Total Synthesis of (−)-Epibatidine Using an Asymmetric Diels−Alder Reaction with a Chiral *N*-Acylnitroso Dienophile

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An asymmetric total synthesis of (−)-epibatidine (**1**), isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae, has been achieved by virtue of the development of asymmetric hetero Diels−Alder (D−A) cycloaddition with an *N*-acylnitroso dienophile bearing the optically active 8-arylmenthol as a chiral source. Thus, in situ oxidation of the hydroxamic acid *ent*-**12f** incorporating the (1*S*,2*R*,5*S*)-8-(2-naphthyl)menthyl auxiliary was performed using the Swern conditions to produce the acylnitroso dienophile, which reacted at once with 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**7**) to provide the (1*S*,4*R*)-*meta-aza* cycloadduct **24** as a major diastereoisomer. The observed facial diastereoselectivity is consistent with a transition-state model with the naphthyl group in "stacked" position and with the acylnitroso group in the *s-cis* conformation, wherein π attractive interaction between the naphthyl and nitrosocarbonyl groups may contribute to facial control. Compound **24** underwent hydrogenation followed by removal of the chiral auxiliary with LiH_2NBH_3 and reductive cleavage of the N−O bond with $Mo(CO)_6$ to give the amino alcohol derivative **29**, which was converted to (−)-epibatidine via bromination followed by cyclization.

Introduction

In the mid-1970s a novel class of amphibian alkaloid epibatidine was first isolated by Daly and co-workers at the National Institutes of Health in a trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae.[1] Its structure **1** was elucidated by this research group in 1992,[2] revealing the relative stereochemistry and unprecedented feature with a strained nitrogen-bridged six-membered carbon ring system (7-azabicyclo[2.2.1]heptane) with an exooriented 3-(6-chloropyridyl) substituent. Because of the very small quantities of the natural product (less than 1 mg isolated from 750 frogs), the assignment of absolute stereochemistry was investigated subsequently by Fletcher et al.[3] in 1994, establishing it as 1*R*,2*R*,4*S* as shown.

In preliminary tests on mice, it proved to be at least 200 times more potent than morphine in bioassays of analgesic effects, but its effect was not blocked by the potent opioid receptor antagonist naloxone, confirming that its strong analgesic action evolves via a nonopioid mechanism.[2,4−8] Subsequent studies showed that the remarkable pharmacological activity of epibatidine is attributed to its unique property as an extremely potent nicotinic acetylcholine receptor (nAChR) agonist in the central and autonomic nervous systems.[4,5,7,9−13] A number of nAChR ligands have been reported that are selective for neuronal nAChR subtypes and may have potential in the treatment of Alzheimer's disease and Parkinson's disease.[14]

Due to its outstanding pharmacological action, unique structure, and scarcity in nature, epibatidine has attracted the unprecedentedly great interest of synthetic chemists around the world,[15] and in a relatively short time a vast number of synthetic approaches has been

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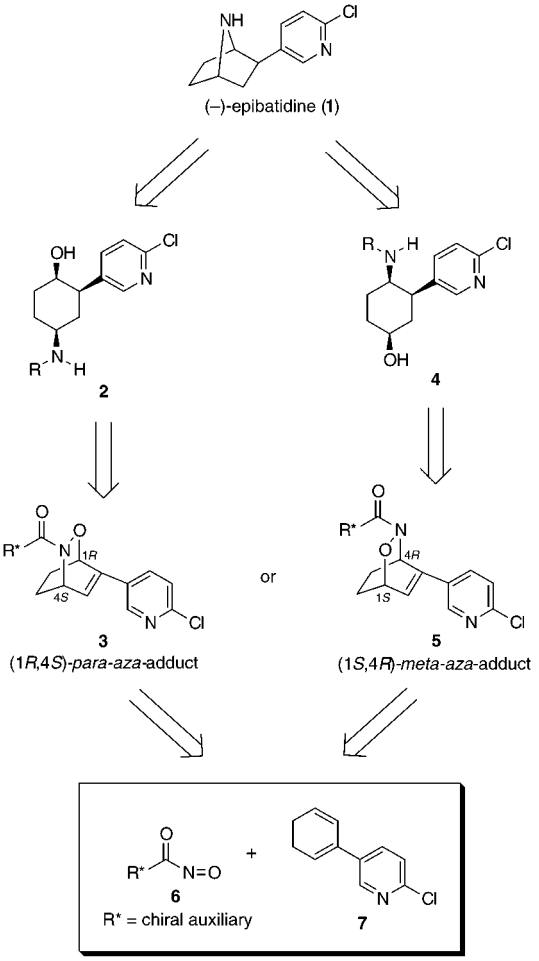
published.[16,17] Furthermore, the fact that the collection of dendrobatid frogs has been prevented by an international treaty[18] enacted in 1984 for the protection of endangered species has also spurred synthetic efforts to prepare needed material for further investigation. Of these synthetic approaches, however, only two asymmetric total syntheses of (−)-epibatidine (**1**), which is the natural enantiomer, have been reported: in one case via Pd-catalyzed desymmetrization reported by Trost[16p] and in the other case via asymmetric protonation reported by Kosugi.[16s] In connection with our ongoing projects related to the use of acylnitroso Diels−Alder methodology in alkaloid synthesis,[19,20] we now report a new asymmetric approach to **1** based on asymmetric hetero Diels−Alder cycloaddition with an acylnitroso dienophile bearing the optically active 8-arylmenthol as a chiral source.[21]

Results and Discussion

Our strategy for the synthesis of **1** is outlined in the retrosynthetic pathway depicted in Scheme 1. The basic approach featured the general methodology for the asymmetric hetero Diels−Alder reaction of 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**7**) with the acylnitroso compound **6** bearing an appropriate chiral auxiliary as the key step, in which either enantioselective pathway, via

Scheme 1



the 1*R*,4*S* adduct **3** or 1*S*,4*R* adduct **5**, is available depending on the *para-aza* or *meta-aza* regioselectivity, respectively, in the cycloaddition. Although the pathway involving (1*S*,4*R*)-*meta-aza*-cycloadduct **5** was actually employed in the present synthesis of **1**, at the beginning of the project, it was difficult to determine which one of these pathways would be operative for the synthesis of **1**, since *para*/*meta* regioselectivity in the acylnitroso cycloaddition with the 2-substituted 1,3-cyclohexadiene was uncertain and unpredictable.

On the basis of this retrosynthetic argument, our initial efforts were directed at developing a general methodology for the asymmetric hetero Diels−Alder reaction with acylnitroso dienophiles bearing appropriate chiral auxiliaries. We have recently recognized[22] efficient asymmetric conjugate allylation of *N*-acyl-2,3-dihydro-4-pyridones using the 8-arylmenthol moiety as a chiral inducer, wherein the presence of π attractive interaction between the aromatic ring and the enamido portion was suggested for control of the facial selectivity. Since introduction of 8-phehylmenthol by Corey in 1975,[23] cyclohexyl-based chiral auxiliaries of the 8-phenylmenthol type[24] have proved to behave as effective chiral inductors in a variety of different types of asymmetric reactions, including Diels−Alder reaction, ene reaction, and conjugate addition to enoates, which are suggested

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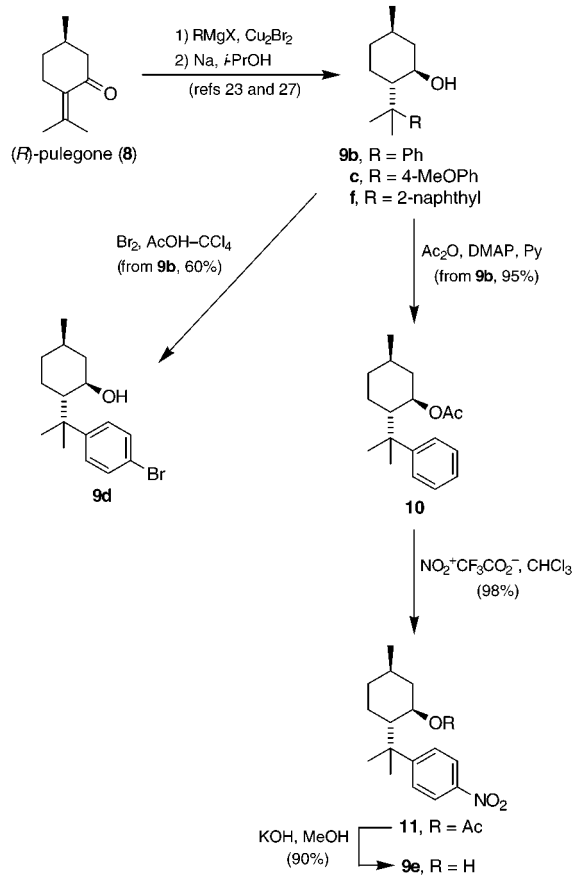
Scheme 2



to lie in π-stacking interactions between the aromatic ring and the π system.[25] In consideration of these results, we envisioned the use of (1*R*,2*S*,5*R*)-(−)-menthol **9a** and its 8-substituted derivatives **9b**−**f** as chiral inducers in the asymmetric hetero Diels−Alder reaction with acylnitroso dienophiles for evaluating the effect of these chiral inducers and the stereochemistry of the cycloadducts.[26] The auxiliaries **9b**,**c**,**f** were prepared from (*R*)-(+)-pulegone (**8**) in analogy with Corey's procedure,[23,27] and the auxiliaries **9d**,**e** were derived from 8-phenylmenthol (**9b**), as shown in Scheme 2. Thus, 8-(4-bromophenyl)menthol (**9d**) was readily available by the usual bromination (Br_2, AcOH−CCl_4) of **9b** in 60% yield. Otherwise, conversion of **9b** to 8-(4-nitrophenyl)menthol (**9e**) was accomplished via protection of the hydroxy group as an acetate **10**, followed by nitration with nitronium trifluoroacetate and subsequent deprotection of **11** in 84% overall yield from **9b**.

