $(BOC)_2O$ in dioxane/sodium hydroxide solution at room temperature and the resulting alcohol **11** subjected to Swern oxidation conditions to afford ketone **12**. This compound was reduced in a stereoselective manner by use of the sterically hindered L-Selectride in an analogous manner to that used to convert norcamphor to *endo*-norborneol.[11] This gave a new alcohol, the *endo*-derivative **13**, *via* delivery of hydride from the *exo*-face of the bicyclic ketone. Deprotection of the resulting *N*-BOC *endo*-alcohol was carried out using TFA in dichloromethane to afford the crude *N*-H derivative **14** which was benzylated to afford authentic *endo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**9**) in 74% yield. ^{1}H NMR comparison of **9** and **10** (Table 1) established that the product of thermal cyclization is *exo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**10**). This was later shown unambiguously by the X-ray crystal structure obtained of the Mosher's ester of **11** (i.e. **30**, shown in Figure 2).

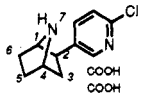
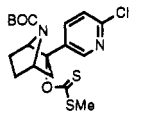
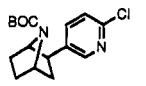
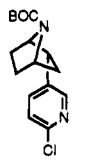
Since the cyclization was initially carried out on a mixture it was not immediately clear how the product was arising. What was apparent, however, is that the *exo*-isomer is the only 7-azabicyclo[2.2.1]heptane derivative formed. With authentic *endo*-derivative **9** in hand it was clear by the use of TLC that this material is not produced. It was considered possible that the *exo*-product arises *via* epimerization of initially formed *endo*-alcohol. To check this, **9** was subjected to the cyclization conditions. This led to the recovery of unchanged material and it was concluded that the thermal cyclization of **8** affords only the *exo*-alcohol **10**. What remained therefore was to determine which component of the mixture was undergoing cyclization.

HPLC on silica was used to separate the *cis*- and *trans*-trifluoroacetamides **15** and **16** (Scheme 4). Because of the presence of amide rotamers it was not possible to establish structure by NMR but the slower eluting component crystallized and was shown by X-ray crystallography[12] to be the *trans*-product **16** (Figure 1). Hydrolysis of the *cis*-trifluoroacetamide **15** using potassium carbonate in methanol at room temperature for 3 days afforded the pure *cis*-benzylamino epoxide **17** in 78% yield. Heating the *cis*-epoxide **17** in *N*-methyl-2-pyrrolidinone at 180 °C for 16 h resulted in cyclization to afford **10**. Hydrolysis of the *trans*-isomer **16** under identical conditions, however, did not give rise to the expected *trans*-benzylamino epoxide. The product obtained in 44% yield was identified as the cyclic carbamate **18**. This was considered to arise from reaction of the initially formed *trans*-amino epoxide **19** with CO_2, generated from K_2CO_3 during the hydrolysis reaction, to give the carbamic acid which induces transannular ring opening of the epoxide. It, thus, became apparent that hydrolysis of the mixture of acetamides **7** results in formation of a 2.5:1 mixture of *cis*-epoxide **17** and carbamate **18** rather than a mixture of *cis*- and *trans*-epoxides. The *cis*-(*N*-benzylamino)cyclohexane 1,2-epoxide undergoes thermal rearrangement to afford *exo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**10**) while the carbamate **18** undergoes thermal decomposition. Hence good yields of **10** are obtained from the mixture of epoxides **7** generated from epoxidation of olefin **6**. Although unexpected, conversion *via* the *cis*-epoxide is advantageous, as formation of this isomer is enhanced in the olefin-oxidation reaction, presumably due to coordination of the

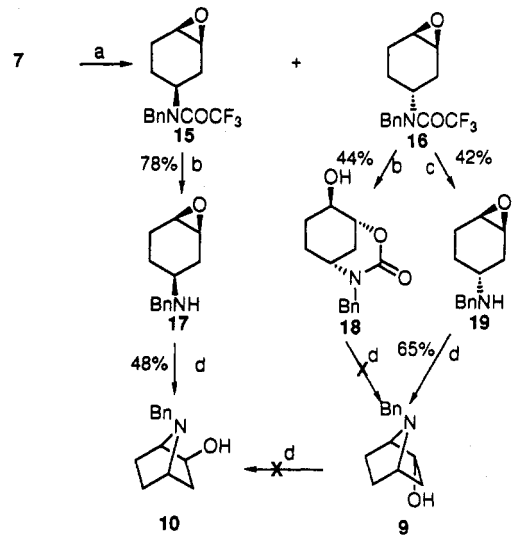
(11) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–61.

(12) Crystal structure details for **16**: $C_{15}H_{16}F_3NO_2$, M_r = 299.295, triclinic, $P\bar{1}$, a = 11.678(2), b = 12.562(2), c = 11.475(2) Å, α = 115.447(9), β = 106.65(1), γ = 92.92(1)°, V = 1426.6(9) Å^3, Z = 4, D_x = 1.393 g cm^{-3}, monochromatized radiation λ(Cu K$_\alpha$) = 1.541838 Å, μ = 0.99 mm^{-1}, F(000) = 624, T = 294 K. Data collected on a Rigaku AFC5R diffractometer to a θ limit of 71° with 3139 observed, at $I \geq 3\sigma(I)$, reflections out of 5586 measured. Structure solved by direct methods and refined using full-matrix least-squares on F using 379 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R = 0.069, R_w = 0.064, S = 3.31, $(\Delta/\sigma)_{max}$ = 0.01. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map is 0.78(5) eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Table 1. NMR Data for the 7-Azabicyclo[2.2.1]heptane Derivatives

