Spirovesamicols: Conformationally Restricted Analogs of 2-(4-Phenylpiperidino)cyclohexanol (Vesamicol, AH5183) as Potential Modulators of Presynaptic Cholinergic Function

S. M. N. Efange,*,†,‡ A. B. Khare,‡ C. Foulon,‡ S. K. Akella,‡ and S. M. Parsons§

Department of Radiology and Department of Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, and Department of Chemistry, University of California, Santa Barbara, California 93106

Received March 30, 1994®

In an effort to develop selective inhibitors of vesicular acetylcholine storage, we have synthesized a series of semirigid vesamicol receptor ligands based on the structure of 2-(4-phenylpiperidino)-cyclohexanol (vesamicol, AH5183, **1**). In these compounds, the planes of the phenyl and piperidyl moieties of the parent ligand **1** are held at right angles by vinyl, ethylene, and propylene bridges to form N-substituted derivatives of spiro[indene-1,4′-piperidine], 2,3-dihydrospiro[indene-1,4′-piperidine], and 3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine], respectively. Preliminary evaluation of these compounds in electric organ synaptic vesicles revealed several potent vesamicol receptor ligands, such as 1′-(2-hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[1*H*-indene-1,4′-piperidine] (**11b**) and 1′-(2-hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[2-bromo-1*H*-indene-1,4′-piperidine] (**14**), which display subnanomolar affinity for this receptor. In general, the vinyl and ethylene bridges yielded the most potent analogs while the propylene-bridged analogs were among the least potent compounds. The increased rigidity of these spiro-fused compounds, relative to the corresponding simple 4-phenylpiperidine derivatives of vesamicol, is expected to confer greater selectivity for the vesamicol receptor.

Introduction

The synthesis of acetylcholine (ACh) takes place in the cytoplasm of cholinergic nerve terminals, and the neurotransmitter is subsequently stored in special organelles called synaptic vesicles. In response to a stimulus, these vesicles fuse with the presynaptic membrane and release their contents into the synapse. Neurotransmitter is characteristically released in discrete amounts or quanta. Therefore, the synaptic vesicle largely defines the unit of ACh release. The release of neurotransmitter is in turn inextricably linked to its storage. Consequently, inhibition of ACh storage provides a useful means of modulating the release of ACh and thereby modulating cholinergic function. The lipophilic amino alcohol 2-(4-phenylpiperidino)cyclohexanol (**1**, vesamicol, AH5183) induces respiratory paralysis, spasms, and death in laboratory animals.[1,2] The pharmacological activity of vesamicol is attributed to its ability to block cholinergic neurotransmission.[3] The latter process is accomplished by the binding of vesamicol to a unique site, the vesamicol receptor (VR), on the cholinergic synaptic vesicle.[4] The VR is functionally linked to the vesicular ACh transporter,[5] a protein complex which transports ACh from the cytoplasm into the vesicle. Occupancy of the VR by vesamicol or related compounds blocks the storage and subsequent release of ACh, thereby effectively shutting down cholinergic neurotransmission (for review, see refs 6–8). Moreover, vesamicol selectively inhibits the storage and release of ACh without affecting the synthesis of this neurotransmitter. The foregoing observations suggest that selective blockade of the VR may provide a means of modulating cholinergic function in animals.

In spite of its potency as an anticholinergic, vesamicol exhibits α-adrenoceptor and local anesthetic activity at higher doses.[3,9,10] The poor selectivity of this compound limits its use as a selective anticholinergic. Consequently, a number of investigators, including us, have attempted to develop more potent and selective ligands for the VR. Previous studies by Rogers et al.[11] have shown that **1a** is the essential fragment for molecular recognition at the VR. In addition, these authors showed that potent VR ligands such as **2** and **3** could be obtained by substitution at the C4-carbon of vesamicol and by ring fusion on the cyclohexyl fragment of vesamicol, respectively. In a subsequent study, Efange et al.[12] reported the synthesis of flexible vesamicol analogs represented by **4**. Although this compound lacks the cyclohexyl moiety found in vesamicol, the former was nevertheless found to be equipotent with vesamicol. The latter observation was attributed to the ability of this flexible analog to adopt a conformation similar to that found in the benzo-fused analog **3a,b**. Further exploration of the structure–activity relationships of VR ligands yielded trozamicol, **5a**,[13] the parent structure for a new class of vesamicol receptor ligands. Although trozamicol itself is a poor ligand for the VR, N-benzylation of trozamicol yields potent ligands such as **6**.[13] In our attempts to expand knowledge of the structure–activity relationships at this receptor, we disclose yet another approach to the development of potent VR ligands for modulating presynaptic cholinergic function.

In a previous study, Rogers et al.[11] found that 2-(4-phenylpiperazinyl)cyclohexanol (**7a**) was 8-fold less active than vesamicol. In contrast, the *o*-methyl-substituted piperazine **7b** was almost equipotent with **1**.

* Address inquiries to this author at: Department of Radiology, Division of Nuclear Medicine, The University of Minnesota Hospital and Clinic, Box 382 UMHC, 420 Delaware Street S. E., Minneapolis, MN 55455.
† Department of Radiology, University of Minnesota.
‡ Department of Medicinal Chemistry, University of Minnesota.
§ University of California.
® Abstract published in *Advance ACS Abstracts,* July 1, 1994.

0022-2623/94/1837-2574$04.50/0

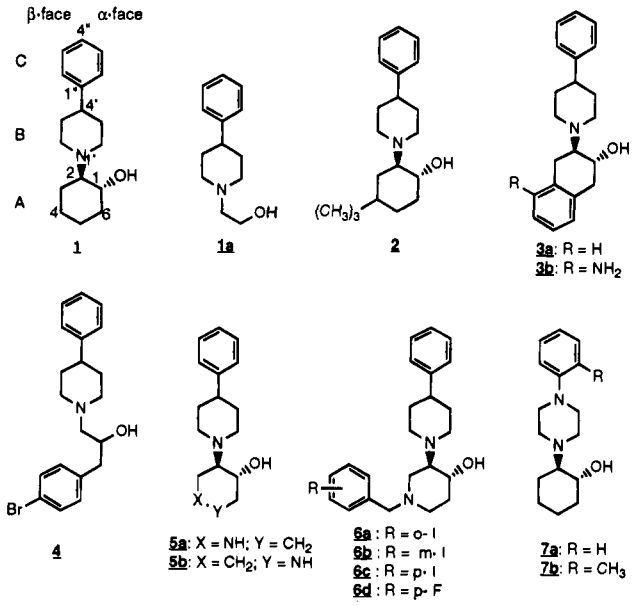


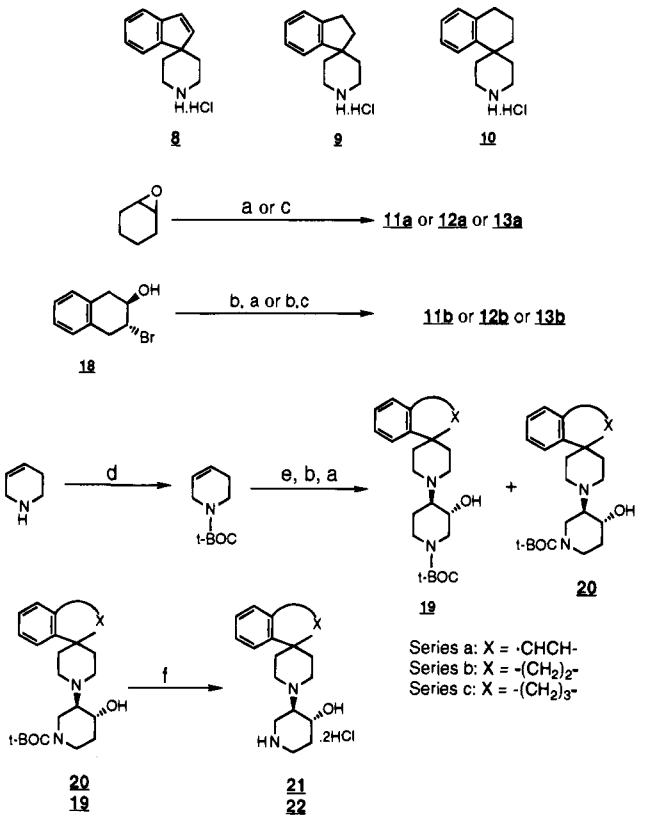
Figure 1. Vesamicol and analogs.

Earlier semiempirical quantum mechanical studies[14] suggest that in the minimum energy conformation of **1**, the plane of fragment B is oriented 45° relative to fragment C. In addition, the barrier to rotation around C4′—C1″ is approximately 1 kcal/mol. To a first approximation, the rotational barrier about N4′—C1″ (**7a**) would be of similar magnitude. In contrast to **1**, where steric interactions between the hydrogen atoms at C3′ and C2″ and C5′ and C6″ predominate, the extension of the π system into fragment B may favor coplanarity between fragments B and C of **7a**. However, the introduction of the *o*-methyl group into **7a** to form **7b** is expected, in a manner similar to that observed earlier for closely related compounds,[14] to significantly increase this barrier and thereby lock the phenyl and piperazyl moieties in an orthogonal orientation. On the basis of this analysis, and the comparable affinities of **1** and **7b**, we surmised that the orthogonal orientation of the phenyl and piperazyl (or piperidyl) moieties was preferred for binding at the VR. Consequently, we proposed that conformationally restricted vesamicol analogs which maintain orthogonality between the phenyl and piperidyl fragments would exhibit high affinity for this receptor. To test this hypothesis, we developed three classes of conformationally restricted vesamicol analogs based on the spiro-fused piperidines **8**–**10**. In these structures, rotation of the phenyl moiety relative to the piperidyl fragment is restricted by a vinyl, ethylene, or propylene bridge. The present report describes the synthesis and affinities of these novel VR ligands which henceforth shall be referred to as *spirovesamicols*.

Chemistry

The target compounds were synthesized as outlined in Schemes **1** and 2. The synthesis of the spiro-fused bases **8**–**10** was reported earlier.[15-17] Similar methods were utilized to produce the brominated spiro-fused indenes **14**–**17** in variable yields. Although two isomeric spiro-fused bases could potentially be obtained from 4-bromoindene, only **27** was recovered as the major product. Formation of the other regioisomer is expected to be hindered by unfavorable steric interactions between the incoming electrophile and the bromine atom.

