Synthesis and Structure Activity Relationships of *cis*- and *trans*-2,3,4,4a,9,9a-Hexahydro-1*H*-indeno[2,1-*c*]pyridines for 5-HT Receptor Subtypes

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A series of *cis*- and *trans*-fused hexahydroindeno[2,1-*c*]pyridines have been prepared and evaluated for affinity and selectivity at the 5-HT_{1A} subtype of the serotonin receptor. Using molecular modeling studies we predicted that the 5-methoxy-*trans*-fused members of this class would exhibit affinity for this site. In agreement with these predictions, *trans*-5-methoxy-*N*-propyl-2,3,4,4a,9,-9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine (**6a**) demonstrated moderate affinity and high selectivity for the 5-HT_{1A} binding site, whereas the *cis*-fused isomer **5a** demonstrated virtually no affinity at this site. Additional *trans*-fused analogs from this series, where the nitrogen was substituted with a variety of alkylene imide containing appendages, demonstrated high (0.60–51 nM) affinity and excellent selectivity for the 5-HT_{1A} site. Certain of these analogs, independent of ring-fusion stereochemistry, also demonstrated high affinity for the 5-HT_2 binding site.

Introduction

At least two distinct structural classes of compounds have been identified which exhibit high affinity for the 5-HT_{1A} subclass of the serotonin receptor. The prototypical agents 8-hydroxy-2-(di-*n*-propylamino)tetralin (**1**) and the arylpiperazines buspirone, gepirone, and ipsapirone (**2**–**4**) are examples from these two classes (Figure 1). Hibert et al.[1,2] have described a steric model for the 5-HT_{1A} binding site which sets two structural features as a minimum requirement for interaction with this site, the one being the presence of an aromatic ring and the other a basic nitrogen at a distance of approximately 5.6 Å from the center of the aromatic ring. The nitrogen atom is nearly coplanar with the ring and the nitrogen lone pair nearly perpendicular to the plane of the aromatic ring. Studies by Huff et al.[3] have similarly concluded that the nitrogen lone pair of various arylpiperazines exists nearly exclusively in an axial orientation, perpendicular to the aromatic ring. These, however, are only a minimum requirement, and additional sites of interaction with the receptor appear to be required for the attainment of high-affinity binding. In the case of the aminotetralins, the presence of an 8-OH or O-Me functionality significantly enhances receptor affinity.[4] And, in the case of the arylpiperazines, the presence of specific side chains on the basic nitrogen results in significantly enhanced affinity for the 5-HT_{1A} binding site.[5,6]

Herein, we report the synthesis and pharmacological characterization of a series of *cis* and *trans*-fused hexahydroindeno[2,1-*c*]pyridines **5** and **6**, a structurally unique class of agents which combines features from both the aminotetralin and pyrimidinylp iperazine class into a single chemical entity. High affinity for the 5-HT_{1A} site is observed only with the *trans*-fused analogs from this class.

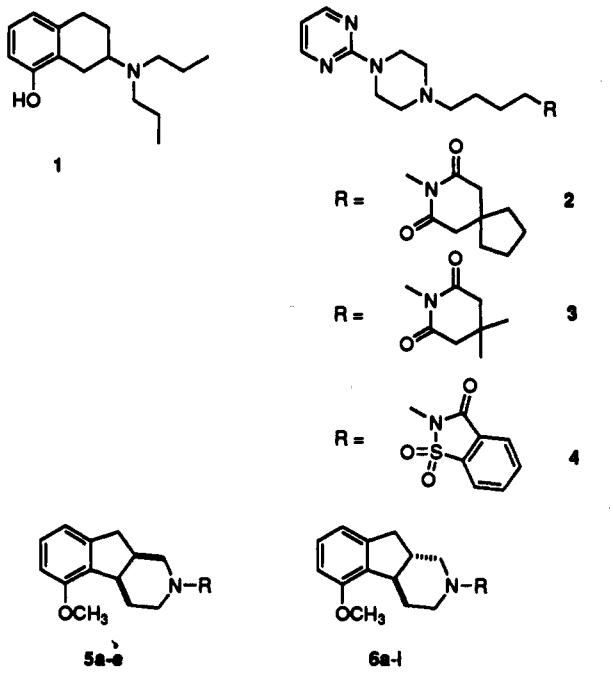

Figure 1.

Results and Discussion

Design of 5-HT_{1A} Selective Agonists. The *cis* and *trans* hexahydroindenopyridine ring systems were constructed within CHEMX.[7] For simplicity, the *N*-methyl analogs were modeled. The DGEOM subroutine from within CHEMX was used to generate 100 random conformations for both the *cis*- and *trans*-fused ring systems. Minimization, followed by rejection of redundant conformations, yielded two low-energy *trans*-fused conformations and four *cis* conformations.

The *trans* conformations placed the piperidine ring in either a chair or twist boat conformation. The twist boat conformation yielded a calculated energy of 33.17 vs 27.71 kcal/mol for the chair conformation. From these calculations, it was concluded that the chair conformation represented the most relevant structure.

For the *cis*-fused analog, the lowest energy conformation identified (26.05 kcal/mol) also placed the piperidine ring in a chair conformaton. However, three additional twist boat conformations were identified that were within 5 kcal/mol of the chair conformation.

Superimposition of these six conformations with 8-OH-DPAT (**1**) using the least-squares fitting routine within CHEMX, and selecting the oxygen, the basic nitrogen, and a dummy atom at the center of the aromatic ring as the important common atoms, strongly suggested that only

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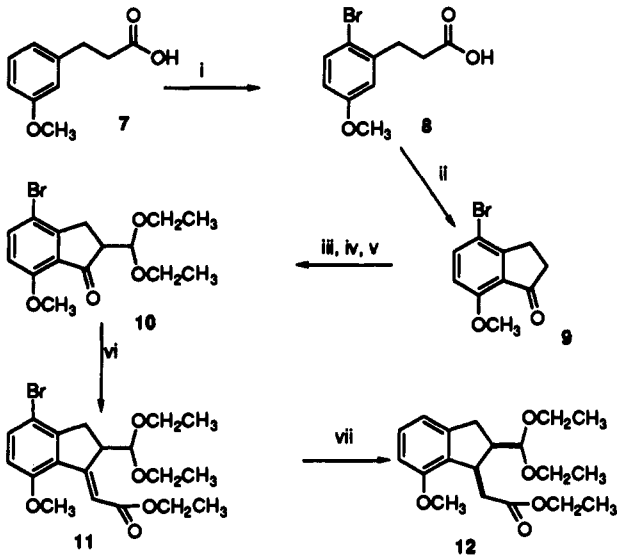
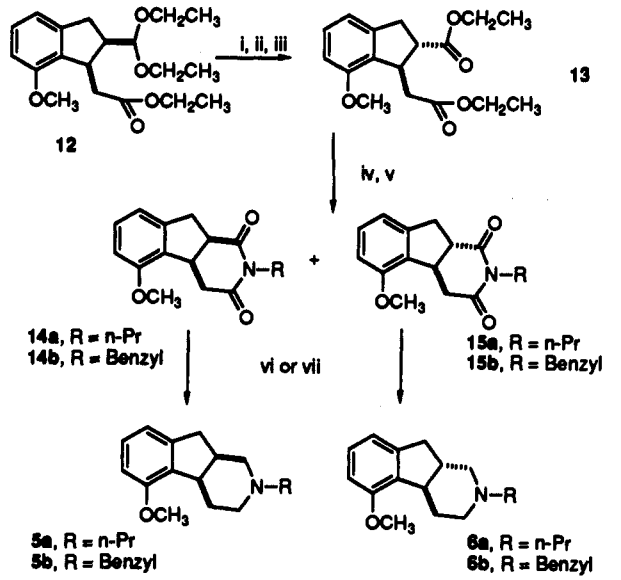
Scheme 1



