Synthesis and Evaluation of 6,11-Ethanohexahydrobenzo[*b*]quinolizidines: A New Class of Noncompetitive *N*-Methyl-D-aspartate Antagonists

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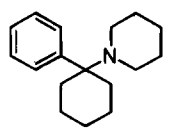
The synthesis and in vitro and in vivo evaluation of 12,13-cycloalkyl-6,11-ethanobenzo[*b*]-quinolizidines, a new class of noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists acting at the PCP site on the NMDA receptor complex, is reported. Structure–activity relationship studies led to the identification of 10-hydroxy-(6α,11α,11aβ,12*R**,13*S**)-1,3,4,6,11,11a,13,14,-15,16-decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline hydrobromide (**5h**) and 9-hydroxy-(6α,11α,11aβ,12*R**,13*S**)-1,3,4,6,11,11a,13,14,15,16-decahydro-12*H*-6,11-[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline hydrobromide (**5i**), the most potent members of this series with K_i values of 2.3 ± 0.2 and 2.3 ± 0.5 nM, respectively. Molecular modeling studies revealed that this series of compounds occupies both lipophilic sites of the Andrews PCP receptor model and shares structural features which are common to other classes of known noncompetitive NMDA antagonists such as MK-801.

Introduction

Overstimulation of excitatory amino acid (EAA) receptors by L-glutamate, an excitatory amino acid, is believed to be the major underlying factor in mediating neuronal cell death that follows cerebral stroke or ischemia.[1] Also, there is enough circumstantial evidence that implicate these EAA receptors in the neuropathology of other chronic neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).[2] Identification of selective and potent antagonists of these receptors might prove useful in the treatment of these disease states.[3] The EAA receptors are of two general types, ionotropic and metabotropic. Due to the pioneering efforts of molecular biologists, at least three types of ionotropic EAA receptors have been identified.[4] These receptors are classified on the basis of the selective agonists *N*-methyl-D-aspartate (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA), and kainic acid (KA) that stimulate them.

Of the various EAA receptors identified, the NMDA receptor ionphore complex is the most extensively studied and best characterized. More than a decade of intense investigations of the ligand sites which control this voltage-sensitive, ligand-gated ionophore has led to the identification of at least seven modulatory sites.[4a,5] A site located within the NMDA receptor is labeled by [^{3}H]TCP and is the binding site for dissociative anesthetics PCP (**1**), ketamine (**2**), and the noncompetitive NMDA antagonist MK-801 (**3**).[6,7] These compounds inhibit Ca^{2+} influx through the NMDA receptor–ion channel complex and have been shown to be neuroprotective in various animal models of focal ischemia.[8] However, a common liability of such compounds has been their undesired psychotomimetic and autonomical side effects.[9] Clearly, compounds that are devoid of such effects would be of improved therapeutic potential. Recently, we reported the identification and characterization of a unique class of NMDA antagonists based on the 6,11-ethanobenzo[*b*]quinolizinium cation template.[10] These compounds (**4a**,**b**) were highly selective for binding to the PCP site on the NMDA receptor complex and were neuroprotective in experimental models of cerebral ischemia. More importantly, they did not produce PCP-like sterotypy or ataxia in conscious rats at antiischemic and higher doses. In order to further characterize compounds that act at the PCP site and further define their role in neurodegenerative diseases, we initiated a program to identify other classes of compounds that bind to the PCP site of the NMDA receptor ionophore complex. Herein, we report that 6,-11-ethanohexahydrobenzo[*b*]quinolizidines **5** are highly potent, noncompetitive NMDA antagonists and bind to the PCP site on the NMDA receptor complex.



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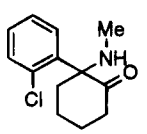

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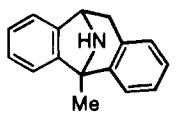

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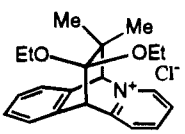
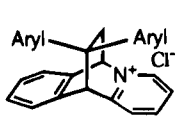
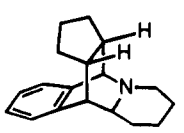


4a



4b



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Chemistry

The lead compound in this series, **5a** (WIN 62407), was identified through substructure search of our compound library based on the structural features common to compounds acting at the PCP site of the

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Scheme 1

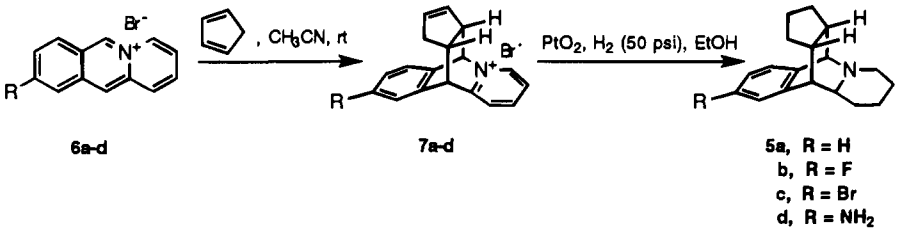
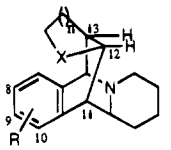


