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Stereocontrolled Synthesis and Pharmacological Evaluation of *cis*-2, 6-Diphenethyl-1-azabicyclo[2.2.2]octanes as Lobelane Analogues

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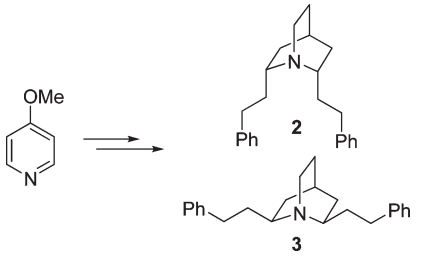

An efficient and highly stereocontrolled approach for the synthesis of the quinuclidine incorporated lobelane analogues, *endo*,*endo*- and *exo*,*exo*-2,6-*cis*-diphenethyl-1-azabicyclo-[2.2.2]octane (**2** and **3**), has been developed. Analogues **2** and **3** were designed to mimic the axial and equatorial geometry, respectively, of the vesicular monoamine transporter-2 (VMAT2) inhibitor, lobelane. The *exo*,*exo* analogue **2** had comparable affinity to lobelane and had greater affinity than the *endo*,*endo* analogue **3** at the tetrabenazine binding site on VMAT2, indicating that the preferred binding mode of lobelane is likely the extended conformation.

Introduction

The brain vesicular monoamine transporter-2 (VMAT2), an integral membrane protein responsible for transporting monoamines from presynaptic cytosol into vesicles, plays an important role in mediating the neurochemical and behavioral effects of psychostimulants.[1] This transporter is considered to be a valid target for the development of drug candidates for the treatment of psychostimulant abuse.[2] *cis*-Lobelane (*N*-methyl-2,6-diphenethylpiperidine; **1**, Figure 1), a minor alkaloid of *Lobelia inflata*,[3] exhibits good affinity and selectivity for the tetrabenazine binding site on VMAT2[4] and good inhibitory potency for vesicular dopamine uptake. Importantly, behavioral studies in rats have shown that lobelane is effective in decreasing methamphetamine self-administration without altering food response,[5] suggesting that this molecule has potential as a novel treatment for methamphetamine abuse.

Given the flexibility that lobelane exhibits, it can exist in a range of conformers; the two phenethyl groups attached to the C-2 and C-6 of the central piperidine ring can position themselves either in the axial or in the energetically favorable equatorial orientations. However, the low-energy conformers of ligand molecules may not always be the one that binds to the biological target. Thus, it is of interest to identify the "biologically" active conformation of lobelane that binds to the tetrabenazine binding site on VMAT2. Such knowledge may provide insight into the optimal pharmacophoric requirements for high-affinity binding of lobelane analogues to this transporter. In the present investigation, we designed two model compounds, **2** and **3** (Figure 1), in which a rigid 1-azabicyclo[2.2.2]octane (quinuclidine) moiety has replaced the piperidine ring in the lobelane molecule. The incorporation of the quinuclidine ring into the molecule allows the design of analogues that can mimic the stereochemistry of either the confined axial, axial conformer of lobelane (i.e., the *endo*,*endo* analogue **2**) or the fully extended equatorial, equatorial lobelane conformer (i.e., the *exo*,*exo* analogue **3**). Restriction of conformational flexibility is an extensively used tactic in medicinal chemistry to predispose a ligand into

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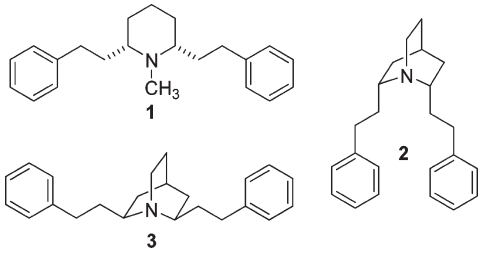
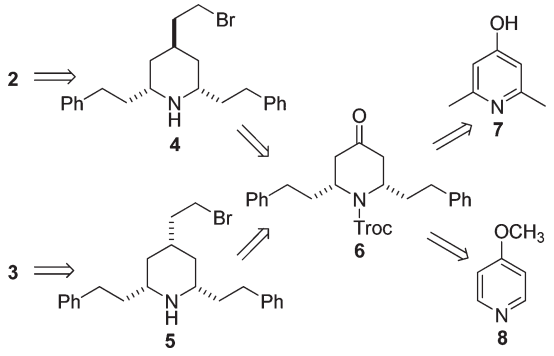


FIGURE 1. Lobelane (**1**) and the conformationally restricted analogues **2** and **3**.