no.	structure	δ (360 MHz, $CDCl_3$)	NMR data for C2 stereochemistry
1		8.30 (1H, d, J = 2.2, $H_{6'}$), 7.79 (1H, dd, J = 8.4, 2.2, $H_{4'}$), 7.49 (1H, d, J = 8.4, $H_{3'}$), 4.58 (1H, d, J = 4.0, H_1), 4.39 (1H, dd, J = 4.0, 4.0 H_4), 3.50 (1H, dd, J = 9.7, 6.2, H_{2endo}), 2.46 (1H, dd, J = 13.7, 9.7, H_{3endo}), 1.86–2.15 (5H). (Spectrum recorded in D_2O).	^3J (Hz): H_{2endo}, H_{3endo} = 9.7, H_{2endo}, H_{3exo} = 6.2 and coupling to H_1 and H_4 confirms there are only 3 *exo* protons
9		7.29 (5H, m, Ph), 4.33 (1H, dddd, J = 10.2, 4.5, 3.4, 1.3, H_{2exo}), 3.59 (1H, d, J = 13.3), 3.57 (1H, d, J = 13.3), 3.28 (1H, dd, J = 4.5, 4.5, H_1), 3.22 (1H, dd, 4.8, 4.8, H_4), 2.21 (1H, dddd, J = 12.5, 10.2, 4.8, 3.0, H_{3exo}), 2.10 (1H, ddd, J = 12.7, 9.3, 4.6, H_{6endo}), 1.94 (1H, ddddd, J = 12.3, 12.1, 4.8, 4.6, 3.0, H_{5exo}), 1.75 (1H, ddddd, J = 12.7, 12.1, 4.5, 4.2, 1.3, H_{6exo}), 1.48 (1H, ddd, J = 12.3, 9.3, 4.2, H_{5endo}), 0.93 (1H, dd, J = 12.5, 3.3, H_{3endo})	assignments confirmed by COSY including ^4J between H_{2exo}, H_{6exo} and H_{3exo}, H_{5exo}. Coupling to H_1 and H_4 confirms there are 4 *exo* protons
10		7.2–7.4 (5H, m, Ph), 3.62 (1H, dd, J = 6.6, 1.3, H_{2endo}), 3.50 (2H, s), 3.27 (1H, dd, J = 5.5, 2.2, H_4), 3.17 (1H, d, J = 4.0, H_1), 2.47 (1H, bs, O*H*), 1.81 (2H, m, H_{5exo}, H_{6exo}), 1.69 (1H, dd, J = 13.3, 6.6, H_{3endo}), 1.50 (1H, ddd, J = 13.3, 3.1, 1.8, H_{3exo}), 1.21 (2H, m, H_{5endo}, H_{6endo})	^3J (Hz): H_{2endo}, H_{3endo} = 6.6, H_{2endo}, H_{3exo} = ca. 1.4 and coupling to H_1 and H_4 confirms there are only 3 *exo* protons
24		8.39 (1H, d, J = 2.2, $H_{6'}$), 7.65 (1H, dd, J = 8.4, 2.2, $H_{4'}$), 7.26 (1H, d, J = 8.4, $H_{3'}$), 5.13 (1H, bs, H_1), 4.35 (1H, bs, H_4), 2.56 (1H, m, H_{3exo}), 2.48 (3H, s, SCH_3), 2.16 (1H, d, J = 13.6, H_{3endo}), 2.06 (1H, m), 1.85 (2H, bm), 1.66 (1H, m), 1.42 (9H, s, Boc)	NOE: SCH_3 to H_{3endo}, $H_{4'}$ to H_1, $H_{6'}$ to H_1
27		8.25 (1H, d, J = 2.3, $H_{6'}$), 7.63 (1H, dd, J = 8.3, 2.3, $H_{4'}$), 7.24 (1H, d, J = 8.3, $H_{3'}$), 4.37 (1H, bs, H_4), 4.16 (1H, bs, H_1), 2.86 (1H, dd, J = 9.0, 4.9, H_{2endo}), 1.99 (1H, dd, J = 12.4, 9.0, H_{3endo}), 1.82 (3H, m), 1.55 (2H, m), 1.43 (9H, s, Boc)	COSY confirmed assignments NOE: H_{2endo} to $H_{6'}$, $H_{4'}$, H_1, H_{3endo} and H_{6endo}
28		8.26 (1H, d, J = 2.4, $H_{6'}$), 7.47 (1H, dd, J = 8.4, 2.4, $H_{4'}$), 7.29 (1H, d, J = 8.4, $H_{3'}$), 4.32 (2H, m, H_1,H_4), 3.46 (1H, ddd, J = 11.3, 5.4, 5.4, H_{2exo}), 2.30 (1H, dddd, J = 11.3, 11.3, 5.4, 5.4, H_{3exo}), 1.84 (1H, m, H_{5exo}), 1.59 (2H, m, H_{6exo}, H_{3endo}), 1.48 (9H, s, Boc), 1.43 (2H, m, H_{5endo}, H_{6endo})	COSY confirmed assignments NOE: H_{2exo} to H_{3exo}, $H_{4'}$, H_1

Scheme 4[a]



[a] Reagents: (a) HPLC; (b) K_2CO_3, MeOH, 3 days; (c) KOH, MeOH, 18 h; (d) 1-methyl-2-pyrrolidinone, 180 °C, 16 h.

m-CPBA with the trifluoroacetamide group of **6** favoring *cis*-epoxidation.

Naturally we were intrigued to know what would be the outcome of thermolysis of the *trans*-amino epoxide **19**. To this end the *trans*-acetamide **16** was hydrolyzed using KOH in methanol thereby preventing formation of the cyclic carbamate. In this way the *trans*-epoxide **19** was obtained in 42% yield (Scheme 4). Heating **19** at 180 °C in *N*-methyl-2-pyrrolidinone for 16 h resulted in formation of *endo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**9**) in 65% yield. Although not pursued, it thus became apparent that both *cis*- and *trans*-epoxides **17** and **19** may be used in the preparation of epibatidine.

It is interesting to speculate on the mechanism of the conversion of **17** to **10** (Scheme 5). Although relatively rare, examples of *syn*-opening of epoxides *via* the intermediacy of a carbenium ion have been reported[13] and this may be how **10** arises. Another possibility is the presence of an unidentified nucleophile in the reaction medium which causes initial 1,2-diaxial ring opening of the epoxide. Transannular displacement of this nucleophile by the 4-amino substituent would then lead to formation of **10** and regeneration of the nucleophile. Attempts to further elucidate the reaction pathway have been unsuccessful. However, although the mechanism of formation remains unclear, *via* the process outlined in Scheme 2 we were able to obtain multigram quantities of *exo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol (**10**) as a key intermediate in the total synthesis of epibatidine.

Because of anticipated difficulties in removal of an *N*-benzyl protecting group in the final stages of the synthesis with the 2-chloropyridine group present, an alternative protecting group was selected. *N*-BOC protection was considered to be most compatible with the subsequent reaction steps. Thus the *N*-benzyl derivative **10** was converted, as described above (Scheme 3), to the *N*-BOC ketone **12** required for the key coupling reaction. The ensuing loss of stereochemistry at C-2 means, of course, that ironically it is synthetically irrelevant whether the *cis*- or *trans*-epoxide undergoes cyclization or whether the product of ring opening is the *exo*- or the *endo*-alcohol.[14]

(13) Rickborn, B. *Comprehensive Organic Synthesis*; Pergamon: London, 1991; Vol. 3, pp 733–775.

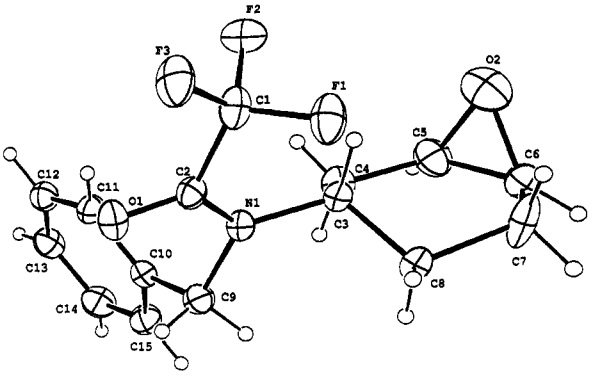
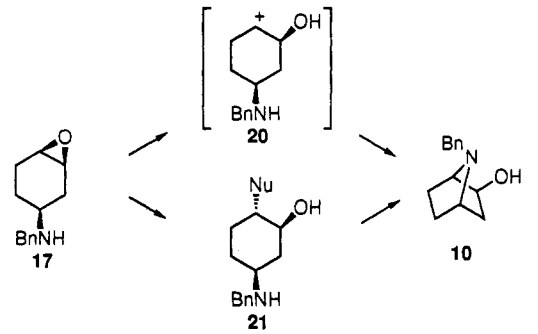