[a] Conditions: (i) Br_2, CH_2Cl_2; (ii) PPA, 60 °C; (iii) $(EtO)_3CH$; (iv) BF_3·Et_2O; (v) ethyldiisopropylamine; (vi) ethyl(trimethylsilyl)acetate, LiHMDS; (vii) H_2/Pd.

Scheme 2



[a] Conditions: (i) aqueous HCl; (ii) AgO; (iii) EtOH, H_2SO_4; (iv) Me_3Al, RNH_2; (v) pTsOH, xylene; (vi) $LiAlH_4$; (vii) BH_3, THF

the chair conformation of the *trans*-fused indenopyridine demonstrated good overlap in this model. Furthermore, the modeling studies demonstrated that the chair conformation of the *trans*-fused hexahydroindenopyridine ring system was in accord with the Hibert[1] agonist model for the 5-HT_{1A} site, with an interatomic distance of 5.53 Å from the center of the aromatic ring to the basic nitrogen, and the nitrogen lone pair perpendicular to the aromatic ring and the nitrogen nearly coplanar with the ring. In contrast, the lowest energy *cis*-fused ring conformation placed the nitrogen approximately 3 Å below the plane of the aromatic ring with an interatomic distance of 4.76 Å from the center of the aromatic ring to the basic nitrogen. Although one of the *cis* conformations (twist boat) showed an interatomic distance of 5.48 Å and a minimum energy of 28.00 kcal/mol, the overlap studies suggested that the nitrogen lone pair would be required to exist orthogonal to that required by the Hibert model. From these modeling studies, we predicted that the *trans*-fused ring system should show affinity for the 5-HT_{1A} site, whereas the *cis*-fused system should be significantly less active. To test the validity of these modeling studies, the *cis*-and *trans*-hexahydroindenopyridine ring systems were prepared, and various N-substituted analogs were examined.

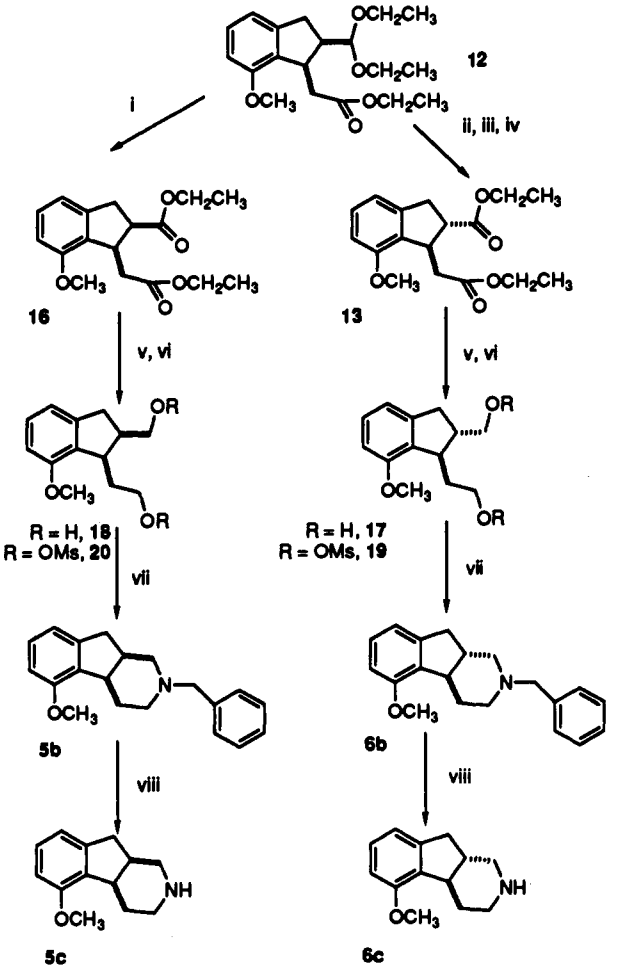
Chemistry. Scheme 1 describes the synthesis of intermediate ester acetal **12**, from which both the *cis*- and *trans*-indenopyridine ring systems were generated. The indanone **9** was prepared in two steps from the 3-(3-methoxyphenyl)propanoic acid **7**, with the required regiochemistry being assured by blockade of the para position of the aromatic ring with bromine. The keto acetal **10** was prepared by the method of Mock and Tsou.[8] Peterson olefination of **10** to yield **11**, followed by concomitant hydrogenation of the double bond and hydrogenolysis of the bromine completed the five step sequence to **12** in 32% overall yield. NMR analysis of **12** strongly suggested the presence of a single isomer, but the NMR studies were ambiguous in terms of assignment of the relative stereochemistry.

Scheme 2 outlines the initially developed synthetic approach to the *cis*- and *trans*-fused indenopyridine ring systems. The ester acetal **12** was converted to the diester intermediate **13** via hydrolysis to the aldehyde, AgO oxidation to the acid, and esterification to the diester. NMR indicated the product to be >90% of a single isomer of unknown configuration. Treatment of the diester with 3 equiv of dimethylaluminum *n*-propylamide (prepared by treatment of trimethylaluminum with 1 equiv of *n*-propylamine in toluene) followed by heating of the intermediate diamide with 1 equiv of *p*-TsOH in xylene yielded a 3:2 mixture of the cyclic *cis* and *trans* imides **14a** and **15a**. The imides were separated chromatographically and their structures elucidated by NMR (see below). The imides were reduced without epimerization to the *n*-propylindenopyridines **5a** and **6a**. Repetition of the above sequence with benzylamine resulted in an unfavorable ratio of *cis* to *trans* imides **14b** and **15b** with the *cis* predominating by greater than 10:1. Again, BH_3 reduction yielded the amines **5b** and **6b**, respectively. Because of the highly unfavorable ratio of *cis* to *trans* products, a more workable general synthesis of the *trans* ring system was needed.