SCHEME 1. Retrosynthetic Analysis of Analogues 2 and 3



a desired conformation.[6] The constrained positional and stereochemical orientations of compounds **2** and **3** could provide a preliminary structural model to probe the spatial and conformational requirements for the binding of lobelane analogues at VMAT2.

Results and Discussion

A retrosynthetic analysis of analogues **2** and **3** in Scheme 1 shows that both should be accessible from a S_N2-type cyclization of intermediates **4** and **5**, respectively. We expected that **4** and **5** could be obtained via a Horner−Wadsworth−Emmons (HWE) reaction of **6**, followed by the stereoselective reduction method developed by Watson et al.,[7] and finally bromination.

We originally planned to prepare the piperidinone intermediate **6** from 2,6-dimethyl-4-hydroxypyridine (**7**) (Scheme 2). **7** was reacted with excess benzaldehyde in acetic anhydride under reflux to form the conjugated product **9** (38% yield).[8] Reduction of the two double bonds in **9** by Pd/C-catalyzed hydrogenation (quantitative yield), followed by treatment of the resulting product **10** with BnBr in the presence of K_2CO_3 in DMF (87% yield), afforded the *O*-benzylated product **11**. *N*-Benzylation of **11** by treatment with excess BnBr (20 equiv) in ACN afforded the quaternary ammonium product **12**.[9] Reduction of **12** with $NaBH_4$ in EtOH afforded the tetrahydropyridine product **13** (89% yield), which upon treatment with CF_3COOH in DCM/H_2O yielded piperidinone **14** (92% yield). The *N*-benzyl group in **14** was then replaced with an *N*-Troc group by initial Pd/C-catalyzed hydrogenolysis (96% yield), followed by reaction of the *N*-deprotected product with 2,2,2-trichloroethyl chloroformate (TrocCl) (92% yield), to afford the desired intermediate **6**.

Although the above synthetic approach afforded the requisite intermediate **6**, it suffered from a somewhat lengthy procedure, poor overall yield, and more importantly, it lacked the flexibility for preparing nonsymmetrical analogues, i.e., with different substituents at C-2 and C-6 of the central piperidine ring. In this respect, we were particularly interested in preparing analogues in which the ethylene linkers between the phenyl rings and the central ring have been replaced with different carbon linker lengths.[10] Thus, we turned to the preparation of **6** utilizing a strategy developed by the Comins group,[11] which involves sequential stereoselective nucleophilic additions to *N*-acyl pyridinium salts of 4-methoxypyridine (**8**). The synthesis commenced with an in situ preparation of the *N*-acyl pyridinium salt formed on treatment of **8** with TrocCl. Phenethyl magnesium chloride (PEMgCl) was then added to the pyridinium salt, and after the reaction was completed, the resulting mixture was treated with aqueous HCl to furnish 2-phenethyl-3,4-dihydro-4-pyridone **15** (78% yield) (Scheme 3).[11a] **15** was also prepared via hydrogenation of compound **16** (94% yield), which was readily prepared from **8** (70% yield) by adapting a method of CuI-catalyzed direct alkyne addition to an *N*-acylated aza-aromatic ion.[12]

With **15** in hand, we first attempted the Cu-mediated conjugate addition with PEMgCl in the presence of $CuBr\cdot SMe_2$ and $BF_3\cdot OEt_2$, a frequently used condition that was introduced by Comins to selectively generate *cis*-2,6-disubstituted piperidinones.[13] Disappointingly, the reaction yielded a mixture of cis/trans isomers (i.e., **6** and the trans isomer **17**) in an approximate ratio of 60:40 (determined by ^1H NMR of the crude mixture, entry 1 in Table 1).[14] The two

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(8) (a) The reaction was completed in 12 days, reduced to 5 days when the reaction temperature was increased by using propionic anhydride; however, the yield dropped to ca. 25%. (b) The isolation and purification of 9 turned out to be tedious.

