Discovery of a Novel Class of Substituted Pyrrolooctahydroisoquinolines as Potent and Selective δ Opioid Agonists, Based on an Extension of the Message−Address Concept

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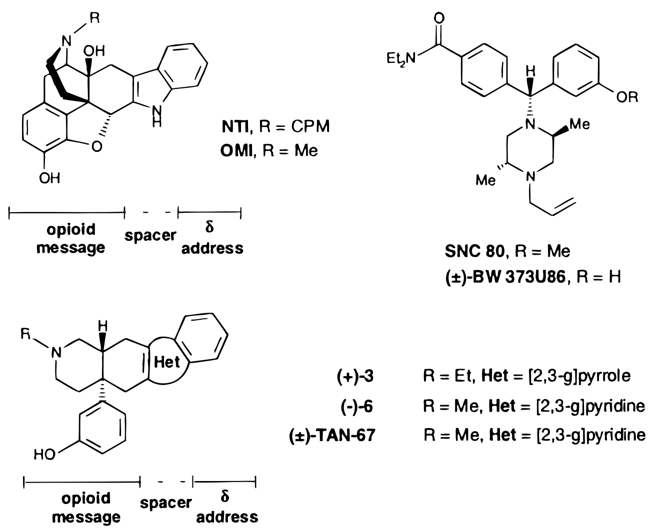
This paper describes the design and synthesis of compounds belonging to a novel class of substituted pyrrolooctahydroisoquinolines which are potent and selective δ opioid agonists. Molecular modeling studies performed on known, selective δ ligands such as **(+)-3** and the potent δ agonist SNC 80 led to the identification of the carboxamido moiety of the latter as a putative nonaromatic δ address. Insertion of this moiety onto the octahydroisoquinoline opioid message resulted in **(±)-5b**, a potent and selective δ ligand. The active enantiomer, **(−)-5b**, displayed nanomolar affinity for the δ receptor ($K_i = 0.9$ nM) with good μ/δ and κ/δ binding selectivity ratios (140 and 1480, respectively). In addition, **(−)-5b** behaved as a full δ agonist in the mouse vas deferens bioassay having an $IC_{50} = 25$ nM and being antagonised in the presence of 30 nM naltrindole (NTI). These studies, based on the message−address concept, indicated that the nonaromatic (*N*,*N*-diethylamino)carbonyl moiety is a viable alternative to the classical benzene ring as a δ opioid address. Preliminary *in vivo* studies showed that **(±)-5b** produced a dose-related antinociception in the mouse abdominal constriction test after intracerebroventricular administration ($ED_{50} = 1.6$ μg/mouse).

The therapeutically useful effects and adverse side issues associated with morphine are primarily due to an interaction with μ opioid receptors. Following the great interest shown over the past 10 years in κ opioid agonist-induced antinociception,[1] attention has shifted recently toward the potential of analgesics acting *via* δ opioid receptors[2] which might lack the negative properties associated with morphine. Considerable evidence derived from animal models shows that existing δ opioid agonists, predominantly peptides, produce antinociception with relatively little effect on gastrointestinal motility or respiratory depression and have little physical dependence liability in comparison with μ agonists.[3] There is very little clinical evidence concerning their therapeutic utility, although the δ selective peptide [D-Ala²,D-Leu⁵]enkephalin (DADLE) has been shown to cause effective pain relief when given intrathecally to cancer patients.[4] Widespread clinical proof of concept studies await, therefore, the identification and development of nonpeptidic drugs which act selectively as δ opioid receptor agonists but which have more favorable metabolism and pharmacokinetic properties than the existing δ selective peptides.

The established rationale for the design of peptidomimetic drugs acting as selective δ receptor ligands has been based on the message−address concept originally proposed by Schwyzer[5] and subsequently re-elaborated by Portoghese.[6] This concept attributes the role of the opiate message to the Tyr[1] residue of the tetrapeptidic sequence of the endogenous peptides (Tyr[1]-Gly[2]-Gly[3]-Phe[4]-...), whereas the δ address resides in the amino acid sequence which starts with Phe[4]. In this context, the residues Gly[2]-Gly[3] represent a spacer maintaining an appropriate distance between Tyr[1] and Phe[4].

Chart 1



Following this rationale the first nonpeptidic δ opioid antagonist, naltrindole (NTI) (see Chart 1), was synthesized[6] as well as the closely related *N*-methyl analogue, oxymorphindole (OMI), which has a partial δ agonist profile *in vitro*.[6] Recently, a novel class of octahydroisoquinolines, formally derived from OMI fragmentation,[7] including the δ antagonist **(+)-3** (SB 205588)[7,8] and the δ agonists TAN67[9] and **(−)-6** (SB 213698),[8] has been described. In addition, two piperazine derivatives, (±)-BW373U86[10] and one of its methoxy analogues SNC 80,[11] which show clear structural differences compared to the previously known δ ligands, have been identified as potent and selective δ agonists. These piperazines do not apparently display the classical moieties responsible for interactions with the δ receptor outlined in the message−address concept.

The present report describes molecular modeling studies that have extended the message−address con-

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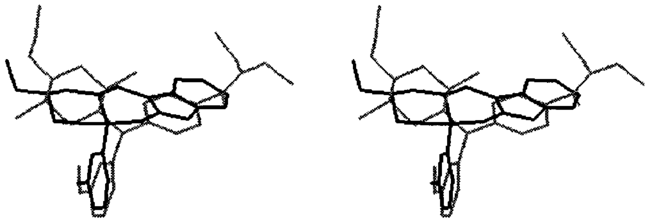


Figure 1. Stereoview of the superimposition between SNC 80 (gray) and **(+)-3** (black). Points used were the basic nitrogens, the centroids of the oxygenated rings, and the centroid of the second benzene ring of SNC 80 with that of the pyrrole nucleus of **(+)-3** (RMS = 0.533).

cept to nonaromatic δ address moieties. In addition, details of the synthesis of novel pyrrolooctahydroisoquinoline derivatives are given, together with preliminary pharmacological results which show them to be δ selective agonists.