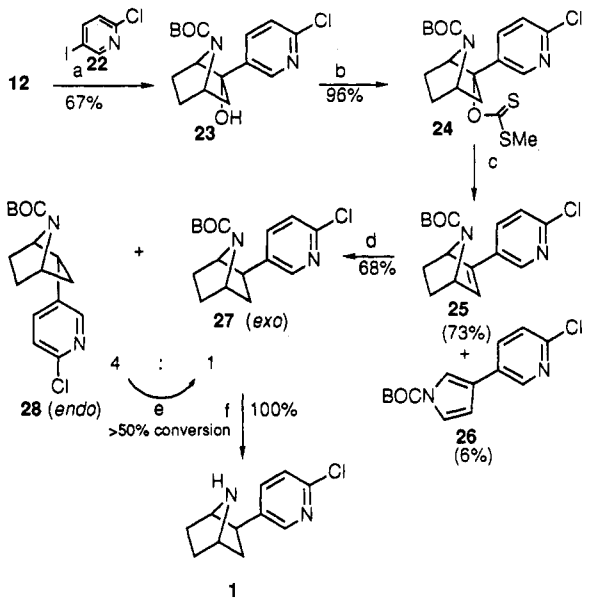
Figure 1. Perspective view (ORTEP) of **16** showing the atomic numbering scheme. Non-hydrogen atoms are drawn as 20% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principle axes indicated; the isotropic atoms are represented as simple circles. The relative orientation of C-4 substituent and the epoxide can be seen to be *trans*.

Scheme 5



It has been shown that lithiation of aromatic systems containing both a chlorine and an iodine atom results in transmetalation of the iodine atom.[15] We thus anticipated that the previously unreported 5-lithio derivative of 2-chloropyridine, required for coupling with ketone **12**, could be generated by metalation of 2-chloro-5-iodopyridine. Treatment of 2-chloro-5-iodopyridine (**22**)[16] with *n*-BuLi at −70 °C followed by reaction with ketone **12** afforded the tertiary alcohol **23** in 67% yield (Scheme 6). No products derived from metalation at other positions of the pyridine ring were detected. Methods of removal of the hydroxyl group were next considered. Thionyl chloride has been used on similar systems to afford the chloride which may be eliminated or removed *via* a one-electron process[8] but this was not considered appropriate in this case. Rather, the alcohol was converted to the *S*-methyl xanthate **24** in 96% yield by treatment with potassium hydride and subsequent quenching with carbon disulfide and methyl iodide. Tertiary xanthates are not generally regarded as isolable species[17] thus the steric constraints imposed on **24** must enhance stability since the compound could be isolated, chromatographed, and proved to be stable at room temperature for long periods. ^{1}H NMR of **24** established the xanthate group to be in the *endo*-orientation thereby confirming the *endo*-orientation

Scheme 6[a]



[a] Reagents: (a) *n*-BuLi, Et_2O/THF, −70 °C; (b) KH, THF, 0 °C, CS_2, MeI; (c) toluene, 110 °C, 2 h; (d) PtO_2, EtOAc, H_2 (40 psi); (e) *t*-BuOH, K*t*-BuO, 100 °C, 30 h; (f) HCl, EtOAc.

of the precursor alcohol **23**. An NOE was observed between the bridgehead proton at C-1 and the 6-pyridyl proton. Additionally an NOE was detected between the *S*-methyl protons and the H_{3endo} proton. Thermolysis of the xanthate **24** in toluene at reflux for 2 h resulted in smooth elimination to give olefin **25** in 73% yield. Interestingly, another product obtained in this reaction was the pyrrole **26** arising from a *retro*-Diels–Alder reaction. Attempts to improve the yield of the desired product by lowering the reaction temperature were not successful. Hydrogenation of **25** in ethyl acetate (40 psi H_2) using Adams' catalyst produced a 4:1 mixture of *endo*:*exo*-isomers in 68% yield from which the desired, more-polar, *exo*-derivative **27** was isolated in 11% yield by column chromatography. The undesired *endo*-isomer **28** was successfully epimerized using potassium *tert*-butoxide in *t*-butyl alcohol at reflux for 30 h in an iterative procedure to afford the *exo*-isomer in greater than 50% yield (based on **28**). ^{1}H NMR was used to firmly establish the identity of the *exo*- and *endo*-isomers **27** and **28** (Table 1). Deprotection of the N-BOC *exo*-isomer **27** was achieved in quantitative yield using HCl in EtOAc at room temperature to afford racemic epibatidine as a colorless solid, which was characterized as the hydrogen oxalate salt.

In view of the somewhat unpredictable nature of resolution by crystallization of diastereomeric salts, we decided to first attempt the preparation of the (+)- and (−)-enantiomers of epibatidine *via* the separation of diastereomeric esters of an alcohol produced in the racemic synthesis. Partial separation of the camphanic esters of the *exo*-alcohol **11** was possible by crystallization. Resolution of **11** was, however, best achieved by formation of diastereomeric esters with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-(−)-Mosher's acid chloride) (**29**). Crystallization from hexane afforded a single diastereomer in 32% yield based on alcohol **11**. Chromatographic purification of the mother liquors then afforded a further 11% of this material and the other diastereomer in 42% yield. Deprotection of the esters **30** and **31** with potassium hydroxide in ethanol gave efficient

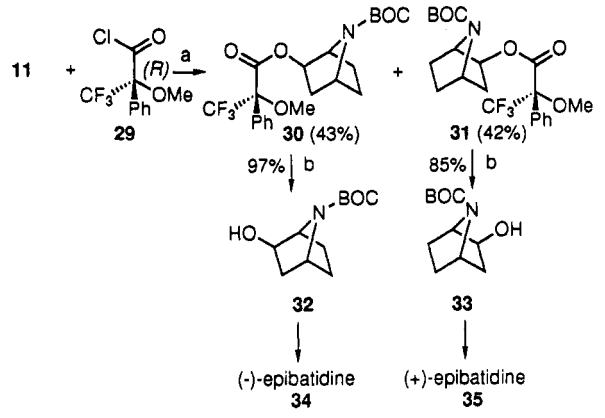
(14) In our initial communication (ref 4), in the absence of X-ray structural data, we incorrectly assigned the ring-opened product as the *endo*-alcohol **9**.

(15) Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339–66.

(16) (a) Magidson, O.; Menschikoff, G. *Chem. Ber.* **1925**, *58*, 113–8. (b) Ger. Patent, 491,681, 1924.

(17) Barton, D. H. R.; Pareckh, S. I.; Tse, C.-L. *Tetrahedron Lett.* **1993**, *34*, 2733–6.