(9) Compound **12** was obtained in only 36% yield even after reflux for 4 days, along with the recovery of 45% of the starting material **11**. Similar results were observed when acetone was used as the solvent. When alcohols were used as solvent, only the debenzylation product (i.e., compound **10**) could be detected. For example, a quantitative amount of **10** was obtained when **11** was treated with BnBr in 4-methyl-2-pentanol (bp 131−134 °C) under reflux for 4 h.

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(13) For examples, see: (a) Reference 11b. (b) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889–5892. (c) Comins, D. L.; Dehghani, A. *J. Org. Chem.* **1995**, *60*, 794–795. (d) Comins, D. L.; Lamunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182–8187. (e) Mancheño, O. G.; Arrayás, R. G.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 10294–10297. (f) McCall, W. S.; Grillo, T. A.; Comins, D. L. *Org. Lett.* **2008**, *10*, 3255–3257.

(14) For examples of low selective Grignard addition under the treatment of CuBr and BF_3, see: (a) Klegraf, E.; Follmann, M.; Schollmeyer, D.; Kunz, H. *Eur. J. Org. Chem.* **2004**, *69*, 3346–3360. (b) Richards, S.; Sorensen, B.; Jae, H.; Winn, M.; Chen, Y.; Wang, J.; Fung, S.; Monzon, K.; Frevert, E. U.; Jacobson, P.; Sham, H.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6241–6245.

SCHEME 2. Synthesis of Intermediate 6 from 7

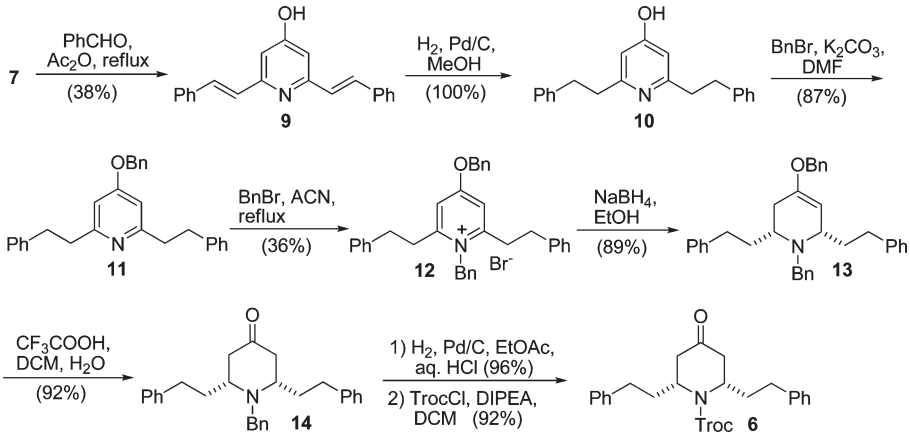


TABLE 1. Grignard Addition of 15 and 16

		reagents (equiv)					product ratio[a]		
entry		$PhCH_2CH_2MgCl$	$CuBr\cdot SMe_2$	CuI	$BF_3\cdot OEt_2$	Me_3SiCl	cis (%)	trans (%)	yield[c] (%)
1	**15**	2.0	2.0		2.0		60	40	91
2		2.0		2.0	2.0		50	50	81
3		2.0	2.0				100	0[b]	75
4		2.0	2.0			5.0	100	0[b]	90
5		2.0			1.5		45	55	86
6	**16**	3.0	3.0		2.0		69	31	84
7		3.0	3.0				100	0[b]	70
8		2.0	2.0			5.0	91	9	ND[d]
9		2.0			1.5		27	73	ND[d]

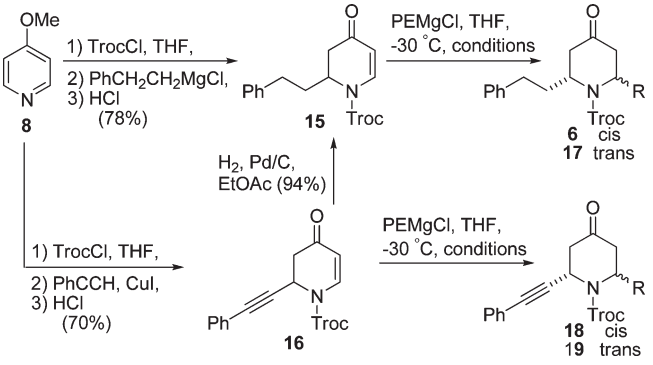
[a]Estimated by ^{1}H NMR integrations of the crude reaction mixtures. [b]No trans product observed from NMR analysis. [c]Combined yield of cis and trans products after column chromatography separation. [d]Not determined.

isomers were readily separable by silica gel flash chromatography, and the structure of the trans isomer **17** was confirmed by X-ray crystallography.