Molecular Modeling

The aims of this study were as follows: (i) trying to identify molecular similarities between the classical δ ligands based on the message−address concept and the novel piperazine derivatives; (ii) identifying which moieties conferred agonist activity to SNC 80, and finally (iii) combining the above findings to design novel structures of putative δ selective agonists. As a starting point for these studies, two representatives of those classes of δ ligands for which crystallographically derived molecular structures were known, i.e. **(+)-3** (a fragment of OMI possessing 4a*S*,11a*R* absolute configuration) and SNC 80,[11] where chosen. The three-dimensional coordinates of **(+)-3** were used as input geometries to build its 3D model while SNC 80 was built according to its absolute stereochemistry.[11] Energy minimization using the MM2 force field and subsequent extensive conformational searches were performed on the above models to ensure that all conformers studied were at their global minima.

The basic nitrogen bearing the allylic group and the oxygenated benzene ring were identified as features that could represent the opioid message in the piperazine derivative SNC 80. These moieties were then superimposed to the corresponding fragments of **(+)-3** (RMS = 1.11). A better fit was obtained using also the centroid of the second benzene ring of SNC 80 with that of the pyrrole nucleus that served as a spacer in the octahydroisoquinoline derivatives (Figure 1; RMS = 0.533). In this case the amidic moiety of SNC 80 lay approximately in the same region of space as that occupied by the classical, aromatic δ address. On the basis of these overlaps, it was hypothesized that the amidic moiety might be responsible for the δ opioid selectivity shown by SNC 80 by playing the role of a nonaromatic δ address. It was also possible that the same moiety may confer agonist activity on SNC 80.

To confirm the validity of these hypotheses, the putative nonaromatic δ address was attached to the well-established opioid message represented by the octahydroisoquinoline framework. Examination of the superimposition shown in Figure 1 revealed that the best position to insert a carboxamido moiety in the octahydroisoquinoline nucleus was adjacent to the indolic nitrogen of **(+)-3**. In addition, the presence of a methyl group in position 3 of the target molecule induced the amidic moiety to adopt a preferential conformation outside the plane of the pyrrole ring, ensuring a good fit with SNC 80. Thus, a model of compound **5b** was built, and after subsequent conformational search, the resulting minimum energy conformation showed a good match with SNC 80 (Figure 2, RMS = 0.490). Therefore, **5b**[12] appeared a suitable tool with which to test our hypothesis. Initially, the racemic pyrrolooctahydroisoquinolines **(±)-5a−c** were synthesized and their opioid binding affinities were evaluated. The agonist/antagonist properties of selected compounds of interest were subsequently determined in the mouse vas deferens (MVD), and their antinociceptive activity was evaluated *in vivo*.

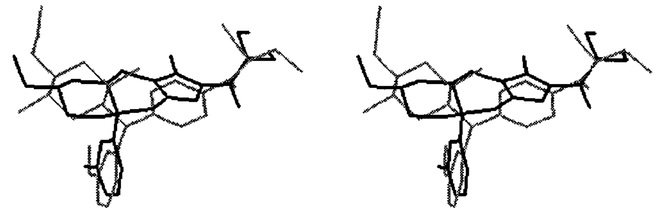


Figure 2. Stereoview of the superimposition between SNC 80 (gray) and **5b** (black). Points used were the basic nitrogens, the centroids of the oxygenated benzene rings, the centroids of the second benzene ring of SNC 80 with that of pyrrole nucleus of **5b** and the two carbon atoms of the amidic moieties (RMS = 0.490).

Chemistry

Compound **(±)-1a** is known and was prepared according to the literature.[13] Synthesis of compound **(±)-1b** was achieved according to the same method. Fractional crystallization in absolute EtOH of the optically active *p*-toluoyltartaric acid salts obtained from the racemic ketone **(±)-1b** and subsequent saponification gave the two corresponding pure enantiomers **(+)-1b** and **(−)-1b** in quantitative yield. Compound **(±)-1c** was obtained by de-ethylation of **(±)-1b** with vinyl chloroformate[14] and subsequent alkylation with (bromomethyl)cyclopropane.

Compounds **2** (see Scheme 1) were obtained by Fischer indole synthesis of the corresponding ketones **1b** with phenylhydrazine hydrochloride in refluxing MeOH saturated with HCl.

Compounds **4a−c** were obtained by Knorr synthesis of the corresponding ketones **1a−c** with *N*,*N*-diethyl-2-phenylhydrazono-3-oxobutyramide[15] in the presence of zinc dust in acetic acid buffered with NaOAc.[16]

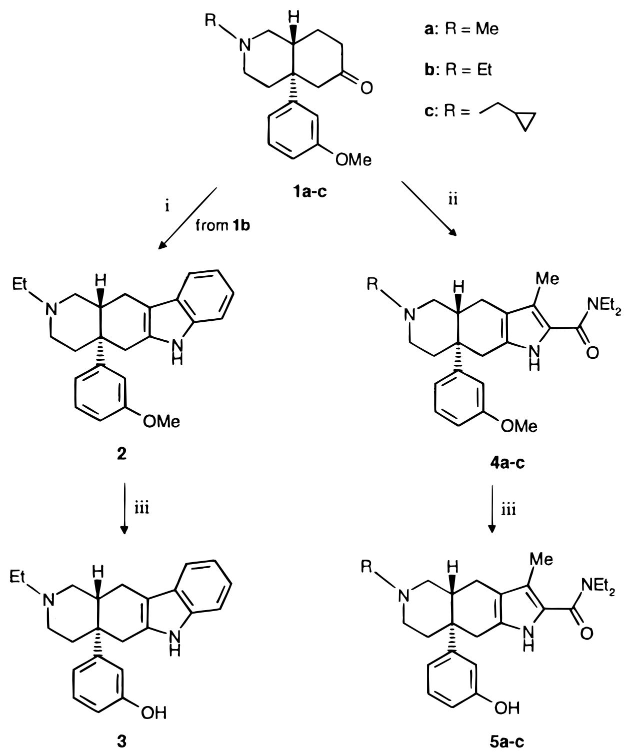
Compounds **2** and **4a−c** were demethylated to the corresponding phenols **3** and **5a-c** with boron tribromide in dry chloroform at room temperature.[17]

Results and Discussion

The δ, μ, and κ opioid receptor binding affinities, along with binding selectivity ratios for compounds **3** and **5a−c**, are shown in Table 1. For comparative purposes, the opioid binding profiles of NTI, OMI, and SNC 80 are also reported.

