Examination of the D_2/5-HT_2 Affinity Ratios of Resolved 5,6,7,8,9,10-Hexahydro-7,10-iminocyclohept[*b*]indoles: An Enantioselective Approach toward the Design of Potential Atypical Antipsychotics†

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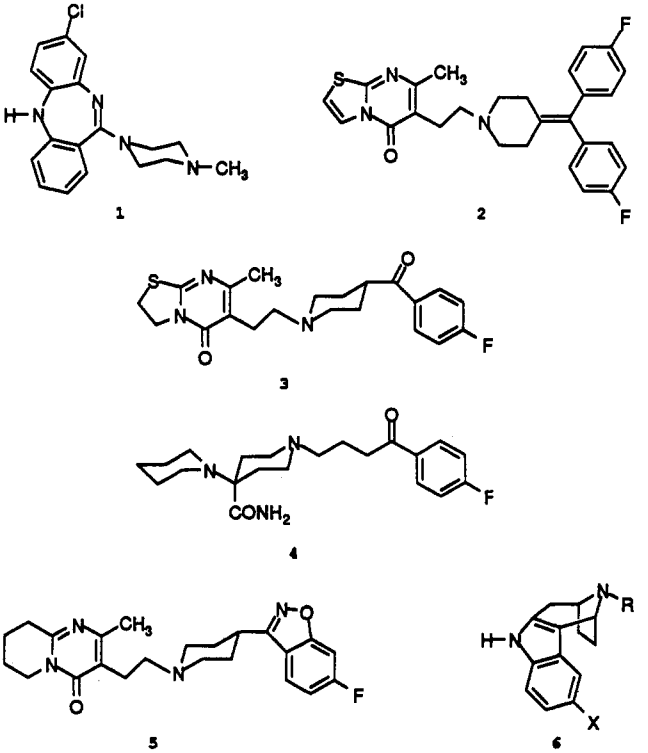
Enantiomers of several *N*-substituted 5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indoles were obtained by the resolution of 2-fluoro-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole and 5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole followed by *N*-alkylation. These, as well as the racemates, were evaluated for their affinity for the 5-HT_2 and D_2 receptors. Those compounds possessing the 7*S*,10*R* stereochemistry were consistently recognized by the 5-HT_2 and D_2 receptors as the eutomer. 2-Fluoro-11-[4-(4-fluorophenyl)-4-oxobutyl]-5,6,7,8,9,10-hexahydro-7*S*,10*R*-iminocyclohept[*b*]indole [(7*S*,10*R*)-8] had the highest affinity for the 5-HT_2 receptor (K_i = 0.80 nM), while its distomer (7*R*,10*S*)-8 was the most selective member of this class of bridged γ-carbolines (D_2/5-HT_2 = 562). Incorporation of a benzoyl or isosteric benzisoxazole moiety tethered by a four-carbon spacer to a bridged γ-carboline nucleus, possessing the 7*S*,10*R* absolute configuration, produced high affinity ligands for the 5-HT_2 and D_2 receptors.

Introduction

The discovery of clozapine (1, Chart I), in the mid-1960s, resulted in an improved antipsychotic for treating schizophrenia without producing extrapyramidal side effects (EPS) or tardive dyskinesia. Though the use of clozapine is restricted, due to drug-induced agranulocytosis, clozapine's clinical effectiveness has led investigators on a quest toward clarifying the biological basis of schizophrenia in order to develop improved, side-effect-free antipsychotics.[1] Due to clozapine's interactions with a variety of receptors, particularly the 5-HT_2 and D_2 receptors, it has been suggested that its effectiveness may stem from its ability to modulate the dopaminergic and serotonergic systems in an integrated fashion.[2-4] Potential atypicality has been correlated with the ratio of D_2/5-HT_2 receptor binding; e.g. clozapine-like antipsychotics show a ratio >1 whereas typical neuroleptics show a ratio <1. Clinical studies of ritanserin[5] (2), setoperone[6] (3), and pipamperone[7] (4) have provided evidence that blockade of the 5-HT_2 receptors may ameliorate EPS associated with dopamine D_2 receptor blockade. More recently, another putative antipsychotic, risperidone (5), which has both D_2 and 5-HT_2 antagonistic properties, was reported to improve positive and negative symptoms of schizophrenia with little propensity to produce EPS.[8]

In two recent papers,[9,10] we have reported the discovery and properties of a series of bridged γ-carbolines (6) which can be structurally tailored to possess high affinity for the σ binding site and serotonin 5-HT_2 and dopamine D_2 receptors. In this paper, we report the preparation of a series of enantiomers of *N*-substituted 5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indoles and their affinity for the 5-HT_2 and D_2 receptors. This study was prompted by the known chiral discriminatory properties of drug-receptor interactions,[11] which impelled us to further investigate whether the 5-HT_2 and D_2 receptor affinities of this bridged γ-carboline series were associated with isomers having the same or different absolute stereochemistry. Concomitantly, we were interested in discerning the structural factors necessary to vary the D_2/5-HT_2 affinity ratio, since the right balance of 5-HT_2 and D_2 antagonism may play an important role for the successful therapeutic treatment of schizophrenia.