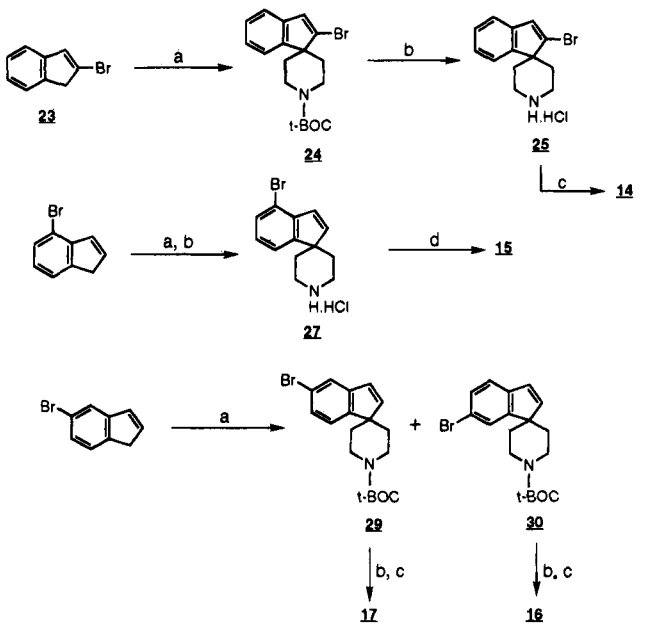
Scheme 1. Synthesis of Spirovesamicols[a]



[a] (a) Spiro-fused piperidine, EtOH, Et_3N, reflux; (b) aqueous NaOH, $CHCl_3$, reflux; (c) Et_3Al, CH_2Cl_2; (d) di-*tert*-butyl dicarbonate; (e) *N*-bromosuccinimide, THF, H_2O; (f) HCl(g), EtOAc.

The absence of similar interactions in 5-bromoindene led to the formation a 50:50 mixture of **29** and **30**. The reaction of cyclohexene oxide with the spiro-fused bases **8**–**10** yielded the corresponding amino alcohols **11a**, **12a**, and **13a**, respectively. The yields ranged from 55% to 80%. For the synthesis of the benzo-fused compounds **11b**, **12b**, **13b**, and **14**–**17**, the bromohydrin **18**, obtained from the reaction of 1,4-dihydronaphthalene with NBS in aqueous THF, was used as a stable source of 1,4-dihydronaphthalene oxide. Treatment of **18** with base followed by reaction of the resulting epoxide with **8**–**10**, **25**, and **27** yielded the target amino alcohols **11b**, **12b**, **13b**, **14**, and **15**, respectively. Similarly, deprotection of the equimolar mixture of **29** and **30** and subsequent reaction of the resulting secondary amines with 1,4-dihydronaphthalene oxide provided a 50:50 mixture of **16** and **17**. The latter were separated by chromatography on silica gel. The assignment of structure for these two regioisomers was based on splitting patterns and chemical shifts obtained from ^1H NMR. For compound **17**, the following signals were identified for the indenyl fragment: a doublet (C7-H) at δ 7.27, a doublet of doublets (C6-H) at δ 7.36, and a doublet (C4-H) at δ 7.48. In contrast, the following signals were recorded for the indenyl fragment of **16**: a doublet (C4-H) at δ 7.18, a doublet of doublets (C5-H) at δ 7.38, and a doublet (C7-H) at δ 7.53. In compound **17**, these chemical shifts span a range of 0.21 ppm, consistent with a similar value reported for 5-bromoindene. In contrast, the difference in chemical shifts calculated for **16** is 0.35 ppm. A similar difference in the range of chemical shifts for these protons has already been reported for 5-iodoindene ($\Delta\delta$ = 0.8 ppm) and 6-iodo-

Scheme 2. Synthesis of Brominated Spirovesamicols[a]



[a] (a) $LiN(SiMe_3)_2$, $BOCN(CH_2CH_2Cl)_2$, 0 °C; (b) HCl(g), EtOAc; (c) 1,4-dihydronaphthalene oxide, EtOH, Et_3N, reflux; (d) 1,4-dihydronaphthalene oxide, Et_3Al, CH_2Cl_2.

indene ($\Delta\delta$ = 1.2 ppm).[18] The target compounds **11c–f**, **12c–f**, and **13c–f** were synthesized from the key intermediates **21a–c**, respectively. The synthesis of the latter (Scheme 1) followed a sequence earlier described for **5a**.[12] In that study, it was found that epoxidation of *N*-benzoyl-1,2,3,6-tetrahydropyridine and subsequent reaction of the resulting epoxide with 4-phenylpiperidine yields a 50:50 mixture of regioisomeric amino alcohols. Subsequent removal of the benzoyl group with refluxing 6 N HCl yielded **5a,b**. To facilitate deprotection, the *tert*-butoxycarbonyl (*t*-BOC) group was utilized in the present study. Surprisingly, this substitution led to a significant change in the regioisomer ratio, from 50:50 to approximately 2–3:1 in favor of **20a–c**. In a previous study,[13] we showed that potent VR ligands are derived only from **5a**. Thus, the change from a benzoyl to a *t*-BOC protecting group also results in a significant improvement of the synthetic sequence. Since the epoxide and the N^1-BOC moiety are not linked directly, we attribute the effect of the latter group on the regioisomer ratio to a transannular interaction between these two groups. Such an interaction would favor attack of the epoxide by an incoming nucleophile at the C3 position of the piperidine ring.

Results and Discussion

The structure of vesamicol may be divided into three major fragments: cyclohexyl (fragment A), piperidyl (fragment B), and phenyl (fragment C). In addition, the molecule is characterized by a long axis, C4″–C1″–C4′–N1′–C2–C5, which divides the structure into two faces designated α and β. In their original investigation, Rogers et al.[11] carried out extensive modification of all three fragments with varying results. In reviewing these data, we were intrigued by the observation that 2-(4-phenylpiperazinyl)cyclohexanol (**7a**) was eight-fold less active than vesamicol while the *o*-methyl-substituted piperazine **7b** was practically equipotent with **1**. On the basis of this observation and our subsequent analysis of the conformational requirements for binding at the VR (vide supra), we proposed that conformationally restricted vesamicol analogs in which fragment B is held orthogonal to fragment C would exhibit high affinity for the VR. To test this hypothesis, analogs of the spiro-fused bases **8–10** were synthesized and tested in vitro for binding at the VR.

Table 1. Inhibitory Potency of Spirovesamicols

compound	K_i (nM)	compound	K_i (nM)
(−)-**1**	1.0 ± 0.5[a]	**12c**	0.98 ± 0.28
(−)-**3b**	0.0065 ± 0.0005[a]	**12d**	0.66 ± 0.19
3a	0.055 ± 0.010	**12e**	0.80 ± 0.26
(+)-**6a**	0.147 ± 0.029	**12f**	0.36 ± 0.10
(+)-**6b**	0.063 ± 0.013	**13a**	24.25 ± 5.71
(+)-**6c**	0.050 ± 0.013	**13b**	18.36 ± 14.03
11a	6.93 ± 2.05	**13c**	5.80 ± 1.08
11b	0.121 ± 0.032	**13d**	0.856 ± 0.211
11c	0.798 ± 0.187	**13e**	0.638 ± 0.089
11d	0.264 ± 0.078	**13f**	2.638 ± 0.692
11e	0.762 ± 0.398	**14**	0.41 ± 0.079
11f	0.248 ± 0.025	**15**	0.212 ± 0.063
12a	7.59 ± 0.99	**16**	1.40 ± 0.30
12b	0.36 ± 0.15	**17**	0.271 ± 0.056

[a] Data from ref 19.

Support for our hypothesis is clearly evident in Table 1. With the exception of compounds **11a**, **12a**, and **13a–c**, all spirovesamicols examined display low nanomolar to subnanomolar affinity for the VR. The success of the conformational restriction approach is also evident when the affinities of these novel compounds are compared to those of known VR ligands. For example, the indene (±)-**11a** is 6-fold less potent than (−)-**1**, while the benzo-fused analog **11b** is only slightly less potent than **3a**. Since the steric requirements of the vinyl bridge would be minimal, these results support the view that the preferred orientation of fragment B relative to C at the VR is orthogonal. For the cyclohexyl-substituted analogs, reduction of the vinyl bridge has no efffect on the affinity (**11a** vs **12a**). However, a noticeable reduction in affinity is obtained by increasing the length of the bridge from two to three carbons, resulting in a rank order of potency of **11a** ≥ **12a** > **13a**. A slightly different rank order is obtained for the benzo-fused analogs where **11b** > **12b** ≫ **13b**. Although the ethylene bridge is slightly more flexible than the vinyl bridge, the steric requirements of these two fragments are similar. Therefore, it would be reasonable to attribute the diminution in affinity following the reduction of the double bond to the loss of the extended π system. However, the absence of a similar trend among the cyclohexyl-substituted (**11a** and **12a**) and halobenzyl analogs (series **c–f**) provides little support for this view. Since the flexibility and steric demands of the core structure increase with the introduction of a propylene bridge, the reduced affinity of the propylene-bridged compounds (**13a,b**) relative to the corresponding ethylene-bridged analogs (**12a,b**) may be partly attributed to these factors. However, the high affinity of compound **14** suggests a more complex picture. Since the presence of the bromine atom in compound **14** adds to the steric bulk of the vinyl bridge, the higher affinity of this compound relative to **13b** also suggests that receptor site topography is an important factor. In this connection, it is worth noting that an overlay of the minimum energy structures of compounds **1**, **11b**, and **13b** reveals that the introduction of the propylene bridge causes a significant displacement of the phenyl ring from its original position in **1**. More-