Compounds **(±)-5a−c** exhibited high affinity for δ receptors with K_i values ranging from 1.7 to 2.1 nM. Furthermore, the *N*-ethyl derivative **(±)-5b** was far less potent at the μ and κ receptors, resulting in μ/δ and κ/δ selectivity ratios of 210 and 690, respectively, while **(±)-5a** and **(±)-5c** displayed low selectivity toward the δ receptor. Thus, **(±)-5b** was selected for further

Scheme 1[a]



[a] Reagents and conditions: (i) $PhNHNH_2 \cdot HCl$, MeOH/HCl, reflux; (ii) $MeCOC(NNHPh)CONEt_2$, Zn, AcOH, AcONa, reflux; (iii) BBr_3, $CHCl_3$, room temperature.

evaluation in the MVD functional bioassay to assess its agonist/antagonist properties. Activity of SNC 80 is also reported for comparison (Table 2). Importantly, and as predicted, insertion of a carboxamido group conferred full δ agonist activity to compound **(±)-5b** which had an IC_{50} value of 34 nM in this *in vitro* assay. In the presence of 30 nM NTI, there was a 10-fold rightward shift of the concentration−response curve for **(±)-5b**, confirming the role of the δ receptors in the response seen.

The binding of the indolooctahydroisoquinoline derivatives **(−)-3** and **(+)-3** to the δ receptor was clearly enantiospecific (eudismic ratio = 900), and this prompted the synthesis of the two corresponding enantiomers of compound **(±)-5b**. As shown in Table 1, compound **(−)-5b** (SB 219825) was a very potent δ ligand with a K_i of 0.9 nM and μ/δ and κ/δ binding selectivity ratios of 140 and 1480, respectively. Enantioselectivity was also evident in this class of pyrrolooctahydroisoquinolines with the δ binding activity residing predominantly in the (−)-enantiomer (eudismic ratio = 3700). Compound **(−)-5b** also behaved as a full δ agonist in the MVD assay causing a complete, concentration-dependent inhibition of electrically induced phasic contraction with an IC_{50} = 25 nM. There was a 18-fold shift of the concentration−response curve in the presence of 30 nM NTI (Table 2).

The antinociceptive activity of **(±)-5b** has been determined using the mouse abdominal constriction model following intracerebroventricular (icv) administration. For comparative purposes the antinociceptive potency of SNC 80 was also determined. Both compounds produced dose-related antinociception with the highest doses employed causing complete protection. Compound **(±)-5b** exhibited an ED_{50} of 1.6 (1.0−2.6) μg/mouse and was thus 5 times more potent than SNC 80 in this model [ED_{50} = 9.5 (4.6−17.2) μg/mouse].

Conclusions

The present molecular modeling studies have demonstrated how the message−address concept may be extended to include nonaromatic moieties, such as N,N-disubstituted carboxamido groups. This led to the synthesis of compounds belonging to a novel class of pyrrolooctahydroisoquinolines which behaved as potent and selective δ opioid receptor ligands. The dialkylamidic moiety was also able to confer full δ agonist activity when it replaced the aromatic δ address in the framework of the δ antagonist **(+)-3**. Compound **(−)-5b** therefore represents the prototype of a new class of nonpeptidic, δ selective agonists which might serve as tools to study further the pharmacology associated with activation of the δ opioid receptors.

Preliminary studies with the racemate **(±)-5b** have already indicated that the compound is a potent and efficaceous antinociceptive agent when injected icv in the mouse.

Experimental Section

Binding Assays: Cell Culture and Preparation of the Crude Membrane Fraction. NG108-15 neuroblastoma x glioma hybrid cells (provided by European Collection of Animal Cell Cultures, ECACC) were grown at 37 °C in 5% CO_2−95% humidified air atmosphere in Dulbecco's MEM nutrient mixture (without sodium pyruvate, using 4.5 g/L glucose) supplemented with 10% foetal calf serum, 2 mM glutamine, 2% HAT, 50 μg/mL streptomycin, and 50 units/mL penicillin. Cells at confluence were harvested with 1 mM EDTA in Ca/Mg-free phosphate-buffered saline with mechanical stirring and centrifuged at 1000 rpm for 8 min. The pellets were stored at −80 °C for a maximum of a month without any discernible loss of binding activity. Prior to binding experiments, the cells were suspended in ice cold 50 mM Tris-HCl, pH 7.4, buffer (3×10^7 cells/10 mL buffer) and homogenized by a PBI politron (setting 5 for 15 s). The homogenate was centrifuged at 53000*g* for 15 min at 4 °C. The resultant pellets were resuspended in the same volume of buffer, incubated at 37 °C for 45 min, and centrifuged at 53000*g* for 15 min. The pellets obtained were finally resuspended in buffer, and 1.9 mL aliquots (membranes from 3×10^5 cells) were used for the assay.

Preparation of Mouse Brain Membranes. Whole brains without cerebellum from male CD-1 mice (Charles River; 25−30 g) were homogenized in 10 volumes (w/v) of ice cold 50 mM Tris-HCl, pH 7.4, using a PBI tissue dispergerate (setting 5 for 15 s). The homogenate was centrifuged at 48000*g* for 10 min. The resulting pellets were resuspended in the same volume of buffer, incubated at 37 °C for 45 min, and centrifuged at 48000*g* for 10 min. The pellets obtained were resuspended in 100 volumes (original wet weight) of buffer and used for the assay (1.9 mL sample).

Binding Assays. The radiolabeled ligands employed in the binding assays are as follow: $[^3H]$[D-Ala^2, D-Leu^5]enkephalin ($[^3H]$DADLE; sp act. 32.3 μCi/nmol, New England Nuclear) has been used to label δ binding sites in NG108-15 cell membranes at the concentration of 1 nM, $[^3H]$[D-Ala^2,MePhe^4,Gly-ol^5]-enkephalin ($[^3H]$DAMGO; sp act. 55.5 μCi/nmol, New England Nuclear) at the concentration of 0.7 nM and $[^3H]$U69593 (sp act. 56.0 μCi/nmol, Amersham) at the concentration of 1.2 nM have been used to label μ and κ binding sites, respectively, in mouse brain membranes. The nonspecific binding was determined in presence of naloxone 10 μM (Salars, Como, Italy).