Table 1. [^{3}H]TCP Binding Affinity of Hexahydrobenzo[*b*]quinolizidines **5a–k** and **8**



compd	R	X	*n*	formula[b]	mp (°C)	[^{3}H]TCP binding affinity[a] K_i (nM) ± SEM
5a	H	CH_2	1	$C_{18}H_{23}N$·HBr	273–275	15 ± 2
5b	9-F	CH_2	1	$C_{18}H_{22}FN$·$C_4H_4O_4$	272–274	20 ± 1
5c	9-Br	CH_2	1	$C_{18}H_{22}BrN$·HBr	233–243	41 ± 6
5d	9-NH_2	CH_2	1	$C_{18}H_{24}N_2$	116–117	12 ± 1
5e	H	12,13-des cyclopentyl		$C_{15}H_{19}N$	96–97	240
5f	H	CH_2	2	$C_{19}H_{25}N$	113–116	134
5g	H	O	1	$C_{17}H_{21}NO$·HBr	270–273	600
5h	10-OH	CH_2	1	$C_{18}H_{23}NO$·HBr	amorph powder	2.3 ± 0.2
5i	9-OH	CH_2	1	$C_{18}H_{23}NO$·HBr	289–292	2.3 ± 0.5
5j	8-OH	CH_2	1	$C_{18}H_{23}NO$·HBr	>300	23 ± 8
5k	11-Me, 12,13-*endo*-cyclopentyl			$C_{19}H_{25}N$	oil	46 ± 6
8		H		$C_{13}H_{17}N$		10 000
3		MK-801				2.2

[a] The binding affinity was determined as described in ref 17. [b] All compounds were characterized by ^{1}H NMR and provided elemental analysis within ±0.4% of the theoretical value, unless otherwise noted in the Experimental Section.

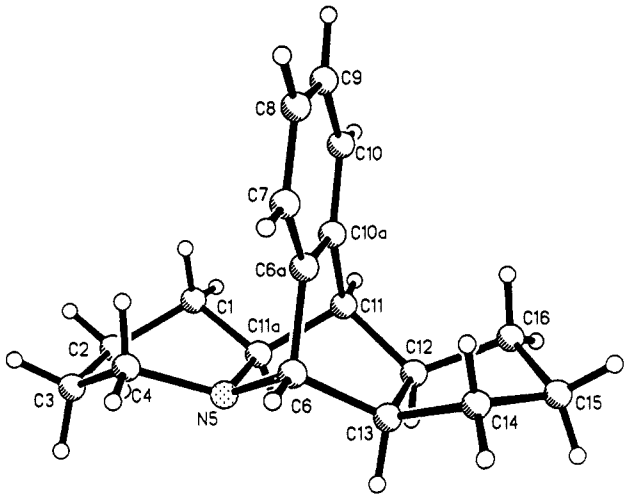


Figure 1. ORTEP drawing and atomic numbering scheme for **5a**.

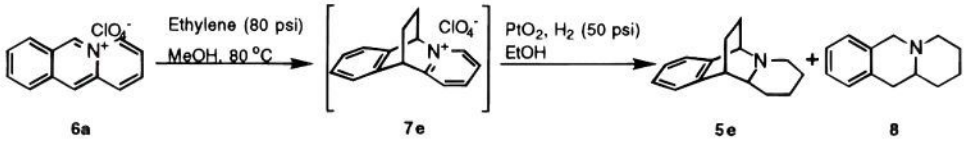
NMDA–ion channel receptor complex. Compound **5a** has a K_i = 12 nM for displacing [^{3}H]TCP from rat brain membranes and was prepared from the known pyridinium bromide **7a**[11] by hydrogenation in the presence of PtO_2 (Scheme 1). The structural identity of this compound was established unequivocally by single-crystal X-ray analysis. As shown in Figure 1, the cyclopentyl portion of **5a** is syn to the benzo ring and the piperidine ring is in a boat conformation.

In order to better understand the structural requirements of this class of compounds and improve the potency for binding to the [^{3}H]TCP site, a series of analogs (Table 1) were prepared. The synthesis of compounds **5b–k** is shown in Schemes 1–6. The analogs **5b–d** with halo or amino substituents in the benzo ring of **5a** were prepared from the readily available[12] benzo[*b*]quinolizinium cations **6b–d**. Thus, inverse electron demand Diels–Alder reaction[11] of **6** with cyclopentadiene followed by hydrogenation (PtO_2/H_2) of the intermediate adducts **7b–d** led to the desired quinolizidines **5b–d**, which were isolated as either their acid addition salt or free base (Scheme 1).