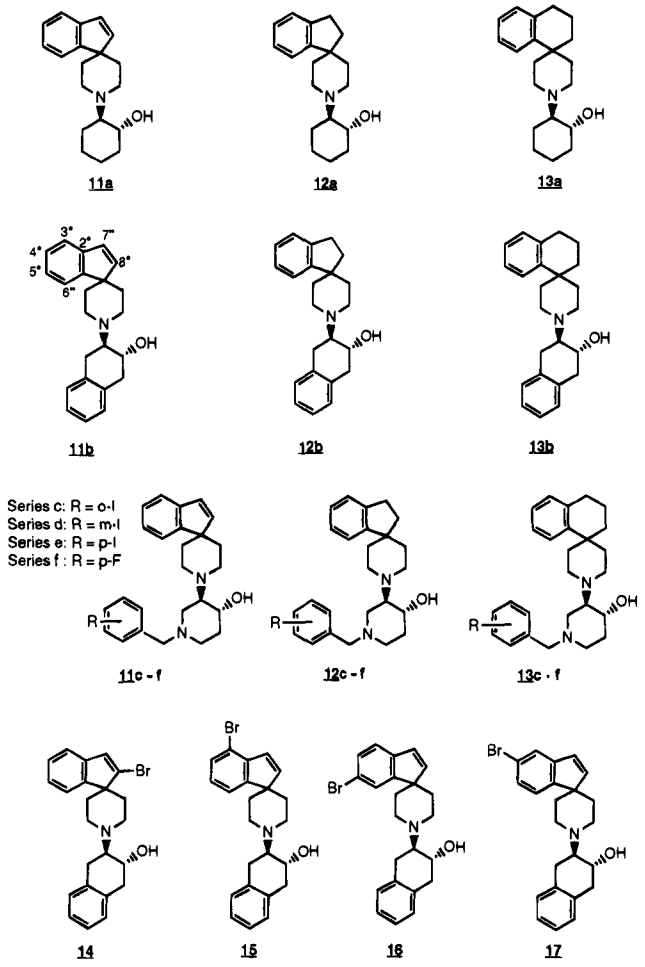


Figure 2. Spirovesamicols.

over, **13b** is distinguished from **11b** in that the middle carbon atom of the propylene bridge is out of the plane of fragment C. These alterations in the shape of the core structure may also be responsible for the differences observed. The introduction of a bromine atom at the C3″, C4″, and C5″ positions of **11b** also yielded high-affinity VR ligands. Compound **15** is equipotent with **17**, and both compounds are approximately half as potent as **11b**. However, **16** is approximately 12-fold less potent than **11b**, suggesting a less than favorable interaction between the receptor and substituents at the C5″ position of **11b**. The introduction of a chlorine atom into the C4″ position of vesamicol results in a 2-fold reduction in affinity for the VR (vide supra). Since the bromine atom in **17** occupies a position corresponding to the C4″ position of vesamicol, the comparable affinity of **17** and **11b** suggests a similar mode of interaction for spirovesamicols and simple vesamicol analogs with the VR. On the basis of the latter conclusion, spirovesamicols may be regarded as constrained C2″,C4′-disubstituted vesamicol analogs. The latter view is supported by the affinities of the halobenzyl analogs **11c–f**, **12c–f**, and **13c–f**. These compounds were synthesized in an effort to combine previous modifications[13] of fragment A with the conformational restriction of fragments B and C. Although the affinities of compounds **12c–f** are 2–5 times lower than those of (+)-**6a–c**, the corresponding analogs of **5a**, these spirovesamicols are nevertheless potent ligands for the VR, displaying dissociation constants at or below 1 nM. With the exception of series **e**, the rank order of potency for a given substitution pattern (e.g., *o*-iodobenzyl) is generally vinyl ≃ ethylene > propylene. Furthermore, the dissociation constants of all propylene-bridged halobenzyl analogs except **13d,e** were above 1 nM. Although compounds **11c–f**, **12c–f**, and **13c–f** represent simultaneous modification of fragments A–C, the similarity between the rank order of potency observed for these compounds and the cyclohexyl and tetrahydronaphthyl analogs (vide supra) is consistent with the view that the role of the bridge (vinyl, ethylene, propylene) is largely to restrict fragments B and C in energetically favored orientations. In spite of the anomalous behavior of compounds **13d,e**, it is clear that while conformational restriction does yield potent VR ligands, the optimal length of the bridge is two carbons. Since conformational restriction has also been used as a strategy for increasing selectivity, it is expected that these compounds will be more selective than **1** or previously reported flexible analogs (e.g., **4**). Accordingly, studies have been initiated to investigate the selectivity of these and previously reported vesamicol analogs.

ExperimentalSection

General Section. Synthetic intermediates were purchased from Aldrich, Inc. (Milwaukee, WI) and used as received. Solvents were distilled immediately prior to use. Commercially available reagents were used without subsequent purification.

All air-sensitive reactions were carried out under nitrogen. Standard handling techniques for air-sensitive materials were employed throughout this study. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. The specific rotation was determined on an automatic polarimeter (Autopol III; Rudolph Research, Flanders, NJ). ^{1}H NMR spectra were recorded on an IBM-Brucker spectrometer at 200 MHz. NMR spectra are referenced to the deuterium lock frequency of the spectrometer. Under these conditions, the chemical shifts (in ppm) of residual solvent in the ^{1}H NMR spectra were found to be as follows: $CHCl_3$, 7.26; DMSO, 2.56; HOD, 4.81. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Both low- and high-resolution MS were performed on an AEI MS-30 instrument. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Unless otherwise indicated, these values are within ±0.4% of the theoretical.

Column chromatography was performed using Baker Analyzed silica gel (60–200 mesh). Preparative chromatography was performed on either a Harrison Research chromatotron using Merck 60 PF_{254} silica gel or a preparative HPLC column (Rainin Instrument Co.) using a 41.1 mm i.d. Dynamax silica gel column (at a solvent delivery rate of 80 mL/min). Enantiomeric purity was determined by HPLC with a Chiralcel OD column (isopropyl alcohol:hexane, 10:90; flow rate 2–4 mL/min). The isopropyl alcohol used for HPLC contained 1% Et_3N. Analytical TLC was performed on Analtech glass TLC plates coated with silica gel GHLF, and the plates were visualized with UV light and/or methanolic iodine. All target compounds were checked for purity by HPLC (silica gel, 10–20% isopropyl alcohol–hexanes, trace Et_3N).

Procedure A. 1′-(2-Hydroxycyclohex-1-yl)spiro[1*H*-indene-1,4′-piperidine] Hydrochloride (11a). Spiro[1*H*-indene-1,4′-piperidine] hydrochloride was prepared by the method described earlier by Evans et al.[15] A mixture of commercially available cyclohexene oxide (0.22 g, 2.24 mmol) and spiro[1*H*-indene-1,4′-piperidine] hydrochloride in EtOH (20 mL) and triethylamine (5 mL) was refluxed for 21 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in a minimum volume of CH_2Cl_2, and the solution was applied onto a short column of silica gel which was subsequently eluted with acetone(20):hexanes(79):Et_3N(1). The

eluent was concentrated in vacuo to yield a dark red syrup (0.35 g, 55%) which was judged by TLC to be greater than 95% pure. The syrup was dissolved in MeOH and cooled in an ice bath. Dry HCl gas was then bubbled through this solution, thereby converting the free base to the corresponding hydrochloride. The solvent was removed in vacuo to yield a solid which was recrystallized from isopropyl alcohol to provide a light tan solid: mp 280–283 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–2.29 (m, 12, piperidyl, cyclohexyl), 2.74 (d, 2, piperidyl α-H, J = 5.6 Hz), 2.95 (d, 2, piperidyl), 3.45 (m, 1, cyclohexyl CH_2-C*H*NCHOH), 3.70 (m, 1, cyclohexyl $CH_2CHNCHOH$), 6.72 (d, 1, indenyl C2-H, J = 5.7 Hz), 6.82 (1, d, indenyl C3-H, J = 5.7 Hz), 7.16–7.39 (m, 5, aryl). Anal. ($C_{19}H_{25}NO$·HCl)

Procedure B. 1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[1*H*-indene-1,4′-piperidine] Hydrochloride (11b). A biphasic mixture of the bromohydrin (1.14 g, 5.0 mmol) in 2 M aqueous NaOH (100 mL) and $CHCl_3$ (100 mL) was refluxed for 2.5 h. TLC (silica gel, 50% hexane–CH_2Cl_2) confirmed that formation of the epoxide was complete. The mixture was cooled to room temperature, and the two layers were separated. The aqueous phase was re-extracted with $CHCl_3$ (2 × 30 mL) and discarded. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude epoxide as a pale yellow syrup which was redissolved in EtOH (30 mL) and Et_3N (2 mL). Spiro[1*H*-indene-1,4′-piperidine] hydrochloride (1.11 g, 5.0 mmol) was added to this solution, and the resulting mixture was refluxed overnight. After 17 h, heating was stopped. The mixture was cooled to room temperature and concentrated to a residue in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (30 mL). The aqueous extract was washed with CH_2Cl_2 (30 mL) and discarded. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to a residue. The latter was dissolved in a minimum volume of CH_2Cl_2 and applied to a short column of silica gel which was subsequently eluted with 25% acetone–hexane. Concentration of the eluent yielded the product (0.91 g, 55%) as a brown syrup. The latter was estimated by TLC (silica gel, acetone(25):hexane(74):Et_3N(1)) to be greater than 97% pure. The corresponding hydrochloride was prepared in MeOH as outlined for (**11a**) above and recrystallized from isopropyl alcohol: mp 254–257 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 2, piperidyl β-H_{eq}, J = 12.8 Hz), 2.17 (m, 2, piperidyl β-H_{ax}), 2.86–3.49 (m, 8, tetrahydronaphthyl C1-H, C3-H, C4-H, piperidyl α-$H_{ax,eq}$), 3.93–4.20 (m, 3, piperidyl α-H_{eq}, C*H*OH), 6.79 (d, 1, indenyl C2-H, J = 5.6 Hz), 6.90 (d, 1, indenyl C3-H, J = 5.7 Hz), 7.03–7.42 (m, 8, aryl).