To improve selectivity for the cis isomer **6**, a number of conditions were examined for the Grignard addition reaction (Table 1). When PEMgCl was treated with CuI and $BF_3\cdot OEt_2$,[11b] an increased amount of trans isomer was detected (ca. 50:50 cis/trans, entry 2) . When PEMgCl was treated with $CuBr\cdot SMe_2$ in the absence of $BF_3\cdot OEt_2$, only the cis product (**6**) was detected (75% yield, entry 3).[15] The yield was improved to 90% in the presence of chlorotrimethylsilane (TMSCl) (entry 4).[16] Since $BF_3\cdot OEt_2$ appears to cause an increase in trans-isomer production, we next attempted the reaction without Cu(I). The reaction proceeded smoothly and the ratio of trans product (**17**) was increased (ca. 45:55 of cis/trans, entry 5). Similar results were obtained when the above conditions were applied to compound **16** (entries 6−9).[17]

As evidenced by the X-ray crystal structure of **16** (see Supporting Information), the phenethyl group at C-2 of **15** and the phenethynyl group at C-2 of **16** prefer to occupy the axial/pseudoaxial positions, due to their strong $A^{(1,3)}$-interactions[18] with the *N*-Troc group. The crystal structure of **16** also indicates that these molecules adopt a sofa conformation, in which C-3, C-4, C-5, C-6, and the *N*-acyl group are approximately coplanar. The Grignard conjugate addition of the α,β-enone system in **20** (**15** and **16**) (Figure 2) favors axial attack owing to stereoelectronic effects.[11b,19] As shown in Figure 2, addition of the nucleophile (R^2M) to the bottom face of **20** (path b) affords the unfavorable twisted-boat-like conformation product, **22** (2,6-*trans*-), while top face attack (path a) leads to the stable chair conformation product

SCHEME 3. Synthesis of Intermediate 6 from 8



(15) For example of copper-mediated cis selective Grignard addition in the absence of BF_3, see: Heintzelman, G. R.; Fang, W.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2001**, *123*, 8851−8853 and **2002**, *124*, 3939−3945.

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(17) The stoichiometries of PEMgCl and additives, as listed in Table 1, were adjusted to ensure the completion of the reactions, but were not fully optimized.

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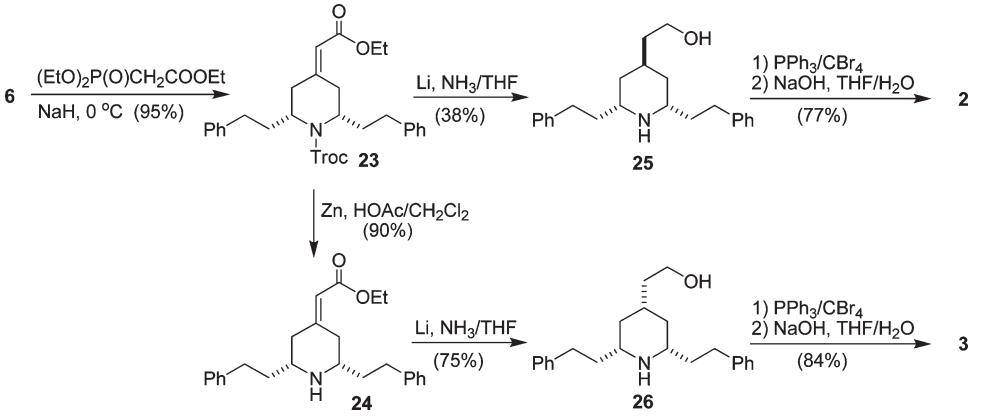
SCHEME 4. Synthesis of the Final Products 2 and 3



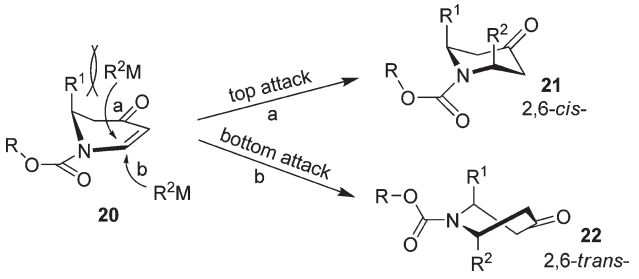


FIGURE 2. Stereochemical course of the conjugated addition reaction.