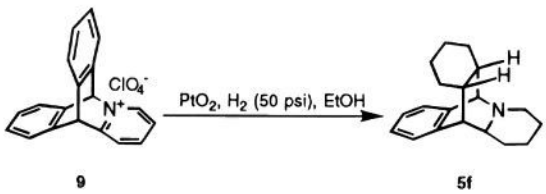
Synthesis of the descyclopentyl compound **5e** proved to be very challenging. Although the Diels–Alder reaction between ethylene and the quinolizinium cation **6a** was evident from ^{1}H NMR, the intermediate adduct **7e** was very unstable. To overcome this problem, compound **7e** was hydrogenated without isolation to give **5e** in low yield after tedious chromatographic purification. A major byproduct in this reaction was the known[13] benzo[*b*]quinolizine **8**, which must arise from hydrogenation of **2** (Scheme 2).

Interestingly, hydrogenation of **9**[14] led to the overreduced adduct **5f** as the only isolable product (Scheme 3). The tetrahydrofuryl analog **5g** was prepared in a manner similar to that of **5a** by using dihydrofuran as the dienophile in the initial Diels–Alder reaction (Scheme 4). The hydroxy analogs **5h–j** were prepared from the appropriate methoxybenzo[*b*]quinolizinium cations **6h–j**[15] (Scheme 5). Demethylation[16] of the aromatic methyl ethers in adducts **7h–j** using 48% HBr led to the desired phenols **5h–j**. The 11-methyl analog **5k** was prepared as shown in Scheme 6. Thus treatment of 6-methylbenzo[*b*]quinolizinium perchlorate (**10**)[15] with cyclopentadiene, followed by hydrogenation of the intermediate adduct **11**, gave the quinolizidine **5k** in moderate yield.

Scheme 2



Scheme 3



Biological Test Results and Discussion

The ability of 6,11-ethanohexahydrobenzo[*b*]quinolizidines to displace [^{3}H]TCP from rat brain membranes was determined as described by Vignon.[17] The results are shown in Table 1. As seen, among this class of noncompetitive NMDA antagonists, only derivatives with a cyclopentyl ring (compounds **5a**−**d**,**h**−**k**) showed good activity, and the nature of the 12,13-substituent demonstrated exceptional sensitivity for [^{3}H]TCP binding affinity. In order to better understand the structure−activity relationships (SAR) observed with these compounds, the computer-generated[18] lowest energy structure of the protonated form of **5a** was fitted to the PCP pharmacophore model as described by Andrews et al.[19] and Mallanack et al.[20] The geometry-optimized structure of **5a** was found to match closely its solid state structure (rms = 0.05 Å) as determined by X-ray crystallography. The computer-generated lowest energy conformer of PCP and the low-energy structure of MK-801 are shown as reference compounds. As seen in Figure 2, the cyclopentyl group of **5a** occupies the upward lipophilic cleft of the PCP receptor model. It has been reported that this "upward" directed cleft in the receptor is a secondary binding site for liphophilic

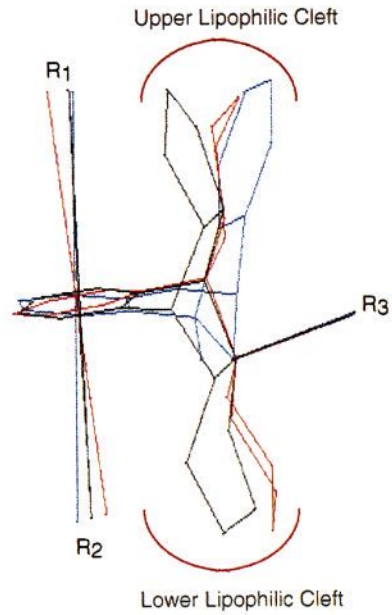
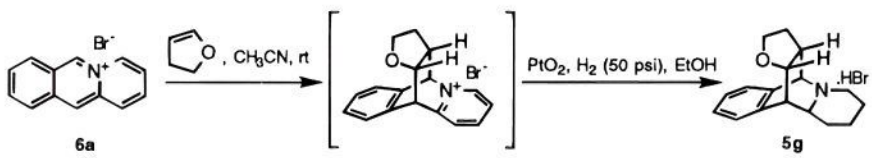


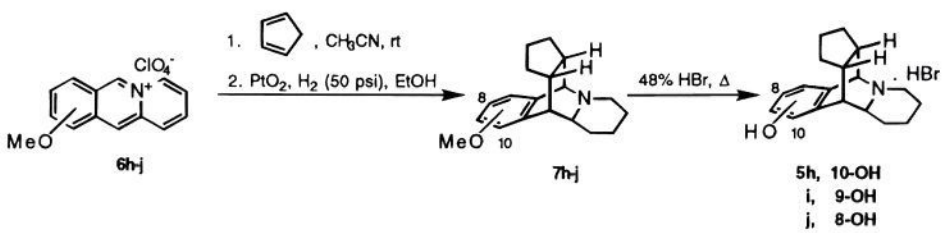
Figure 2. Overlay of compound **5a** (green), MK-801 (blue), and PCP (red) on the Andrews and Mallanack PCP receptor model. R_1, R_2, and R_3 detail the position of the receptor points described in ref 20.