Chart I



Chemistry

The syntheses of all racemic compounds, including the key intermediates 6 and 7, as well as the resolution of 6

† This paper is dedicated to Dr. Carl Kaiser, a mentor and friend, whose interest in medicinal chemistry has resulted in over 250 publications and patents.

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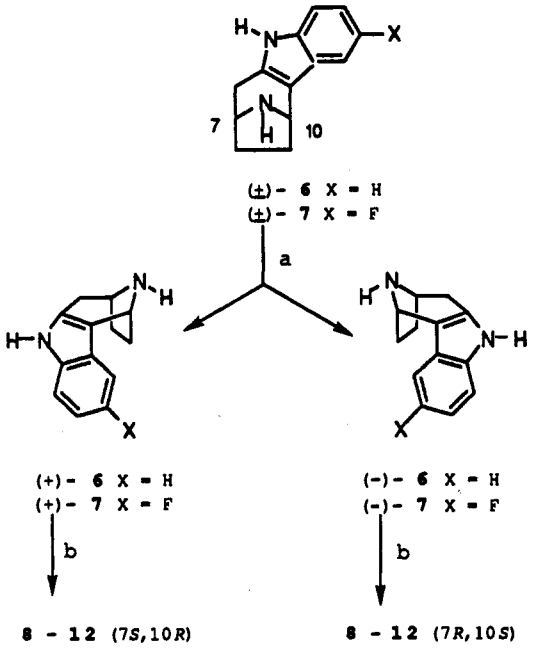
Scheme I[a]



[a] Reagents and conditions: (a) Classical resolution using L- and D-tartaric acid; (b) RBr(Cl) (KI), K_2CO_3, DMF.

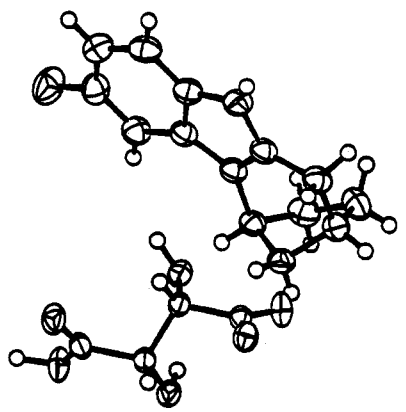
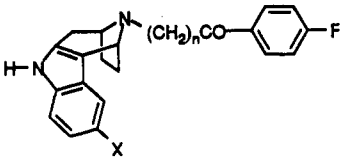


Figure 1. ORTEP drawing of (+)-7·D-tartrate.

were reported previously.[9] The resolution of **7** was achieved similarly to that of **6**, to afford the diastereomeric tartrate salts of **7**. Recrystallization of the tartrate salts from a mixture of ethanol/water provided enantiomerically enriched isomers of **7** (Scheme I).

An HPLC analysis was performed to determine the optical purity of (-)- and (+)-**7** in a fashion similar to that previously described for **6**[9,12] (see Experimental Section). Coupling of the liberated free bases with (*R*)-(+)-*O*-methylmandelic acid (Aldrich, >99.5 ± 0.5% optical purity) provided the corresponding *O*-methylmandeloylamides, which were resolved by analytical HPLC (reverse phase, C_{18}, 40% acetonitrile–60% water). The optical purities of (-)- and (+)-**7** were observed to be >98.2% and >99.3%, respectively. The absolute configuration of (+)-**6** was established to be 7*S*,10*R* through single-crystal X-ray crystallographic analysis of its (*R*)-*O*-methylmandeloylamide as previously reported.[9] Conclusive assignment of the absolute stereochemistry of (+)- and (-)-**7** was established by an X-ray crystallographic analysis of the D-tartrate salt of (+)-**7**. As a result, the stereocenters of (+)- and (-)-**7** were observed to be 7*S*,10*R* and 7*R*,10*S*, respectively. The ORTEP drawing of (+)-**7** is shown in Figure 1 and the cell parameters and characteristics are shown in Table IV.