Procedure C. Preparation of 1′-[1-(Butoxycarbonyl)-3-hydroxypiperidin-4-yl]spiro[1*H*-indene-1,4′-piperidine] (19a) and 1′-[1-(Butoxycarbonyl)-4-hydroxypiperidin-3-yl]spiro[1*H*-indene-1,4′-piperidine] (20a). A solution of 1,2,3,6-tetrahydropyridine in CH_2Cl_2 (10 mL) was added to a stirring solution of di-*tert*-butyl dicarbonate in CH_2Cl_2 (40 mL). The resulting mixture was treated with Et_3N (1 mL) and stirred overnight. After 30 h, the reaction mixture was concentrated to provide a clear colorless liquid which was redissolved in THF (100 mL). To this solution were added *N*-bromosuccinimide (4.45 g, 25.0 mmol) and water (25 mL). The resulting biphasic mixture was stirred at room temperature for 23 h, diluted with water (40 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to a syrup. The latter was triturated with hot hexane and cooled to cause precipitation of succinimide. The precipitate was removed by filtration and discarded. The filtrate was concentrated to provide a mixture of the isomeric bromohydrins as a yellow syrup (6.8 g, 98%). A fraction of this syrup (3.64 g, 13.0 mmol) was refluxed for 2 h in a biphasic mixture of $CHCl_3$ (100 mL) and 2.5 M aqueous NaOH (100 mL). The mixture was allowed to cool to room temperature, and the layers were separated. The aqueous layer was re-extracted with $CHCl_3$ (2 × 30 mL) and discarded. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to yield *N*-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine oxide (2.72 g) as an orange liquid. A mixture of the crude epoxide (2.72 g) and **8** (2.22 g, 10.0 mmol) in EtOH (60 mL) and Et_3N (15 mL) was refluxed for 24 h, cooled, and concentrated to a residue. The latter was partitioned between CH_2Cl_2 (50 mL) and water (40 mL). Following separation of the layers, the aqueous phase was re-extracted with CH_2Cl_2 (50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated to a minimum volume, and passed through a short column of silica gel (eluting with acetone(20):hexane(79):Et_3N(1)). Concentration of the eluent provided a red syrup which was subjected to preparative HPLC (5:94:1 *i*-PrOH:hexane:Et_3N; flow rate 80 mL/min). Concentration of the more mobile fraction yielded **19a** (0.61 g, 16%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.45 (br s, 9, (CH_3)-C), 1.70–1.90 (m, 2, piperidyl), 2.01 (td, 1, piperidyl), 2.11–2.28 (m, 2, piperidyl), 2.38–2.70 (m, 2, piperidyl), 2.76–3.00 (m, 3, piperidyl), 3.47 (m, 1, piperidyl), 3.67 (m, 1, piperidyl), 3.91–3.40 (m, 2, piperidyl), 4.15 (m, 1, N-C*H*-CHOH), 4.28 (br s, 1, *H*C-OH), 4.45 (br s, 1, OH), 6.74 (d, 1, J = 6 Hz, Ph-CH=C*H*), 6.80 (d, 1, J = 6 Hz, Ph-C*H*=CH), 7.20–7.39 (m, 4, phenyl). The less mobile fraction, **20a** (1.90 g, 49%), was obtained as the major component: ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 11, $(CH_3)_3$-C, piperidyl), 1.99–2.35 (m, 4, piperidyl), 2.40 (td, 1, piperidyl), 2.61 (td, 1, piperidyl), 2.72–2.82 (m, 3, piperidyl), 2.92 (m, 1, piperidyl), 3.07 (m, 2, piperidyl), 3.63 (m, 1, N-C*H*-CHOH), 4.13 (br s, 1, *H*C-OH), 4.38 (br s, 1, OH), 6.74–6.80 (complex dd, 2H, indyl), 7.18–7.41 (m, 4, phenyl). Anal. ($C_{23}H_{32}N_2O_3$) C, H, N.

Resolution of 20a. Racemic **20a** was resolved on a Chiralcel OD column (20% *i*-PrOH–hexane) to yield 0.8 g of (+)-**20a** and 0.8 g of (−)-**20a** (64% recovery). (+)-**20a**: retention time, 14.6 min; $[\alpha]_D$ = +38.72° (c = 0.02, MeOH). (−)-**20a**: retention time, 20.3 min; $[\alpha]_D$ = −38.95° (c = 0.02, MeOH).

(+)-1′-(4-Hydroxypiperidin-3-yl)spiro[1*H*-indene-1,4′-piperidine] Dihydrochloride ((+)-21a) and (−)-1′-(4-Hydroxypiperidin-3-yl)spiro[1*H*-indene-1,4′-piperidine] Dihydrochloride ((−)-21a). Solutions of (+)- and (−)-**20a** in EtOAC (20 mL) were cooled down to 0 °C. Dry HCl gas was bubbled through these solutions for 30 min with stirring. The stirring was continued for an additional 30 min at 0 °C. The solutions were concentrated under reduced pressure to yield (+)-**21a** (0.62 g, 84%) and (−)-**21a** (0.69 g, 93%), respectively: mp 279–282 °C.

Procedure D. 1′-[4-Hydroxy-1-(2-iodobenzyl)piperidin-3-yl]spiro[1*H*-indene-1,4′-piperidine] Dihydrochloride (*11c*). A mixture of sodium bicarbonate (0.42 g, 5.0 mmol), 2-iodobenzyl chloride (0.23 g, 0.92 mmol), and 1′-(4-hydroxypiperidin-3-yl)spiro[1*H*-indene-1,4′-piperidine] dihydrochloride (0.30 g, 0.84 mmol) in EtOH (13 mL) and water (6 mL) was refluxed for 23 h. The resulting mixture was cooled and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (30 mL) and water (25 mL). After separation of the layers, the aqueous layer was re-extracted with CH_2Cl_2 (2 × 30 mL) and discarded. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to a residue which was purified by radial flow chromatography on silica gel (13:86:1 acetone:hexane:triethylamine) to yield 0.13 g (31%) of the free base as a pale yellow syrup. The latter was converted to the corresponding hydrochloride in methanol as described above and recrystallized from *i*-PrOH to give a white solid, mp 242–245 °C. The yield was increased to 71% when procedure E was used: ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 2, piperidyl), 1.66 (dt, 1, piperidyl), 2.04–2.27 (m, 5, piperidyl), 2.57 (t, 1, piperidyl), 2.64 (dt, 1, piperidyl), 2.70–3.52 (m, 5, piperidyl), 3.57–3.62 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 6.73 (d, J = 6 Hz, 1, Ph-CH=C*H*), 6.80 (d, J = 6 Hz, 1, Ph-C*H*=CH), 6.96 (t, J = 9 Hz, 1, iodophenyl), 7.21–7.44 (m, 6 H, iodophenyl, phenyl), 7.84 (d, 1, J = 6 Hz, iodophenyl).

Procedure E. 1′-[4-Hydroxy-1-(3-iodobenzyl)piperidin-3-yl]spiro[1*H*-indene-1,4′-piperidine] Dihydrochloride (11d). A mixture of **21b** (0.30 g, 0.84 mmol), 3-iodobenzyl bromide (0.25 g, 0.84 mmol), and K_2CO_3 (0.4 g, 2.89 mmol) was stirred in DMF (20 mL) at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), filtered, and diluted with H_2O (100 mL), the organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried over

Na_2SO_4 and concentrated under reduced pressure to obtain a liquid residue. The residue was purified by passing through a short silica gel column (33% acetone–hexane). The eluent was concentrated under reduced pressure to obtain a yellow syrup (0.29 g, 71%). The free base was converted to the dihydrochloride using methanolic HCl: mp 226–228 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 2, piperidyl), 1.64 (dt, 1, piperidyl), 1.93–2.25 (m, 5, piperidyl), 2.54 (t, 1, piperidyl), 2.66 (dt, 1, piperidyl), 2.79–3.10 (m, 5, piperidyl), 3.40–3.56 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 6.72 (d, J = 6 Hz, 1, Ph-CH=C*H*), 6.80 (d, J = 6 Hz, 1, Ph-C*H*=CH), 7.06 (t, J = 9 Hz, 1, iodophenyl), 7.20–7.36 (m, 5, iodophenyl, phenyl), 7.58 (d, 1, iodophenyl), 7.69 (s, 1, iodophenyl).

1′-[4-Hydroxy-1-(4-iodobenzyl)piperidin-3-yl]spiro[1*H*-indene-1,4′-piperidine] Dihydrochloride (11e). Procedure E: yield, 52%; mp (ether–isopropyl alcohol) 243–245 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 2, piperidyl), 1.62 (dt, 1, piperidyl), 1.92–2.30 (m, 5, piperidyl), 2.56 (m, 2, piperidyl), 2.86–3.07 (m, 5, piperidyl), 3.40–3.57 (m, 3, benzyl, piperidyl), 3.81 (br s, 1, OH), 6.72 (d, 1, J = 6 Hz, Ph-CH=C*H*), 6.79 (d, 1, J = 6 Hz, Ph-C*H*=CH), 7.07 (d, 2, J = 8 Hz, iodophenyl), 7.17–7.36 (m, 4, phenyl), 7.64 (d, 2, J = 8 Hz, iodophenyl).

1′-[4-Hydroxy-1-(2-fluorobenzyl)piperidin-3-yl]spiro-[1*H*-indene-1,4′-piperidine] Dihydrochloride (11f). Procedure E: yield, 66%; mp (acetone) 126–128 °C.; ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 2, piperidyl), 1.64 (dt, 1, piperidyl), 1.94–2.16 (m, 6, piperidyl), 2.62 (t, 1, piperidyl), 2.79–3.13 (m, 5, piperidyl), 3.40–3.56 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 6.75 (d, J = 6 Hz, 1, Ph-CH=C*H*), 6.78 (d, J = 6 Hz, 1, Ph-C*H*=CH), 7.01 (t, J = 8 Hz, 2, fluorophenyl), 7.18–7.36 (m, 6, fluorophenyl, phenyl).