substituents, and the presence of such groups is an essential requirement for good activity.[20] Consistent with this hypothesis is the >20-fold loss of activity observed for the descyclopentyl derivative **5e**. Removal of the ethano bridge altogether (compound **8**) results in total loss of activity. Interestingly, replacement of the cyclopentyl ring of **1** with a cyclohexyl group (compound

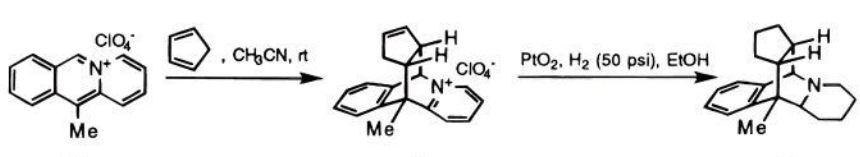
Scheme 4



Scheme 5



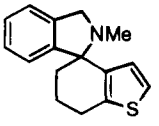
Scheme 6



5f) also led to a 20-fold drop in binding affinity (vs **5a**). It is conceivable that either the increased entropy or the additional volume consumption when compound **5f** is fit to the pharmacophoric model is responsible for the observed results.

The tetrahydrofuryl analog **5g** was >50-fold less potent than **5a**. This reduction in potency is probably due to an adverse electronic effect of the tetrahydrofuranyl oxygen. A similar result has been reported for MK-801 derivatives with oxygen (OMe and OH) substituents in the benzo ring that occupies the upward lipophilc cleft in the PCP receptor model.[21] The SAR for compounds with substituents in the benzo ring of **5a** parallels that of substituted MK-801[21] and PCP derivatives.[22] The 10- and 9-OH analogs (compounds **5h,i**) with K_i = 2 nM were the most potent among this class. The improved activity of **5h,i** could be attributed to interaction of these hydroxy substituents with the optional hydrogen bond-accepting site on the receptor.[20] Compounds **5b–d** with amino and halogen substituents were 2–4-fold less active than **5a**. It has been reported that in the case of MK-801, the bridgehead methyl group improves PCP site affinity.[21] A similar exercise in our series (compound **5k**) led to a 3-fold drop (vs **5a**) in activity.

As described in the Introduction, a liability generally associated with compounds acting at the PCP site of the NMDA receptor complex is their ability to produce undesired behavioral and autonomical side effects. However, spiroindoline **12**,[23] a potent noncompetitive NMDA antagonist (IC_{50} for [^{3}H]TCP displacement = 490 nM), has been reported to be devoid of some of the MK-801- and PCP-like psychotomimetic effects (such as body rolling, ataxia, and hyperlocomotion) at doses which produced neuroprotective effects in a gerbel model of ischemia. Although one could argue that the substantial drop in potency (8-fold vs PCP) of **12** could be responsible for this lack of behavioral effects, an analogous spiroindoline, **13** (IC_{50} = 980 nM), was found to elicit PCP- and MK-801-like behavioral effects in MK-801-trained rats. These results suggest that it is possible to separate the beneficial neuroprotective effects of compounds acting at the PCP site from their psychostimulant liabilities. In order to assess the effect of our class of compounds in such studies, the lead member in our series (compound **5a**) was evaluated in various behavioral models described by Sturgeon.[24,25]



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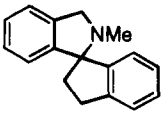

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Male Swiss–Webster mice were injected bilaterally (iv) with test compound. The mice were rated once every 10 min for a 90 min observation period on three different rating scales (ataxia, stereotypy, and locomotor activity) by an observer who was blind to the individual treatments. The rating scales were modified from the methods of Sturgeon and quantified for the amount of locomotion, stereotypy, and ataxia observed following drug treatment. As shown in Figure 3, compound **5a** exhibited the various MK-801 type effects and was equipotent to MK-801 in producing such effects.

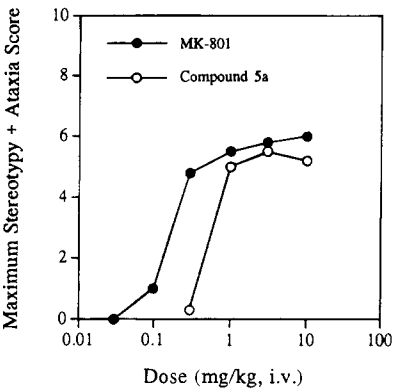

Figure 3. Effect of compound **5a** in eliciting ataxia and stereotypical behavior in male Swiss–Webster mice.