Scheme 3

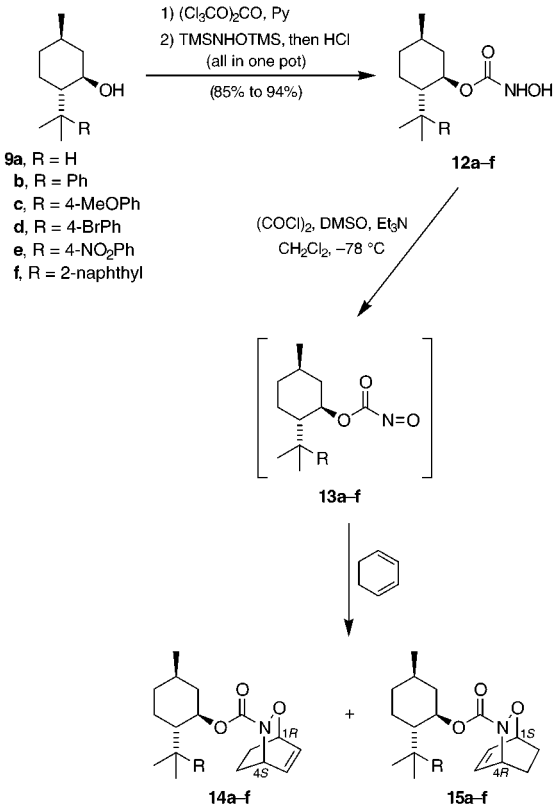


Table 1. Asymmetric Hetero Diels−Alder Reaction of *N*-Acylnitroso Compounds with 1,3-Cyclohexadiene

entry	hydroxamic acid **12** (% yield from **9**)	major adduct **14**	**14**/**15** ratio[a]	yield (%)[b]
1	**12a**, R = H (85)	**14a**	1.2:1	96
2	**12b**, R = Ph (94)	**14b**	8.9:1	95
3	**12c**, R = 4-MeOPh (89)	**14c**	9.1:1	94
4	**12d**, R = 4-BrPh (85)	**14d**	13.2:1	95
5	**12e**, R = 4-NO_2Ph (92)	**14e**	22.7:1	94
6	**12f**, R = 2-naphthyl (88)	**14f**	14.0:1	95

[a] Determined by HPLC analysis: Shim-pack CLC-SIL column; hexanes−EtOAc = 16:1 (entries 1, 2), 9:1 (entries 3, 4), 6:1 (entry 5); UVdetector, 254 nm. [b] Isolated combined yield of **14** and **15**.

(1*R*,2*S*,5*R*)-Menthol (**9a**) and its 8-substituted derivatives **9b**−**f** thus obtained were treated with triphosgen and pyridine in dichloromethane to form the chloroformates, which immediately underwent reaction with *N*,*O*-bis(trimethylsilyl)hydroxylamine followed by acid treatment in the same reaction vessel, affording the corresponding hydroxamic acids **12a**−**f** in 85−94% overall yields (see Scheme 3 and Table 1). In a preliminary experiment, in situ oxidation of **12f** in the presence of 1,3-cyclohexadiene was performed using Pr_4NIO_4 in chloroform at room temperature to produce the acylnitroso dienophile **13f**, which reacted at once with 1,3-cyclohexadiene to give the (1*R*,4*S*)- and (1*S*,4*R*)-cycloadducts, **14f** (vide infra) and **15f**, with a 5.6:1 ratio in 73% combined yield. When this cycloaddition of **13f** with 1,3-cyclohexadiene was performed at −78 °C by using the Swern oxidation protocol,[26i] both the diastereoselectivity and chemical yield were found to be remarkably enhanced to 14.0:1 and 95%, respectively (Table 1, entry 6). The molecular structure with the 1*R*,4*S* absolute configuration of the major

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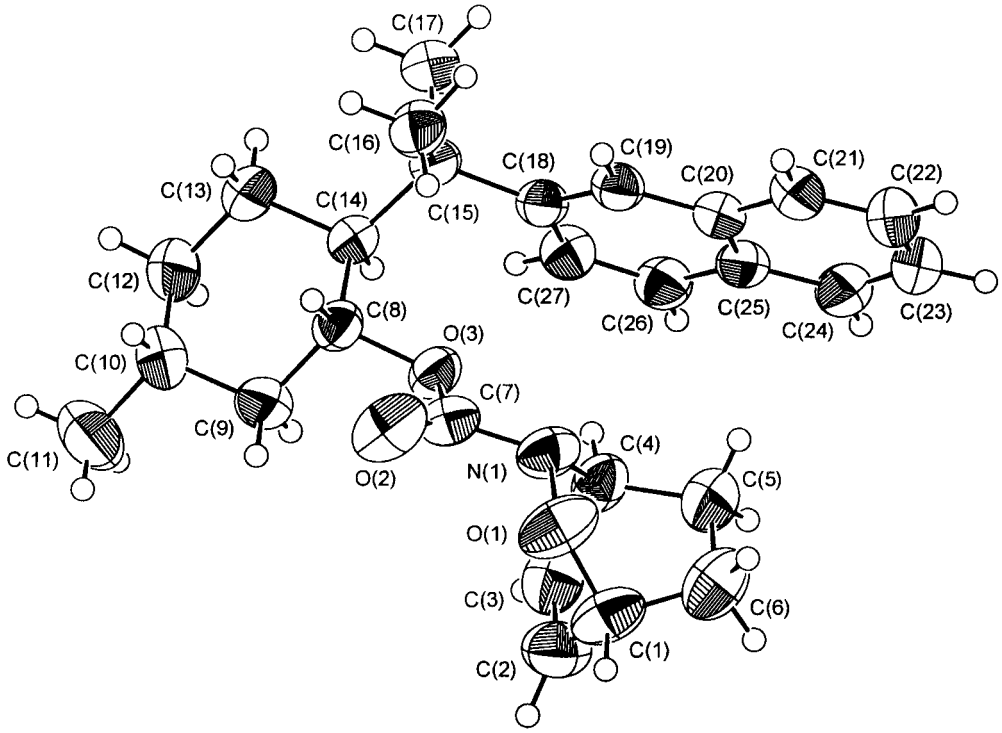


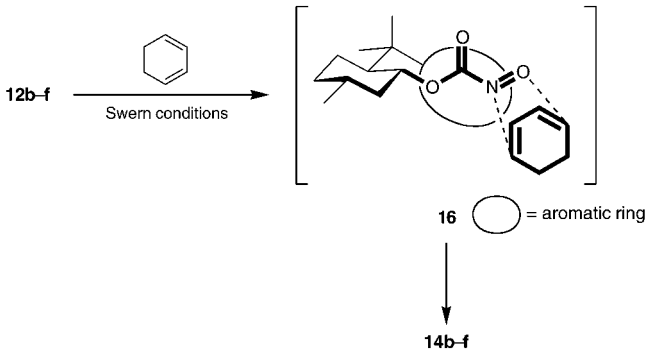
Figure 1. ORTEP drawing of **14f** (ellipsoids at 50% probability).

cycloadduct **14f** was unambiguously established by single-crystal X-ray analysis (Figure 1).

On the basis of the above experimental results, we employed the Swern oxidation conditions for the cycloaddition with the rest of the hydroxamic acids **12a**−**e**, and the results are presented in Table 1. In entry 1, **12a** lacking the aryl substituent group at C(8) shows almost no selectivity in the cycloaddition. On the other hand, as can be seen in entries 2−5, the reactions with **12b**−**e** provide the (1*R*,4*S*)-cycloadducts **14b**−**e** as major diastereomers in good to very high diastereoselectivity and excellent yield; these results clearly demonstrate the importance of the aromatic moiety of the menthol auxiliary to attain high levels of asymmetric induction.

Each ^{1}H NMR spectrum of the major cycloadducts **14b**−**e** with the 8-arylmenthyl moiety shows the chemical shift attributed to the C(4) bridgehead proton at higher field (δ 3.5−4.1) as a characteristic very broad singlet, in contrast to that observed for **14a** with no aryl group where the corresponding proton resonance occurs at δ 4.72. It appears that the upfield shifts observed for these protons in **14b**−**e** are due to the influence of the anisotropic shielding effect of the aromatic rings, indicating that **14b**−**e** adopt a conformation with the aryl group in "stacked" position (vide infra) consistent with the solid-state conformation of **14f** elucidated by X-ray analysis as depicted in Figure 1.