1′-Benzyl-2,3-Dihydrospiro[indene-1,4′-piperidine] (31). 4-(2-Phenylethyl)pyridine (8.5 g, 46 mmol) and benzyl chloride (11.64 g, 92 mmol) were refluxed in acetone for 48 h. The precipitated 1-benzyl-4-(2-phenylethyl)pyridinium chloride was filtered, washed with acetone, and dried in vacuo at 50 °C to obtain 9.35 g (65%) off the white solid. 1-Benzyl-4-(2-phenylethyl)pyridinium chloride (9.0 g, 29.0 mmol) was suspended in MeOH (100 mL) and cooled to 0 °C in an ice bath. $NaBH_4$ (4.73 g, 207.2 mmol) was added portionwise with vigorous stirring over 40 min. After cooling and stirring for an additional 1 h, the reaction mixture was concentrated under reduced pressure and partitioned between H_2O (50 mL) and CH_2Cl (50 mL). The layers were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide 7.1 g (91%) of 1-benzyl-4-(2-phenylethyl)-1,2,3,6-tetrahydropyridine as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.14 (br s, 2, N-CH_2-C*H*$_2$-CH=), 2.27 (t, 2, J = 8 Hz, N-C*H*$_2$-CH_2), 2.57 (t, 2, J = 6 Hz, Ph-C*H*$_2$-CH_2), 2.73 (m, 2, Ph-CH_2-C*H*$_2$), 2.97 (br s, 2, N-C*H*$_2$-CH=), 3.59 (s, 2, Ph-CH_2-N), 5.41 (m, 1, CH=C), 7.14–7.38 (m, 10, phenyl). 1-Benzyl-4-(2-phenylethyl)-1,2,3,6-tetrahydropyridine (7.1 g, 25.6 mmol) was refluxed in 85% H_3PO_4 (50 mL) for 80 h. The reaction mixture was made basic with 6 N NH_4OH and extracted with ether (2 × 100 mL). The ethereal extracts were dried over $MgSO_4$ and concentrated under reduced pressure to a residue. The crude product was purified by radial flow chromatography on silica gel (hexane(9)acetone(1)) to yield 2.3 g (32%) of 1′-benzyl-2,3-dihydrospiro[indene-1,4′-piperidine] as a straw-colored liquid: ^{1}H NMR ($CDCl_3$) δ 1.53 (br d, 2, piperidyl β-H_{eq}), 1.96 (dt, 2, piperidyl β-H_{ax}), 2.02 (t, 2, Ph-CH_2-C*H*$_2$, J = 6 Hz), 2.20 (dt, 2, piperidyl α-H_{ax}), 2.90 (m, 4, Ph-C*H*$_2$-CH_2, piperidyl α-H_{eq}), 3.59 (s, 2, benzyl), 7.14–7.40 (m, 9, phenyl).

2,3-Dihydrospiro[1*H*-indene-1,4′-piperidine] Hydrochloride (9). 1′-Benzyl-2,3-dihydrospiro[1*H*-indene-1,4′-piperidine] (0.50 g, 1.80 mmol) was dissolved in dichloroethane (6 mL). The resulting solution was cooled to 0 °C and 1-chloroethylchloroformate (0.258 g, 1.80 mmol) was added in one batch. Cooling was continued for 10 min after which the reaction mixture was refluxed for 1 h, cooled to room temperature, and concentrated under reduced pressure. The residue was redissolved in MeOH (10 mL) and refluxed for 2 h. The resulting solution was concentrated under reduced pressure to obtain 0.40 g (quantitative) of a pale yellow crystalline solid: mp 256–257 °C (lit.[15] mp 288–290 °C); ^{1}H NMR ($CDCl_3$) δ 1.74 (br d, 2, piperidyl β-H_{eq}), 2.10 (td, 2, piperidyl β-H_{ax}), 2.13 (t, 2, Ph-CH_2-C*H*$_2$, J = 6 Hz), 2.94 (t, 2, J = 6 Hz, Ph-C*H*$_2$-CH_2), 3.12–3.38 (m, 4, piperidyl α-$H_{ax,eq}$), 7.19 (br s, 4, phenyl); MS (EI) m/e 187.2 (M^+ of free base).

2,3-Dihydro-1′-(2-Hydroxycyclohex-1-yl)spiro[1*H*-indene-1,4′-piperidine] Hydrochloride (12a). Procedure A: yield, 60%; mp 264–267 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (br d, 2, piperidyl β-H_{eq} (N-CH_2-C*H*$_2$)), 1.76–2.94 (m, 15, cyclohexyl, piperidyl), 2.00 (t, 2, J = 6 Hz, Ph-CH_2-C*H*$_2$), 2.77 (t, 2, J = 6 Hz, Ph-C*H*$_2$-CH_2), 3.40 (m, 1, C*H*-OH), 4.17 (br s, 1, OH), 7.25 (s, 4, phenyl).

1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)-2,3-dihydrospiro[1*H*-indene-1,4′-piperidine] Hydrochloride (12b). Procedure B: yield, 48%; mp 267–269 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (br d, 2, piperidyl β-H_{eq}), 2.04 (td, 2, piperidyl β-H_{ax}), 2.08 (t, 2, J = 6 Hz, Ph-CH_2-C*H*$_2$), 2.45 (td, 1, piperidyl α-H_{ax}), 2.84 (m, 9, piperidyl α-H_{eq}, tetrahydronaphthyl C1-H, C3-H, C4-H, Ph-C*H*$_2$-CH_2), 3.33 (dd, 1, piperidyl α-H_{ax}), 3.92 (m, 1, C*H*-OH), 4.47 (br s, 1, OH), 7.15 (s, 4, phenyl(spiro)), 7.32 (m, 5, phenyl).

1′-[1-(*tert*-Butoxycarbonyl)-3-hydroxypiperidin-4-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] (19b) and 1′-[1-(*tert*-Butoxycarbonyl)-4-hydroxypiperidin-3-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] (20b). Procedure C. **19b**: yield, 14%; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H, *tert*-butyl), 1.56 (m, 2, piperidyl), 1.86 (m, 4, piperidyl), 1.97 (t, J = 6 Hz, 2, Ph-CH_2-C*H*$_2$), 2.32 (m, 2, piperidyl), 2.55 (m, 3, piperidyl), 2.88 (t, J = 6 Hz, 2, Ph-C*H*$_2$-CH_2), 3.85 (m, 1, piperidyl), 3.95 (m, 1, piperidyl), 4.22 (br d, 1, piperidyl), 4.40 (br d, 1, piperidyl), 7.17 (s, 4, phenyl). **20b**: yield, 25%; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H, *tert*-butyl), 1.56 (m, 2, piperidyl), 1.74–2.11 (m, 7, Ph-CH_2-C*H*$_2$, piperidyl), 2.38 (m, 2, piperidyl), 2.60 (m, 4, piperidyl), 2.89 (t, J = 6 Hz, 2, Ph-C*H*$_2$-CH_2),3.58 (m, 1, piperidyl), 3.68 (m, 1, piperidyl), 4.13 (m, 1, piperidyl), 4.27 (br d, 1, piperidyl), 7.18 (s, 4, phenyl).

Resolution of 20b. Racemic **20b** (0.6 g, 1.55 mmol) was resolved on Chiralcel OD column (30:70 *i*-PrOH:hexane (trace Et_3N)) to yield 0.22 g of (+)-**20b** and 0.23 g of (−)-**20b** (75% recovery). (+)-**20b**: retention time, 12.5 min $[\alpha]_D$ = +28.74° (c = 0.02, MeOH). (−)-**20b**: retention time, 18.2 min; $[\alpha]_D$ = −28.87° (c = 0.02, MeOH).

(+)-1′-(4-Hydroxypiperidin-3-yl)-2,3-dihydrospiro[indene-1,4′-piperidene] Hydrochloride ((+)-21b) and (−)-1′-(4-Hydroxypiperidin-3-yl)-2,3-dihydrospiro[indene-1,4′-piperidene] Hydrochloride ((−)-21b). Solutions of (+)- and (−)-**20b** in EtOAC (20 mL) were cooled down to 0 °C. Dry HCl gas was bubbled through these solutions for 30 min with stirring. The stirring was further continued for an additional 30 min at 0 °C. The solutions were concentrated under reduced pressure to yield the corresponding deprotected hydrochlorides, (+)-**21b** (92%) and (−)-**21b** (90%): mp 280–283 °C.

(±)-1′-(4-Hydroxypiperidin-3-yl)-2,3-dihydrospiro[indene-1,4-piperidine] Dihydrochloride (21b). Method 2. A mixture of **21a** (1.2 g, 3.35 mmol) and 10% Pd–C (0.2 g) in MeOH (50 mL) was hydrogenated for 3 h at 50 psi. The catalyst was filtered, and the filtrate was concentrated under reduced pressure to yield an off-white solid (1.12 g, 93%): mp 280–283 °C. ^{1}H NMR δ 1.79 (d, 2, piperidyl), 1.96 (dt, 1, piperidyl), 2.14 (t, J = 8 Hz, 2, Ph-CH_2-C*H*$_2$), 2.35 (m, 4, piperidyl), 2.95 (t, J = 8 Hz, 2, Ph-C*H*$_2$-CH_2), 3.10–3.74 (m, 9, piperidyl), 4.05 (d, 1, piperidyl), 4.28 (dt, 1, piperidyl), 7.11–7.39 (m, 4, phenyl).

1′-[4-Hydroxy-1-(2-iodobenzyl)piperidin-3-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] Dihydrochloride (12c). Procedure E: yield, 39%; mp (*i*-PrOH–ether) 246–249 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2, piperidyl), 1.80–2.10 (m, 8, piperidyl, indane), 2.31 (t, 1, piperidyl), 2.51 (t, 1, piperidyl), 2.67–3.10 (m, 7, piperidyl, indane), 3.40–3.54 (m, 3, benzyl, piperidyl), 4.05 (br s, 1, OH), 6.95 (t, 1, iodophenyl), 7.16–7.30 (m, 5, iodophenyl, phenyl), 7.32 (d, 1, iodophenyl), 7.81 (s, 1, iodophenyl).

1′-[4-Hydroxy-1-(3-iodobenzyl)piperidin-3-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] Dihydrochloride (12d). Procedure E: yield, 73%; mp (*i*-PrOH–ether) 243–246 °C; ^{1}H

NMR ($CDCl_3$) δ 1.50 (m, 2, piperidyl), 1.78 (dt, 1, piperidyl), 1.88–2.02 (m, 7, piperidyl, indane), 2.31 (t, 1, piperidyl), 2.54 (t, 1, piperidyl), 2.67–3.00 (m, 7, piperidyl, indane), 3.40–3.51 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 7.03 (t, J = 9 Hz, 1, iodophenyl), 7.14–7.28 (m, 5, iodophenyl, phenyl), 7.57 (d, 1, iodophenyl), 7.66 (s, 1, iodophenyl).

1′-[4-Hydroxy-1-(4-iodobenzyl)piperidin-3-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] Dihydrochloride (12e). Procedure E: yield, 50%; mp (*i*-PrOH–ether) 248–249 °C; ^1H NMR ($CDCl_3$) δ 1.51 (m, 2, piperidyl), 1.67–1.93 (m, 8, piperidyl, indane), 2.35 (t, 1, piperidyl), 2.57 (dt, 1, piperidyl), 2.75–3.04 (m, 7, piperidyl, indane), 3.41–3.54 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 7.06 (d, 2, J = 8 Hz, iodophenyl), 7.17–7.35 (m, 4, phenyl), 7.64 (d, J = 8 Hz, iodophenyl).