Scheme 3 describes the elaboration of **12** stereoselectively to either the *cis*- or *trans*-fused indenopyridine ring systems. The ester acetal **12** was converted in a single step to the *cis* diester (*vide infra*) **16** via *m*-CPBA oxidation in the presence of a catalytic amount of H_2SO_4. Acid-catalyzed *m*-CPBA oxidation of acetals to esters has previously been reported,[9] and according to the the mechanism proposed by Grieco et al., the stereochemical integrity at C-2 should be retained (see Figure 3). By contrast, aqueous acid-catalyzed hydrolysis of the acetal produces the aldehyde which can then epimerize via the enol tautomer. Elaboration of the diester to the *N*-benzylindenopyridine yielded a product identical to the *cis*-indenopyridine **5b** prepared as described in Scheme 2. The diester **16** was of opposite stereochemistry to the diester prepared in Scheme 2. Therefore, it was inferred that the originally prepared diester **13** was in fact *trans*.

Having established that the original route to the diester **13** described in Scheme 2 yielded a product which was nearly exclusively *trans*, we were then able to utilize the route described in Scheme 3 for the preparation of the *trans*-indenopyridine **6c**. Since the conditions required for the conversion of **12** to **13** should allow equilibration

Scheme 3



[a] Conditions: (i) *m*-CPBA, H_2SO_4; (ii) aqueous HCl; (iii) AgO; (v) EtOH, H_2SO_4; (v) $LiAlH_4$; (vi) CH_3SO_2Cl, Et_3N; (vii) benzylamine; (viii) H_2/Pd.

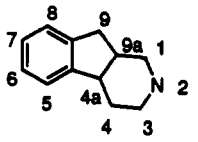


Figure 2. Numbering scheme for indeno[2,1-*c*]pyridine ring system.

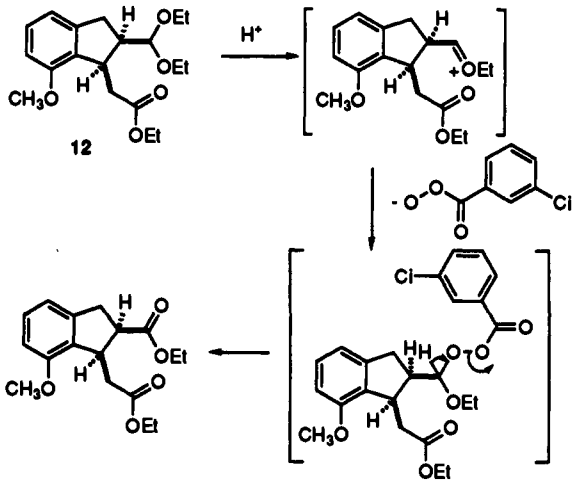


Figure 3. Proposed mechanism for *m*-CPBA oxidation of 12.

Table 1. Properties of Indenopyridine Analogs

	mp, °C	recrystn solvent	formula
5a	175–7	EtOAc–Et_2O	$C_{16}H_{23}NO$·HCl
6a	>260	EtOH–Et_2O	$C_{16}H_{23}NO$·HCl
5d	170–2	EtOAc–Et_2O	$C_{25}H_{34}N_2O_3$·HCl
6d	221–3	CH_2Cl_2–Et_2O	$C_{25}H_{34}N_2O_3$·HCl
5e	amorphous	H_2O (lyophilized)	$C_{26}H_{36}B_2O_3$·HCl
6e	222–4	EtOAc	$C_{26}H_{36}N_2O_3$·HCl
6f	252–3	CH_2Cl_2–Et_2O	$C_{23}H_{26}N_2O_4S$·HCl
6g	228–30	CH_2Cl_2–Et_2O	$C_{24}H_{23}N_2O_4S$·HCl
6h	242–4	EtOAc	$C_{22}H_{23}N_2O_2F$·HCl
6i	250–2	EtOAc	$C_{26}H_{34}N_2O_3$·HCl

to a thermodynamically favored mix of isomers, equilibrium must strongly favor the *trans* relative stereochemistry.

Elaboration of the *cis* and *trans* diesters **16** and **13** to the indenopyridine ring systems proceeded in a straightforward manner, involving reduction to the diols, conversion to the bis-mesylates, and double displacement with benzylamine to afford the *cis*- and *trans*-*N*-benzylhexahydroindeno[2,1-*c*]pyridines in 62 and 60% overall yields, respectively. Catalytic debenzylation of the hydrochloride salts produced the secondary amines in nearly quantitative yields. Alkylation of the amines with the appropriate alkyl bromides then provided the target compounds (Scheme 3).

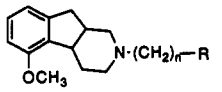
NMR Structural Assignment of *Cis* and *Trans* Ring Fusions. The *cis*- and *trans*-2-propyl-5-methoxy-2,3,4,-4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine-1,3-diones (**14a** and **15a**) were used for assignment of the ring fusion stereochemistry of final products reported in this study. Using standard decoupling experiments, the two bridgehead methines for **14a** were assigned (4a-methine at δ 3.71 and 9a-methine at δ 3.42) (see Figure 2). A moderate NOE enhancement was observed between the two methine resonances, suggesting a *cis* ring juncture. Similarly, the two bridgehead methines for **15a** were assigned (4a-methine at δ 3.33 and 9a-methine at δ 2.81). Whereas no significant NOE enhancement was observed between these two resonances, a small NOE was observed between the 4a-methine and one of the benzylic methylene protons at C-9, suggesting a 1,3 diaxial interaction supportive of the *trans* ring fusion assignment.

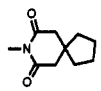
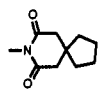
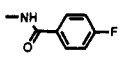
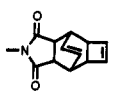
Biological. Competition against [^{3}H]Serotonin and [^{3}H]Ketanserin. Compounds were evaluated for their affinity to 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 binding sites. The results are summarized in Table 2. *Trans*-fused isomers invariably showed significantly higher affinity for the 5-HT_{1A} binding site than the respective *cis*-fused analogs, as well as excellent selectivity for the 5-HT_{1A} site vs the 5-HT_{1B} site. Although the *N*-propyl analog **6a** showed moderate affinity and good selectivity for the 5-HT_{1A} site, inclusion of various alkylene imide side chains resulted in significant increases in affinity for the 5-HT_{1A} site. Affinity for the 5-HT_2 binding site was significant for a number of the alkylene imide containing compounds, with the stereochemistry of the ring fusion not being a particularly important determinant.