21 (2,6-*cis*-). Thus the formation of the cis product via top face attack should be preferential. However, when the size of the nucleophile is large, the facial selectivity may be decreased[20] or reversed.[21] In addition, the selectivity could also be dramatically affected by reaction conditions, as indicated in the present study, and in the literature.[11b] In the present study, $BF_3 \cdot OEt_2$ appears to promote the bottom face attack to form the trans isomers. It is well-established that $BF_3 \cdot OEt_2$ generates kinetically more reactive organocuprates, and therefore increases the reaction rate of nucleophilic additions,[22] which may explain the increased amount of the kinetically controlled product (i.e., trans isomer).

HWE olefination of **6** with triethyl phosphonoacetate furnished the corresponding α,β-unsaturated ester **23** (95% yield) (Scheme 4). It is worth mentioning that reduction of the double bond in **23**, by catalytic hydrogenation with various catalysts, was unsuccessful. However, the double bond in **24**, which was obtained by removing the Troc protecting group in **23** (90% yield), was readily reduced by hydrogenation to afford a mixture of two inseparable isomers in a ratio of approximately 7 to 3 (cis to trans).[23] Dissolving metal reduction of compound **23**, a procedure developed by Watson et al.,[7] provided the 2,4-trans-isomer **25** with high stereoselectivity (16:1, trans:cis, as measured by HPLC) (38% yield). The Troc group was also removed during the reaction. In contrast, compound **24** furnished exclusively the 2,4-cis-isomer **26** under similar reaction conditions (75% yield).[24] Compounds **25** and **26**, both of which contained small amounts of Birch reduction products, were purified by silica gel column chromatography after treatment with MnO_2. Bromination of **25** and **26** with CBr_4/PPh_3 followed by cyclization afforded the desired lobelane analogues **2** (77% yield) and **3** (84% yield), respectively.

TABLE 2. Inhibition Constants (K_i) for Analogues at the [^{3}H]DTBZ Binding Site (VMAT2) on Rat Synaptic Vesicle Membranes

compd	K_i, μM (±SEM)[a]
lobelane (**1**)	0.97 ± 0.19
2	9.83 ± 2.42
3	1.36 ± 0.19

[a]Each K_i value represents data from four independent experiments, each performed in duplicate.

The ability of compounds **2** and **3** to interact with VMAT2 (Table 2) was assessed by determining inhibition of [^{3}H]-dihydrotetrabenazine ([^{3}H]DTBZ) binding to rat brain vesicle preparations, using a high-throughput 96-well assay.[10] The *exo*,*exo* analogue **3** exhibited similar affinity for VMAT2 as lobelane (**1**), while the *endo*,*endo* analogue **2** displayed 10-fold less potency compared to lobelane in inhibiting [^{3}H]DTBZ binding. These results suggest that lobelane binds to VMAT2 likely in a fully extent form, in which the two phenethyl substituents at C-2 and C-6 of piperidine ring are in an equatorial, equatorial conformation.

Conclusion

In conclusion, two conformational restricted quinuclidine-containing lobelane analogues were synthesized via an efficient and highly stereocontrolled synthetic route. Although no improvement in binding affinity at VMAT2 was observed with these rigidified analogues, we expected analogue **3** to have improved selectivity for VMAT2; this work is currently under investigation.

Experimental Section

{*cis*-*N*-[(2,2,2-Trichloroethoxy)carbonyl]-2,6-diphenethylpiperidine-4-ylidene}acetic Acid Methyl Ester (23). To a suspension of NaH (160 mg, 60% dispersion in mineral oil, 4.01 mmol) in

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(23) As measured by HPLC, after DIBAL-H reduction to a mixture of hydroxyl compounds (i.e., **25** and **26**).