Scheme 7[a]



[a] Reagents: (a) DMAP, CH_2Cl_2, 18 h; (b) KOH, EtOH, 2 h.

conversion to the enantiomers **32** and **33** (Scheme 7). Since the absolute configuration at the bridgehead protons was now fixed, each enantiomer could be taken through the reaction sequence developed for the racemate to afford the (−)- and (+)-enantiomers of epibatidine (**34** and **35**). In this manner, materials were obtained, of >99% ee as determined by chiral HPLC.[5]

To determine the absolute configuration of epibatidine, we obtained an X-ray structure[18] of the crystalline Mosher's ester **30** prepared from (*R*)-(−)-Mosher's acid chloride **29**. This material ultimately afforded (−)-epibatidine hydrogen oxalate salt (**34**). The structure obtained (Figure 2) shows that the configuration at the bridgehead carbon C-1 is *S* and at C-4 is *R*, based on the known configuration of the starting Mosher's acid chloride. We have previously reported that the (+)-enantiomer **35** corresponds to the natural product.[5] Thus, the configuration at C-1 and C-4 of epibatidine is *R* and *S*, respectively. Since the pyridyl group at C-2 is in the *exo*-orientation the configuration of C-2 is *R*. Thus, the absolute configuration of epibatidine is 1*R*,2*R*,4*S*.

Conclusion

A synthetic route has been developed for the preparation of epibatidine. An X-ray crystal structure determination has established the absolute configuration of the natural product to be 1*R*,2*R*,4*S*. This latter information may well be significant in enabling comparison with other chemical series once the biochemical mechanism of action of epibatidine has been discovered.

Experimental Section

Elemental analyses were performed by Butterworth Laboratories, Middlesex, TW11 8LG, U.K. ^{1}H NMR spectra were recorded on a Bruker AM-360 spectrometer. ^{1}H Chemical shifts

(18) Crystal structure details for **30**: $C_{21}H_{26}F_3NO_5$, M_r = 429.440, orthorhombic, $P2_12_12_1$, a = 12.368(2), b = 19.376(2), c = 9.080(2) Å, V = 2176(1) Å^3, Z = 4, D_x = 1.311 g cm^{-3}, monochromatized radiation λ(Cu K_α) = 1.541838 A, μ = 0.91 mm^{-1}, $F(000)$ = 904, T = 294 K. Data collected on a Rigaku AFC5R diffractometer to a θ limit of 71° with 1024 observed, at $I \geq 3\sigma(I)$, reflections out of 2338 measured. Structure solved by direct methods and refined using full-matrix least-squares on F using 196 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R = 0.051, R_w = 0.043, S = 1.56, $(\Delta/\sigma)_{max}$ = 0.01. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map is 0.18(5) eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

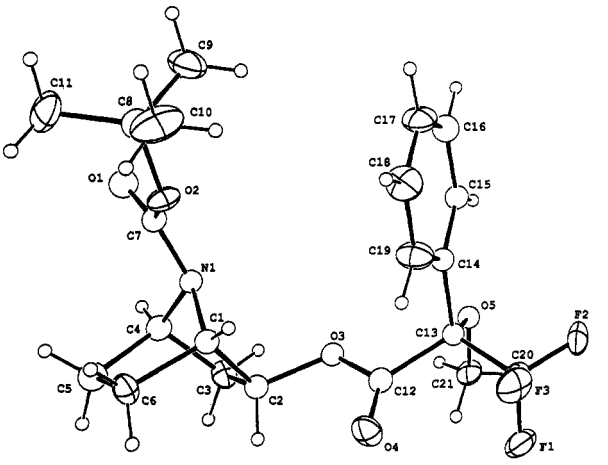


Figure 2. Perspective view (ORTEP) of **30** showing the atomic numbering scheme. Non-hydrogen atoms are drawn as 20% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principle axes indicated, the isotropic atoms are represented as simple circles. The absolute configuration at C1 is shown to be *S* and C4 to be *R*, and the substituent at C2 is *exo*.

are reported in ppm referenced to tetramethylsilane (TMS) as internal standard (0 ppm). Mass spectra were obtained on a VG Quattro instrument using desorption chemical ionization (DCI). Optical rotations were obtained using a Perkin-Elmer 241 polarimeter and melting points (uncorrected) were determined using a Reichert Thermovar hot stage microscope. HPLC was performed analytically on an HP-1090 high performance chromatograph and preparatively on a Shimadzu LC-8A system. Silica gel thin-layer chromatography (TLC) plates (No. 5719, Kieselgel 60 F_{254}) and the Kieselgel 60 silica gel used for column chromatography were purchased from Merck. 3-Cyclohexenecarboxylic acid was purchased from Lancaster Synthesis, 2-chloro-5-aminopyridine from Aldrich, and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (**29**) from Fluka. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere using commercially available anhydrous solvents.

(±)-1-[*N*-(Phenylmethyl)-*N*-(trifluoroacetyl)amino]cyclohex-3-ene (6). A stirred solution of *N*-[(trifluoroacetyl)amino]cyclohex-3-ene[10] (50 g, 0.26 mol), benzyl bromide (67 mL, 0.56 mol), and cesium carbonate (176 g, 0.54 mol) in DMF (600 mL) was heated at 70 °C for 40 h. The solution was cooled to room temperature and partitioned between water (700 mL) and ether (700 mL). The organic layer was separated and the aqueous phase extracted with ether (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* and the residue was purified by flash column chromatography on silica, eluting with petroleum ether (60/80):ether (85:15). Amide **6** (48 g, 66%) was isolated as a pale yellow oil which solidified on standing: mp 41–44 °C; ^{1}H NMR ($CDCl_3$) δ 7.28–7.19 (5H, m), 5.69–5.47 (2H, m), 4.65 (1H, d, J = 16 Hz), 4.61 (1H, d, J = 16 Hz), 4.26–4.02 (1H, m), 2.25–1.65 (6H, m); MS (Cl, NH_3) 301 (MNH_4^+). Anal. Calcd for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69; N, 4.94. Found: C, 63.53; H, 5.64; N, 4.84.

Mixture of (±)-*cis*-1,2-Epoxy-4-[*N*-(Phenylmethyl)-*N*-(trifluoroacetyl)amino]cyclohexane and (±)-*trans*-1,2-Epoxy-4-[*N*-(phenylmethyl)-*N*-(trifluoroacetyl)amino]cyclohexane (7). *m*-CPBA (80%, 8.2 g, 38 mmol) was added portionwise to a stirred solution of **6** (10.8 g, 38 mmol) in CH_2Cl_2 (100 mL) at 0 °C. When the addition was complete the cooling bath was removed and the mixture stirred at room temperature for 4 h, during which time a colorless solid precipitated. The mixture was treated with aqueous potassium iodide (10%, 5 mL) followed by aqueous sodium sulfite (10%, 40 mL). CH_2Cl_2 (100 mL) was added and the organic phase separated and then washed with saturated aqueous $NaHCO_3$ (3 × 100 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated. The residual oil was chromatographed on silica, eluting with petroleum ether (60/80):ether (3:1 → 2:1), to give the epoxides **7** (8.5 g, 74%) as

a 2.4:1 *cis*:*trans*-mixture, isolated as a pale yellow oil: R_f 0.75 and 0.7 (silica; ether); ^{1}H NMR ($CDCl_3$) (2.4:1 combination of **15** and **16**). Anal. Calcd for $C_{15}H_{16}F_3NO_2$: C, 60.20; H, 5.39; N, 4.68. Found: C, 60.27; H, 5.42; N, 4.67.