Conclusion

A series of *cis*- and *trans*-fused hexahydroindenopyridines were prepared and evaluated as selective ligands for the 5-HT_{1A} receptor binding site. The goal of this study was to design a rigid core structure which would mimic the requirements for interaction with the 5-HT_{1A} site proposed by Hibert and defined by the prototypical agonist 8-OH-DPAT (**1**). Modeling studies suggested that the *trans*-fused indenopyridine system met the minimum

Table 2. *In Vitro* Pharmacology[a]



	ring fusion	n	R	K_i (nM) (n) (lower, upper 95% confidence limit) 5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_2$
1				1.59 (9) (0.643, 3.93)	2570 (8) (1730, 3830)	>10000 (1)[b]
2				46.1 (4) (29.9, 71.1)	17,400 (4) (12200, 24700)	391 (1)
5a	*cis*	3	H	1410 (3) (572, 3460)	48500 (3) 48500 (3) (572, 3460)	965(3) 965 (3) (14800, 159000) (389, 2390)
6a	*trans*	3	H	76.2 (3) (29.7, 195)	5010 (3) (1480, 17000)	688 (3) (264, 1800)
5d	*cis*	3		692 (3) (476, 1010)	96400 (3) (90300, 103000)	17.4 (3) (9.88, 30.5)
6d	*trans*	3		51.2 (3) (16.9, 155)	7360 (3) (4620, 11700)	15.9 (3) (10.2, 24.6)
5e	*cis*	4		54.5 (3) (52.6, 56.4)	13600 (3) (6020, 30800)	35.9 (3) (18.7, 69.1)
6e	*trans*	4		1.65 (4) (1.03, 2.66)	800 (4) (292, 2200)	9.30 (4) (5.12, 28.9)
6f	*trans*	3		0.891 (3) (0.725, 1.09)	845 (3) (308, 2310)	3.00 (3) (1.64, 5.47)
6g	*trans*	4		1.98 (3) (1.09, 3.61)	325 (3) (246, 431)	33.4 (3) (24.0, 46.3)
6h	*trans*	2		0.588 (2) (0.558, 0.621)	888 (3) (714, 1100)	28.9 (3) (23.4, 35.7)
6i	*trans*	4		3.60 (4) (1.41, 9.14)	1310 (4) (793, 2180)	2.58 (3) (0.887, 7.60)

[a] Values represent the geometric mean. [b] Estimated value.

requirements of appropriate aromatic ring to basic nitrogen interatomic distance and spatial orientation of the basic nitrogen. Furthermore, the presence of an oxygen substituent at the 5-position of the indenopyridine nucleus as well as a site for attachment of appropriate side chain appendages offered two additional favorable sites for interaction with the 5-HT$_{1A}$ receptor. As predicted by the modeling studies, the *cis*- and *trans*-fused analogs from this series of indenopyridines show markedly different activities at the 5-HT$_{1A}$ binding site, with the *trans*-fused analogs showing significantly higher affinity. In agreement with Hibert's model, inclusion of appropriate side chains from the basic nitrogen offered an additional site of interaction with the 5-HT$_{1A}$ receptor, resulting in greatly enhanced affinity for this site. A final interesting observation derives from the high affinity of certain of these analogs for the 5-HT$_2$ binding site. We have previously[10,11] characterized the activity of compounds from this series as showing predominantly agonist activity at the 5-HT$_{1A}$ receptor. Their structures would suggest that these compounds should be antagonists for the 5-HT$_2$ receptor. It has been proposed that there exists an opposing role for for the 5-HT$_{1A}$ and 5-HT$_2$ receptors in biological systems.[12-15] Therefore, an agent which combines agonist activity at the 5HT$_{1A}$ site with antagonist activity at the 5-HT$_2$ site may exhibit a synergistic activity. Work is in progress to further elucidate this potential interaction.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. All spectral and analytical data were obtained through the Abbott analytical department. Analytical thin-layer chromatography was performed using 5-cm × 10-cm plates coated with a 0.25-mm thickness of silica gel containing F-254 indicator (E. Merck). Flash chromatography was performed with silica gel 60 (E. Merck 9285, 230–400 mesh).

Pharmacological Methods. Assays for the binding of [^{3}H]-5-HT to 5-HT$_1$ receptors followed methods previously described by Pedigo et al.[16] The component of binding which constituted the 5-HT$_{1A}$ receptor was identified by masking the 5-HT$_{1A}$ sites with 1 μM *S*-spiroxatrine.[17,18] Binding to the 5-HT$_2$ site was performed as previously descriibed.[19] The data were analyzed as previously reported[20] and represent the geometric mean.

3-(2-Bromo-5-methoxyphenyl)propanoic Acid (8). To a solution of 25.0 g of 3-(3-methoxyphenyl)propanoic acid (7, 139 mmol) in 350 mL CH_2Cl_2 at 0 °C was added 7.5 mL of bromine (139 mmol) over 30 min. After an additional 15 min, the reaction mixture was poured into H_2O and extracted with an additional 100-mL portion of CH_2Cl_2. The combined organic extracts were washed with H_2O (3×) and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting solid was triturated with hexane and filtered to yield 32.8 g (91%) of a

white solid: mp: 81–3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8 Hz, 1 H), 6.83 (d, J = 2.5 Hz, 1 H), 6.66 (dd, J = 2.5, 8 Hz, 1 H), 3.78 (s, 3 H), 3.03 (t, J = 8 Hz, 2 H), 2.71 (t, J = 8 Hz, 2H).

4-Bromo-7-methoxyindan-1-one (9). The acid 8 (30 g, 116 mmol) was added over 30 min to polyphosphoric acid (500 g) preheated to 60 °C. The reaction mixture was stirred at 60 °C for 1 h, and then the reaction was quenched on ice. The crude product was collected by filtration, dissolved in CH_2Cl_2 (200 mL), washed successively with H_2O, aqueous 5% $NaHCO_3$ solution, and saturated brine, and dried over $MgSO_4$. After evaporation of the solvent, the product was recrystallized from methanol to yield 18.5 g (66%) of light yellow needles: mp 130–3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 1 H), 6.63 (d, J = 8 Hz, 1 H), 3.95 (s, 3 H), 3.01 (m, 2 H), 2.72 (m, 2 H).

2-(Diethoxymethyl)-4-bromo-7-methoxyindan-1-one (10). Sixty-six milliliters (400 mmol) of triethyl orthoformate was cooled to −30 °C, and a solution of 60 mL of BF_3·Et_2O in 200 mL of CH_2Cl_2 was added over 15 min. The reaction mixture was warmed to 0 °C for 15 min and then cooled to −78 °C. To the reaction mixture was then added a solution of 48.22 g (200 mmol) of the ketone 9 in 200 mL CH_2Cl_2 followed by addition of 77.6 mL (445 mmol) of ethyldiisopropylamine over 15 min. The reaction mixture was warmed to −15 °C for 2 h, and then the reaction was quenched in 5% $NaHCO_3$ solution, extracting with two portions of CH_2Cl_2. The organic extracts were washed with ice-cold 5% H_2SO_4 and saturated brine and then dried over $MgSO_4$. The solvent was removed at reduced pressure, and the product was crystallized from hexane to yield 62.7 g (91%) of the title compound as an off-white solid: mp 77–9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 8 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H), 4.98 (d, J = 2 Hz, 1 H), 3.93 (s, 3 H), 3.55–3.80 (m, 3 H), 3.48 (m, 1 H), 3.27 (m, 1 H), 3.02 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.05 (t, J = 7 Hz, 3 H).