The facial diastereoselectivity observed in the cycloadditions of the hydroxamic acids **12b**−**f** with aromatic menthyl auxiliaries is consistent with a transition-state model **16** with the aryl group in "stacked" position[28] and with the acylnitroso group in the *s-cis* conformation with respect to the C−N bond, wherein the aromatic ring shields selectively the face of the nitroso group by π attractive interaction between the aryl and nitrosocarbonyl groups, forcing the diene to "endo approach"[26e,f,h] preferentially from the front side. The *s-cis*/*s-trans*



arrangement, as well as the exo/endo mode approach, is a crucial factor dictating the sense of the asymmetric induction; however, this aspect is generally not well-understood in the [4 + 2] cycloaddition with acylnitroso dienophiles. One reason for this may be that the RCON=O species are very short-lived and hence spectroscopically undetectable.[29] However, in the case of 8-phenylmenthyl glyoxalates, the glyoxalate moiety has been proved to lie in the *s-cis* arrangement, wherein π attractive interaction is presumed to hold the two carbonyl groups in the *s-cis* conformation.[30] A similar situation should be expected for the acylnitroso compounds **13a**−**f**, whose structural and electronic features are similar to those of the 8-phenylmenthyl glyoxalates, to show the *s-cis* preference in the cyclization of transition state **16**.

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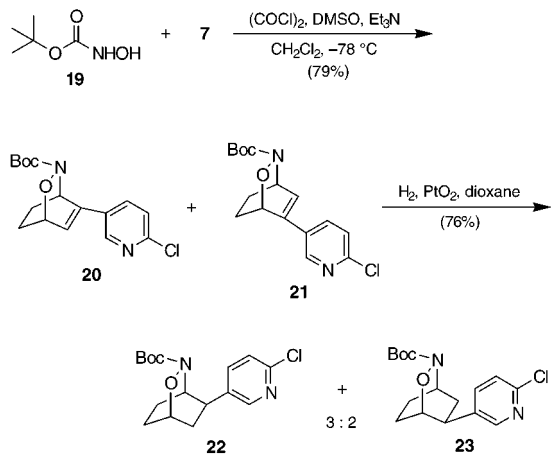
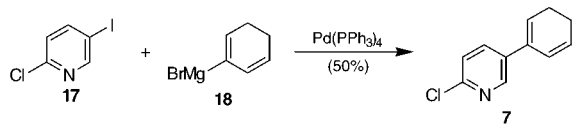
Scheme 4

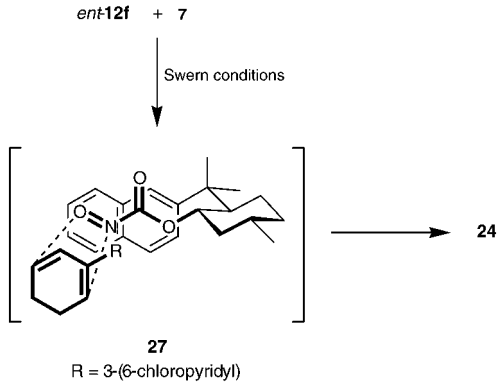


Having established the feasibility of the asymmetric cycloaddition with a menthol-based chiral auxiliary, in an attempt to apply this method to the asymmetric synthesis of epibatidine, we next examined the regioselectivity in the cycloaddition using 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**7**) as a diene component. Thus, palladium-catalyzed cross-coupling of 2-chloro-5-iodopyridine (**17**)[31] with 2-(1,3-cyclohexadienyl)magnesium



bromide (**18**), prepared from 2-bromo-1,3-cyclohexadiene[32] led to **7** in 50% yield. The cycloaddition of **7** with commercially available *tert*-butyl *N*-hydroxycarbamate **19** was performed utilizing Swern conditions as described above to give a chromatographically unseparable mixture of the cycloadducts **20** and **21** in 79% combined yield (Scheme 4). This mixture underwent catalytic hydrogenation over PtO_2 to furnish the regioisomers **22** and **23** in a 3:2 ratio (76% combined yield) with complete endo selectivity. The major isomer **22** was crystallized, and X-ray crystallographic analysis revealed its regio- and stereochemistry as shown in Figure 2. These results indicate that the *meta-aza* regioisomer is favored over the *para-aza* one in this cycloaddition with a strongly electron-withdrawing 2-substituted cyclohexadiene such as **7**. This finding is in contrast to that reported for the cycloaddition of acylnitroso compounds to an electron-deficient 2-substituted 1,3-cyclohexadiene, which predominantly affords *para-aza* adducts consistent with either a normal (HOMO-diene controlled) or inverse electron demand (LUMO-diene controlled) Diels−Alder reaction.[33]

Considering the diastereo- and regioselectivities observed in these cycloadditions with the hydroxamic acids **12f** and **19**, respectively, we employed the asymmetric approach to (−)-epibatidine based on the retrosynthetic route depicted in Scheme 1 via the (1*S*,4*R*)-*meta-aza*-cycloadduct **5** rather than the (1*R*,4*S*)-*para-aza*-cycloadduct **3**. The need for **5** suggested the use of the (1*S*,2*R*,5*S*)-menthyl auxiliary for inducing the correct sense of chirality. Thus, due to the ease of preparation and providing high π-facial discrimination, the 2-naphthyl group[34] was selected as a C(8) substitution, and (1*S*,2*R*,5*S*)-8-(2-naphthyl)menthol (*ent*-**9f**) was prepared from (*S*)-(−)-pulegone (*ent*-**8**)[35] according to the known procedure.[23,27] Conversion of *ent*-**9f** to the hydroxamic acid *ent*-**12f** was achieved in the same manner as described above for the preparation of **12f**. Oxidation of *ent*-**12f** in the presence of **7** under the Swern conditions resulted in cylcloaddition to form **24** (42%), **25** (20%), and **26** (4%) (Scheme 5).[36] The major product **24** resulted from the *meta-aza* regioselective process and the opposite asymmetric induction to that obtained with the hydroxamic acids **12** (via transition state **16**), which results are in agreement with the prediction based on the π-attractive transition-state model **27**.



The (1*S*,4*R*)-*meta-aza* isomer **24** thus obtained was hydrogenated over PtO_2 to give the exo product **28** (81%) as a single diastereomer (Scheme 6), which underwent removal of the chiral auxiliary with LiH_2NBH_3, prepared from $BH_3{\cdot}NH_3$ and BuLi,[37] followed by *tert*-butoxycarbonylation to give (−)-**22** (58% from **28**), identical with the above-described compound **22**, except for the optical rotation. After reductive cleavage of the N−O bond with molybdenum hexacarbonyl,[38] the resulting *N*-Boc amino alcohol **29** (85%) was brominated with triphenylphosphine and carbon tetrabromide with inversion of configuration to afford the bromide **30** (42%), which was then deprotected with trifluoroacetic acid to give the bromoamine **31** in 96% yield. Finally, refluxing of **31** in chloroform for 3 days provided (−)-epibatidine, mp 61−62 °C; $[\alpha]^{27}_D$ −6.26 (*c* 0.80, $CHCl_3$), in 97% yield, which was identical with the spectral data (^1H and ^{13}C NMR) reported in the literature.[15a]

(31) (a) Ogura, F.; Otsubo, T.; Aso, T.; Nobuhara, Y.; Hama, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1683. (b) Magidson, O.; Menschikoff, G. *Chem. Ber.* **1925**, *58*, 113.

(32) (a) Sonnenberg, J.; Winstein, S. *J. Org. Chem.* **1961**, *27*, 748. (b) Bottini, A. T.; Schear, W. *J. Org. Chem.* **1965**, *30*, 3205.

(33) (a) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.

(34) The efficiency of the menthol chiral auxiliary bearing a naphthalene nucleus has been demonstrated. (a) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500. (b) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293. See also ref 22.

(35) A sample of (*S*)-(−)-pulegone was kindly provided by Takasago International Co.

(36) In this cycloaddition, the use of *ent*-**12e** is expected to lead to a better selectivity for the desired (1*S*,4*R*)-*meta-aza* isomer, since, as can be seen from the results summarized in Table 1, **12e** gives the best diastereoselectivity in the cycloaddition with 1,3-cyclohexadiene. Work in this area is underway in our laboratory.

(37) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

(38) Cicchi, S.; Goti, A.; Guarna, A.; De Salo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