Conclusion

In conclusion, we have identified a new class of compounds that bind to the PCP site of the NMDA–ion channel complex. The SAR in this series correlates well with the PCP receptor pharmacophore described by Andrews and Mallanack. The phenols **5h,i** with K_i = 2.0 nM were the most potent compounds in this series and are among the most potent PCP site ligands reported to date. Compound **5h** also displayed affinity for the [^{3}H]naloxone sites (K_i = 78 ± 9 nM) of the opiate receptor. This, coupled with the undesired PCP- and MK-801-like psychotomimetic effects observed with the lead compound in this series, precluded further development of this class of noncompetitive NMDA antagonists.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20SX FTIR spectrometer. NMR spectra were acquired in the indicated solvent on a JEOL-FX270, General Electric QE-300, or Bruker-AC200 FTNMR spectrometer, and the chemical shifts are expressed in δ units from tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Nermag R10/10 spectrometer coupled to a Varian 3400 gas chromatograph or on a JEOL JMS-01SC spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values, except where indicated by individual analyses. Thin layer chromatography (TLC) was performed on E. Merck 5 × 20, Kieselgel 60 F-254 plates. Preparative chromatography was performed using a Buchi B680 MPLC system coupled to an ISCO UV-detector and fraction collector or by the flash method as described by Still.[26] Columns were packed with Kieselgel 60, 230–400 mesh. All solvents and reagents were reagent grade unless otherwise noted.

(6α*,11α*,11a*β,12*R**,13*S**)-1,3,4,6,11,11a,13,14,15,16-Decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido-[1,2-*b*]isoquinoline Hydrobromide (5a).** A solution of quinolizinium derivative **7a** (26.0 g, 0.08 mol) in 4:1 EtOH/water (250 mL) was hydrogenated at 50 psi in the presence of PtO_2 (0.2 g) until no more hydrogen uptake was observed. The catalyst was filtered, the filtrate concentrated in vacuo, and the residue dissolved in hot ethanol (100 mL). The resulting solution was passed through a pad of Supercel, eluting with ethanol (100 mL). The eluents were concentrated in vacuo, and the crude product was purified by crystallization from MeOH/tBuOMe to give 10.45 g (40%) of **5a** as a colorless solid: mp 273–275 °C; ^{1}H NMR (DMSO-d_6) δ 0.62–1.25 (m, 6H), 1.42–1.85 (m, 6H), 2.30–2.37 (m, 2H), 2.42–2.58 (m, 2H), 2.65–2.82 (m, 2H), 3.22 (m, 1H), 3.62 (d, J = 1.5 Hz, 1H), 7.05–7.25 (m, 4H). Anal. ($C_{18}H_{23}N$·HBr) C, H, N.

Free Base of 5a. To a suspension of **5a** (2.0 g, 0.006 mol) in CH_2Cl_2 (200 mL) was added saturated $NaHCO_3$ (100 mL).

Table 2. Summary of Crystallographic Data for (6α*,11α*,11aβ*,12R*,13S*)-1,3,4,6,11,11a,13,14,15,16-Decahydro-12H-6,11[1′,2′]-*endo*-cyclopenta-2H-pyrido[1,2-*b*]isoquinoline (**5a**)

formula	$C_{18}H_{23}N$
fw	253.4
color, habit	fragment of colorless prism
crystal size (mm)	0.16 × 0.40 × 0.56
crystal system	orthorhombic
space group	*P*bca (No. 61)
unit cell dimensions (Å)	a = 8.568 (2)
	b = 12.111 (2)
	c = 27.744 (5)
V (Å^3)	2882.1 (10)
Z	8
d_{calcd} (g cm^{-3})	1.168
wave length (Å)	1.54178
abs coeff (mm^{-1})	0.501
F(000)	1104
no. of reflections	2295
no. with $F > 4.0\sigma(F)$	1644
final R indices (obsvd data) (%)	R = 5.66, R_w = 10.07
R indices (all data) (%)	R = 6.33, R_w = 10.72

After stirring for 10 min, the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Crystallization of the residue from an ethyl acetate solution by vapor phase diffusion of pentane gave X-ray quality crystals of the free base of **5a**.

X-ray Crystallography. Colorless prisms of **5a** were obtained as described above and mounted by means of epoxy resin to a glass fiber which was attached to a goniometer head. The crystal was coated with epoxy resin. A Siemens R3m/v diffractometer was used for data collection. By means of a graphite monochromator, the Cu Ka doublet (λ = 1.54178 Å) of a sealed X-ray tube was employed as the radiation source. The reflections were measured in an ω-scan mode at a variable scan speed of 1.0−29.3°/min in ω. The ω-range was 1.20°. Twenty-five reflections were selected from a rotation photograph and centered using standard software procedures of the Siemens R3m diffractometer. From these reflections, the unit cell parameters were calculated. Table 2 contains a summary of the crystal structure data. The background was measured with stationary crystal and stationary counter at the beginning and end of each scan, each for 50% of the total scan time. Four reflections were measured as standards after every 60 reflections. The 2θ-range was 3.0−130.0° ($0 < h < 9$; $0 < k < 13$; $0 < l < 30$); 2295 reflections were collected at room temperature (21 °C), of which 1964 were independent reflections; 1644 reflections were observed [$F > 4.0\sigma(F)$]. No absorption correction was applied.