The samples, in triplicate, containing NG108-15 or mouse brain membranes, tritiated and unlabeled ligands (final volume 2 mL) were incubated at 25 °C. The time necessary to reach equilibrium conditions was 60 min for $[^3H]$-DADLE and 50 min for $[^3H]$DAMGO and $[^3H]$U69593. The incubation was terminated by rapid filtration through Whatman GF/B

Table 1. Binding Affinities to δ, μ and κ Receptors

compd	binding affinities (K_i nM)[a] δ	μ	κ	selectivity ratios μ/δ	κ/δ
(±)-3	7.1 ± 0.8	2093 ± 365	334 ± 13	290	50
(−)-3	1971 ± 190	1631 ± 130	167 ± 11	1	0.1
(+)-3	2.2 ± 0.4	2618 ± 190	771 ± 160	1190	350
(±)-5a	2.1 ± 0.1	93 (n = 2)	500 (n = 2)	43	240
(±)-5b	1.9 ± 0.4	407 ± 25	1298 ± 120	210	690
(+)-5b	3535 ± 310	>5000	6005 ± 530	>1	2
(−)-5b	0.9 ± 0.2	129 ± 30	1340 ± 490	140	1480
(±)-5c	1.7 ± 0.6	14.1 ± 0.9	63.1 ± 8.7	8	37
NTI	0.5 ± 0.1	15 ± 2.6	9.5 ± 2.8	35	20
OMI	0.8 ± 0.1	66 ± 5.6	77 ± 6.3	80	90
SNC 80	1.7 ± 0.5	1300 ± 280	1348 ± 330	760	790

[a] Each value represents the mean ± SEM of independent experiments, each performed in triplicate (n = 3) unless otherwise indicated in parentheses.

Table 2. Effect of **(±)-5b**, **(−)-5b**, and SNC 80 in the MVD Bioassay

compd	IC_{50} (nM)[a]	IC_{50} (nM)[a] + 30 nM NTI	IC_{50} ratio
(±)-5b	34 (23−50)	330 (192−569)	9.7
(−)-5b	26 (18−37)	462 (342−625)	17.8
SNC 80	8 (5−13)	634 (293−1373)	79.2

[a] 95% confidence limits are reported in parentheses.

filters using a Brandel cell harvester system. Filters used for [^{3}H]U69593 were presoaked in buffer containing polyethylenimine 0.05%. The radioactivity on the discs was measured by liquid scintillation counting on a Camberra Packard 2500TR beta counter. All the experiments were performed in triplicate.

Mathematical Analysis of Binding Data. Binding parameters deriving from competition experiments (IC_{50} values) were calculated by nonlinear regression analysis using the software package RS/1 (BBN Software Products, Corp.).[18] K_i values were calculated from IC_{50} using the Cheng−Prusoff relationship.[19]

MVD Isolated Tissue Bioassay. Vasa deferentia were obtained from CD-1 mice weighing 25−35 g and were suspended in a Mg^{2+}-free, oxygenated (95% O_2, 5% CO_2) Krebs buffer at 37 °C. For the δ agonist/antagonist studies, the tissues were electrically stimulated with pulse trains having the following parameters: train duration 50 ms, stimulus duration 2 ms, frequency of stimuli 50 Hz, maximal voltage 60−70 V, train frequency 0.1 Hz. Concentration−response curves for each compound were constructed cumulatively.

Linear regression analysis and IC_{50} concentrations were evaluated according to Tallarida and Murray.[20]

***In Vivo* Antinociceptive Studies.** Male Swiss mice (Charles River; 20−35 g) were used throughout these studies. The mouse phenyl-*p*-benzoquinone-induced (PPQ) abdominal constriction test (MAC) was performed according to the procedure described by Siegmund *et al.*[21] modified by Milne and Twomey.[22] The icv injection was performed according to the method of Domino *et al.*[23] by insertion of a disposable 30 gauge $^1/_2$ in. needle mated to a 50 μL luer syringe (Hamilton), through the soft bone 1.5 mm to the right bregma on the coronal suture. The needle was inserted through a stainless-steel tube that acted as a stopper (needle protrusion, 3.5 mm). Drugs were injected 5 min before the intraperitoneal (ip) administration of an aqueous solution of PPQ (2 mg/kg at 37 °C, in a final volume of 10 mL/kg). The treated mice were placed in a compartemented perpex box maintained at room temperature and were observed for a period of 8 min. During this period the number of abdominal constriction responses for each animal was recorded.

Data Evaluation. The degree of graded antinociceptive protection afforded by the drug was determined according to the method described by Locke *et al.*[24]

ED_{50} values, and their 95% confidence intervals (in parentheses), were determined using the method of Finney.[25]

Chemistry

Melting points were determined on a Büchi 512 hot stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker ARX-300 spectrometer at 303 K. Chemical shifts were recorded in parts per million (δ units) downfield from tetramethylsilane (TMS). Mass spectral data were obtained on a Finnigan MAT TSQ-700 spectrometer. IR spectra were recorded in KBr with a Perkin-Elmer 1420 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at 20 °C at the sodium D line. Silica gel used for flash column chromatography was Kieselgel 60 (230−400 mesh) (E. Merck AG, Darmstadt, Germany). Enantiomeric excesses were measured by chiral HPLC methodology using Shimadzu LC9 equipment and Lichrocart (25 cm × 4.6 mm) Chiradex (5 μm); 0.1 M phosphate buffer (pH 4.0)/MeOH; 0.8 mL/min; concentration 100 γ/mL; UV detector 220 nm. Elemental analyses are indicated only by the symbols of the elements; analytical results were within 0.4% of the theoretical values unless otherwise indicated.