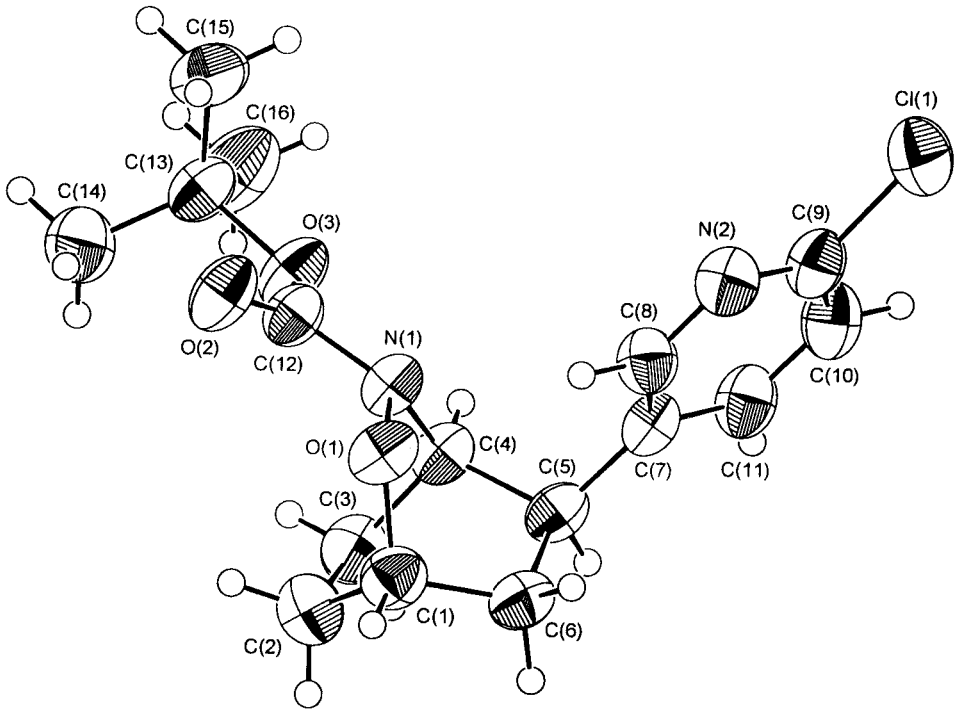
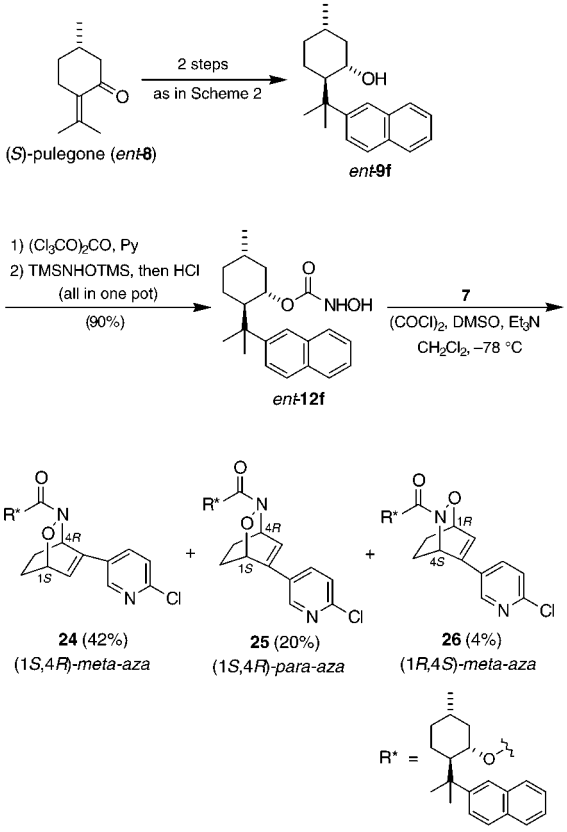
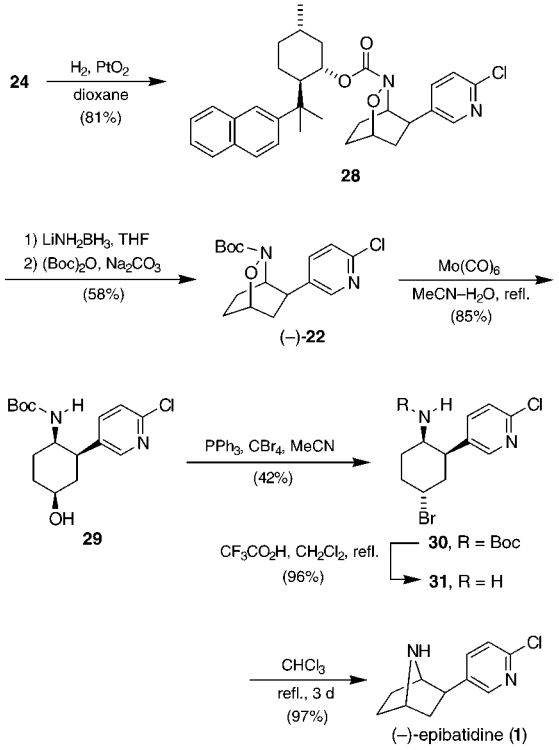


Figure 2. ORTEP drawing of **22** (ellipsoids at 50% probability).

Scheme 5



Scheme 6



In conclusion, the asymmetric synthesis of (−)-epibatidine has been accomplished by a ten-step route in 5.9% overall yield from *ent*-**9f** based on asymmetric hetero Diels−Alder cycloaddition with an acylnitroso dienophile incorporating (1*S*)-8-(2-naphthyl)menthol as a chiral inducer, wherein π-attracting interaction between the naphthyl and nitrosocarbonyl groups may contribute to facial control.

Experimental Section

General Procedures. All melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz using residual $CHCl_3$ (7.26 ppm) as reference. ^{13}C NMR spectra were recorded at 100.6 MHz with $CDCl_3$ (77.05 ppm) as reference. Mass spectra were measured at an ionizing voltage of 70 eV. Organic solvents used were dried by standard methods. Commercially obtained reagents were used without further purification. Silica gel 60 (230−400 mesh, Merck) was used for column chromatography, and silica gel 70 FM plates (0.25 mm, Wako) were used for TLC. HPLC analysis was performed with a Shim-pack CLC−SIL column.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-bromophenyl)-ethyl]cyclohexanol (9d). To a cooled (0 °C), stirred solution of (−)-8-phenylmenthol (**9b**) (360 mg, 1.55 mmol) in CCl_4 (1.5 mL) and acetic acid (7 mL) was added bromine (0.99 g, 6.2 mmol), and the mixture was stirred at room temperature. After 5 h, 20% aqueous K_2CO_3 (50 mL) was added and the resulting mixture was extracted with ether (2 × 100 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 50:1) to give **9d** (288 mg, 60%) as a colorless oil: $[\alpha]^{26}_D$ −8.0 (*c* 0.25, $CHCl_3$); IR (film) 3413 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77−1.04 (4H, m), 0.88 (3H, d, J = 6.6 Hz), 1.28 (3H, s), 1.32−1.45 (1H, m), 1.40 (3H, s), 1.58−1.66 (3H, m), 1.83−1.88 (1H, m), 3.49 (1H, td, J = 10.2, 4.2 Hz), 7.25 (2H, dt, J = 8.7, 2.3 Hz), 7.42 (2H, dt, J = 8.7, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 22.0, 25.3, 26.6, 28.0, 31.6, 34.8, 39.9, 45.8, 54.2, 73.1, 119.4, 127.8 (2C), 131.3 (2C), 150.6; EIMS *m*/*z* (rel intens) 312 (M^+ + 2, 5), 310 (M^+, 5), 197 (100).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acetate (10). A mixture of **9b** (1.57 g, 6.76 mmol), acetic anhydride (1.38 g, 13.5 mmol), and 4-(dimethylamino)-pyridine (0.90 g, 7.4 mmol) in pyridine (8 mL) was stirred at room temperature for 22 h. The mixture was poured into 5% aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed sequentially with 5% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 30:1) to give **10** (1.76 g, 95%) as a colorless oil: $[\alpha]^{26}_D$ −6.4 (*c* 2.47, $CHCl_3$); IR (film) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82−0.99 (2H, m), 0.87 (3H, d, J = 6.5 Hz), 1.11 (1H, qd, J = 12.9, 3.3 Hz), 1.21 (3H, s), 1.31 (3H, s), 1.40−1.54 (1 H, m, including 3H, s at δ 1.54), 1.63−1.68 (1H, m), 1.72 (1H, qd, J = 13.3, 3.5 Hz), 1.83−1.88 (1H, m), 2.01 (1H, ddd, J = 12.3, 10.6, 3.6 Hz), 4.79 (1H, td, J = 10.7, 4.5 Hz), 7.11−7.16 (1H, m), 7.25−7.32 (4H, m); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.8, 24.5, 26.5, 28.3, 31.3, 34.6, 39.6, 41.8, 50.4, 74.0, 125.0, 125.4 (2C), 127.9 (2C), 151.7, 170.4; EIMS *m*/*z* (rel intens) 274 (M^+, 7), 214 (38), 119 (100).

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-nitrophenyl)ethyl]cyclohexyl Acetate (11). To a cooled (0 °C), stirred solution of **10** (560 mg, 2.04 mmol) in $CHCl_3$ (3 mL) was added ammonium nitrate (324 mg, 4.06 mmol) and trifluoroacetic anhydride (3.00 g, 14.3 mmol). After being stirred at room temperature for 4.5 h, the mixture was poured into water (10 mL) and then extracted with $CHCl_3$ (4 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane−EtOAc, 20:1) gave **11** (640 mg, 98%) as a pale yellow oil: $[\alpha]^{26}_D$ +33.3 (*c* 3.84, $CHCl_3$); IR (film) 1732, 1519, 1348 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82−1.02 (2H, m, including 3H, d, J = 6.5 Hz at δ 0.88), 1.16 (1H, qd, J = 12.9, 3.4 Hz), 1.22 (3H, s), 1.34 (3H, s), 1.42−1.53 (1H, m, including 3H, s at δ 1.45), 1.70 (1H, m), 1.87 (1H, m), 2.06 (1H, ddd, J = 12.2, 10.6, 3.5 Hz), 4.77 (1H, td, J = 10.7, 4.4 Hz), 7.45 (2H, dt, J = 9.0, 2.4 Hz), 8.15 (2H, dt, J = 9.0, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.7, 23.5, 26.3, 28.7, 31.2, 34.4, 40.4, 41.6, 50.4, 73.9, 123.1 (2C), 126.3 (2C), 145.6, 160.0, 170.0; EIMS *m*/*z* (rel intens) 319 (M^+, 1), 165 (97), 164 (82), 155 (58), 118 (42), 95 (89), 91 (31), 43 (100).