Siemen's programs SHEXTL PLUS (release 4.21/V) were used for phase determination and structure refinement. The application of direct methods of phase determination led to an electron density map which showed all the nonhydrogen atoms. They were refined isotropically at first. Finally coordinates and anisotropic temperature factors for all nonhydrogen atoms were refined by full matrix least squares procedures. All the hydrogen atoms could be located in difference electron density maps. They were included in the calculations with coordinates riding on the coordinates of the atoms to which they are attached. Three separate isotropic temperature factors were refined for the secondary, tertiary, and aromatic hydrogen atoms. The refinement converged with R = 6.46%; R_w = 11.82%. Background features in the Fourier difference map, some high thermal displacement coefficients, and chemical considerations led to refinement of the model with the N5 atom and the C-11a-H methine exchanged in some of the sites. This, in effect, replaces a molecule by its enantiomer at these sites. The refinement of this model calculated a population parameter of 57% and converged with R = 5.66% and R_w = 10.07%. An R-factor ratio test[27] applied $\mathcal{R}_{obs}$ = 1.17378 and $\mathcal{R}_{12,1456,0.005}$ = 1.00969. This indicates that the improvement obtained from the disordered model is significant at the 0.5% level. The largest feature in the Fourier difference map was 0.25 eÅ^{-3}. Tables of atomic coordinates and bond distances and angles are given in the supplementary material.

9-Fluoro-(6α*,11α*,11aβ*,12R*,13S*)-1,3,4,6,11,11a,13,14,15,16-decahydro-12H-6,11[1′,2′]-*endo*-cyclopenta-2H-pyrido[1,2-*b*]isoquinoline Fumarate (5b). To a solution of 9-Fluorobenzo[*b*]quinolizinium perchlorate (**6b**) (7.35 g, 0.025 mol) in CH_3CN (75 mL) was added freshly distilled cyclopentadiene (10 mL). After stirring at room temperature for 12 h, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was triturated with ethyl acetate and filtered. The filter cake was dissolved in MeOH (200 mL), and PtO_2 (0.5 g) was added. The resulting mixture was hydrogenated at 50 psi of hydrogen pressure in a Parr apparatus for 5 h. The catalyst was filtered and the filtrate evaporated to dryness. The residue was dissolved in water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried and evaporated to dryness in vacuo. The crude product was dissolved in acetone; fumaric acid (2.8 g, 0.024 mol) was added and the mixture refluxed for 1 h. The solids that precipitated upon cooling were collected and recrystallized from iPrOH to give 3.75 g (38%) of **5b** as a colorless solid: mp 272−274 °C; ^{1}H NMR (DMSO-d_6) δ 0.52−1.15 (m, 5H), 1.32−1.80 (m, 6H), 2.05−2.25 (m, 1H), 2.41−2.52 (m, 2H), 2.71−2.92 (m, 1H), 3.12 (s, 1H), 3.52 (m, 1H), 4.2 (s, 1H), 6.5 (s, 2H), 7.05−7.25 (m, 2H), 7.35−7.42 (m, 1H). Anal. ($C_{18}H_{22}FN\cdot C_4H_4O_4$) C, H, N.

9-Bromo-(6α*,11α*,11aβ*,12R*,13S*)-1,3,4,6,11,11a,13,14,15,16-decahydro-12H-6,11[1′,2′]-*endo*-cyclopenta-2H-pyrido[1,2-*b*]isoquinoline Hydrobromide (5c). To a suspension of 9-bromobenzo[*b*]quinolizinium bromide (**6c**) (7.7 g, 0.0227 mol) in 3:3:1 CH_3CN:$MeNO_2$:MeOH (180 mL) was added cyclopentadiene (10.0 g, 0.15 mol). After stirring at room temperature for 12 h, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was triturated with CH_3CN; the solids were collected by filtration and crystallized from EtOH to give 7.2 g (78%) of adduct **7c** as a colorless solid. Anal. ($C_{18}H_{15}BrN\cdot Br$) C, H, N.

A solution of **7c** (6.5 g, 0.016 mol) in MeOH (200 mL) was hydrogenated in the presence of PtO_2 (0.2 g) until no more hydrogen uptake was observed. The reaction mixture was filtered, the filtrate concentrated in vacuo, and the residue crystallized from CH_3OH/EtOAc to give 4.7 g (71%) of **5c** as a colorless solid: mp 233−243 °C; ^{1}H NMR (DMSO-d_6) δ 0.52−1.25 (m, 6H), 1.32−2.02 (m, 8H), 2.12−2.35 (m, 1H), 3.02−3.25 (m, 2H), 3.65−3.88 (m, 1H), 4.35 (m, 1H), 7.25−7.55 (m, 2H), 7.55−7.75 (m, 1H), 10.2 (br s, 1H); HRMS calcd for $C_{18}H_{23}BrN$ [(M + H)$^+$ − HBr] 332.1014, found 332.1012.