Ethyl (2-(diethoxymethyl)-4-bromo-7-methoxyindan-1-ylidene)acetate (11). Ethyl (trimethylsilyl)acetate (40.41 g, 252 mmol) was added to 300 mL of THF and cooled to −78 °C. To the reaction mixture was added 252 mL of a 1.0 M solution of lithium hexamethyldisilazide in THF. After 30 min, a solution of 61.8 g (256 mmol) of 10 in 250 mL of THF was added. The reaction mixture was stirred at −78 °C for 2.5 h and then warmed to 0 °C. The reaction was then immediately quenched in aqueous NH_4Cl and extracted with two portions of diethyl ether. The combined organic extracts were washed successively with water (2×) and saturated brine and then dried over $MgSO_4$. Solvent was removed at reduced pressure, and the product was dissolved in 500 mL of a 3:1 mixture of hexane and ethyl acetate. Silica gel (200 g) was added, and after several minutes, the mixture was filtered and the solvent removed. The product was then crystallized from hexane to yield 48.2 g (65%) of an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8 Hz, 1 H), 6.62 (d, J = 8 Hz, 1 H), 4.77 (d, J = 2 Hz, 1 H), 4.22 (q, J = 7 Hz, 2 H), 3.90 (s, 3 H), 3.65 (m, 4 H), 3.27 (t, J = 18 Hz, 1 H), 3.25 (m, 1 H), 2.90 (dd, J = 8, 18 Hz, 1 H), 1.35 (t, J = 7 Hz, 3 H), 1.27 (t, J = 7 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H).

***cis*-Ethyl 2-(Diethoxymethyl)-7-methoxyindan-1-acetate (12).** The unsaturated ester 11 (48.0 g, 116 mmol) was dissolved in 500 mL of ethanol; 17.5 g of NaOAc·3H_2O (129 mmol) and 9.6 g of 10% Pd/C was added, and the mixture was shaken on a Parr hydrogenation apparatus under 4 atm of H_2 pressure until the theoretical amount of hydrogen was consumed. The reaction mixture was filtered and the filtrate evaporated. The product was dissolved in ether, extracted with 5% $NaHCO_3$ solution (2×) and saturated brine, and then dried over $MgSO_4$. The solvent was removed to yield 35.7 g (91%) of a colorless oil which was homogeneous by TLC (85:15 hexane–ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 8 Hz, 1 H), 6.80 (d, J = 7 Hz, 1 H), 6.65 (d, J = 7 Hz, 1 H), 4.74 (d, J = 5 Hz, 1 H), 4.04 (q, J = 7 Hz, 2 H), 3.79 (s, 3 H), 3.45–3.75 (m, 6 H), 2.86 (m, 2 H), 2.70 (dd, J = 7, 14 Hz, 1 H), 2.49 (dd, J = 5, 14 Hz, 1 H), 1.20 (m, 9 H).

***cis*-Ethyl 2-Carbethoxy-7-methoxyindan-1-acetate (16).** A solution of 80 mL of CH_2Cl_2 and 1 drop of 96% H_2SO_4 was prepared and cooled to 0 °C. The ester acetal 12 (3.36 g, 10 mmol) was dissolved in 20 mL of CH_2Cl_2 and added to the above solution. A solution of 2.46 g of *m*-chloroperbenzoic acid in 50 mL of CH_2Cl_2 was then added. After 1 h at 0 °C, the reaction was quenched in 5% $NaHCO_3$ solution and extracted with two additional portions of CH_2Cl_2. The combined organic extracts were washed with 10% $Na_2S_2O_3$ solution and 5% $NaHCO_3$ solution and then dried over $MgSO_4$. The solvent was removed to yield 2.87 g (94%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 7 Hz, 1 H), 6.81 (d, J = 7 Hz, 1 H), 6.68 (d, J = 7 Hz, 1 H), 4.1 (m, 5 H), 3.79 (s, 3 H), 3.4 (m, 2 H), 3.02 (dd, J = 8, 15 Hz, 1 H), 2.70 (dd, J = 5, 16 Hz, 1 H), 2.61 (dd, J = 8, 16 Hz, 1 H), 1.29 (t, J = 7 Hz, 3 H), 1.24 (t, J = 7 Hz, 3 H).

***trans*-Ethyl 2-Carbethoxy-7-methoxyindan-1-acetate (13).** The ester acetal 12 (27.0 g, 80.3 mmol) was dissolved in 300 mL of THF, and 60 mL of 6.0 M aqueous HCl was added. The reaction mixture was stirred at 25 °C for 2.5 h and then quenched in H_2O. The product was extracted with three portions of diethyl ether, and the combined organic extracts were washed successively with 5% $NaHCO_3$ solution and saturated brine and then dried over $MgSO_4$. After evaporation under reduced pressure, the impure aldehyde was dissolved in 250 mL of ethanol and a solution of 22 g (130 mmol) $AgNO_3$ in 50 mL of H_2O was added. To this solution was then added a solution of 18 g (320 mmol) of KOH in 250 mL of H_2O over 15 min. After an additional 30 min, the reaction mixture was filtered, washing several times with H_2O. The filtrate was extracted with one portion of diethyl ether (discarded), and the aqueous solution was acidified to pH 1 with 6 N HCl. The mixture was extracted with CH_2Cl_2 (3×), and the combined organic extracts were washed with saturated brine, dried over $MgSO_4$, and evaporated to dryness at reduced pressure. The crude product was dissolved in 500 mL of ethanol, and 5 g 96% H_2SO_4 was added. The reaction mixture was heated to reflux for 2 h and evaporated to approximately $^1/_2$ volume, and the reaction was quenched in H_2O. The product was extracted with diethyl ether (2×), and the combined organic extracts were washed with 5% $NaHCO_3$ solution and saturated brine, dried over $MgSO_4$, and evaporated to dryness at reduced pressure to yield 12.15 g of a light yellow oil. The product was purified by flash chromatography eluting with 85:15 hexane–ethyl acetate to yield 9.93 g (40%) of the diester as a colorless oil, which was calculated to be >90% trans isomer by NMR: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 7 Hz, 1 H), 6.80 (d, J = 7 Hz, 1 H), 6.68 (d, J = 7 Hz, 1 H), 4.17 (q, J = 7 Hz, 2 H), 4.13 (q, J = 7 Hz, 2 H), 4.06 (m, 1 H), 3.80 (s, 3 H), 3.10–3.35 (m, 3 H), 3.07 (dd, J = 4, 15 Hz, 1 H), 2.52 (dd, J = 9, 15 Hz, 1 H), 1.27 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H).