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-nitrophenyl)ethyl]cyclohexanol (9e). To a solution of **11** (4.31 g, 13.5 mmol) in MeOH (23 mL) was added 33% aqueous KOH (20 mL), and the mixture was refluxed for 3.5 h. Water (50 mL) and EtOAc (150 mL) was added to this mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography on silica gel (hexane−EtOAc, 20:1) gave **9e** (3.37 g, 90%) as a pale yellow solid: mp 63−64 °C; $[\alpha]^{28}_D$ −20.7 (*c* 0.56, $CHCl_3$); IR (KBr) 3442, 1515, 1347 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78−1.04 (2H, m), 0.89 (3H, d, J = 6.5 Hz), 1.34 (3H, s), 1.36−1.72 (6H, m, including 3H, s at δ 1.47), 1.87 (1H, m), 3.50 (1H, m), 7.51 (2H, td, J = 9.0, 2.4 Hz), 8.15 (2H, td, J = 9.0, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.9, 25.8, 26.7, 27.4, 31.7, 34.7, 40.9, 46.2, 54.3, 73.0, 123.3 (2C), 126.7 (2C), 145.7, 160.0; EIMS *m*/*z* (%) 277 (M^+, 2), 165 (100), 148 (83), 118 (39).

General Procedure for the Preparation of Hydroxamic Acids 12. The preparation of [[(1*R*,2*S*,5*R*)-5-methyl-2-isopropylcyclohexyl]oxy]carbonylhydroxylamine (**12a**) is representative. To a solution of **9a** (600 mg, 3.84 mmol) in CH_2Cl_2 (18 mL) was added pyridine (402 mg, 5.08 mmol), and the mixture was cooled to 0 °C. To this was added a solution of triphosgene (456 mg, 1.54 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at 0 °C. After 30 min, to this mixture were successively added pyridine (608 mg, 7.69 mmol) and *N*,*O*-bis(trimethylsilyl)hydroxylamine (820 mg, 4.62 mmol), and the mixture was stirred at 0 °C. After 2 h, the reaction was quenched by addition of 1 N HCl (20 mL), and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 7:1) to provide **12a** (703 mg, 85%) as a white solid: mp 138−139 °C; $[\alpha]^{26}_D$ −82.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3346, 1696, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (3H, d, J = 7.0 Hz), 0.87 (3H, d, J = 7.1 Hz), 0.89 (3H, d, J = 6.6 Hz), 0.92−1.10 (3H, m), 1.28−1.35 (1H, m), 1.41−1.53 (1H, m), 1.66 (2H, br d, J = 12.2 Hz), 1.83−1.91 (1H, m), 2.02 (1H, br d, J = 11.9 Hz), 4.63 (1H, td, J = 10.9, 4.4 Hz), 7.29 (1H, br s), 7.58 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 16.3, 20.7, 22.0, 23.5, 26.2, 31.4, 34.1, 41.1, 47.2, 76.6, 159.6; CIMS (isobutane) *m*/*z* (rel intens) 216 (M^+ + 1, 12), 139 (100).

[[(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-phenylethyl]cyclohexyl]oxy]carbonylhydroxylamine (12b) was prepared from **9b** according to the general procedure in 94% yield as a colorless oil: $[\alpha]^{26}_D$ −40.0 (*c* 1.0, $CHCl_3$); IR (film) 3306, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, J = 6.5 Hz), 0.81−1.01 (2H, m), 1.16 (1H, m), 1.22 (3H, s), 1.31 (3H, s), 1.42−1.54 (1H, m), 1.69 (1H, m), 1.82−1.93 (2H, m), 2.04 (1H, m), 4.71 (1H, td, J = 10.8, 4.4 Hz), 6.24 (1H, br s), 7.15−7.20 (1H, m), 7.30−7.35 (4H, m); ^{13}C NMR ($CDCl_3$) d 21.8, 22.8, 26.2, 29.3, 31.3, 34.5, 39.4, 41.7, 51.0, 76.3, 124.8, 125.5 (2C), 127.9 (2C), 152.5, 158.4; CIMS (isobutane) *m*/*z* (rel intens) 292 (M^+ + 1, 10), 215 (100).

[[(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-methoxyphenyl)-ethyl]cyclohexyl]oxy]carbonylhydroxylamine (12c) was prepared from **9c** according to the general procedure in 89% yield as a colorless oil: $[\alpha]^{26}_D$ −23.7 (*c* 2.7, $CHCl_3$); IR (film) 3316, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81−1.01 (2H, m), 0.87 (3H, d, J = 6.5 Hz), 1.10 (1H, qd, J = 12.9, 3.2 Hz), 1.20 (3H, s), 1.28 (3H, s), 1.40−1.52 (1H, m), 1.66 (1H, m), 1.77 (1H, m), 1.88−1.97 (2H, m), 3.79 (3H, s), 4.71 (1H, td, J = 10.8, 4.4 Hz), 6.84−6.87 (2H, m), 7.19−7.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.9, 26.4, 28.8, 31.3, 34.5, 38.9, 41.8, 51.0, 55.3, 76.5, 113.1 (2C), 126.4 (2C), 144.2, 156.9, 158.6; EIMS *m*/*z* (rel intens) 321 (M^+, 2), 149 (100).

[[(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-bromophenyl)-ethyl]cyclohexyl]oxy]carbonylhydroxylamine (12d) was prepared from **9d** according to the general procedure in 85% yield as a white solid: $[\alpha]^{24}_D$ −4.9 (*c* 1.0, $CHCl_3$); IR (film) 3305, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81−0.99 (2H, m), 0.87 (3H, d, J = 6.5 Hz), 1.05−1.15 (1H, m), 1.20 (3H, s), 1.28 (3H, s), 1.39−1.53 (1H, m), 1.66 (1H, m), 1.74 (1H, m), 1.88−1.96 (2H, m), 4.71 (1H, td, J = 10.7, 4.4 Hz), 6.42 (2H, br s), 7.16 (2H, d, J = 8.6 Hz), 7.42 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.9, 26.4, 28.3, 31.2, 34.4, 39.5, 41.8, 51.0, 76.5, 118.6, 127.4 (2C), 130.9 (2C), 151.1, 158.4; CIMS (isobutane) *m*/*z* (rel intens) 372 (M^+ + 3, 5), 370 (M^+ + 1, 5), 295 (94), 293 (100).

[[(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-nitrophenyl)-ethyl]cyclohexyl]oxy]carbonylhydroxylamine (12e) was prepared from **9e** according to the general procedure in 94% yield as a pale yellow solid: mp 146−147 °C; $[\alpha]^{26}_D$ −13.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3349, 1718, 1516, 1348 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83−1.00 (2H, m), 0.88 (3H, d, J = 6.5 Hz), 1.10−1.21 (1H, m), 1.25 (3H, s), 1.36 (3H, s), 1.42−1.55 (1H, m), 1.65−1.79 (2H, m), 1.87−1.93 (1H, m), 1.98−2.04 (1H, m), 4.73 (1H, td, J = 10.8, 4.4 Hz), 6.31 (1H, br s), 7.44 (2H, d, J = 8.9 Hz), 8.15 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.7, 26.4, 28.4, 31.2, 34.3, 40.4, 41.7, 51.1, 76.4, 123.2 (2C), 126.3

(2C), 145.5, 158.0, 159.9; EIMS *m/z* (rel intens) 337 ($M^+ + 1$, 1), 150 (100), 109 (34).

[[(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]-cyclohexyl]oxy]carbonylhydroxylamine (12f) was prepared from **9f** according to the general procedure in 88% yield as a white solid: mp 69−70 °C; $[\alpha]^{27}_D$ −31.5 (*c* 2.0, $CHCl_3$); IR (KBr) 3305, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79−1.03 (2H, m), 0.88 (3H, d, J = 6.5 Hz), 1.19 (1H, qd, J = 13.0, 3.3 Hz), 1.31 (3H, s), 1.43 (3H, s), 1.48 (1H, m), 1.64−1.71 (1H, m), 1.81−1.92 (2H, m), 2.10−2.16 (1H, m), 4.79 (1H, td, J = 10.7, 4.4 Hz), 5.88 (1H, br s), 7.41−7.48 (3H, m), 4.52 (1H, dd, J = 8.7, 1.7 Hz), 7.66 (1H, s), 7.78−7.83 (3H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.4, 26.4, 28.6, 31.3, 34.5, 39.7, 41.8, 50.7, 76.4, 122.7, 125.2, 125.5, 126.2, 127.1, 127.3, 127.8, 131.1, 133.1, 149.6, 158.0; EIMS *m/z* (rel intens) 341 (M^+, 3), 169 (100), 141 (39); HRMS calcd for $C_{21}H_{27}NO_3$ (M^+) 341.1991, found 341.1991.

General Procedure for Asymmetric Hetero Diels−Alder Reaction of *N*-Acylnitroso Compounds 14 with 1,3-Cyclohexadiene (Entries 1−6 in Table 1). A representative experiment is as follows. To a cooled (−78 °C), stirred solution of oxalyl chloride (1.5 mmol) in CH_2Cl_2 (7 mL) was added a solution of dimethyl sulfoxide (3.0 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at −78 °C for 30 min. To this mixture was added a solution of the hydroxamic acid **14** (1.0 mmol) in CH_2Cl_2 (7 mL), and stirring was continued at −78 °C. After 15 min, 1,3-cyclohexadiene (10 mmol) was added via syringe followed by Et_3N (6.0 mmol), and the mixture was stirred for an additional 1 h. The reaction was quenched by addition of water (10 mL) at −78 °C. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (30 mL × 3). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to HPLC analysis for determination of diastereoisomer ratios. Reported yields listed in Table 1 are based on material isolated by column chromatography on silica gel using hexane−EtOAc as the eluent system.