9-Amino-(6α*,11α*,11aβ*,12R*,13S*)-1,3,4,6,11,11a,13,14,15,16-decahydro-12H-6,11[1′,2′]-*endo*-cyclopenta-2H-pyrido[1,2-*b*]isoquinoline (5d). A mixture of 9-nitrobenzo[*b*]quinolizinium perchlorate (**6d**) (12.6 g, 0.0388 mol) and cyclopentadiene (13.6 g, 0.2 mol) in acetonitrile (80 mL) was stirred at room temperature for 12 h and filtered. The filtrate was concentrated in vacuo and the residue triturated with CH_3CN, and the solids were collected by filtration to give the Diels−Alder adduct **7d** (6.0 g, 40%).

A solution of **7d** (5.71 g, 0.0146 mol) in EtOH (200 mL) and 3 N HCl (1 mL) was hydrogenated in the presence of PtO_2 (0.2 g) until no more hydrogen uptake was observed. The reaction mixture was filtered and the filtrate concentrated in vacuo, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was crystallized from CH_3CN to give 0.35 g (9%) of **5d** as a colorless solid: mp 166−167 °C; ^{1}H NMR (DMSO-d_6) δ 0.51−1.65 (m, 12H), 2.25−2.41 (m, 4H), 2.75−2.82 (m, 1H), 3.15−3.25 (m, 2H), 4.70 (br s, 2H), 6.21−6.35 (m, 2H), 6.58 (d, J = 7.1 Hz, 1H). Anal. ($C_{18}H_{24}N_2$) C, H, N.

(6α*,11α*,11aβ*,12R*,13S*)-1,3,4,6,11,11a,13,14,15,16-Decahydro-12H-6,11[1′,2′]-ethano-2H-pyrido[1,2-*b*]isoquinoline (5e). A 600 mL Parr reaction vessel was charged with benzo[*b*]quinolizinium perchlorate (**6a**) (20.0 g, 0.072 mol) in MeOH (300 mL) and pressurized to 80 psi with ethylene gas. The contents were heated at 70 °C for 6 h and cooled to room temperature. After flushing the reaction vessel with

nitrogen, PtO_2 (0.5 g) was added and the mixture hydrogenated at 50 psi of H_2 pressure for 8 h and filtered. The filtrate was concentrated in vacuo, dissolved in water, basified with 3 N NaOH, and extracted with pentane. The organic layer was dried and concentrated in vacuo. Purification by flash chromatography followed by crystallization from pentane gave 0.9 g (6%) of **5e** as a colorless solid: mp 96–97 °C; ^{1}H NMR ($CDCl_3$) δ 0.72–0.95 (m, 1H), 1.10–1.25 (m, 1H), 1.35–1.60 (m, 5H), 1.71–1.95 (m, 2H), 2.11–2.35 (m, 2H), 2.41–2.55 (m, 1H), 2.7 (br s, 1H), 3.01–3.15 (m, 1H), 3.58–3.62 (m, 1H), 7.05–7.35 (m, 4H). Anal. ($C_{15}H_{19}N$) C, H, N.

(6α*,6aβ*,10aβ*,11α*,11aα)-1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-6,11[1′,2′]-benzeno-2*H*-pyrido[1,2-*b*]isoquinoline (5f). To a solution of 12,13-benzo-1,2,3,4,6,11-hexahydro-6,11-ethanobenzo[*b*]quinolizidine perchlorate (**9**) (1.4 g, 0.004 mol) in THF (100 mL) was added PtO_2 (0.3 g), and the mixture was hydrogenated at 50 psi of H_2 pressure until hydrogen uptake ceased (7 h). The catalyst was filtered off and the filtrate concentrated in vacuo. The residue was dissolved in water, basified with 6 N KOH, and extracted with EtOAc. The organic phase was dried (K_2CO_3) and concentrated in vacuo. The residue was dissolved in pentane, treated with DARCO, and filtered through Supercel, eluting with pentane. The eluents were combined and concentrated under reduced pressure. The crude product was crystallized from pentane to give 0.32 g (30%) of **5f** as a colorless solid: mp 113–116 °C; ^{1}H NMR ($CDCl_3$) δ 0.45–1.12 (m, 8H), 1.42–1.57 (m, 6H), 2.11–2.41 (m, 2H), 2.52 (m, 1H), 3.22 (m, 1H), 3.40 (d, J = 1.5 Hz, 1H), 7.05–7.25 (m, 4H). Anal. ($C_{19}H_{25}N$) C, H, N.

(6α*,11α*,11aβ*,12*R,16*R**)-1,3,4,6,11,11a,12,14,15,16-Decahydro-6,11[3′,2′]-furano-2*H*-pyrido[1,2-*b*]isoquinoline Hydrobromide (5g).** To a solution of benzo[*b*]quinolizinium bromide (**6a**) (2.6 g, 0.009 mol) in sulfolane (10 mL) was added dihydropyran (10 mL). The resulting mixture was heated at 80 °C for 2 h, cooled to room temperature, and concentrated in vacuo. The residue was triturated with EtOAc (50 mL) and filtered. The filter cake was hydrogenated as described above for **5a** to give after crystallization (EtOH/Et_2O) 0.28 g (5%) of **5g** as a colorless solid: mp 270–273 °C; ^{1}H NMR (DMSO-d_6) δ 0.72–1.05 (m, 2H) 1.42–2.25 (m, 7H), 2.61 (m, 1H), 3.21–3.33 (m, 3H), 3.50 (d, J = 2.0 Hz, 1H), 3.71 (m, 1H), 4.32 (m, 1H), 4.80 (br s, 1H), 7.44 (m, 4H), 10.01 (br s, 1H). Anal. ($C_{17}H_{21}NO$·HBr) C, H, N.