***cis*- and *trans*-2-Propyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine-1,3-dione (14a and 15a).** Propylamine (0.99 mL, 12 mmol) was dissolved in toluene (20 mL). Trimethylaluminum in toluene (6.0 mL of a 2.0 M solution, 12 mmol) was added to the amine solution. After 1 h, the diester 13 (1.16 g, 3.8 mmol) in 5 mL of toluene was added, and the reaction mixture was heated under reflux for 2.5 h. The reaction was cooled to 0 °C and quenched with 2.3 mL of H_2O. The reaction mixture was then added to 100 mL of 5% aqueous HCl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The resulting intermediate diamide product was suspended in 75 mL of xylene, and 0.75 g of pTsOH (3.94 mmol) was added. The reaction mixture was refluxed for 48 h, and the solvent was then evaporated. The residue was dissolved in EtOAc (150 mL) and filtered through silica gel, washing with 2 × 100 mL of EtOAc. The solvent was evaporated and the product chromatographed over silica eluting with 80:20 hexane–EtOAc to yield 0.205 g (20%) of the faster moving *trans* product (15a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 7 Hz, 1H), 6.93 (d, J = 7 Hz, 1H), 6.72 (d, J = 7 Hz, 1H), 3.82 (s, 3H), 3.68–3.90 (m, 3H), 3.33 (m, 1H, 4a methine), 3.16 (dd, J = 7, 16 Hz, 1H, C-9 methylene), 3.05 (dd, J = 11, 16 Hz, 1H, C-9 methylene), 2.81 (m, 1H, 9a methine), 2.73 (dd, J = 13, 18 Hz, 1H), 1.60 (m, 2H), 0.91 (t, J = 7 Hz, 3H). Further elution yielded 0.622 g (60%) of the slower moving *cis* product (14a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 7 Hz, 1H), 6.87 (d, J = 7 Hz, 1H), 6.71 (d, J = 7 Hz, 1H), 3.82 (s, 3H), 3.72 (m, 2H), 3.70 (m, 1H, 4a methine), 3.44 (dd, J = 9, 19 Hz, 1H, C-9 methylene), 3.42 (m, 1H, 9a methine), 3.23 (dd, J = 11, 19 Hz, C-9 methylene, 1H), 3.01 (dd, J = 6, 16 Hz, 1H, C-4 methylene), 2.74 (dd, J = 10, 16 Hz, 1H, C-4 methylene), 1.50 (m, 2H), 0.82 (t, J = 7 Hz, 3H).

***cis*-5-Methoxy-2-propyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (5a).** The amide (**14a**, 0.60 g, 2.20 mmol) was dissolved in THF (20 mL) and treated with 1.0 M BH_3·THF (10 mL). After 4 h at reflux, the reaction was quenched by the additon of methanol (5 mL) and evaporated to dryness. The residue was dissolved in methanol (10 mL) and isopropyl alcohol saturated with anhydrous HCl (5 mL), and the resulting solution was refluxed for 2 h. Solvent was evaporated, and the resulting product was recrystallized from 1:4 ethanol–ether to yield 0.34 g (55%) of a white solid: mp 175–7 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.15 (t, J = 7 Hz, 1H), 6.84 (d, J = 7 Hz, 1H), 6.78 (d, J = 7 Hz, 1H), 3.78 (s, 3H), 1.95–3.55 (m, 10H), 1.20 (m, 4H), 0.90 (t, 3H). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***trans*-5-Methoxy-2-propyl-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (6a).** The amide (**15a**, 1.20 g, 4.40 mmol) was dissolved in THF (40 mL) and treated with 1.0 M BH_3·THF (20 mL). After 4 h at reflux, the reaction was quenched by the addition of methanol (10 mL) and evaporated to dryness. The residue was dissolved in methanol (20 mL) and isopropyl alcohol saturated with anhydrous HCl (10 mL), and the resulting solution was refluxed for 2 h. Solvent was evaporated, and the resulting product was recrystallized from ethanol and ether to yield 0.95 g (77%) of a white solid: mp >260 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.14 (t, J = 7 Hz, 1H), 6.87 (d, J = 7 Hz, 1H), 6.81 (d, J = 7 Hz, 1H), 3.75 (s, 3H), 1.85–3.70 (m, 12H), 1.73 (m, 2H), 0.92 (t, 3H). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*- and *trans*-2-Benzyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine-1,3-dione (14b and 15b).** Benzylamine (4.82 g, 45 mmol) was dissolved in toluene (60 mL). Trimethylaluminum in toluene (22.5 mL of a 2.0 M solution, 45 mmol) was added to the amine solution. After 1 h, the diester **13** (4.59 g, 15 mmol) in 25 mL of toluene was added, and the reaction mixture was refluxed for 2.5 h. The reaction was cooled to 0 °C and quenched with 2.3 mL of H_2O. The reaction mixture was then added to 100 mL of 5% aqueous HCl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The resulting intermediate diamide product was suspended in 300 mL of xylene, and 3.14 g of pTsOH·H_2O (49.5 mmol) was added. The reaction mixture was refluxed for 72 h, and the solvent was then evaporated. The residue was dissolved in EtOAc (150 mL) and filtered through silica gel, washing with 2 × 100 mL of EtOAc. The solvent was evaporated and the product chromatographed over silica eluting with 80:20 hexane–EtOAc to yield 0.380 g (8%) of the faster moving *trans* product (**15b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.4 (m, 5H), 7.21 (t, J = 7 Hz, 1H), 6.92 (d, J = 7 Hz, 1H), 6.72 (d, J = 7 Hz, 1H), 4.97 (dd, J = 14,25 Hz, 2H), 3.80 (s, 3H), 3.75 (dd, J = 4, 17 Hz, 1H, C-4 methylene), 3.37 (ddd, J = 4,13,17 Hz, 1H, 9a methine), 3.16 (dd, J = 7, 15 Hz, 1H, C-9 methylene), 3.05 (dd, J = 11,15 Hz, 1H, C-9 methylene), 2.81 (ddd, J = 7,11,13 Hz, 1H, 4a methine), 2.77 (dd, J = 13, 17 Hz, 1H, C-4 methylene). Further elution yielded 3.75 g (78%) of the slower moving *cis* product (**14b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 6H), 6.84 (d, J = 7 Hz, 1H), 6.71 (d, J = 7 Hz, 1H), 4.95 (s, 2H), 3.81 (s, 3H), 3.72 (ddd, J = 6, 8, 13 Hz, 1H, 4a methine), 3.42 (m, 2H, 9a methine plus C-9 methylene), 3.24 (dd, J = 7, 15 Hz, 1H, C-9 methylene), 3.03 (dd, J = 6, 16 Hz, 1H, C-4 methylene), 2.82 (dd, J = 9, 16 Hz, 1H, C-4 methylene).

***cis*-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-7-methoxyindan (18).** The *cis* diester **16** (9.05 g, 29.5 mmol) was dissolved in 50 mL of THF and added over 15 min to a suspension of 4.56 g of $LiAlH_4$ (120 mmol) in 150 mL of THF. After 2 h, the reaction was quenched by sequential addition of 4.5 mL of H_2O, 4.5 mL of 15% NaOH, and 13.5 mL of H_2O. The reaction mixture was filtered through Celite, washing the salts with several portions of hot THF, and the combined filtrates were evaporated to dryness. The product was purified by chromatography over silica gel, eluting with ethyl acetate to yield 4.98 g (76%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 7 Hz, 1 H), 6.88 (d, J = 7 Hz, 1 H), 6.71 (d, J = 7 Hz, 1 H), 3.79–3.96 (m, 2 H), 3.86 (s, 3 H), 3.66 (m, 1 H), 3.53 (m, 2 H), 2.64–2.95 (m, 3 H), 1.80–2.20 (br s, 2 H), 1.96 (m, 1 H), 1.40 (m, 1 H).