(24) The stereochemistry at C-4 of **25** and **26** was confirmed by NOESY experiments of their corresponding cyclization products **2** and **3**.

THF (20 mL) at 0 °C was added triethyl phosphonoacetate (899 mg, 4.01 mmol) in THF (10 mL) and the resulting mixture was stirred for 30 min. A solution of **6** (1.29 g, 2.67 mmol) in THF (10 mL) was added dropwise, and the reaction was stirred at 0 °C for 4 h before quenching with saturated aqueous NH_4Cl and dilution with water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica (hexanes/EtOAc 10:1) to afford **23** (1.40 g, 95%) as a colorless oil: ^{1}H NMR (300 MHz) δ 1.30 (t, J = 7.2 Hz, 3H), 1.65−1.98 (m, 4H), 2.22−2.35 (m, 2H), 2.51−2.70 (m, 4H), 2.75−2.90 (m, 1H), 4.07 (br d, J = 12.9 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.48−4.72 (m, 3H), 4.94 (br t, J = 12.9 Hz, 1H), 5.85 (s, 1H), 7.05−7.32 (m, 10H); ^{13}C NMR (75 MHz) δ 14.6, 31.3, 33.8, 34.1, 37.0, 37.4, 38.1, 39.3, 53.8, 54.0, 60.2, 75.4, 95.8, 118.8, 126.0, 126.2, 128.39, 128.43, 128.5, 141.2, 141.7, 153.0, 153.9, 165.9; MS (EI) m/z 551/553/555, 446/448/450, 400/402/404 (100), 342/344/346, 181, 117, 91; HRMS calcd for $C_{28}H_{32}{}^{35}Cl_3NO_4$ (M^+) m/z 551.1396, found 551.1383.

(*cis*-2,6-Diphenethylpiperidine-4-ylidene)acetic Acid Methyl Ester (24). To a solution of **23** (1.04 g, 1.88 mmol) in HOAc/CH_2Cl_2 (3/1, 20 mL) at 0 °C was added zinc dust (1.0 g) in portions and the resulting suspension was stirred vigorously at room temperature for 6 h. The mixture was filtered, concentrated, neutralized with saturated aqueous K_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica (hexanes/EtOAc 2:1) to afford **24** (639 mg, 90%) as a colorless oil: ^{1}H NMR (300 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 1.44 (br s, 1H), 1.62−1.90 (m, 5H), 1.97 (t, J = 12.0 Hz, 1H), 2.24 (d, J = 12.6 Hz, 1H), 2.51−2.73 (m, 6H), 3.95 (d, J = 13.5 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 5.63 (s, 1H), 7.14−7.33 (m, 10H); ^{13}C NMR (75 MHz) δ 14.6, 32.6, 32.7, 36.7, 38.8, 39.0, 44.3, 57.1, 57.6, 59.9, 114.3, 126.0, 126.1, 128.4, 128.5, 128.6, 141.8, 141.9, 159.3, 166.7; MS (EI) m/z 377 (M^+), 348, 332, 272 (100), 250, 226, 117, 91; HRMS calcd for $C_{25}H_{31}NO_2$ (M^+) m/z 377.2354, found 377.2353.

(*cis*-2,6-Diphenethylpiperidine-*trans*-4-yl)ethanol (25). To a solution of anhydrous liquid NH_3 (40 mL) and THF (30 mL) at −78 °C was added lithium wire (500 mg, 72 mmol), cut into small pieces. The resulting blue solution was stirred for 30 min. A solution of **23** (400 mg, 0.72 mmol) in THF (10 mL) was added dropwise and the reaction temperature was allowed to slowly increase to −30 °C over 1 h, and maintained at this temperature for another 30 min. The reaction was then quenched with solid NH_4Cl (4.15 g, 79 mmol) and with continual stirring at room temperature until the ammonia was completely evaporated. The residue was taken up into water and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was filtered through a short silica column, eluted with CH_2Cl_2/MeOH/NH_4OH (10:1:0.2). The resulting product was dissolved in $CHCl_3$ (20 mL) and MnO_2 (120 mg) was added. After being stirred for 24 h at room temperature, the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was chromatographed on silica (CH_2Cl_2/MeOH/NH_4OH 30:1:0.2) to afford **25** (92 mg, 38%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.78 (m, 11H), 1.97−2.04 (m, NH), 2.62 (t, J = 8.1 Hz, 4H), 2.63−2.77 (m, 2H), 3.67 (t, J = 6.9 Hz, 2H), 7.10−7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 32.8, 35.4, 37.1, 39.3, 51.3, 61.7, 126.0, 128.46, 128.54, 142.3; MS (EI) m/z 337 (M^+) 336, 319, 290, 246, 232 (100), 91; HRMS calcd for $C_{23}H_{31}NO$ (M^+) m/z 337.2405, found 337.2406.