(1*R*,2*S*,5*R*)-5-Methyl-2-isopropylcyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14a). Colorless oil; $[\alpha]^{26}_D$ −39.4 (*c* 0.9, $CHCl_3$); IR (film) 1740, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3H, d, J = 7.0 Hz), 0.78−1.08 (3H, m), 0.86 (3H, d, J = 7.1 Hz), 0.88 (3H, d, J = 6.5 Hz), 1.32−1.53 (4H, m), 1.62−1.68 (2H, m), 1.82−1.89 (1H, m), 1.97−2.03 (1H, m), 2.08−2.22 (2H, m), 4.60 (1H, td, J = 10.9, 4.4 Hz), 4.72 (1H, m), 4.78 (1H, m), 6.49−6.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.5, 20.4, 20.6, 22.0, 23.7 (2C), 26.3, 31.4, 34.3, 41.0, 47.1, 50.3, 70.8, 76.3, 131.5, 132.1, 158.8; EIMS *m/z* (rel intens) 293 (M^+, 4), 83 (76), 79 (100); HRMS calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1991, found 293.1969.

(1*R*,2*S*,5*R*)-5-Methyl-2-isopropylcyclohexyl (1*S*,4*R*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (15a). Colorless oil; $[\alpha]^{26}_D$ −77.2 (*c* 0.65, $CHCl_3$); IR (film) 1738, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74−1.09 (3H, m), 0.77 (3H, d, J = 7.0 Hz), 0.88 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 7.0 Hz), 1.33−1.52 (4H, m), 1.62−1.79 (2H, m), 1.82−2.03 (2H, m), 2.08−2.23 (2H, m), 4.61 (1H, td, J = 10.9, 4.3 Hz), 4.71−4.80 (2H, m), 6.48−6.59 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.2, 20.6, 20.8, 22.0, 23.4, 23.6, 26.3, 31.4, 34.3, 41.1, 47.1, 50.3, 70.8, 76.4, 131.6, 131.8, 158.6; EIMS *m/z* (rel intens) 293 (M^+, 4), 111 (34), 83 (95), 79 (100).

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-phenylethyl]cyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14b). Colorless oil; $[\alpha]^{26}_D$ −24.6 (*c* 1.3, $CHCl_3$); IR (film) 1735, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76−1.08 (3H, m), 0.85 (3H, d, J = 6.5 Hz), 1.13−1.63 (5H, m), 1.21 (3H, s), 1.30 (3H, s), 1.87−2.20 (4H, m), 3.9 (1H, very br s), 4.62−4.72 (2H, m), 6.38−6.50 (2H, m), 7.10−7.16 (1H, m), 7.27−7.30 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.8, 23.7, 26.8, 31.2, 34.6, 39.8, 41.7, 49.7, 50.8, 70.8, 76.7, 124.9, 125.5 (2C), 127.9 (2C), 131.3, 132.0, 151.6, 157.8; EIMS *m/z* (rel intens) 369 (M^+, 2), 119 (58), 105 (100); HRMS calcd for $C_{23}H_{31}NO_3$ (M^+) 369.2304, found 369.2284.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-methoxyphenyl)-ethyl]cyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14c). Colorless oil; $[\alpha]^{26}_D$ −23.8 (*c* 1.0, $CHCl_3$); IR (film) 1729, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72−1.05 (3H, m), 0.84 (3H, d, J = 6.5 Hz), 1.19 (3H, s), 1.22−1.62 (5H, m), 1.27 (3H, s), 1.86−1.98 (3H, m), 2.08−2.18 (1H, m), 3.78 (3H, s), 4.0 (1H, very br s), 4.61−4.69 (2H, m), 6.42−6.50 (2H, m), 6.82 (2H, d, J = 8.8 Hz), 7.18 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.8, 23.7, 26.8, 31.2, 34.6, 39.2, 41.8, 49.8, 50.9, 55.1, 70.8, 76.7, 113.1 (2C), 126.4 (2C), 131.4, 132.0, 143.7, 156.9, 157.8; EIMS *m/z* (rel intens) 399 (M^+, 2), 149 (77), 135 (100), 121 (38); HRMS calcd for $C_{24}H_{33}NO_4$ (M^+) 399.2410, found 399.2393.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-bromophenyl)-ethyl]cyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14d). Colorless oil; $[\alpha]^{26}_D$ −15.2 (*c* 1.5, $CHCl_3$); IR (film) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79−1.12 (3H, m), 0.85 (3H, d, J = 6.5 Hz), 1.16 (3H, s), 1.20−1.75 (5H, m), 1.25 (3H, s), 1.88−2.01 (3H, m), 2.08−2.15 (1H, m), 3.8 (1H, very br s), 4.59−4.68 (2H, m), 6.33−6.48 (2H, m), 7.15 (2H, d, J = 8.6 Hz), 7.39 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.7, 23.7, 26.3, 31.2, 34.6, 39.5, 41.6, 49.9, 50.8, 70.8, 76.5, 118.5, 127.4 (2C), 130.9 (2C), 131.4, 131.7, 151.2, 157.6; EIMS *m/z* (rel intens) 447 (M^+, 0.2), 183 (34), 111 (40), 80 (51), 79 (100); HRMS calcd for $C_{23}H_{30}NO_3Br$ (M^+) 447.1409, found 447.1397.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(4-nitrophenyl)ethyl]cyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14e). Pale yellow solid; mp 182−183 °C; $[\alpha]^{26}_D$ −22.7 (*c* 1.0, $CHCl_3$); IR (KBr) 1728, 1510, 1344 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80−0.96 (2H, m), 0.85 (3H, d, J = 6.5 Hz), 1.05−1.36 (3H, m), 1.21 (3H, s), 1.31 (3H, s), 1.40−1.53 (1H, m), 1.63−1.78 (3H, m), 1.86−1.92 (1H, m), 2.02−2.08 (2H, m), 3.7 (1H, very br s), 4.57 (1H, br s), 4.64 (1H, td, J = 10.7, 4.2 Hz), 6.27−6.44 (2H, m), 7.43 (2H, d, J = 8.8 Hz), 8.13 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.0, 21.7, 23.5, 26.4, 28.6, 31.1, 34.4, 40.3, 41.5, 49.8, 51.0, 70.8, 76.2, 123.2 (2C), 126.3 (2C), 131.5 (2C), 145.4, 157.1, 160.2; EIMS *m/z* (rel intens) 414 (M^+, 0.5), 164 (65), 111 (53), 79 (100); HRMS calcd for $C_{23}H_{30}N_2O_5$ (M^+) 414.2155, found 414.2157.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]-cyclohexyl (1*R*,4*S*)-2-Oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (14f). Colorless needles ($CHCl_3$−hexane); mp 122−123 °C; $[\alpha]^{26}_D$ −40.5 (*c* 1.0, $CHCl_3$); IR (KBr) 1729, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81−1.17 (5H, m), 0.86 (3H, d, J = 6.5 Hz), 1.22−1.54 (2H, m), 1.29 (3H, s), 1.41 (3H, s), 1.59−1.72 (2H, m), 1.85−1.99 (2H, m), 2.17 (1H, m), 3.5 (1H, very br s), 4.52 (1H, d, J = 3.0 Hz), 4.74 (1H, td, J = 10.7, 4.2 Hz), 6.29 (2H, br s), 7.38−7.46 (2H, m), 7.50−7.54 (1H, m), 7.66 (1H, s), 7.75−7.83 (3H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 21.8, 23.5, 26.7, 31.2, 34.6, 39.8, 41.8, 49.6, 50.4, 70.7, 76.6, 123.0, 124.9, 125.1, 125.7, 127.2 (2C), 128.2, 131.1, 131.4, 131.8, 133.5, 149.4, 157.7; EIMS *m/z* (rel intens) 419 (M^+, 1), 169 (62), 155 (100), 141 (37). Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H,7.93; N, 3.34. Found: C, 77.29; H, 7.94; N, 3.64. An X-ray crystal structure was obtained: monoclinic, space group $P2_1$, a = 17.78(1) Å, b = 6.062(4) Å, c = 11.292(6) Å, β = 102.20(4)°, V = 1190(1) Å^3, Z = 2, D_x = 1.169 g cm^{-3}, λ(Cu Kα) = 1.541 78 Å. Final R = 0.048 for 2176 observed reflections.

2-Chloro-5-(1,5-cyclohexadienyl)pyridine (7). To a benzene (40 mL) solution containing **17** (6.08 g, 25.4 mmol) and $(Ph_3P)_4Pd$ (880 mg, 0.76 mmol) was added 2-(1,3-cyclohexadienyl)magnesium bromide (**18**) prepared in 50 mL of THF from 2-bromo-1,3-cyclohexadiene (4.00 g, 25.2 mmol) and magnesium shavings (0.674 g, 27.7 mmol). After being stirred at room temperature for 10 h, the mixture was diluted with ether (400 mL), washed with 5% aqueous NH_4Cl (100 mL) and brine (50 mL), and dried ($MgSO_4$). Concentration in vacuo followed by purification by column chromatography on silica gel (hexane−EtOAc, 100:1) afforded **7** (2.42 g, 50%) as a colorless oil: IR (film) 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15−2.23 (2H, m), 2.30−2.36 (2H, m), 6.04 (1H, dt, J = 9.7, 4.3 Hz), 6.10 (1H, t, J = 4.6 Hz), 6.19 (1H, dd, J = 9.7, 1.7 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.60 (1H, dd, J = 8.3, 2.5 Hz), 8.38 (1H, d, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.7, 123.8, 124.3, 125.1, 129.0, 132.0, 135.0, 135.5, 146.6, 149.5; EIMS *m/z* (rel intens) 193 ($M^+ + 2$, 34), 191 (M^+, 100), 154 (41), 128 (50), 126 (46); HRMS calcd for $C_{11}H_{10}NCl$ (M^+) 191.0502, found 191.0502.