(±)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-6-one Hydrochloride [(±)-1b·HCl]. This product was obtained according to the method described for its N-Me analogue **(±)-1a**.[13] The free base was taken up in MeOH, and the resulting solution was brought to acidic pH with HCl/Et_2O. The solvent was removed *in vacuo*, and the resulting solid was crystallized from acetone. The precipitate was filtered, washed, and dried to yield **(±)-1b**·HCl: mp 243−244 °C; IR (KBr) 3460, 2480, 1715, 1465 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.20 (br s, 1H), 7.26 (dd, J = 8.1, 8.1 Hz, 1H), 7.07 (dd, J = 8.1, 1.0 Hz, 1H), 6.94 (dd, J = 2.0, 1.0 Hz, 1H), 6.82 (dd, J = 8.1, 2.0 Hz, 1H), 3.75 (s, 3H), 3.54 (br d, J = 11.2 Hz, 1H), 3.36−3.22 (m, 2H), 3.11−3.01 (m, 2H), 2.82−2.70 (m, 1H), 2.77 (d, J = 13.5 Hz, 1H), 2.62−2.50 (m, 1H), 2.58 (d, J = 13.5 Hz, 1H), 2.43−2.13 (m, 5H), 2.10−1.98 (m, 1H), 1.23 (t, J = 8.1 Hz, 3H). Anal. ($C_{18}H_{25}NO_2$·HCl) C, H, N, Cl.

(−)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-6-one Hydrochloride [(−)-1b·HCl]. A solution of 5.97 g (20.77 mmol) of **(±)-1b** in 80 mL of EtOH was added to a solution of 8.02 g (20.77 mmol) of (+)-di-*O,O'*-*p*-toluoyl-D-tartaric acid in 80 mL of EtOH. After a gentle warming, the resulting solution was filtered and the less soluble diastereomeric salt crystallized from the filtrate on standing. The salt was recrystallized from EtOH, up to a constant optical activity, to give 5.62 g of (+)-di-*O,O'*-*p*-toluoyl-D-tartrate: mp 161−163 °C; $[\alpha]^{20}_D$ = +57.42 (c = 2, MeOH). Anal. ($C_{38}H_{43}NO_{10}$) C, H, N.

The tartrate salt was transformed into the free base by dissolving it in 5% NaOH solution, extracting with CH_2Cl_2, and evaporating the solvent, yielding 2.3 g (77%) of **(−)-1b** as an oil. $[\alpha]^{20}_D$ = −83.85 (c = 2, $CHCl_3$). The corresponding hydrochloride salt was formed and crystallized as described above for **(±)-1b**·HCl. IR and ^{1}H NMR matched those of the racemate **(±)-1b**·HCl.

(+)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-6-one Hydrochloride [(+)-1b·HCl]. The mother liquors obtained from the first crystallization of the preceding description were evaporated to dryness. The residue was treated with 5% NaOH solution, extracted with CH_2Cl_2, and evaporated to afford 2.75 g (9.6 mmol) of the enriched free base which was dissolved in 45 mL of EtOH. A solution of 3.78 g (9.6 mmol) of (−)-di-*O,O′-p*-toluoyl-L-tartaric acid, dissolved in 45 mL of EtOH, was added to the hot solution of the free base and the diastereomeric salt crystallized on standing. The salt was recrystallized until constant optical activity to give 5.82 g of (−)-di-*O,O′-p*-toluoyl-L-tartrate: mp 162−163 °C; $[\alpha]^{20}_D = -55.36$ (*c* = 2, MeOH). Anal. ($C_{38}H_{43}NO_{10}$) C, H, N.

The tartrate salt was transformed into the free base by dissolving it in 5% NaOH solution, extracting with CH_2Cl_2, and evaporating the solvent, yielding 2.4 g (80%) of **(+)-1b** as an oil, $[\alpha]^{20}_D = +82.20$ (*c* = 2, $CHCl_3$). The corresponding hydrochloride salt was formed and crystallized as described for **(±)-1b**·HCl. IR and ^1H NMR matched those of the racemate **(±)-1b**·HCl.

(±)-*trans*-2-(Cyclopropylmethyl)-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-6-one Hydrochloride [(±)-1c·HCl]. A solution of 1.2 g (4.2 mmol) of **(±)-1b** and 1.8 g (12.6 mmol) of Proton-Sponge (Aldrich) in 34 mL of 1,2-dichloroethane was treated with 1.4 mL (16.8 mmol) of vinyl chloroformate at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min and then refluxed for 3 h. The solvent was removed *in vacuo*, and the residue was taken up in water and extracted with Et_2O. The organic layer was washed with 3% HCl and then was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was then dissolved in EtOH, treated with an excess of HCl/EtOH, and refluxed for 1 h. The solvent was removed *in vacuo*, obtaining 0.88 g (3.08 mmol) of the de-ethylated intermediate which was dissolved in 15 mL of DMF; 0.44 g (3.23 mmol) of (bromomethyl)cyclopropane were added together with 0.64 g (4.6 mmol) of K_2CO_3 and a catalytical amount of KI. The reaction mixture was stirred at 60 °C for 2 h, then the solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (AcOEt/MeOH/concentrated NH_4OH, 90:10:0.8). The resulting solid was dissolved in acetone and treated with an excess of HCl/Et_2O. The precipitate was filtered, washed, and dried to yield 280 mg (30%) of **(±)-1c**·HCl: mp 78 °C dec; IR (KBr) 3400, 2940, 1715, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.00 (br s, 1H), 7.27 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.93 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.81 (dd, *J* = 7.9, 2.0 Hz, 1H), 3.74 (s, 3H), 3.62 (br d, *J* = 11.6 Hz, 1H), 3.46−3.35 (m, 2H), 3.05−2.93 (m, 2H), 2.78 (d, *J* = 14.3 Hz, 1H), 2.65−2.40 (m, 2H), 2.59 (d, *J* = 14.3 Hz, 1H), 2.33−2.00 (m, 6H), 1.12−1.02 (m, 1H), 0.64−0.57 (m, 2H), 0.39−0.32 (m, 2H), MS (EI) *m/z* 314.2 (MH$^+$). Anal. ($C_{20}H_{27}NO_2$·HCl) H, N, Cl; C: calcd, 68.65; found, 68.07.