1′-[4-Hydroxy-1-(4-fluorobenzyl)piperidin-3-yl]-2,3-dihydrospiro[indene-1,4′-piperidine] Oxalate (12f). Procedure E: yield, 84%; mp (*i*-PrOH–ether) 129–131 °C; ^1H NMR ($CDCl_3$) δ 1.62 (m, 3, piperidyl), 1.78–2.06 (m, 7, piperidyl, indane), 2.37 (t, 1, piperidyl), 2.59 (dt, 1, piperidyl), 2.76–3.05 (m, 7, piperidyl,indane), 3.41–3.58 (m, 3, benzyl, piperidyl), 3.80 (br s, 1, OH), 7.01 (t, 2, fluorophenyl, J = 8Hz), 7.14–7.28 (m, 6, fluorophenyl, phenyl).

Procedure F. 3,4-Dihydro-1′-(2-hydroxycyclohex-1-yl)spiro[naphthalene-1,4′-piperidine] Hydrochloride (13a). A flask containing a mixture of **10** (505 mg, 2.51 mmol) in dichloromethane (2 mL) was maintained at 0 °C while Et_3Al (1.32 mL, 2.51 mmol) was added dropwise. The solution was stirred at room temperature for 35 min. The flask was then placed in an ice bath, and a solution of cyclohexene oxide (255 mL, 2.51 mmol) in dichloromethane (75 mL) was added. The resulting mixture was stirred at room temperature for 18 h, while the disappearance of the epoxide was monitored by TLC (silica gel, ethyl acetate:hexanes, 50:50). When the reaction was complete (the solution became white), 5 N KOH (2 mL) was added and stirring was prolonged for 2 h. Water (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 20 mL). After extraction, the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The desired compound, 13a, was obtained as a white crystalline solid (598 mg, 80%); no impurities were observed by TLC (silica gel, ethyl acetate:hexanes, 50:50). The hydrochloride was prepared in methanolic HCl, and the white solid was recrystallized from 50% ethyl acetate–hexanes: mp 306.6 °C; ^1H NMR ($CDCl_3$) δ 2.24–1.22 (3m, 16, piperidine, cyclohexanol), 2.46–2.52 (m, 2, Ph-CH_2), 2.65–2.79 (m, 4, Ph-CH_2-CH_2-CH_2), 2.98–3.02 (dt, 1, CHN), 3.42–3.47 (s, 1, C*H*-OH), 4.18 (s, 1, OH), 7.05–7.26 (m, 3, arom), 7.45–7.49 (d, 1H, arom, J = 7.7 Hz). Anal. ($C_{20}H_{29}NO$·HCl) C, H, N.

3,4-Dihydro-1′-(2-hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[naphthalene-1(2*H*),4′-piperidine] Hydrochloride (13c). Crude 1,4-dihydronaphthalene (340 mg, 2.3 mmol), obtained from the corresponding bromohydrin as outlined for **11b** above, was reacted with **10** following procedure F to yield, after purification on silica gel (ethyl acetate:hexanes: triethylamine, 50:50:1), a white solid (583 mg, 72%). The hydrochloride was prepared in methanolic HCl and recrystallized from ethyl acetate: mp 274.2 °C; ^1H NMR ($CDCl_3$) δ 1.23–2.24 (m, 16, piperidyl, cyclohexyl), 2.73–2.79 (m, 4, Ph-CH_2-CH_2-CH_2), 2.85–3.02 (dt, 1, CHN), 3.30–3.45 (m, 1, C*H*OH), 4.18 (s, 1, OH), 7.05–7.26 (m, 7, arom), 7.48–7.52 (d, 1, arom, J = 7.6 Hz). Anal. ($C_{24}H_{29}NO$·HCl) C, H, N.

1′-[1-(*tert*-(Butoxycarbonyl)-3-hydroxypiperidin-4-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (19c) and 1′-[1-(*tert*-Butoxycarbonyl)-4-hydroxypiperidin-3-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (20c). A mixture of the hydrochloride of **10** (4.9 g, 20.6 mmol) and 5.8 g (21 mmol) of the isomeric bromohydrins derived from 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine (see procedure F above) in absolute ethanol (25 mL) and triethylamine (15 mL) was refluxed for 24 h. Since TLC (silica gel, hexanes: ethyl acetate, 50:50) failed to show any progress in the reaction, solid potassium carbonate (7.26 g, 52.5 mmol) was added and the mixture was refluxed for 4 more days. After cooling, the salts were filtered off and the volatiles were removed under reduced pressure. The remaining brown oil was dissolved in ethyl acetate (30 mL), and the organic layer was successively washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated. The mixture of **19c** and **20c** was obtained as an orange oil (6.7 g, 84%). The regioisomers were separated by preparative HPLC on a gel column (hexanes:isopropyl alcohol, 98:2) to afford 1.58 g (20%) of **19c** (retention time, 7 min) and 3.70 g (46%) of **20c** (retention time, 8 min). **19c**: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9, *tert*-butoxy), 1.58–1.84 (m, 8, NCH_2-CH_2), 1.92–2.25 (m, 2, Ar-CH_2, CH_2-CH_2), 2.35–2.54 (m, 6, CH_2CH_2N(t-BOC)-CH_2), 2.72–2.78 (m, 4, Ar-CH_2CH_2-CH_2), 2.87–2.98 (t, 1, CH-N, J = 11.8 Hz), 3.38–3.50 (m, 1, C*H*-OH), 7.05–7.22 (m, 3, arom), 7.43–7.46 (d, 1, arom, J = 7.7 Hz). **20c:** ^1H NMR ($CDCl_3$) δ 1.47 (s, 9, 3 CH_3), 2.18–1.57 (2m, 8, 2 N-CH_2-CH_2), 2.38–2.30 (dt, 2, CH_2-CHOH, J = 3.6, 13.6 Hz), 2.57–2.49 (t, 2, Ar-CH_2, J = 9.9 Hz), 2.64–2.58 (d, 2, N-CH_2- CHN, J = 11.9 Hz), 2.78–2.75 (m, 4, Ar-CH_2-CH_2-CH_2), 3.09–2.98 (t, 2, CH_2-CH_2-N-t-BOC, J = 11.2 Hz), 3.66–3.54 (dt, 1, CH-N, J = 4.6, 10.3 Hz), 3.83 (s, 1, C*H*-OH), 7.21–7.03 (m, 3, arom), 7.45–7.42 (d, 1, arom, J = 7.7 Hz).

Resolution of 20c. Separation of the two enatiomers, (+)- and (−)-**20c**, was performed on a 250 mm × 10 mm i.d. Chiralcel OD column (hexanes:isopropyl alcohol:triethylamine, 70:30:0.3) to afford (+)-**20c** (retention time, 10 min) and (−)-**20c** (retention time, 18 min) as white crystalline solids. (+)-**20c**: $[\alpha]_D$ = +30.2° (**c** = 1.0, MeOH). (−)-**20c:** $[\alpha]_D$ = −30.9° (*c* = 1.0, MeOH).

1′-(4-Hydroxypiperidin-3-yl)-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] Dihydrochloride (21c). HCl gas was bubbled for 30 min through a solution of **20c** (800 mg, 2.1 mmol) in EtOAc (10 mL) while the flask was maintained in an ice bath. The resulting solution was subsequently stirred at room temperature for 30 min, and the volatiles were removed under reduced pressure. The white solid thus obtained was recrystallized from 50% isopropyl alcohol–hexanes to provide the hydrochloride of **21c** as a white powder (80%).

1′-[1-(2-Iodobenzyl)-4-hydroxypiperidin-3-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (13c). A mixture of the dihydrochloride of **21c** (250 mg, 0.67 mmol), DMF (10 mL), potassium carbonate (463 mg, 3.35 mmol), and 2-iodobenzyl chloride (1.00 mmol, 254 mg) was stirred at room temperature for 18 h. Water (25 mL) and dichloromethane (2 × 25 mL) were added, and the organic layer was extracted, washed with brine (25 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel, hexanes:ethyl acetate, 50:50) to afford **13c** as a yellow oil. The latter was converted to the corresponding hydrochloride in saturated HCl/ether and recrystallized twice from 50% *i*-PrOH–hexanes to yield 0.20 g (33%) of **13c**: mp 258.8 °C; ^1H NMR ($CDCl_3$) δ 1.50–2.21 (2m, 8, 2 N-CH_2-CH_2), 2.45–2.57 (m, 2H, Ar-CH_2-CH_2, J = 10.2 Hz), 2.60–2.76 (m, 2, CH_2-CHOH), 2.84 (m, 4, Ar-CH_2-CH_2-CH_2), 2.88–3.00 (t, 2, CH_2-CH_2-CHOH, J = 11.2 Hz), 3.09–3.13 (d, 2, N-CH_2-CHN, J = 8.7 Hz), 3.50–3.64 (m, 3, Ar-CH_2-N, CH-N), 3.85 (s, 1, C*H*-OH), 4.67 (s, 1, OH), 6.96–7.49 (m, 8H, arom), 7.83–7.87 (d, 1H, arom, J = 6.8 Hz).

1′-[1-(3-Iodobenzyl)-4-hydroxypiperidin-3-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (13d). A mixture of **21c** and **22c** (676 mg, 1.81 mmol), 3-iodobenzyl bromide (2.17 mmol, 645 mg), and triethylamine (10 mL) in absolute EtOH (20 mL) was refluxed for 18 h. Volatiles were removed under reduced pressure, and the red residue was treated with water. After extraction in dichloromethane (3 × 30 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a dark red semisolid residue. Chromatographic purification (silica gel, 50% ethyl acetate–hexanes) afforded 276 mg (30%) of the crude product as a yellow oil. The two regioisomers were separated by HPLC (silica gel, hexane:Isopropyl alcohol:triethylamine, 98:2:0.02), and **13d** was obtained as a white crystalline solid (166 mg, 18%). Only a trace of the other isomer was recovered. The hydrochloride of **13d** was prepared in saturated methanolic HCl and subsequently recrystallized from 50% *i*-PrOH–hexanes to provide a white powder: mp 245 °C; ^1H NMR ($CDCl_3$) δ 1.59–2.06 (m, 8, 2 N-CH_2-CH_2), 2.41–2.48 (m, 2, Ar-CH_2-CH_2), 2.52–2.62 (m, 2, CH_2-CHOH), 2.75–2.78 (m, 4,

Ar-CH_2-CH_2-CH_2), 2.83–2.92 (m, 2, CH_2-CH_2-CHOH), 3.01–3.06 (d, 2, N-CH_2-CHN, J = 10.0 Hz), 3.38–3.56 (m, 3, Ar-CH_2-N, CH-N), 3.85 (s, 1, CH-OH), 7.02–7.31 (m, 5, arom), 7.44–7.48 (d, **1**, arom, J = 7.8 Hz), 7.58–7.62 (d, 1, arom, J = 7.9 Hz), 7.68 (s, 1, arom).