(*cis*-2,6-Diphenethylpiperidine-*cis*-4-yl)ethanol (26). Starting from **24** (118 mg, 0.31 mmol), **26** was prepared as a colorless oil (79 mg, 75%) utilizing a similar procedure to that described above for **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (q, J = 11.4 Hz, 2H), 1.45−1.63 (m, 3H), 1.65−1.78 (m, 6H), 1.80−2.10 (m, NH), 2.54 (ddt, J = 8.7, 6.6, 2.1 Hz, 2H), 2.62 (t, J = 8.1 Hz, 4H), 3.67 (t, J = 6.6 Hz, 2H), 7.12−7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7, 32.9, 38.7, 39.3, 40.1, 56.4, 60.4, 125.9, 128.4, 128.5, 142.1; MS (EI) m/z 337 (M^+) 336, 319, 290, 246, 232 (100), 91; HRMS calcd for $C_{23}H_{31}NO$ (M^+) m/z 337.2405, found 337.2406.

***endo*,*endo*-2,6-Diphenethyl-1-azabicyclo[2.2.2]octane (2).** To a solution of **25** (92 mg, 0.27 mmol) and CBr_4 (136 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of PPh_3 (108 mg, 0.41 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for 30 min and poured into hexanes/EtOAc (4:1) (60 mL). The resulting suspension was filtered through a silica column, and eluted with hexanes/EtOAc (4:1) and then CH_2Cl_2/MeOH (30:1). The combined filtrates were concentrated. The crude product was dissolved in THF/H_2O (3:1, 25 mL) and 15% aqueous NaOH (5 mL) was added. The resulting mixture was heated under reflux for 24 h. Brine (20 mL) was added to the mixture and the aqueous phase was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica (CH_2Cl_2/MeOH/NH_4OH 20:1:0.2) to afford **2** (66 mg, 77%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17−1.34 (m, 2H), 1.43−1.57 (m, 2H), 1.72−1.96 (m, 5H), 2.05−2.21 (m, 2H), 2.67 (t, J = 7.8 Hz, 4H), 2.70−3.03 (m, 4H), 7.07−7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.4, 34.0, 35.0, 40.8, 54.5, 57.8, 125.9, 128.5, 128.6, 142.2; MS (EI) m/z 319, 304, 278, 228, 214 (100), 124, 91; HRMS calcd for $C_{23}H_{29}N$ (M^+) m/z 319.2300, found 319.2299.

***exo*,*exo*-2,6-Diphenethyl-1-azabicyclo[2.2.2]octane (3).** Compound **3** (62 mg, 84%) was prepared as a colorless oil utilizing a similar procedure to that described above for **2**, from starting material **26** (79 mg, 0.23 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (dt, J = 13.2, 3.0 Hz, 2H), 1.42 (br t, J = 6.6 Hz, 2H), 1.66−1.86 (m, 5H), 2.07−2.21 (m, 2H), 2.70 (t, J = 7.8 Hz, 4H), 2.68−2.82 (m, 2H), 2.91 (t, J = 7.8 Hz, 2H), 7.10−7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 27.0, 32.8, 33.0, 35.7, 37.2, 58.2, 125.9, 128.4, 128.6, 142.3; MS (EI) m/z 319, 304, 278, 228 (100), 214, 186, 117, 91; HRMS calcd for $C_{23}H_{29}N$ (M^+) m/z 319.2300, found 319.2300.

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Supporting Information Available: Full experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for all compounds, crystal structures, and crystallographic information files (CIFs) for compounds **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.