(±)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(±)-2·HCl]. A solution of 470 mg (1.64 mmol) of **(±)-1b** and 357 mg (2.47 mmol) of phenylhydrazine hydrochloride in 33 mL of MeOH saturated with HCl was refluxed under a nitrogen atmosphere for 3 h and then cooled at room temperature. The reaction mixture was evaporated to dryness, the residue was dissolved in AcOEt and treated with an excess of 1 N NaOH, and the aqueous phase was counterextracted with AcOEt. The combined extracts were dried (Na_2SO_4) and evaporated. The solid residue was purified by flash chromatography (CH_2Cl_2/MeOH/concentrated NH_4OH, 94:5:0.5), yielding 457 mg of **(±)-2**, which were dissolved in 10 mL of acetone and treated with an excess of HCl/Et_2O. The precipitate was filtered, washed, and dried to yield 400 mg (61%) of **(±)-2**·HCl: mp 273−275 °C; IR (KBr) 3400, 3200, 1605, 1460 cm^{-1}; ^1H NMR (free base, $CDCl_3$) δ 7.67 (br s, 1H), 7.44 (m, 1H), 7.21 (m, 1H), 7.11−7.00 (m, 5H), 6.62 (br d, *J* = 8.1 Hz, 1H), 3.69 (s, 3H), 3.10 (d, *J* = 15.7 Hz, 1H), 3.10 (dd, *J* = 12.5, 2.1 Hz, 1H), 3.01−2.85 (m, 4H), 2.68−2.57 (m, 2H), 2.50 (q, *J* = 6.7 Hz, 2H), 2.41 (m, 1H), 2.10−1.98 (m, 2H), 1.14 (t, *J* = 6.7 Hz, 3H). Anal. ($C_{24}H_{28}N_2O$·HCl) C, H, N, Cl.

(+)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(+)-2·HCl]. This compound was prepared from **(−)-1b** using the same procedure reported for **(±)-2**: yield 43%; mp 274−277 °C; $[\alpha]^{20}_D = +147.0$ (*c* = 2, MeOH); IR and ^1H NMR matched those of the racemate **(±)-2**·HCl. Anal. ($C_{24}H_{28}N_2O$·HCl) C, H, N, Cl.

(−)-*trans*-2-Ethyl-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(−)-2·HCl]. This compound was prepared from **(+)-1b** using the same procedure reported for **(±)-2**: yield 47%; mp 273−276 °C; $[\alpha]^{20}_D = -143.1$ (*c* = 2, MeOH); IR and ^1H NMR matched those of the racemate **(±)-2**. Anal. ($C_{24}H_{28}N_2O$·HCl) C, H, N, Cl.

***N,N*-Diethyl-2-phenylhydrazono-3-oxobutyramide.** A solution of 15.7 g (0.1 mol) of *N,N*-diethyl-3-oxobutyramide, 12 g (0.14 mol) of AcONa in 20 mL of water, and 75 mL of EtOH was cooled to 10 °C, and 0.1 mol of a freshly prepared solution of phenyldiazonium chloride were added dropwise. The precipitated solid was filtered and dried *in vacuo* yielding 22.6 g (87%) of product: mp 63−65 °C; IR (KBr) 2970, 1720, 1620, 1605, 1560, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.30 (s, 1H), 7.41−7.22 (m, 5H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.22 (q, *J* = 6.4 Hz, 2H), 2.51 (s, 3H), 1.35 (t, *J* = 6.4 Hz, 3H), 1.20 (t, *J* = 6.4 Hz, 3H), MS (TSP) *m/z* 262.1 (MH$^+$).

(±)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(±)-4b·HCl]. Under a nitrogen atmosphere, 1.4 g (4.9 mmol) of **(±)-1b** and 1.54 g (5.8 mmol) of *N,N*-diethyl-2-phenylhydrazono-3-oxobutyramide were dissolved in a mixture of 5 mL of glacial AcOH and 0.48 g (5.8 mmol) of AcONa. The solution was heated to 60 °C, and then 1.47 g (22.5 mmol) of zinc dust was added portionwise. The resulting mixture was refluxed for 2 h then cooled to room temperature. The precipitate was removed by decantation and washed with 5 mL of glacial AcOH. The combined acidic solutions were diluted with iced water (50 mL), the pH was adjusted to 8 with 20% NaOH, and then the solution was extracted with AcOEt. The organic layer was dried (Na_2SO_4), and the solvent was evaporated, affording a residue that was purified by flash chromatography (AcOEt/MeOH/concentrated NH_4OH, 90:10:1). The resulting solid was dissolved in acetone and the solution treated with an excess of Et_2O/HCl. The solvent was evaporated and the solid triturated with Et_2O, yielding 1.5 g (67%) of **(±)-4b**·HCl: mp 272−274 °C dec; IR (KBr) 3410, 3200, 2920, 2500, 1600, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.84 (br s, 1H), 10.39 (s, 1H), 7.19 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.91 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.76 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.69 (s, 3H), 3.50 (br d, *J* = 11.0 Hz, 1H), 3.42−3,22 (m, 6H), 3.12 (m, 1H), 3.03 (m, 2H), 2.95 (d, *J* = 15.0 Hz, 1H), 2.78−2.50 (m, 5H), 2.18 (ddd, *J* = 11.2, 11.2, 2.0 Hz, 1H), 1.98 (s, 3H), 1.22 (t, *J* = 6.4 Hz, 3H), 1.02 (t, *J* = 6.4 Hz, 6H), MS (TSP) *m/z* 424.2 (MH$^+$). Anal. ($C_{26}H_{37}N_3O_2$·HCl) C, H, N, Cl.

(−)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(−)-4b·HCl]. This compound was prepared from **(−)-1b** using the same procedure reported for **(±)-4b**: yield 85%; mp 273−276 °C dec; $[\alpha]^{20}_D = -20.32$ (*c* = 1, MeOH); IR and ^1H NMR matched those of the racemate **(±)-4b**·HCl. Anal. ($C_{26}H_{37}N_3O_2$·HCl) C, H, N, Cl.