General Method for the Preparation of Phenol Hydrobromides 5h–j. A solution of the methoxybenzo[*b*]-quinolizinium perchlorates **6h–j** (1 equiv) and freshly distilled cyclopentadiene (5 equiv) in MeOH (10 mL/g of **6**) was stirred at room temperature for 12–24 h. The resulting reaction mixture was evaporated to dryness. The residue was triturated with EtOAc (to remove cyclopentadiene dimer), and the solids were collected by filtration to give the Diels–Alder adducts, which without further purification were hydrogenated as described above for **5a** to give the methyl ethers **7h–j**.

The methyl ethers from above were dissolved in 48% HBr (10 mL/g) and heated at 100 °C for 24 h. After cooling to room temperature, the mixture was evaporated to dryness and the residue crystallized from the noted solvents to give the phenol hydrobromides **5h–j**.

10-Hydroxy-(6α*,11α*,11aβ*,12*R,13*S**)-1,3,4,6,11,11a,-13,14,15,16-decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline hydrobromide (5h):** yield 33%, amorphous powder; ^{1}H NMR (DMSO-d_6) δ 0.65–1.21 (m, 5H), 1.45–1.85 (m, 6H), 2.25–2.65 (m, 4H), 3.15 (m, 1H), 3.45 (m, 1H), 3.85 (m, 1H), 4.25 (d, J = 1.8 Hz, 1H), 6.8 (d, J = 6.8 Hz, 1H), 7.0 (d, J = 7.0 Hz, 1H), 7.2 (t, J = 6.7 Hz, 1H), 7.4 (s, 1H). Anal. ($C_{18}H_{23}NO$·HBr·1.0H_2O) C, H, N.

9-Hydroxy-(6α*,11α*,11aβ*,12*R,13*S**)-1,3,4,6,11,11a,-13,14,15,16-decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline hydrobromide (5i):** yield 80%; mp (EtOH) 289–292 °C; ^{1}H NMR (DMSO-d_6) δ 0.55–1.10 (m, 6H), 1.42–1.85 (m, 6H), 2.35 (m, 1H), 2.81–3.1 (m, 3H), 3.22–3.34 (m, 2H), 3.62 (m, 1H), 4.5 (br s, 1H), 6.82 (m, 2H), 7.3 (d, J = 7.5 Hz, 1H), 9.62 (br s, 1H). Anal. ($C_{18}H_{23}$-NO·HBr) C, H, N.

8-Hydroxy-(6α*,11α*,11aβ*,12*R,13*S**)-1,3,4,6,11,11a,-13,14,15,16-decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline hydrobromide (5j):** yield 15%; mp (MeOH) >300 °C; ^{1}H NMR (DMSO-d_6) δ 0.61–1.22 (m, 6H), 1.55–1.82 (m, 6H), 2.42 (m, 2H), 3.25 (m, 1H), 3.52 (m, 2H), 3.85 (m, 1H), 4.2 (d, J = 1.5 Hz, 1H), 6.6 (d, J = 1.2 Hz, 1H), 6.8 (dd, J = 7.2, 1.5 Hz, 1H), 7.1 (d, J = 7.2 Hz, 1H), 9.1 (s, 1H), 10.8 (br s, 1H). Anal. ($C_{18}H_{23}NO$·HBr) C, H, N.

11-Methyl-(6α*,12*R,13*S**)-1,3,4,6,11a,13,14,15,16-decahydro-12*H*-6,11[1′,2′]-*endo*-cyclopenta-2*H*-pyrido[1,2-*b*]isoquinoline (5k).** This compound was prepared by a procedure similar to the one described above for **5a**. The crude material was purified by chromatography (1:1 EtOAc/hexanes containing 1% iPrOH) to give 40% yield of **5k** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.35–0.42 (m, 2H), 0.59–0.68 (m, 2H), 1.05–1.12 (m, 2H), 1.25 (s, 3H), 1.38–1.81 (m, 6H), 2.35–2.42 (m, 2H), 2.45–2.60 (m, 2H), 2.71–2.78 (m, 2H), 3.5 (d, J = 1.5 Hz, 1H), 7.05–7.30 (m, 4H); HRMS calcd for $C_{19}H_{26}N$ [$(M + H)^+$] 268.2065, found 268.2065.

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Supplementary Material Available: Tables of atomic coordinates and bond distances and angles for compound **5a** (5 pages). Ordering information is given on any current masthead page.

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