***trans*-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-7-methoxyindan (17).** The *trans* diester **13** (6.75 g, 22.0 mmol) was treated in an analogous manner as described for **16** to yield 3.96 g (81%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7 Hz, 1 H), 6.82 (d, J = 7 Hz, 1 H), 6.68 (d, J = 7 Hz, 1 H), 3.83 (s, 3 H), 3.72 (m, 2 H), 3.52 (m, 2 H), 3.34 (dd, J = 1.5, 8, 1 H), 3.20 (dd, J = 8, 16, 1 H), 2.59 (dd, J = 2, 16, 1 H), 2.47 (m, 1 H), 1.95–2.20 (br s, 2 H), 1.99 (m, 1 H), 1.74 (m, 1 H).

***cis*-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-7-methoxyindanbismesylate (20).** The diol **18** (1.28 g, 5.76 mmol) was dissolved in 50 mL of CH_2Cl_2 and 4.09 mL of triethylamine. The reaction mixture was cooled to 0 °C, and 1.38 mL (17.3 mmol) of methanesulfonyl chloride was added. After 1 h at 0 °C, the reaction was poured into 5% $NaHCO_3$ solution and extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with saturated brine and dried over $MgSO_4$, and the solvent was removed to yield 2.10 g (96%) of the intermediate bismesylate **20**, which was used in the next step without purification.

***trans*-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-7-methoxyindanbismesylate (19).** The diol **17** (0.85 g, 3.82 mmol) was dissolved in CH_2Cl_2 (50 mL) and triethylamine (2.70 mL). The reaction mixture was cooled to 0 °C, and methanesulfonyl chloride (0.91 mL, 11.4 mmol) was added. After 1 h at 0 °C, the reaction mixture was poured into 5% $NaHCO_3$ solution and extracted with CH_2Cl_2 (2×). The combined organic extracts were washed with saturated brine and dried over $MgSO_4$, and the solvent was removed to yield 1.35 g (94%) of the intermediate bismesylate **19**, which was used in the next step without purification.

***cis*-2-Benzyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (5b). Method A.** The imide **14b** (2.35 g, 7.32 mmol) was dissolved in THF (100 mL), and $LiAlH_4$ (2.25 g, 59 mmol) was added. The reaction mixture was stirred at 25 °C for 3 h, the reaction was quenched (Fieser workup), and the reaction mixture was filtered through Celite and evaporated to dryness. The resulting product was purified by flash chromatography eluting with 8:2 hexane–diethyl ether to yield 1.01 g (47%) of a white solid: mp 76–8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5 H), 7.11 (t, J = 7 Hz, 1 H), 6.86 (d, J = 7 Hz, 1 H), 6.68 (d, J = 7 Hz, 1 H), 3.80 (s, 3 H), 3.54 (d, J = 13 Hz, 1 H), 3.45 (d, J = 13 Hz, 1 H), 3.12 (m, 1 H), 3.05 (dd, J = 9, 15 Hz, 1 H), 2.71 (m, 2 H), 2.58 (m, 1 H), 2.47 (m, 1 H), 2.35 (dd, J = 5, 12 Hz, 1 H), 2.10 (m, 1 H), 1.97 (m, 1 H), 1.70 (m, 1 H). The resulting solid was dissolved in diethyl ether and treated with an excess of ethereal HCl. Solvent was removed and the salt was recrystallized from ethyl acetate–diethyl ether: mp 222–3 °C; ^{1}H NMR (300 MHz, d_6 DMSO) δ 7.70 (m, 1H), 7.58 (m, 1H), 7.40 (m, 3H), 7.16 (m, 1H), 6.85 (m 2H), 4.18–4.44 (m, 3H), 3.78 (s, 3H), 2.00–3.55 (m, 8H), 1.70 (m, 1H). Anal. ($C_{20}H_{23}NO$·HCl) C, H, N.

***cis*-2-Benzyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (5b). Method B.** The bismesylate **20** (2.47 g, 6.52 mmol) was dissolved in 5 mL of benzylamine, and the solution was heated to 75 °C for 2 h. The reaction was quenched in 2% aqueous NaOH solution and extracted with diethyl ether (3×). The combined organic extracts were washed with saturated brine, dried over K_2CO_3, evaporated to dryness, and then heated to 60 °C under high vacuum to remove excess benzylamine. The resulting product was purified by flash chromatography eluting with 8:2 hexane–diethyl ether to yield 1.56 g (82%) of a white solid: mp 76–8 °C. The ^{1}H NMR spectrum was identical to that of material from method A. The resulting solid was dissolved in diethyl ether and treated with an excess of ethereal HCl. Solvent was removed, and the salt was recrystallized from ethyl acetate–diethyl ether: mp 222–3 °C. The ^{1}H NMR spectrum was identical to that of material from method A. Anal. ($C_{20}H_{23}NO$·HCl) C, H, N.

***trans*-2-Benzyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (6b). Method A.** The imide **15b** (1.00 g, 3.11 mmol) was treated in an analogous manner as described above for the *cis* imide **14b** to yield 0.81 g of **6b** as a white solid: mp 104–6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H), 7.10 (t, J = 7 Hz, 1 H), 6.83 (d, J = 7 Hz, 1 H), 6.68 (d, J = 7 Hz, 1 H), 3.78 (s, 3 H), 3.67 (d, J = 13 Hz, 1 H), 3.56 (d, J = 13 Hz, 1 H), 3.09 (m, 2 H), 2.74 (m, 1 H), 2.35–2.60 (m, 3 H), 2.00–2.05 (m, 3 H), 1.75 (m, 1 H). The product was converted to its HCl salt as described above to yield 0.865 g of a white solid: mp >260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62 (m, 2 H), 7.48 (m, 3 H), 7.13 (t, 1 H), 6.84 (d, 1 H), 6.80 (d, 1 H), 4.34 (dd, 2 H),

3.73 (s, 3 H), 2.38–3.55 (m, 8 H), 2.28 (m, 1 H), 1.95 (m, 1 H). Anal. ($C_{20}H_{23}NO$·HCl) C, H, N.

***trans*-2-Benzyl-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (6b). Method B.** The bismesylate **19** (2.50 g, 6.60 mmol) was treated in an analogous manner as described above for the *cis* bismesylate to yield the free base of **6b** (1.62 g, 84%) as a white solid: mp 104–6 °C. The ^{1}H NMR spectrum was identical to that of material from method A. The resulting solid was dissolved in diethyl ether and treated with an excess of ethereal HCl. Solvent was removed, and the salt was recrystallized from ethanol/diethyl ether to yield 1.61 g of a white solid: mp >260 °C. The ^{1}H NMR spectrum was identical to that of material from method A. Anal. ($C_{20}H_{23}$-NO·HCl) C, H, N.

***cis*-5-Methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]-pyridine Hydrochloride (5c).** The amine **5b** (1.80 g) was combined with 0.90 g of 20% Pd/C in 100 mL of methanol and hydrogenated at 4 atm for 4 h. The reaction mixture was filtered and evaporated to yield 1.08 g of a white solid: mp 140–3 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.15 (t, 1H), 6.84 (d, 1H), 6.80 (d, 1H), 3.77 (s, 3H), 2.78–3.30 (m, 7H), 2.60 (m, 1H), 2.02 (m, 1H), 1.70 (m, 1H). Anal. ($C_{13}H_{17}NO$·HCl) C, H, N.