***tert*-Butyl (1*S**,4*R**,5*R**)-5-(6-Chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]octane-3-carboxylate (22) and *tert*-Butyl (1*S**,4*R**,6*S**)-6-(6-Chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]octane-3-carboxylate (23).** To a cooled (−78 °C), stirred solution of oxalyl chloride (1.99 g, 15.6 mmol) in CH_2Cl_2 (65 mL) was added dropwise a solution of dimethyl sulfoxide (2.42 g, 31.0 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at −78 °C for 30 min. To this was added a solution of **19** (1.40 g, 10.5 mmol) in CH_2Cl_2 (27 mL), and the mixture was stirred at −78 °C. After 15 min, a solution of **7** (1.00 g, 5.22 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe, followed by addition of Et_3N. The mixture was stirred for 1 h at −78 °C and then quenched by addition of water (10 mL) at −78 °C. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (hexane−EtOAc, 4:1) to give a mixture of the cycloadducts **20** and **21** as a colorless oil (1.33 g, 79%), which was subjected to catalytic hydrogenation. Thus, a part of the cycloadducts **20**/**21** (225 mg) was dissolved in dioxane (8 mL), PtO_2 (11 mg) was added to this solution, and the mixture was stirred under 1 atm of hydrogen at room temperature. After 22 h the mixture was filtered through a Celite pad to remove the catalyst and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane−EtOAc, 10:1) to afford **22** (105 mg, 46%) as a white solid, which was recrystallized from $CHCl_3$−hexane to give colorless cubics and **23** (68 mg, 30%) as a white solid.

Data for **22**: mp 174−175 °C; IR (KBr) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (9H, s), 1.73−1.88 (2H, m), 2.12−2.30 (4H, m), 3.19 (1H, dd, J = 10.8, 2.9 Hz), 4.04 (1H, br s), 4.37 (1H, br s), 7.27 (1H, d, J = 8.1 Hz), 7.80 (1H, br d, J = 8.1 Hz), 8.30 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 24.3 (2C), 28.2 (3C), 32.6, 39.1, 53.2, 71.3, 81.5, 124.2, 138.0, 138.7, 149.4, 149.8, 155.3; CIMS (isobutane) *m*/*z* (rel intens) 327 (M^+ + 3, 33), 325 (M^+ + 1, 100), 269 (52). Anal. Calcd for $C_{16}H_{21}N_2O_3Cl$: C, 59.17; H, 6.52; N, 8.62. Found: C, 59.04; H, 6.49; N, 8.65. An X-ray crystal structure was obtained: monoclinic, space group $P2_1/a$, a = 22.666(7) Å, b = 10.999(2) Å, c = 12.992(3) Å, β = 94.43(2)°, V = 3229(1) Å^3, Z = 8, D_x = 1.336 g cm^{-3}, λ(Cu Kα) = 1.541 78 Å. Final R = 0.049 for 4803 observed reflections.

Data for **23**: mp 112−113 °C; IR (KBr) 1728, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.64−1.77 (1H, m), 1.86−1.95 (1H, m), 2.07 (1H, ddt, J = 13.9, 7.2, 2.5 Hz), 2.15−2.28 (2H, m), 2.33 (1H, ddd, J = 13.8, 10.9, 3.6 Hz), 2.95 (1H, dd, J = 10.9, 7.3 Hz), 4.10 (1H, br s), 4.18 (1H, br s), 7.28 (1H, d, J = 8.3 Hz), 7.92 (1H, dd, J = 8.3, 2.4 Hz), 8.27 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 22.0, 25.4, 28.3 (3C), 34.1, 38.1, 48.9, 75.7, 81.7, 124.4, 138.3, 138.8, 149.0, 149.9, 156.7; EIMS *m*/*z* (rel intens) 324 (M^+ + 2, 0.5), 324 (M^+, 1.4), 57 (100); HRMS calcd for $C_{16}H_{21}N_2O_3Cl$ (M^+) 324.1241, found 324.1259.

[[(1*S*,2*R*,5*S*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl]oxy]carbonylhydroxylamine (*ent*-12f). Title compound, having $[\alpha]^{26}_D$ +30.1 (*c* 1.6, $CHCl_3$), was prepared in 90% yield from *ent*-**9f** according to the general procedure for the preparation of hydroxamic acid **14**.

Acylnitroso Cycloaddition of Hydroxamic Acid *ent*-12f and Diene 7. Compound *ent*-**12f** (2.80 g, 8.20 mmol) and **7** (2.08 g, 10.9 mmol) was treated in a manner similar to that used for the cycloaddition of **19** with **7**, and the resulting crude product was chromatographed on silica gel (hexane−EtOAc, 10:1). The first fraction afforded (1*S*,2*R*,5*S*)-5-methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*R*,4*S*)-5-(6-chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**26**) (190 mg, 4%) as a white solid: ^1H NMR ($CDCl_3$) δ 0.75−1.12 (4H, m), 0.78 (3H, d, J = 6.4 Hz),, 1.20−2.00 (8H, m), 1.35 (3H, s), 1.44 (3H, s), 2.12−2.18 (1H, m), 4.60 (1H, m), 4.82 (1H, td, J = 10.7, 4.5 Hz), 5.03 (1H, d, J = 2.4 Hz), 6.61 (1H, dd, J = 6.0, 2.1 Hz), 7.32 (1H, d, J = 8.3 Hz), 7.39−7.45 (2H, m), 7.50 (1H, dd, J = 8.7, 1.5 Hz), 7.64 (1H, s), 7.76−7.85 (4H, m), 8.46 (1H, d, J = 2.4 Hz).

The second fraction afforded (1*S*,2*R*,5*S*)-5-methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*S*,4*R*)-6-(6-chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**25**) (888 mg, 20%) as a white solid: mp 84−85 °C; $[\alpha]^{24}_D$ +65.5 (*c* 2.2, $CHCl_3$); IR (KBr) 1728, 1703, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80−1.13 (4H, m), 0.85 (3H, d, J = 6.4 Hz), 1.18−1.75 (6H, m), 1.25 (3H, s), 1.34 (3H, s), 1.92 (1H, br d, J = 11.4 Hz), 2.00−2.25 (2H, m), 4.74 (1H, td, J = 10.6, 4.0 Hz), 5.02 (1H, br s), 6.61 (1H, br s), 7.24−7.55 (5H, m), 7.64 (1H, s), 7.76−7.82 (3H, m), 8.32 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.7, 21.8, 23.7, 26.8, 29.7, 31.3, 34.6, 39.9, 41.8, 49.8, 50.0, 50.4, 71.9, 72.2, 77.3, 123.0, 124.2, 124.8, 125.2, 125.8, 127.2, 127.3, 128.2, 130.2, 131.4, 133.5, 134.9, 135.0, 139.0, 146.3, 149.0, 150.9, 157.4; EIMS *m*/*z* (rel intens) 532 (M^+ + 2, 0.2), 530 (M^+, 0.5), 169 (89), 155 (100), 141 (74). The third fraction afforded (1*S*,2*R*,5*S*)-5-methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*S*,4*R*)-5-(6-chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**24**) (1.83 g, 42%) as a white solid: mp 73−74 °C; $[\alpha]^{24}_D$ −26.1 (*c* 1.7, $CHCl_3$); IR (KBr) 1730, 1657, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (3H, d, J = 6.0 Hz), 0.77−0.94 (2H, m), 1.10−1.70 (7H, m), 1.20 (3H, s), 1.36 (3H, s), 1.91 (2H, br s), 2.15 (1H, td, J = 11.4, 3.2 Hz), 2.9 (1H, very br s), 4.57 (1H, td, J = 10.4, 3.2 Hz), 4.65 (1H, br s), 6.53 (1H, br s), 7.30 (1H, d, J = 8.3 Hz), 7.38−7.47 (3H, m), 7.60 (1H, d, J = 7.3 Hz), 7.70 (1H, br s), 7.78 (1H, d, J = 8.0 Hz), 7.84 (1H, br s), 8.20 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 18.7, 21.6, 23.8, 26.2, 31.0, 34.4, 39.4, 41.4, 50.4, 50.6, 71.0, 77.1, 122.9, 123.9, 124.8, 125.2, 125.9, 127.2 (2C), 128.2, 129.6, 131.3, 133.6, 135.0, 139.0, 146.6, 150.3, 150.9, 157.2; EIMS *m*/*z* (rel intens) 532 (M^+ + 2, 0.6), 530 (M^+, 1.2), 169 (78), 155 (100), 141 (42); HRMS calcd for $C_{32}H_{35}N_2O_3Cl$ (M^+) 530.2336, found 530.2354.