Hydrolysis of 7 to 8. To a stirred solution of the trifluoroacetates **7** (21.0 g, 0.07 mol) in MeOH (180 mL) at room temperature was added a solution of K_2CO_3 (24.0 g, 0.18 mol) in water (60 mL). After 3 days the solvents were removed *in vacuo* and the residue partitioned between CH_2Cl_2 (3 × 200 mL) and water (200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica, eluting with CH_2Cl_2:MeOH (95:5), to give **8** (13.2 g, 88% (based on conversion to **17** and **18**)) as a pale yellow oil. This was found to be a 2.5:1 mixture of **(±)-*cis*-1,2-Epoxy-4-[*N*-(phenylmethyl)amino]cyclohexane (17)** and **(±)-*exo*-8-Hydroxy-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (18)**: ^{1}H NMR ($CDCl_3$) (2.5:1 combination of **17** and **18**). Anal. Calcd for $2.5(C_{13}H_{17}NO)\cdot C_{14}H_{17}NO_3$: C, 73.93; H, 7.94; N, 6.49. Found: C, 74.16; H, 8.21; N, 6.80.

(±)-*exo*-7-(Phenylmethyl)-7-azabicyclo[2.2.1]heptan-2-ol (10). A solution of **8** (1.9 g, 9.4 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was heated at 180 °C for 16 h. The solvent was then evaporated *in vacuo* and the residue purified by chromatography on silica, eluting with CH_2Cl_2:MeOH (9:1) to afford **10** (1.16 g, 61%) as a pale yellow oil: ^{1}H NMR (see Table 1); MS (CI, NH_3) 204 (MH^+). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89: Found; C, 76.80; H, 8.35; N, 6.81.

(±)-*exo*-7-[(1,1-Dimethylethoxy)carbonyl]-7-azabicyclo-[2.2.1]heptan-2-ol (11). A solution of **10** (4.6 g, 23 mmol) in EtOH (100 mL) and 5 N HCl (5 mL), containing palladium hydroxide on carbon (Pearlman's catalyst) (2.2 g, 48% (w/w)) was hydrogenated (40 psi H_2) at 40 °C for 6 h. The catalyst was filtered off and the filtrate evaporated. The residue was azeotroped with toluene (2 × 30 mL). A solution of the resulting crude amine hydrochloride and di-*tert*-butyl dicarbonate (7.3 g, 33.6 mmol) in dioxane:1 N NaOH (2:1; 150 mL) was stirred vigorously at room temperature for 18 h. After this time the solvents were evaporated and the residue partitioned between CH_2Cl_2 (4 × 100 mL) and water (100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (1:1) to give the BOC-protected derivative **11** as a colorless oil (3.8 g, 79%), which solidified on standing: mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 4.23 (1H, t, J = 4.4 Hz), 4.11 (1H, d, J = 5.5 Hz), 3.86 (1H, dd, J = 6.9, 2.0 Hz), 1.90–1.57 (4H, m), 1.46 (9H, s), 1.29–1.22 (2H, m); MS (CI, NH_3) 214 (MH^+). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.03; H, 9.31; N, 6.54.

(±)-7-[(1,1-Dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]-heptan-2-one (12). To a stirred solution of oxalyl chloride (0.76 mL, 8.7 mmol) in CH_2Cl_2 (21 mL) at −70 °C was added a solution of DMSO (1.2 mL, 17.6 mmol) in CH_2Cl_2 (5 mL) dropwise. After addition, the mixture was stirred at −70 °C for 10 min and then a solution of alcohol **11** (1.55 g, 7.3 mmol) in CH_2Cl_2 (16 mL) was added dropwise. The mixture was stirred for a further 20 min and then triethylamine (5 mL, 36 mmol) was added dropwise. The mixture was allowed to attain room temperature and then washed with water (40 mL). The organic layer was separated and the aqueous phase reextracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (9:1). Ketone **12** (1.39 g, 90%) was isolated as a colorless oil which solidified on standing: mp 60–2 °C; ^{1}H NMR ($CDCl_3$) δ 4.55 (1H, t, J = 4.5 Hz), 4.24 (1H, d, J = 4.9 Hz), 2.50–2.43 (1H, m), 2.09–1.51 (5H, m), 1.53 (9H, s); MS (CI, NH_3) 212 (MH^+). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.73; H, 8.24; N, 6.54.

(±)-*endo*-7-[(1,1-Dimethylethoxy)carbonyl]-7-azabicyclo-[2.2.1]heptan-2-ol (13). To a stirred solution of ketone **12** (100 mg, 0.47 mmol) in THF (6 mL) at −55 °C, was added L-Selectride (0.57 mL of a 1.0 M solution in THF, 0.57 mmol) dropwise. The solution was allowed to warm to room temperature and then stirred for a further 30 min. After this time the solution was cooled to 0 °C and EtOH (0.7 mL) was added, followed by saturated aqueous NH_4Cl solution (0.7 mL). The mixture was allowed to attain room temperature and then partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chroamtographed on silica, eluting with petroleum ether (60/80):EtOAc (5:1 → 1:1), to afford *endo*-alcohol **13** (84 mg, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.38–4.32 (1H, m), 4.14–4.11 (2H, m), 2.24–1.44 (15H, m). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.75; H, 9.36; N, 6.53.

(±)-*endo*-7-(Phenylmethyl)-7-azabicyclo[2.2.1]heptan-2-ol (9). A solution of alcohol **13** (80 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) was stirred with TFA (1 mL) at room temperature for 3 h. The solvent was removed *in vacuo* and the residue azeotroped with toluene (2 × 20 mL). The crude amine salt **14** was isolated as a colorless oil and used directly without further purification. To a stirred solution of amine salt **14** in DMF (6 mL) was added K_2CO_3 (114 mg, 0.83 mmol) and benzyl bromide (54 mL, 0.45 mmol). The mixture was heated at 60 °C for 3 h then cooled to room temperature and partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was separated and the aqueous phase reextracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residual oil was chromatographed on silica, eluting with CH_2Cl_2:MeOH (95:5) followed by CH_2Cl_2:MeOH:NH_3 (90:10:1) to afford *endo*-alcohol **9** (56 mg, 74%) as a colorless oil: ^{1}H NMR (see Table 1); MS (CI, NH_3) 204 (MH^+). Anal. Calcd for $C_{13}H_{17}NO\cdot 0.1H_2O$: C, 76.14; H, 8.45; N, 6.83. Found: C, 76.21; H, 8.33; N, 6.85.