(+)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(+)-4b·HCl]. This compound was prepared from **(+)-1b** using the same procedure reported for **(±)-4b**: yield 74%; mp 273−275 °C dec; $[\alpha]^{20}_D = +20.65$ (*c* = 1, MeOH); IR and ^1H NMR matched those of the racemate **(±)-4b**·HCl. Anal. ($C_{26}H_{37}N_3O_2$·HCl) C, H, N, Cl.

(±)-*trans*-2-[(Diethylamino)carbonyl]-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo-[2,3-*g*]isoquinoline Hydrochloride [(±)-4a·HCl]. This compound was prepared from **(±)-1a**[13] using the same procedure reported for **(±)-4b**: yield 15%; mp 250 °C dec; IR (KBr) 3410, 3200, 2915, 2510, 1605, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.47 (br s, 1H), 10.43 (s, 1H), 7.06 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.87−6.81 (m, 2H), 6.60 (dd, *J* = 7.9, 2.0 Hz, 1H), 3.71 (s, 3H), 3.45 (br d, *J* = 11.2 Hz, 1H), 3.43−3,12 (m, 5H), 2.94 (d, *J* = 15.9 Hz, 1H), 2.74 (br s, 3H), 2.67−2.42 (m, 6H), 2.42 (d, *J* = 13.7

Hz, 1H) 2.04 (ddd, J = 13.7, 13.7, 1.0 Hz, 1H), 1.91 (s, 3H), 1.00 (t, J = 6.4 Hz, 6H), MS (TSP) m/z 410.7 (MH^+). Anal. ($C_{25}H_{35}N_3O_2$·HCl) C, H, N, Cl.

(±)-*trans*-6-(Cyclopropylmethyl)-2-[(diethylamino)carbonyl]-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(±)-4c·HCl]. This compound was prepared from **(±)-1c** using the same procedure reported for **(±)-4b**: yield 62%; mp 190−195 °C. IR (KBr) 3400, 3200, 2915, 2580, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.58 (br s, 1H), 10.40 (s, 1H), 7.20 (dd, J = 7.9, 7.9 Hz, 1H), 7.04 (dd, J = 7.9, 1.0 Hz, 1H), 6.91 (dd, J = 2.0, 1.0 Hz, 1H), 6.76 (dd, J = 7.9, 2.0 Hz, 1H), 3.69 (s, 3H), 3.50 (br d, J = 11.2 Hz, 1H), 3.50−3,22 (m, 5H), 3.01−2.93 (m, 4H), 2.78−2.50 (m, 5H), 2.18 (m, 1H), 1.94 (s, 3H), 1.05−0.98 (m, 2H), 1.02 (t, J = 6.4 Hz, 6H), 0.62−0.58 (m, 2H), 0.42−0.38 (m, 2H), MS (EI) m/z 450.5 (MH^+). Anal. ($C_{28}H_{39}N_3O_2$·HCl) C, H, N, Cl.

(±)-*trans*-2-Ethyl-4a-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(±)-3·HCl]. To a stirred solution of 0.55 mL (5.8 mmol) of boron tribromide in 17 mL of dry $CHCl_3$ was added dropwise, a solution of 383 mg (0.96 mmol) of **(±)-2**·HCl in 5 mL of $CHCl_3$ under a nitrogen atmosphere and at room temperature. After 30 min the solution was poured onto 17 g of ice containing 2 mL of concentrated NH_4OH and stirred for 30 min. The precipitate was collected by filtration; the filtrate was extracted with CH_2Cl_2, dried (Na_2SO_4), evaporated, and combined with the precipitate. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH/concentrated NH_4OH, 79:15:1), and the resulting solid was dissolved in 5 mL of MeOH and treated with an excess of HCl/Et_2O. The precipitate was filtered, washed, and dried to yield 120 mg (33%) of **(±)-3**·HCl: mp >300 °C; IR (KBr) 3450, 3260, 3200, 1600, 1450 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.60 (s, 1H), 10.30 (br s, 1H), 9.25 (s, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.03 (dd, J = 7.4, 7.4 Hz, 1H), 6.97 (dd, J = 7.8, 2.0 Hz, 1H), 6.95−6.89 (m, 3H), 6.53 (dd, J = 7.8, 2.0 Hz, 1H), 3.66 (br d, J = 11.4 Hz, 1H), 3.42 (br d, J = 11.4 Hz, 1H), 3.29 (ddd, J = 11.4, 11.4, 9.5 Hz, 1H), 3.20-3.02 (m, 3H), 3.00−2.80 (m, 3H), 2.72−2.60 (m, 1H), 2.60−2.48 (m, 2H), 2.11 (dd, J = 13.8, 13.8 Hz, 1H), 1.21 (t, J = 6.4 Hz, 3H). Anal. ($C_{23}H_{26}N_2O$·HCl) H, N, Cl, C: calcd, 72.14; found, 71.69.

(+)-(4a*S*,11a*R*)-*trans*-2-Ethyl-4a-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(+)-3·HCl]. This compound was prepared from **(+)-2·HCl** using the same procedure reported for **(±)-3**: yield 63%; mp > 300 °C; $[\alpha]^{20}_D$ = +141.1 (c = 1, MeOH); ee >99.5% (HPLC; 0.1 M phosphate buffer (pH 4.0)/MeOH = 60:40); IR and ^{1}H NMR matched those of the racemate **(±)-3**·HCl. Anal. ($C_{23}H_{26}N_2O$·HCl) H, N, Cl; C: calcd, 72.14; found, 71.72

(−)-(4a*R*,11a*S*)-*trans*-2-Ethyl-4a-(3-hydroxyphenyl)-1,2,3,4,4a,5,11,11a-octahydroindolo[2,3-*g*]isoquinoline Hydrochloride [(−)-3·HCl]. This compound was prepared from **(−)-2** using the same procedure reported for **(±)-3**: yield 63%; mp >300 °C; $[\alpha]^{20}_D$ = −141.5 (c = 1, MeOH); ee >99.5% (HPLC; 0.1 M phosphate buffer (pH 4.0)/MeOH = 60:40); IR and ^{1}H NMR matched those of the racemate **(±)-3**·HCl. Anal. ($C_{23}H_{26}N_2O$·HCl) H, N, Cl, C: calcd, 72.14; found, 71,62.