Procedure G. 1′-[1-(4-Iodobenzyl)-4-hydroxypiperidin-3-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (13e). A mixture of the hydrochloride of **21c** (250 mg, 0.67 mmol), potassium carbonate (463 mg, 3.35 mmol), and 4-iodobenzyl chloride (298 mg, 1.00 mmol) in absolute ethanol (25 mL) was refluxed for 16 h. When the mixture had cooled, the salts were filtered off and the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (25 mL), and the solution was successively washed with water (25 mL) and brine (25 mL). The organic layer was then dried (Na_2SO_4) and concentrated. The product was purified by chromatography (silica gel, hexanes:ethyl acetate, 50:50), and **13e** was obtained as a colorless oil (226 mg, 52%). The hydrochloride was prepared in a saturated HCl/ether solution and recrystallized twice from 50% isopropyl alcohol–hexanes to yield a yellow powder: mp 256.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.56–2.18 (2m, 8, 2 N-CH_2-CH_2), 2.40–2.45 (d, 2H, Ar-CH_2-CH_2, J = 10.1 Hz), 2.51–2.60 (m, 2, CH_2-CHOH), 2.72–2.78 (m, 4, Ar-CH_2-CH_2-CH_2), 2.84–2.97 (t, 2, N-CH_2-CH_2-CHOH, J = 11.9 Hz), 3.05–3.50 (d, 2, CHN-CH_2-N, J = 10.4 Hz), 3.40–3.55 (m, 4, CH-OH, Ar-CH_2-N, CHN), 3.81 (s, 1, OH), 7.22–7.02 (m, 4, arom), 7.42–7.46 (d, 2, arom, J = 7.7 Hz), 7.63–7.67 (d, 2, arom, J = 8.2 Hz).

1′-[1-(4-Fluorobenzyl)-4-hydroxypiperidin-3-yl]-3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine] (13f). Procedure E: yield, 13%; mp 232.4 °C; ^{1}HNMR ($CDCl_3$) δ 1.50–2.10 (m, 8, 2 N-CH_2-CH_2), 3.47–2.52 (m, 2, Ar-CH_2-CH_2), 2.59–2.64 (dt, 2, CH_2-CHOH, J = 2.1 Hz, J' = 10.1 Hz), 2.68–2.78 (m, 4, Ar-CH_2-CH_2-CH_2), 2.87–2.99 (t, 2, CH_2-CH_2-CHOH, J = 11.0 Hz), 3.05–3.10 (d, 2, N-CH_2 CHN, J = 10.2 Hz), 3.76–3.80 (m, 3, Ar-CH_2-N, CH-N), 3.90 (s, 1, CH-OH), 4.55 (s, 1, OH), 6.75–7.49 (m, 8H, arom).

1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[2-bromo-1*H*-indene-1,4′-piperidine] Hydrochloride (14). Compound 24 was prepared from 2-bromo-1*H*-indene (procedure H) and purified by radial flow chromatography in silia gel (hexanes(94):acetone(5):Et_3N (1)) to yield 3.0 g (57%) of a golden yellow syrup: ^{1}H NMR ($CDCl_3$) δ 1.24–1.29 (d, 2, piperidyl β-H_{eq}), 1.44–1.54 (s, 9, *tert*-butoxy), 2.04–2.12 (m, 2, piperidyl β-H_{ax}), 3.45–3.60 (m, 2, piperidyl α-H_{ax}), 4.21–4.35 (br s, 2, piperidyl α-H_{eq}), 6.85 (s, 1, indenyl C3-H), 7.13–7.31 (m, indenyl C4-H, C5-H, C6-H), 7.80 (d, 1, indenyl C7-H).

Compound **24** (2.8 g, 7.85 mmol) was converted to **25** as described for **21a** above. This product was added to a solution of 1,4-dihydronaphthalene oxide, prepared from the corresponding bromohydrin (9.0 mmol) as described in procedure B above, in EtOH (10 mL) and Et_3N (10 mL). The resulting mixture was refluxed for 40 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (30 mL). After separation of the phases, the aqueous layer was re-extracted wtih CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to a residue. The latter was subjected to radial flow chromatography on silica gel (hexanes(79):acetone(20):Et_3N(1)) to provide 1.92 g (60%) of **14** as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.43 (d, 2, piperidyl β-H_{eq}, J = 10.5 Hz), 2.13–2.32 (m, 2, piperidyl β-H_{ax}), 2.81–3.49 (m, 9, tetrahydronaphthyl C1-H, C3-H, C4-H, piperidyl α-H), 3.96 (m, 1, CHOH), 6.88 (s, 1, indenyl C3-H), 7.02–7.97 (m, 7, aryl), 7.81 (d, 1, indenyl C7-H, J = 7.2 Hz). The corresponding hydrochloride was obtained in cold methanolic HCl and recrystallized from *i*-PrOH as an off-white solid: mp 278–281 °C.

1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[4-bromo-1*H*-indene-1,4′-piperidine] Hydrochloride (15). The reaction of 7-bromo-1*H*-indene (3.50 g, 17.94 mmol) with $LiN[Si(CH_3)_3]_2$ and *tert*-butyl bis(2-chloroethyl)carbamate (procedure H) yielded a mixture of two products (5.85 g, 90%) in a ratio of 85:15, respectively, as revealed by HPLC (silica gel, 2% acetone–hexanes). Deprotection (see **21a**), subsequent neutralization, and extraction into EtOAc yielded, after concentration, 2.2 g (46%) of the crude free base. Trituration of this residue with CH_2Cl_2 yielded **27** as a white solid which was collected by filtration, washed with CH_2Cl_2, and dried at 50 °C in vacuo: mp 310–315 °C (sinters); ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 2, piperidyl α-H_{eq}, J = 13.5 Hz), 2.38 (dt, 2, piperidyl δ-H_{ax}, J = 12.9 Hz, J' = 4.8 Hz), 3.21 (dt, 2, piperidyl α-H_{ax}, J = 13.4 Hz, J' = 2.4 Hz), 3.35 (d, 2, piperidyl α-H_{eq}, J = 11.1 Hz), 6.78 (d, 1, indenyl C2-H, J = 6.0 Hz), 7.14 (t, 1, indenyl C6-H, J = 8.4 Hz), 7.26 (d, 1, indenyl C2-H, J = 6.0 Hz), 7.29 (d, 1, indenyl C5-H, J = 6.0 Hz), 7.40 (d, 1, indenyl C7-H, J = 8.4 Hz).

A solution of 1 M Et_3Al in toluene (0.65 mL) was added dropwise at room temperature under N_2 to a stirring suspension of **27** (0.30 g, 1.13 mmol) in CH_2Cl_2 (13 mL). Complete dissolution occurred at the end of the addition. The resulting solution was stirred at room temperature for 40 min at which time a solution of 1,4-dihydronaphthalene oxide in CH_2Cl_2 (5 mL), prepared from the corresponding bromohydrin (1.35 mmol) as described in procedure B above, was added dropwise over 5 min. Stirring was continued for 21 h. The reaction was quenched by dropwise addition of 4 N NaOH (20 mL). The resulting mixture was stirred vigorously for 2 h, diluted with H_2O (25 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $NaSO_4$ and concentrated to a tan solid which was purified by radial flow chromatography on silica gel (hexanes(79):acetone(20):Et_3N-(1)) to yield an off-white solid (0.30 g, 65%): mp 265–267 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 2, piperidyl β-H_{eq}, J = 12.9 Hz), 2.10–2.28 (m, 2, piperidyl α-H_{ax}), 2.65 (t, 1, piperidyl α-H_{ax}, J = 11.4 Hz), 2.81–3.11 (m, 7, tetrahydronaphthyl C1-H, C4-H, piperidyl), 3.35 (dd, 1, piperidyl α-H_{eq}, J = 16.1 Hz, J' = 5.7 Hz), 3.93 (m, 1, CHOH), 6.87 (d, 1, indenyl C2-H, J = 5.7 Hz), 6.96 (d, 1, indenyl C3-H, J = 5.7 Hz), 7.12 (m, 5, aryl), 7.31 (d, 1, indenyl C5-H, J = 7.4 Hz), 7.38 (d, 1, indenyl C7-H, J = 7.9 Hz).

Procedure H. 5-Bromo-1′-(*tert*-butoxycarbonyl)spiro-[1*H*-indene-1,4′-piperidine] (29) and 6-Bromo-1′-(*tert*-butoxycarbonyl)spiro[1*H*-indene-1,4′-piperidine] (30). A solutionn of 1 M $LiN[Si(CH_3)_3]_2$ in THF (45 mL) was added dropwise over 20 min, under N_2, to a cooled (ice bath) stirring solutionn of 5-bromo-1*H*-indene (3.90 g, 20.0 mmol) in dry THF (15 mL). Following the addition, stirring was continued at 4 °C for 45 min. The dark solution was then transferred via cannula to a precooled (ice bath) solution of *tert*-butyl *N*,*N*-bis(2-choroethyl)carbamate (4.84 g, 20.0 mmol) in dry THF (15 mL). The resulting solution was stirred at 4 °C for 2 h and then at room temperature for 18 h. The dark purple mixture was concentrated in vacuo, and the residue was triturated with a small volume of 20% acetone–hexanes and applied into a short silica gel column. The latter was eluted with the same solvent (300 mL). The eluent was concentrated to yield 6.45 g (88%) of the crude mixture of **29** and **30** which was considered pure enough for use without further purification. However, a small fraction of this material was purified by radial flow chromatography on silica gel (hexanes(89):acetone-(10):Et_3N(1)) to provide an orange-colored syrup: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 2, piperidyl β-H_{eq}, J = 16.8 Hz), 1.50 (s, 9, *tert*-butoxy), 1.96 (dt, 2, piperidyl β-H_{ax}, J = 12.3 Hz, J' = 4.6 Hz), 3.09 (t, 2, piperidyl α-H_{ax}, J = 13.0 Hz), 4.17 (br d, 2, piperidyl α-H_{eq}, J = 13.0 Hz), 6.71 (d, 1, indenyl C2-H, J = 5.78 Hz), 6.85 (m, 1, indenyl C3-H), 7.14–7.45 (m, 3, aryl). Anal. ($C_{18}H_{22}BrNO_2$) C, H, N.