(±)-*cis*-1,2-Epoxy-4-[*N*-(phenylmethyl)-*N*-(trifluoroacetyl)amino]cyclohexane (15) and (±)-*trans*-1,2-Epoxy-4-[*N*-(phenylmethyl)-*N*-(trifluoroacetyl)amino]cyclohexane (16). Separation of the *cis*/*trans*-mixture of epoxides **7** (5.3 g, 0.018 mol) was achieved *via* preparative HPLC on a 5-μm silica column (250 mm × 20 mm i.d.) eluting with hexane:EtOAc (75:25) as eluant at a flow rate of 20 mL/min using a loading of 200 mg/injection. This gave **15** (1.05 g, 20%), a mixture of **15** and **16** (1.05 g, 20%), and **16** (1.8 g, 34%). *Cis*-isomer (**15**): R_f 0.75 (ether); mp 54–6 °C; ^{1}H NMR ($CDCl_3$) δ 7.38–7.16 (5H, m), 4.60 (1H, d, J = 16 Hz), 4.55 (1H, d, J = 16 Hz), 4.15–3.87 (1H, m), 3.14–3.07 (2H, m), 2.26–1.22 (6H, m). Anal. Calcd for $C_{15}H_{16}F_3NO_2$: C, 60.20; H, 5.39; N, 4.68. Found: C, 59.81; H, 5.17; N, 4.94. *Trans*-isomer (**16**): R_f 0.70 (ether); mp 60–61 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 7.42–7.18 (5H, m), 4.68–4.47 (2H, m), 4.27–4.11 and 3.67–3.55 (1H, m), 3.27–3.19 (1H, m), 3.17–3.02 (1H, m), 2.46–1.36 (6H, m). Anal. Calcd for $C_{15}H_{16}F_3NO_2$: C, 60.20; H, 5.39; N, 4.68. Found: C, 60.03; H, 5.24; N, 4.58.

(±)-*cis*-1,2-Epoxy-4-[*N*-(phenylmethyl)amino]cyclohexane (17). Following the procedure described for the preparation of **8**, the *cis*-isomer **15** (0.25 g, 0.88 mmol) was hydrolyzed with K_2CO_3 (0.25 g, 1.8 mmol) in a mixture of MeOH (5 mL) and H_2O (5 mL) at room temperature for 3 days to give **17** (0.14 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (4H, m, Ph), 7.24 (1H, m, Ph), 3.77 (2H, s), 3.12 (2H, m, H_1, H_2), 2.50 (1H, dddd, J = 11.0, 10.8, 6.1, 3.1, H_{4ax}), 2.19 (1H, dddd. J = 15.1, 6.5, 5.1, 2.0, H_{3eq}), 2.16 (1H, dddd, J = 15.1, 4.4, 4.4, 1.1, H_{6eq}), 1.76 (1H, dddd, J = 15.3, 11.5, 5.3, 1.8, H_{6ax}), 1.71 (1H, dd, J = 15.1, 9.9, H_{3ax}), 1.54 (1H, ddddd, J = 13.0, 5.3, 4.4, 3.1, 2.0, H_{5eq}), 1.36 (1H, dddd, J = 13.0, 11.2, 11.1, 4.5, H_{5ax}). Assignments confirmed by COSY. *Trans*-antiperiplanar ^4J H_{3eq}–H_{5eq} (2.0 Hz) confirms twisted chair conformation. Values of ^3J for H_4 show it to be axial: MS (CI, NH_3), 204 (MH^+). Anal. Calcd for $C_{13}H_{17}NO\cdot 0.35(H_2O)$: C, 74.49; H, 8.51; N, 6.68. Found: C, 74.55; H, 8.25; N, 6.72.

Cyclization of 17. Following the procedure described for the preparation of **10**, *cis*-epoxide **17** (90 mg, 0.44 mol) was converted to **10** (43 mg, 48%).

(±)-(*exo*)-8-Hydroxy-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (18). The *trans*-isomer **16** (0.3 g, 1 mmol) was stirred with K_2CO_3 (0.69 g, 5 mmol) in a mixture of MeOH (6 mL) and H_2O (3 mL) at room temperature for 3 days. The solvent was then evaporated and the residue partitioned between CH_2Cl_2 (3 × 15 mL) and 1 N HCl (10 mL). The combined organic phase was evaporated and the residue chromatographed on silica eluting with CH_2Cl_2:MeOH (95:5) to give **18** (110 mg, 44%) as a colorless solid: mp 93–5 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (5H, m, Ph), 4.99 (1H, d, J = 15.1, H_{10d}), 4.47 (1H, m, H_1), 4.14 (1H, m, H_5), 4.12 (1H, d, J = 15.1, H_{10u}), 3.42 (1H, m, H_8), 2.23 (1H, dm, J = 13.6, H_{9e}), 1.78 (3H, m, H_{7e}, H_{9a}, H_{6e}), 1.65 (2H, m, H_{6a}, H_{7a}); MS (Cl^+, NH_3), 204 ((MH^+-CO_2), (Cl^-), 247 ($M^{-\bullet}$); IR (nujol) cm^{-1}

3400 (OH), 1670 (C=O). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.15; H, 7.22; N, 5.68.

(±)-*trans*-1,2-Epoxy-4-[*N*-(phenylmethyl)amino]cyclohexane (19). A solution of **16** (0.3 g, 1 mmol) and KOH (0.17 g, 3 mmol) in MeOH (6 mL) and H_2O (3 mL) was stirred at room temperature for 18 h. The solvent was then evaporated and the residue chromatographed directly on silica eluting with CH_2Cl_2:MeOH (95:5) to give **19** (85 mg, 42%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (5H, m, Ph), 3.77 (1H, d, J = 13.0, PhCH_2), 3.74 (1H, d, J = 13.0, PhCH_2), 3.19 (1H, m, H_2), 3.16 (1H, dd, J = 4.0, 4.0, H_1), 2.75 (1H, m, H_4), 2.29 (1H, dd, J = 14.8, 4.7, H_{3d}), 2.08 (1H, dddd, J = 15.5, 6.2, 5.3, 5.0, H_{6d}), 1.89 (1H, ddd, J = 15.4, 9.3, 6.1, H_{6u}), 1.68 (1H, m, H_{5d}), 1.62 (1H, ddd, J = 14.8, 7.9, 2.9, H_{3u}), 1.21 (1H, dddd, J = 13.3, 9.4, 9.4, 6.3, H_{5u}). Anal. Calcd for $C_{13}H_{17}NO{\cdot}0.25(H_2O)$: C, 75.15; H, 8.49; N, 6.74. Found: C, 75.09; H, 8.21; N, 6.49.

Cyclization of 19. Following the procedure described for the preparation of **10**, *trans*-epoxide **19** (90 mg, 0.44 mol) was converted to **9** (58 mg, 65%).

2-Chloro-5-iodopyridine (22) was synthesized according to the method of Magison and Menschikoff:[16a] mp 97–9 °C (MeOH) (lit.[16] mp 99 °C); ^{1}H NMR ($CDCl_3$) δ 8.61 (1H, d, J = 2.6 Hz), 7.92 (1H, dd, J = 8.4, 2.6 Hz), 7.13 (1H, d, J = 8.4 Hz).