(1*S*,2*R*,5*S*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*S*,4*R*,5*R*)-5-(6-Chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]octane-3-carboxylate (28). To a solution of **24** (600 mg, 1.13 mmol) in dioxane (20 mL) was added PtO_2 (30 mg), and the mixture was stirred under 1 atm of hydrogen at room temperature. After 20 h the reaction mixture was filtered through a Celite pad to remove the catalyst. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane−EtOAc, 5:1) to afford **28** (487 mg, 81%) as a white solid: mp 62−63 °C; $[\alpha]^{23}_D$ +2.7 (*c* 1.0, $CHCl_3$); IR (KBr) 1708, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73−0.93 (2H, m), 0.84 (3H, d, J = 6.4 Hz), 1.00−1.83 (5H, m), 1.20 (3H, br s), 1.37 (3H, s), 1.86−2.28 (5H, m), 2.75 (2H, br s), 4.09−4.25 (1H, m), 4.59 (1H, br s), 7.25 (1H, d, J = 8.1 Hz), 7.37−7.77 (5H, m), 7.68−7.80 (3H, m), 8.13 (1H, br s); EIMS *m*/*z* (rel intens) 534 (M^+ + 2, 1.5), 532 (M^+, 4), 224 (33), 169 (77), 155 (100), 141 (57); HRMS calcd for $C_{32}H_{37}N_2O_3Cl$ (M^+) 532.2493, found 532.2500.

***tert*-Butyl (1*S*,4*R*,5*R*)-5-(6-Chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]octane-3-carboxylate [(−)-22].** To a stirred, cooled (0 °C) suspension of borane−ammonia complex (90%, 119 mg, 3.47 mmol) in THF (5 mL) was added a 1.69 M solution of butyllithium in hexane (3.0 mL, 3.38 mmol). The mixture was stirred at 0 °C for 10 min and then at room temperature for 10 min. After cooling the mixture to 0 °C, a solution of **28** (180 mg, 0.338 mmol) in THF (2 mL) was added dropwise and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of 10% aqueous Na_2CO_3 (1.1 mL), and the mixture was cooled to 0 °C. To this mixture was added dropwise with stirring a solution of di-*tert*-butyl dicarbonate (369 mg, 1.69 mmol) in $CHCl_3$ (2 mL), and stirring was maintained at room temperature for 1 h. After being diluted with $CHCl_3$ (50 mL), the mixture was washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography on silica gel (hexane−EtOAc, 4:1) provided (−)-**22** (64 mg, 58%) as a white solid, $[\alpha]^{25}_D$ −3.2 (*c* 1.4, $CHCl_3$), spectral data of which were identical with those of racemic **22**.

***tert*-Butyl *N*-[(1*R*,2*R*,4*S*)-2-(6-Chloro-3-pyridyl)-4-hydroxycyclohexyl]carbamate (29).** To a solution of (−)-**22** (280 mg, 0.862 mmol) in acetonitrile−water (15:1, 16 mL) was added $Mo(CO)_6$ (182 mg, 0.689 mmol), and the mixture was refluxed for 3 h. The mixture was diluted with $CHCl_3$ (50 mL), washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 3:1) to afford **29** (240 mg, 85%) as a white solid: mp 188−190 °C; $[\alpha]^{25}_D$ −41.1 (*c* 0.9, $CHCl_3$); IR (KBr)

3357, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (9H, s), 1.39 (1H, m), 1.73 (2H, tt, J = 14.2, 3.9 Hz), 1.92−2.10 (3H, m), 2.56 (1H, br s), 2.89 (1H, d, J = 13.0 Hz), 3.76 (1H, br s), 4.01 (1H, br s), 4.85 (1H, br s), 7.23 (1H, d, J = 8.2 Hz), 7.50 (1H, dd, J = 8.2, 2.5 Hz), 8.21 (1H, s); ^{13}C NMR ($CDCl_3$) δ 28.1 (3C), 29.5, 29.7, 34.3, 42.1, 48.4, 69.6, 79.6, 123.8, 136.2, 138.3, 148.6, 149.6, 155.0; EIMS m/z (rel intens) 328 ($M^+ + 2$, 1), 270 (35), 170 (50), 140 (96), 127 (49), 57 (100); HRMS calcd for $C_{16}H_{23}N_2O_3Cl$ (M^+) 326.1397, found 326.1383. Anal. Calcd for $C_{16}H_{23}N_2O_3Cl$: C, 58.80; H, 7.09; N, 8.57. Found: C, 58.76; H, 7.07; N, 8.55.

***tert*-Butyl *N*-[(1*R*,2*R*,4*R*)-4-Bromo-2-(6-chloro-3-pyridyl)-cyclohexyl]carbamate (30).** To a solution of **29** (220 mg, 0.673 mmol) in acetonitrile (22 mL) was added Ph_3P (354 mg, 1.35 mmol) and CBr_4 (448 mg, 1.35 mmol). The mixture was allowed to warm to 70 °C and stirred for 45 min at this temperature. The reaction mixture was diluted with $CHCl_3$ (100 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 10:1) to give **30** (110 mg, 42%) as a white solid: mp 174−175 °C; $[\alpha]^{28}_D$ −25.7 (*c* 1.30, $CHCl_3$); IR (film) 3266, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (9 H, s), 1.35−1.47 (1 H, m), 1.72−2.50 (7 H, m), 3.50 (1 H, br d, J = 10.1 Hz), 3.92−4.15 (1 H, m), 4.80 (1 H, s), 7.27 (1 H, d, J = 8.2 Hz), 7.52 (1 H, br d, J = 8.2 Hz), 8.22 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 26.6, 28.1 (3 carbon), 29.1, 33.4, 38.4, 49.3, 51.8, 79.8, 123.8, 136.0, 138.5, 148.6, 149.7, 155.0; EIMS m/z (rel intens) 392 ($M^+ + 4$, 0.1), 390 ($M^+ + 2$, 0.4), 388 (M^+, 0.3), 336 (M^+, 1), 167 (36), 149 (76), 57 (100); HRMS calcd for $C_{16}H_{22}N_2O_2BrCl$ (M^+) 388.0553, found 388.0550. Anal. Calcd for $C_{16}H_{22}N_2O_2BrCl$: C, 49.31; H, 5.69; N, 7.19. Found: C, 49.24; H, 5.63; N, 7.22.

[(1*R*,2*R*,4*R*)-4-Bromo-2-(6-chloro-3-pyridyl)cyclohexan-1-amine (31). To a cooled (0 °C), stirred solution of **30** (50 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (292 mg, 2.56 mmol), and the mixture was stirred at room temperature for 3 h and concentrated in vacuo. After 10% aqueous K_2CO_3 (1 mL) was added to the residue, the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried (K_2CO_3) and concentrated in vacuo to give a crude residue, which was purified by column chromatography on silica gel ($CHCl_3$−MeOH−concentrated NH_4OH, 100:9:1) to give **31** (35.5 mg, 96%) as a colorless oil: $[\alpha]^{26}_D$ −32.7 (*c* 1.1, $CHCl_3$); IR (film) 3373, 3301 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (2H, br s), 1.64−1.69 (1H, m), 1.87−1.92 (1H, m), 1.98 (1H, dd, J = 14.1, 2.8 Hz), 2.26 (1H, tt, J = 13.5, 3.1 Hz), 2.35 (1H, tt, J = 13.5, 3.1 Hz), 2.66 (1H, ddd, J = 12.9, 12.8, 3.1 Hz), 3.34 (1H, t, J = 2.8 Hz), 3.44 (1H, dt, J = 12.7, 3.0 Hz), 4.87 (1H, t, J = 2.8 Hz), 7.29 (1H, d, J = 8.2 Hz), 7.52 (1H, dd, J = 8.2, 2.5 Hz), 8.28 (1H, d, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.5, 31.9, 39.2, 50.0, 54.2, 124.0, 137.4, 138.3, 149.3, 149.8; EIMS m/z (rel intens) 209 (M^+ − Br, 2), 208 (M^+ − HBr, 5), 69 (100); HRMS calcd for $C_{11}H_{14}N_2BrCl$ (M^+ − Br) 209.0846, found 209.0821.

(−)-Epibatidine (1). A solution of **31** (30 mg, 0.104 mmol) in $CHCl_3$ (2 mL) was refluxed for 3 days and rendered to basic with 10% aqueous K_2CO_3. The organic layer was separated, dried (K_2CO_3), and concentrated in vacuo. Purification of the crude residue by column chromatography on silica gel ($CHCl_3$−MeOH−concentrated NH_4OH, 100:9:1) provided **1** (21 mg, 97%) as a white solid: mp 61−62 °C; $[\alpha]^{27}_D$ −6.26 (*c* 0.8, $CHCl_3$); IR (film) 3269, 2962, 2873, 1582, 1563, 1457, 1104, 1025, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48−1.65 (5H, m), 2.77 (1H, dd, J = 9.0, 4.9 Hz), 3.6 (1H, d, J = 2.0 Hz), 3.80 (1H, t, J = 4.0 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.76 (1H, dd, J = 8.3, 2.5 Hz), 8.27 (1H, d, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.4, 40.4, 44.6, 56.5, 62.8, 124.0, 137.7, 141.1, 148.9, 149.0; EIMS m/z (rel intens) 210 ($M^+ + 2$, 3), 208 (M^+, 8), 179 (4), 149 (4), 140 (13), 104 (4), 77 (7), 69 (100), 68 (55); HRMS calcd for $C_{11}H_{13}N_2Cl$ (M^+) 208.0767, found 208.0761.

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Supporting Information Available: Figures showing ^1H NMR spectra of compounds **1**, **7**, **9d**, **9e**, **10**, **11**, **12a**−**f**, **14a**−**e**, **15a**, **23**−**26**, **28**, and **31** and ORTEP diagrams of **14f** and **22** and tables listing and X-ray data of compounds **14f** and **22** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.JO9813078

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