A sample of the hydrobromide salt was prepared for X-ray analysis. The free base was dissolved in MeOH, and then the resulting solution was brought to acidic pH with 48% HBr. The solvent was removed and the resulting solid crystallized from MeOH, mp >300 °C. Anal. ($C_{23}H_{26}N_2O$·HBr·MeOH) C, H, N, Br.

(±)-*trans*-2-[(Diethylamino)carbonyl]-3,6-dimethyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(±)-5a·HCl]. This compound was prepared from **(±)-4a** using the same procedure reported for **(±)-3**: yield 12%; mp 250 °C dec; IR (KBr) 3450, 3120, 2970, 1600, 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.45 (br s, 1H), 10.40 (s, 1H), 9.30 (s, 1H), 7.06 (dd, J = 7.9, 7.9 Hz, 1H), 6.88−6.82 (m, 2H), 6.59 (dd, J = 7.9, 2.0 Hz, 1H), 3.46 (br d, J = 11.2 Hz, 1H), 3.43−3,12 (m, 5H), 2,94 (d, J = 15.9 Hz, 1H), 2.74 (br s, 3H), 2.67−2.42 (m, 6H), 2.41(d, J = 13.7 Hz, 1H) 2.04 (ddd, J = 13.7, 13.7, 1.0 Hz, 1H), 1.90 (s, 3H), 1.01 (t, J = 6.4 Hz, 6H), MS (TSP) m/z 396.4 (MH^+). Anal. ($C_{24}H_{33}N_3O_2$·HCl) C, H, N, Cl.

(±)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline [(±)-5b]. This compound was prepared from **(±)-4b** using the same procedure reported for **(±)-3**: yield 20%, crystallization solvent EtOH; mp 238−240 °C; IR (KBr) 3200, 2980, 2940, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 9.03 (s, 1H), 6.97 (dd, J = 7.9, 7.9 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.83 (br d, J = 7.9 Hz, 1H), 6.47 (dd, J = 7.9, 2.0 Hz, 1H), 3.45−3.23 (m, 4H), 2.90 (d, J = 15.9 Hz, 1H), 2.83 (dd, J = 10.5, 2.0 Hz, 1H), 2.63−2.42 (m, 6H), 2.35−2.20 (m, 3H), 2.12 (br d, J = 9.6 Hz, 1H), 1.88 (s, 3H), 1.80−1.79 (m, 2H), 1.02 (t, J = 6.4 Hz, 6H), 0.88 (t, J= 6.4 Hz, 3H), MS (TSP) m/z 410.2 (MH^+). Anal. ($C_{25}H_{35}N_3O_2$·0.5H_2O) C, H, N.

(−)-(4a*S*,8a*R*)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline [(−)-5b]. This compound was prepared from **(−)-4b** using the same procedure reported for **(±)-3**: yield 17%, crystallization solvent EtOH; mp 239−241 °C; $[\alpha]^{20}_D$ = −57.94 (c = 1, MeOH); ee >99.5% (HPLC; 0.1 M phosphate buffer (pH 4.0)/MeOH = 85:15); IR and NMR matched those of the racemate **(±)-5b**; MS (TSP) m/z 410.2 (MH^+). Anal. ($C_{25}H_{35}N_3O_2$·0.5H_2O) C, H, N.

(+)-(4a*R*,8a*S*)-*trans*-2-[(Diethylamino)carbonyl]-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrrolo[2,3-*g*]isoquinoline [(+)-5b]. This compound was prepared from **(+)-4b** using the same procedure reported for **(±)-3**: yield 16%, crystallization solvent EtOH; mp 239−240 °C; $[\alpha]^{20}_D$ = +57.49 (c = 1, MeOH); ee >99.5% (HPLC; 0.1 M phosphate buffer (pH 4.0)/MeOH = 85:15); IR and NMR matched those of the racemate **(±)-5b**; MS (TSP) m/z 410.2 (MH^+). Anal. ($C_{25}H_{35}N_3O_2$·0.5H_2O) C, H, N.

(±)-*trans*-6-(Cyclopropylmethyl)-2-[(diethylamino)carbonyl]-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-*g*]isoquinoline Hydrochloride [(±)-5c·HCl]. This compound was prepared from **(±)-4c** using the same procedure reported for **(±)-3**: yield 35%; mp 270−272 °C dec; IR (KBr) 3010, 2700, 1595, 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.50 (br s, 1H), 10.40 (s, 1H), 9.30 (s, 1H), 7.06 (dd, J = 7.9, 7.9 Hz, 1H), 6.90−6.85 (m, 2H), 6.58 (dd, J = 7.9, 2.0 Hz, 1H), 3.61 (br d, J = 11.2 Hz, 1H), 3.45 (br d, J = 11.2 Hz, 1H), 3.40−3,12 (m, 4H), 3.01−2.92 (m, 3H), 2.67−2.42 (m, 6H), 2.14 (ddd, J = 12.0,12.0, 2.0 Hz, 1H), 1.88 (s, 3H), 1.08−1.00 (m, 2H), 1.01 (t, J = 6.4 Hz, 6H), 0.62−0.58 (m, 2H), 0.40−0.36 (m, 2H), MS (EI) m/z 435.3 (M^+). Anal. ($C_{27}H_{37}N_3O_2$·HCl) C, H, N, Cl.

Computer Modeling Studies. Models of compound **5b** and SNC 80 were constructed with standard bond lengths and angles from the fragment database in MacroModel V5.0 (Columbia University, New York, NY 10027) using a Silicon Graphics workstation (Indigo II). The structure of compound **(+)-3** was built by inverting the known X-ray coordinates of the relative counterpart, **(−)-3**. All the compounds have been modeled as free bases and minimized by the MacroModel/BatchMin V5.0 program using the MM2 force field. To perform an extensive conformational search, a MonteCarlo/Energy minimization[26] was carried out ($E_i - E_{min} \leq 40$ kJ/mol). Representative minimum energy conformations of each compound were used to perform superimposition studies. For compound **(−)-5b**, X-ray data agreed favorably with the low-energy conformers used throughout our studies.[27]

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Supporting Information Available: Data for single-crystal X-ray structure analysis of compounds **(−)-3** and **(−)-5b** (14 pages). Ordering information is given on any current masthead page.

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