(±)-*endo*-2-(2-Chloro-5-pyridinyl)-7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]heptan-2-ol (23). To a stirred solution of **22** (1.24 g, 5.2 mmol) in ether (30 mL) and THF (15 mL) at −70 °C was added *n*-BuLi (3.3 mL of a 1.6 M solution in hexanes, 5.2 mmol) dropwise. The mixture was stirred at −70 °C for 20 min before a solution of ketone **12** (1.09 g, 5.2 mmol) in ether (15 mL) was added dropwise. The reaction was stirred at −70 °C for 2 h then warmed to −50 °C and stirred for 30 min. Saturated aqueous NH_4Cl (3 mL) was added and the mixture warmed to room temperature. Water (10 mL) was added and the organic layer separated. The aqueous phase was extracted with EtOAc (20 mL) and the combined organic layers dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (4:1 → 1:1) to give **23** (1.12 g, 67%) as a colorless solid: mp 147–50 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (1H, d, J = 2.6 Hz), 7.86 (1H, dd, J = 8.4, 2.6 Hz), 7.27 (1H, d, J = 8.4 Hz), 4.33 (1H, broad s), 4.23 (1H, broad s), 2.43–2.35 (2H, m), 2.00–1.63 (4H, m), 1.41 (9H, s); MS (CI, NH_3) 325/327 (MH^+). Anal. Calcd for $C_{16}H_{21}ClN_2O_3$: C, 59.17; H, 6.52; N, 8.62. Found: C, 59.01; H, 6.58; N, 8.45.

***O*-[(±)-*endo*-2-(2-Chloro-5-pyridinyl)-7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]heptan-2-yl] *S*-Methyl Xanthate (24).** To a stirred suspension of KH (0.79 g of a 35% (w/w) suspension in mineral oil, 6.8 mmol) in THF (25 mL) at 0 °C was added a solution of **23** (1.5 g, 4.6 mmol) in THF (15 mL). The cooling bath was removed and the mixture stirred at room temperature for 20 min. The solution was recooled to 0 °C and carbon disulfide (0.35 mL, 5.8 mmol) added dropwise, followed after 10 min by methyl iodide (0.36 mL, 5.8 mmol). The cooling bath was removed and the reaction stirred for 20 min at room temperature. Water (10 mL) was added and the solvent evaporated *in vacuo*. The residue was partitioned between water (20 mL) and CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (9:1 → 4:1). Xanthate **24** (1.84 g, 96%) was isolated as a pale yellow foam: ^{1}H NMR (see Table 1); MS (CI, NH_3) 415/417 (MH^+). Anal. Calcd for $C_{18}H_{23}ClN_2O_3S_2$: C, 52.10; H, 5.59; N, 6.75. Found: C, 52.36; H, 5.53; N, 6.59.

(±)-2-(2-Chloro-5-pyridinyl)-7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene (25) and 3-(2-Chloro-5-pyridinyl)-1-[(1,1-dimethylethoxy)carbonyl]pyrrole (26). Xanthate **24** (0.48 g, 1.16 mmol) was heated in toluene (10 mL) at reflux for 2 h. The solvent was evaporated and the residue chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (9:1 → 4:1). The first product eluted was **26** (20 mg, 6%): R_f, 0.7 (petroleum ether (60/80):EtOAc (4:1)); ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, d, J = 2.5 Hz), 7.76 (1H, dd, J = 8.1, 2.5 Hz), 7.53 (1H, t, J = 2 Hz), 7.32–7.30 (2H, m), 6.51–6.50 (1H, m), 1.63 (9H, s); MS (CI, NH_3) 280/278 (MH^+). Further elution afforded alkene **25** (0.26 g, 73%) as a colorless gum: R_f 0.22 (petroleum ether (60/80):EtOAc (4:1)); ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, d, J = 2.5 Hz), 7.64 (1H, dd, J = 8.4, 2.5 Hz), 7.30 (1H, d, J = 8.4 Hz), 6.55 (1H, d, J = 2.3 Hz), 5.03 (1H, d, J = 2.3 Hz), 4.81 (1H, broad s), 2.06–2.00 (2H, m), 1.42 (9H, s), 1.39–1.19 (2H, m); MS (CI, NH_3) 307/309 (MH^+). Anal. Calcd for $C_{16}H_{19}ClN_2O_2{\cdot}H_2O$: C, 59.17; H, 6.52; N, 8.62. Found: C, 58.92; H, 6.39; 8.27.

(±)-*exo*-2-(2-Chloro-5-pyridinyl)-7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (27) and (±)-*endo*-2-(2-Chloro-5-pyridinyl)-7-[(1,1-dimethylethoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (28). To a solution of olefin **25** (0.83 g, 2.7 mmol) in ethyl acetate (40 mL) was added PtO_2 (0.25 g) and the mixture hydrogenated (40 psi) for 1 h. Successive amounts of PtO_2 were then added and hydrogenation continued until starting material had disappeared as evidenced by TLC: **25**, R_f 0.51; **27/28**, R_f, 0.43 (silica, CH_2Cl_2:EtOAc (4:1)). (The hydrogenation was considered to be variable due to the presence of residues from the xanthate elimination step which could poison the catalyst). The catalyst was removed by filtration and the solvent evaporated. The residue was chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (9:1 → 4:1). The *endo*-isomer **28** (0.42 g, 51%) was isolated as a colorless oil which solidified on standing: mp 83–5 °C; R_f 0.23 (silica, petroleum ether (60/80):EtOAc (4:1); ^{1}H NMR (see Table 1); MS (CI, NH_3) 309/311 (MH^+). Anal. Calcd for $C_{16}H_{21}N_2O_2Cl{\cdot}0.25H_2O$: C, 61.34; H, 6.92; N, 8.94. Found: C, 61.56; H, 6.66; N, 8.79. A mixture of **27** and **28** (0.05 g, 6%) was isolated as a colorless oil. The *exo*-isomer **27** (0.093 g, 11%) was isolated as a colorless oil which solidified on standing: mp 67–9 °C; R_f 0.18 (silica, petroleum (60/80):EtOAc (4:1); ^{1}H NMR (see Table 1); MS (CI, NH_3) 309/311 (MH^+). Anal. Calcd for $C_{16}H_{21}N_2O_2Cl$: C, 62.23; H, 6.85; N, 9.07. Found: C, 62.29; H, 6.76; N, 8.74.

Epimerization of 28. To a solution of *endo*-isomer **28** (0.61 g, 1.97 mmol) in *tert*-butyl alcohol (22 mL) was added *t*-BuOK (0.89 g, 7.9 mmol) and the mixture was heated at reflux for 30 h. The solvent was evaporated and the residue chromatographed on silica (twice), eluting with petroleum ether (60/80):EtOAc (9:1 → 4:1) to afford the *endo*-isomer **28** (0.16 g, 26%), a mixture of **27/28** (18 mg, 3.8%), and pure **27** (0.20 g, 33%). The *endo*-isomer and mixture was resubmitted to the epimerization process to afford a 30–35% conversion to **27** on each cycle.