1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[6-bromo-1*H*-indene-1,4′-piperidine] Hydrochloride (16) and 1′-(2-Hydroxy-1,2,3,4-tetrahydronaphth-3-yl)spiro[5-bromo-1*H*-indene-1,4′-piperidine] Hydrochloride (17). HCl-(g) was vigorously bubbled through a cooled (ice bath) solution of **29** and **30** (6.20 g, mmol) in EtOAc (100 mL). The resulting solution was stirred at 4 °C for an additional 45 min and concentrated in vacuo to a brown solid. The latter was triturated with Et_2O, filtered, washed with Et_2O, and dried to afford 4.12 g (80%) of a mixture of isomeric bromospiro[1*H*-indene-1,4-piperidine] hydrochlorides.

A fraction of this mixture (2.0 g, 6.65 mmol) was added to a solutionn of 1,4-dihydronaphthalene oxide, prepared from the

corresponding bromohydrin (1.61 g, 7.1 mmol), in EtOH (50 mL) and Et_3N (20 mL). The mixture was refluxed for 72 h, cooled to room temperature, and concentrated in vacuo to a syrup. The latter was diluted with CH_2Cl_2, and the solution was washed with saturated $NaHCO_3$ (40 mL). The aqueous layer was re-extracted with CH_2Cl_2 (40 mL) and set aside. The combined organic extracts were dried over Na_2SO_4 and concentrated to a residue. Radial flow chromatographic separation (hexanes(89):acetone(10):Et_3N(1)) yielded a small fraction of starting material (0.30 g, 17%) and two products. The more mobile product, **16**, was obtained as a white powder (0.2 g, 10%) which was converted to the hydrochloride in MeOH and recrystallized from isopropyl alcohol: mp 259–263 °C; ^1H NMR ($CDCl_3$) δ 1.44 (d, 2, piperidyl β-H_{eq}, J = 12.8 Hz), 2.08–2.30 (m, 2, piperidyl β-H_{ax}), 2.64 (t, **1**, piperidyl α-H_{ax}, J = 9.8 Hz), 2.59–3.12 (m, 7, tetrahydronaphthyl C1-H, C4-H, piperidyl), 3.35 (dd, 1, piperidyl α-H_{eq}, J = 16 Hz, J' = 5.8 Hz), 3.94 (m, 1, C*H*OH), 6.72 (d, 1, indenyl C2-H, J = 5.6 Hz), 6.90 (d, 1, indenyl C3-H, J = 5.7 Hz), 7.14 (s, 4, tetrahydronaphthyl C5-H, C6-H, C7-H, C8-H), 7.18 (d, 1, indenyl C4-H, J = 8.1 Hz), 7.38 (dd, 1, indenyl C5-H, J = 7.9 Hz, J' = 1.6 Hz), 7.53 (d, 1, indenyl C7-H, J = 1.6 Hz). The less mobile product, **17**, was also obtained in 10% yield and coverted to the hydrochloride in a similar manner: mp 269–270 °C; ^1H NMR ($CDCl_3$) δ 1.43 (d, 2, piperidyl β-H_{eq}, J = 13.2 Hz), 2.16 (m, 2, piperidyl β-H_{ax}), 2.64 (t, 1, piperidyl α-H_{ax}, J = 9.8 Hz), 2.79–3.12 (m, 7, tetrahydronaphthyl C1-H, C4-H, piperidyl), 2.94–3.40 (dd, 1, piperidyl α-H_{eq}, J = 16.1 Hz, J' = 5.7 Hz), 3.94 (m, 1, C*H*OH), 6.72 (d, 1, indenyl C2-H, J = 5.7 Hz), 6.92 (d, 1, indenyl C3-H, J = 5.6 Hz), 7.14 (s, 5, tetrahydronaphthyl C5-H, C6-H, C7-H, C8-H), 7.27 (d, 1, indenyl C7-H, J = 6.6 Hz), 7.36 (dd, 1, indenyl C6-H, J = 7.9 Hz, J' = 1.7 Hz), 7.48 (d, 1, indenyl C4-H, J = 1.6 Hz).

Biological. Dissociation constants of novel compounds were measured by competition against binding of [^{3}H]vesamicol to electric organ synaptic vesicles at 22 °C, after 24 h of incubation, by the method of Rogers et al.[19]

Acknowledgment. Financial support was provided by The National Institute of Neurological Disorders and Stroke (Grant #1R01NS28711). The authors thank Ms. Charla Zaccardi for her assistance in the preparation of this manuscript.

References

(1) Brittain, R. T.; Levy, G. P.; Tyers, M. B. Observations on the neuromuscular blocking action of 2-(4-phenylpiperidino)cyclohexanol (AH 5183). *Br. J. Pharmacol.* **1969**, *37*, 173–174.
(2) Brittain, R. T.; Levy, G. P.; Tyers, M. B. The neuromuscular blocking action of 2-(4-phenylpiperidino)cyclohexanol (AH 5183). *Eur. J. Pharmacol.* **1969**, *8*, 93–99.
(3) Marshall, I. G. Studies on the blocking action of 2-(4-phenylpiperidino)cyclohexanol (AH 5183). *Br. J. Pharmacol.* **1970**, *38*, 503–516.
(4) Bahr, B. A.; Parsons, S. M. Demonstration of a receptor in Torpedo synaptic vesicles for the acetylcholine storage blocker L-trans-2-(4-phenyl[3,4-^{3}H]-piperidino)cyclohexanol. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 2267–2270.
(5) Marien, M. R.; Richard, J. W.; Allaire, C.; Altar, C. A. Suppression of in vivo neostriatal acetylcholine release by vesamicol: evidence for a functional role of vesamicol receptors in brain. *J. Neurochem.* **1991**, *57*, 1878–1883.
(6) Marshall, I. G.; Parsons, S. M. The vesicular acetylcholine system transport system. *Trends Neurosci.* **1987**, *10*, 174–177.
(7) Prior, C.; Marshall, I. G.; Parsons, S. M. The pharmacology of vesamicol: an inhibitor of the vesicular acetylcholine transporter. *Gen. Pharmacol.* **1992**, *23*, 1017–1022.
(8) Parsons, S. M.; Prior, C.; Marshall, I. G. Acetylcholine transport, storage and release. *Int. Rev. Neurobiol.* **1993**, *35*, 279–390.
(9) Wannan, G.; Prior, C.; Marshall, I. G. α-Adrenoceptor blocking properties of vesamicol. *Eur. J. Pharmacol.* **1991**, *201*, 29–34.
(10) Girod, R.; Loctin, F.; Dunant, Y. Local anesthetic activity of vesamicol in the electric organ of Torpedo. *Eur. J. Pharmacol.* **1991**, *195*, 1–9.
(11) Rogers, G.A.; Parsons, S.M.; Anderson, D.C.; Nilsson, L.M.; Bahr, B.A.; Kornreich, W.D.; Kaufman, R.; Jacobs, R.S.; Kirtman, B. Synthesis, in vitro acetylcholine-storage-blocking activities and biological properties of derivatives and analogues of *trans*-2-(4-phenylpiperidino)cyclohexanol (vesamicol). *J. Med Chem.* **1989**, *32*, 1217–1230.
(12) Efange, S. M. N.; Michelson, R. H.; Dutta, A. K.; Parsons, S. M. Acyclic analogues of 2-(4-phenylpiperidino)cyclohexanol (vesamicol): conformationally mobile inhibitors of vesicular acetylchline transport. *J. Med. Chem.* **1991**, *34*, 2638–2643.
(13) Efange, S. M. N.; Khare A. B.; Parsons, S. M.; Bau, R.; Metzenthin, T. Nonsymmetrical bipiperidyls as inhibitors of vesicular acetylcholine storage. *J. Med. Chem.* **1993**, *36*, 985–989.
(14) Efange S. M. N.; Boudreau, R. J. Molecular determinants in the bioactivation of the dopaminergic neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *J. Comput.-Aided Mol. Des.* **1991**, *5*, 405–417.
(15) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight A. K.; Middlemiss, D. N.; Wong, E. H. F. Spiropiperidines as high-affinity, selective sigma ligands. *J. Med. Chem.* **1992**, *35*, 2033–2039.
(16) Evans, B. E.; Leighton, J. L.; Rittle, K. E.; Gilbert, K. F.; Lundell, G. F.; Gould, N. P.; Hobbs, D. W.; DiPardo, R. M.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. Orally active, nonpeptide oxytocin antagonists. *J. Med. Chem.* **1992**, *35*, 3919–3927.
(17) Reimann, E.; Speckbacher, J.; Schünemann, J. Synthese und pharmakologische prüfung homologer und hydroxylierter 3,4-dihydro-1′-methylspiro[naphthalin-1(2*H*),4′-piperidine]. (Intramolecular alkylation of aromatic compounds. XXVIII. Synthesis and pharmacological test of homologated and hydroxylated 3,4-dihydro-1′-methylspiro[naphthalene-1(2*H*),4′-piperidines].) *Arch. Pharm. (Weinheim, Ger.)* **1990**, *323*, 35–39.
(18) Miller, R. B.; Frincke, J. M. Synthesis of isoquinolines from indenes. *J. Org. Chem.* **1980**, *45*, 5312–5315.
(19) Rogers, G. A.; Kornreich, W. D.; Hand, K.; Parsons, S. M. Kinetic and equilibrium characterization of vesamicol receptor-ligand complexes with picomolar dissociation constants. *Mol. Pharmacol.* **1993**, *44*, 633–641.