***trans*-5-Methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (6c).** The amine **6b** (1.40 g) was combined with 0.70 g of 20% Pd/C in 100 mL of methanol and hydrogenated at 4 atm for 4 h. The reaction was mixture was filtered and evaporated to yield 0.88 g of a white solid: mp >260 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.13 (t, 1H), 6.87 (d, 1H), 6.79 (d, 1H), 3.74 (s, 3H), 2.55–3.55 (m, 6H), 1.60–2.10 (m, 4H). Anal. ($C_{13}H_{17}NO$·HCl) C, H, N.

General Procedure for Alkylation of *cis*- and *trans*-5-Methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride. The amine hydrochloride (2.0 mmol) and the appropriate bromoalkane (2.4 mmol) were combined in 5 mL of acetonitrile and 1 mL of ethyldiisopropylamine. The reaction mixture was stirred at 80 °C until TLC indicated reaction was complete (24–48 h). The reaction was quenched in cold dilute NaOH solution and extracted with several portions EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The resulting oil was purified by flash chromatography, eluting with hexane–diethyl ether, and the purified amine product was converted to its hydrochloride salt.

***cis*-2-(3-(3,3-Tetramethyleneglutarimido)propyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (5d):** recrystallized from CH_2Cl_2–diethyl ether; mp 170–2 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.15 (t, 1H), 6.83 (d, 1H), 6.78 (d, 1H), 3.78 (s, 3H), 2.62 (s, 4H), 1.80–3.70 (m, 16H), 1.62 (m, 4H), 1.40 (m, 4H). Anal. ($C_{25}H_{34}N_2O_3$·HCl) C, H, N.

***trans*-2-(3-(3,3-Tetramethyleneglutarimido)propyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (6d):** recrystallized from CH_2Cl_2–diethyl ether; mp 221–5 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.13 (t, 1H), 6.88 (d, 1H), 6.80 (d, 1H), 3.77 (s, 3H), 3.70 (t, 2H), 3.52 (m, 1H), 2.30–3.25 (m, 7H), 2.62 (s, 4H), 2.20 (m, 2H), 1.90 (m, 4H), 1.55 (m, 4H), 1.43 (m, 4H). Anal. ($C_{25}H_{34}N_2O_3$·HCl) C, H, N.

***cis*-2-(4-(3,3-Tetramethyleneglutarimido)butyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride monohydrate (5e):** lyophilized from water, amorphous powder; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.17 (t, 1H), 6.87 (d, 1H), 6.78 (d, 1H), 3.78 (s, 3H), 2.62 (s, 4H), 1.90–3.70 (m, 16H), 1.65 (m, 6H), 1.40 (m, 4H). Anal. ($C_{26}H_{36}N_2O_3$·HCl·H_2O) C, H, N.

***trans*-2-(4-(3,3-Tetramethyleneglutarimido)butyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (6e):** from ethyl acetate; mp 222–4 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.13 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 3.74 (s, 3H), 3.66 (m, 2H), 2.62 (s, 4H), 2.10–3.60 (m, 12H), 1.62 (m, 6H), 1.40 (m, 6H). Anal. ($C_{26}H_{36}N_2O_3$·HCl) C, H, N.

***trans*-2-(3-(1,3,3-Trioxo-1,2-benzisothiazol-2-yl)propyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (6f):** recrystallized from CH_2Cl_2; mp 252–3 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.35 (d, 1H), 8.1 (m, 3H), 7.13 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 3.86 (t, 2H), 3.73 (s, 3H), 3.5–3.8 (m, 2H), 2.95–3.45 (m, 4H), 2.4–2.9 (m, 4H), 2.1–2.3 (m, 4H), 1.8–2.0 (m, 2H). Anal. ($C_{23}H_{28}N_2O_4S$·HCl) C, H, N.

***trans*-2-(4-(1,3,3-Trioxo-1,2-benzisothiazol-2-yl)butyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride (6g):** recrystallized from CH_2Cl_2; mp 228–30 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.32 (d, 1H), 8.1 (m, 3H), 7.13 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 3.86 (t, 2H), 3.73 (s, 3H), 3.5–3.8 (m, 2H), 2.95–3.45 (m, 4H), 2.4–2.9 (m, 4H), 2.1–2.3 (m, 4H), 1.8–2.0 (m, 4H). Anal. ($C_{24}H_{28}N_2O_4S$·HCl) C, H, N.

***trans*-2-(2-(4-Fluorobenzamido)ethyl)-5-methoxy-2,3,4,-4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (6h).** The amine hydrochloride **6c** (0.311 g, 1.30 mmol) was treated with *N*-(2-bromoethyl)phthalimide as described in the General Procedure. The resultant crude product was dissolved in 20 mL of EtOH, 0.083 mL of hydrazine hydrate (2.6 mmol) was added, and the reaction mixture was refluxed for 18 h, cooled to 0 °C, and filtered to remove phthalyl hydrazide. Solvent was evaporated, and the crude amine was disslolved in 20 mL of CH_2Cl_2 and 0.40 mL of triethylamine. The reaction mixture was cooled to −20 °C, and 0.18 mL of 4-fluorobenzoyl chloride was added. After 30 min, the reaction was quenched in 5% $NaHCO_3$ and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. After purification by flash chromatography, the product was converted to the hydrochloride salt and recrystallized from EtOAc to yield 0.170 g: mp 242–4 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.98 (m, 1H), 8.02 (dd, 2H), 7.32 (dd, 2H), 7.15 (t, 1H), 6.87 (d, 1H), 6.81 (d, 1H), 3.78 (s, 3H), 3.6–3.9 (m, 3H), 3.05–3.4 (m, 4H), 2.83 (m, 2H), 2.45–2.75 (m, 2H), 2.3 (m, 2H), 1.9–2.1 (m, 2H). Anal. ($C_{22}H_{25}N_2O_2F$·HCl) C, H, N.

***trans*-2-(4-(3a,4,4a,6a,7,7a-Hexahydro-1,3-dioxo-4,7-etheno-1*H*-cyclobut[*f*]isoindol-2-yl)butyl)-5-methoxy-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*c*]pyridine hydrochloride hemihydrate (6i):** from EtOAc; mp 250–2 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.13 (t, 1H), 6.87 (d, 1H), 6.80 (d, 1H), 5.89 (m, 2H), 5.87 (dd, 2H), 3.74 (s, 3H), 3.45–3.70 (m, 2H), 2.95–3.25 (m, 8H), 2.90 (br s, 2H), 2.6–2.8 (m, 6H), 1.80–2.30 (m, 2H), 1.53 (m, 2H), 1.45 (m, 2H). Anal. ($C_{29}H_{34}N_2O_3$·HCl·$^1/_2H_2O$) C, H, N.

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