(±)-*exo*-2-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]-heptane ((±)-epibatidine) (1). HCl gas was bubbled through a cooled (0 °C) solution of **27** (98 mg, 0.32 mmol) in EtOAc (10 mL) for 10 min. The resulting yellow solution was stirred at 0 °C for 1 h and then evaporated to dryness. The residue was chromatographed on silica, eluting with CH_2Cl_2:MeOH:NH_3 (98:2:1 → 96:4:1). The free base **1** (66 mg, 100%) was obtained as a colorless solid: mp 50–1 °C (lit.[3] mp 50–1 °C); ^{1}H NMR (see Table 1) and converted to the hydrogen oxalate salt in ether: mp 174–6 °C (MeOH/ether); R_f 0.45 (silica, CH_2Cl_2:MeOH:NH_3 (90:10:1)); ^{1}H NMR (DMSO-d_6) δ 8.39 (1H, d, J = 2.5 Hz), 7.86 (1H, dd, J = 8.3, 2.5), 7.46 (1H, d, J = 8.3 Hz), 4.17 (1H, s), 4.08 (1H, s), 3.19 (1H, dd, J = 9.3, 5.8 Hz), 2.17 (1H, dd, J = 12.8, 9.3 Hz), 1.90–1.55 (5H, m); MS (CI, NH_3) 209/211 (MH^+). Anal. Calcd for $C_{11}H_{13}N_2Cl{\cdot}0.8(CO_2H)_2$: C, 53.91; H, 5.24; N, 9.98. Found: C, 53.94; H, 5.20; N, 9.81.

Formation and Separation of the Mosher's Esters 30 and 31. To a stirred solution of **11** (2.6 g, 12.2 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added 4-(dimethylamino)pyridine (DMAP) (1.49 g, 12.2 mmol) followed by (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride [(*R*)-(−)-Mosher's acid chloride] (3.08 g, 12.2 mmol) over 10 min. The mixture was warmed to room temperature and stirred for 18 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), water (20 mL), and brine (30 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated. Trituration and recrystallization of the resultant solid from hexane afforded **30** (1.68 g, 32%) as colorless needles: mp 108–10 °C (hexane); R_f 0.20 (silica, petroleum ether (60/80):EtOAc (1:1)); $[\alpha]^{25}_D$ −21.5° (c = 0.736, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.55–7.50 (2H, m), 7.45–7.35 (3H, m), 4.95–4.90 (1H, m), 4.31 (2H, broad s), 3.52 (3H, s), 2.05–1.50 (6H, m), 1.36 (9H, s); MS (CI, NH_3) 447 (MNH_4^+). Anal. Calcd for $C_{21}H_{26}NO_5F_3$: C, 58.74; H, 6.10; N, 3.26. Found: C, 59.14; H, 5.96; N, 3.12.

The hexane from the trituration and recrystallization mother liquor was combined and concentrated *in vacuo* to give an enriched mixture of diastereomers which could be separated by

column chromatography on silica. Separation was, however, achieved most efficiently *via* preparative HPLC on a Pirkle-type dinitrobenzoylleucine (250 mm × 20 mm i.d.) column eluting with hexane:methyl *tert*-butyl ether (85:15) as eluant at a flow rate of 20 mL/min using a loading of 250 mg/injection. In this way further **30** (0.6 g, 11%) was obtained, and **31** (2.2 g, 42%) was isolated as a colorless oil: R_f 0.25 (silica, petroleum ether (60/80):EtOAc (1:1)); $[\alpha]^{25}_D$ −47.6° (c = 0.618, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.58–7.50 (2H, m), 7.45–7.35 (3H, m), 4.90–4.95 (1H, m), 4.42 (1H, broad s), 4.29 (1H, broad s), 3.57 and 3.52 (3H, 2 × s), 2.10–1.50 (6H, m), 1.39 and 1.37 (9H, 2 × s); MS (CI, NH_3) 447 (MNH_4^+). Anal. Calcd for $C_{21}H_{26}NO_5F_3$: C, 58.74; H, 6.10; N, 3.26. Found: C, 58.93; H, 6.02; N, 3.20.

(+)-*exo*-7-[(1,1-Dimethylethoxy)carbonyl]-7-azabicyclo-[2.2.1]heptan-2-ol (32). To a stirred solution of **30** (1.59 g, 3.7 mmol) in EtOH (50 mL) at room temperature was added powdered KOH (2.07 g, 37 mmol). The mixture was stirred for 2 h and the solvent then evaporated. The residue was partitioned between ether (2 × 40 mL) and water (40 mL). The combined ether layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with petroleum ether (60/80):EtOAc (1:1). Enantiomer **32** (0.767 g, 97%) was obtained as a colorless solid: mp 72–5 °C; $[\alpha]^{25}_D$ +21.1° (c = 0.639, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (as for 11); MS (CI, NH_3) 214 (MH^+). Anal. Calcd for $C_{21}H_{26}NO_5F_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.17; H, 9.22; N, 6.75.

(−)-*exo*-7-[(1,1-Dimethylethoxy)carbonyl]-7-azabicyclo-[2.2.1]heptan-2-ol (33). Following the procedure described for the preparation of **32**, diastereomer **31** (1.59 g, 3.7 mmol) was hydrolyzed to give enantiomer **33** (0.447 g, 85%) as a colorless solid: mp 72–5 °C; $[\alpha]^{25}_D$ −21.6° (c = 0.655, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) as for 11; MS (CI, NH_3) 214 (MH^+). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.09; H, 8.86; N, 6.41.

(−)-Epibatidine Hydrogen Oxalate (34). Following the procedures described for the preparation of 1 replacing 11 with **32**, the hydrogen oxalate salt **34** was obtained as a colorless solid: mp 150 °C dec; $[\alpha]^{24}_D$ −37.4° (c = 0.419, MeOH), [Free base $[\alpha]^{23}_D$ +6.5° (c = 1.0, $CHCl_3$) (lit.[7] $[\alpha]^{23}_D$ +5° (c = 0.35, $CHCl_3$))]; ^{1}H NMR as for 1; MS (CI, NH_3) 209/211 (MH^+). Anal. Calcd for $C_{11}H_{13}N_2Cl\cdot(CO_2H)_2\cdot 0.2H_2O$: C, 51.65; H, 5.13; N, 9.27. Found: C, 51.79; H, 5.25; N, 8.89.

(+)-Epibatidine Hydrogen Oxalate (35). Following the procedures described for the preparation of 1, replacing 11 with **33**, the hydrogen oxalate salt **35** was obtained as a colorless solid: mp 160 °C dec; $[\alpha]^{24}_D$ +37.3° (c = 0.442, MeOH); [Free base $[\alpha]^{24}_D$ −6.7° (c = 0.87, $CHCl_3$) (lit.[7] $[\alpha]^{24}_D$ −5° (c = 0.35, $CHCl_3$))]; ^{1}H NMR as for 1; MS (CI, NH_3) 209/211 (MH^+). Anal. Calcd for $C_{11}H_{13}N_2Cl\cdot(CO_2H)_2$: C, 52.27; H, 5.06; N, 9.38. Found: C, 51.98; H, 4.92; N, 9.18.

Acknowledgment. We would like to thank Dr. John W. Daly for kindly supplying a sample of natural epibatidine.

Supplementary Material Available: HPLC conditions for separation of the (+)- and (−)-enantiomers of epibatidine are provided together with represenatative chromatograms (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.