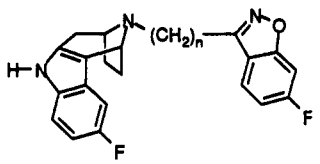
Table I. In Vitro Binding Affinity Data for Derivatives 8–10



compd[b]	*n*	X	K_i (nM)[a] 5HT$_2$ receptor[d]	K_i (nM)[a] D_2 receptor[e]	D_2/5HT$_2$
rac-8[c]	3	F	1.96 ± 0.37	220 ± 31	112
(*S*,*R*)-8	3	F	0.80 ± 0.09	99.3 ± 23.6	124
(*R*,*S*)-8	3	F	2.56 ± 0.13	1440 ± 171	562
rac-9[c]	4	F	2.98 ± 0.70	2.77 ± 1.04	0.93
(*S*,*R*)-9	4	F	1.87 ± 0.37	2.59 ± 1.17	1.38
(*R*,*S*)-9	4	F	109 ± 21.4	755 ± 217	6.93
rac-10[c]	4	H	2.81 ± 0.94	4.43 ± 0.85	1.58
(*S*,*R*)-10	4	H	2.13 ± 0.59	1.70 ± 0.55	0.80
(*R*,*S*)-10	4	H	32.0 ± 8.82	113 ± 42.1	3.53
ritanserin			0.61 ± 0.07	47.0 ± 9.0	77
clozapine			3.68 ± 0.25	168 ± 40	45.6
haloperidol			26.5 ± 2.50	0.47 ± 0.17	0.018

[a] The K_i binding data for Tables I and II were generated as described in Experimental Section. All values are the mean of at least two to four separate determinations. [b] (*S*,*R*) and (*R*,*S*) means (7*S*,10*R*) and (7*R*,10*S*), respectively. [c] *rac* = racemic; compounds were previously prepared as reported in ref 9. [d] Versus [^{3}H]ketanserin. [e] Versus [^{3}H]sulpiride.

Table II. In Vitro Binding Affinity Data for Benzisoxazole Analogues 11 and 12



compd[b]	*n*	K_i (nM)[a] 5HT$_2$ receptor[d]	K_i (nM)[a] D_2 receptor[e]	D_2/5HT$_2$
rac-11[c]	3	8.54 ± 1.85	308 ± 28	36.1
(*S*,*R*)-11	3	4.25 ± 1.75	233 ± 25	54.8
(*R*,*S*)-11	3	6.62 ± 2.85	1840 ± 285	278
rac-12[c]	4	7.98 ± 1.87	2.70 ± 0.74	0.34
(*S*,*R*)-12	4	6.11 ± 3.60	0.71 ± 0.08	0.12
(*R*,*S*)-12	4	170 ± 77	2380 ± 98	14

[a–e] See footnotes of Table I.

The resolved, liberated free bases of **6** and **7** were alkylated with the appropriate side chains in dimethylformamide to afford **8-12** (Tables I–III) as described in the Experimental Section. Compounds were converted either to their corresponding oxalate or hydrochloride salts for biological testing.

Results and Discussion

The in vitro affinity for the 5-HT$_2$ and D_2 receptors was assessed by the ability of all test compounds to displace [^{3}H]ketanserin and [^{3}H]sulpiride, respectively.[13,14]

As indicated in Tables I and II, the 5-HT$_2$ and D_2 receptors consistently recognized the high-affinity ligand in the racemic mixture as the 7*S*,10*R* enantiomer (eutomer), while the lower affinity 7*R*,10*S* enantiomer was distinguished as the distomer.[15,16] The most potent member of this series at the 5-HT$_2$ receptor was (7*S*,10*R*)-**8** (K_i = 0.80 nM), having a D_2/5-HT$_2$ ratio of 124. Though its mirror image, (7*R*,10*S*)-**8**, retained high affinity for the 5-HT$_2$ receptor (K_i = 2.56 nM), low affinity was observed for the D_2 receptor, resulting in the most 5-HT$_2$-selective ligand in this series (D_2/5-HT$_2$ = 562). Another member of this series which possessed excellent selectivity for the 5-HT$_2$ receptor was the benzisoxazole

Table III. Physical Data

compd	abs config	formula[a]	mp, °C	recrys solvent	$[\alpha]^{24}_D$, deg[d]	(c, solvent)	% yield[g]
8	7S,10R	$C_{23}H_{22}F_2N_2O \cdot C_2H_2O_4$	165–169	THF	−13.5	(1, MeOH)[f]	78
8	7R,10S	$C_{23}H_{22}F_2N_2O \cdot C_2H_2O_4$	167–171	THF	+13.0	(1, MeOH)[f]	78
9	7S,10R	$C_{24}H_{24}F_2N_2O \cdot HCl$[c]	104–109	EtOH–Et_2O	+22.8	(1, $CHCl_3$)	93
9	7R,10S	$C_{24}H_{24}F_2N_2O \cdot HCl$[c]	99–105	THF–Et_2O	−20.6	(1, $CHCl_3$)	95
10	7S,10R	$C_{24}H_{25}FN_2O \cdot C_2H_2O_4$	95–100	THF–Et_2O	+18.7	(1, CH_2Cl_2)	79
10	7R,10S	$C_{24}H_{25}FN_2O \cdot C_2H_2O_4$[b]	98–101	THF/Et_2O	−18.6	(2, CH_2Cl_2)	89
11	7S,10R	$C_{23}H_{21}F_2N_3O \cdot C_2H_4O_4$	103–108	THF	+17.9	(2, $CHCl_3$)	86
11	7R,10S	$C_{23}H_{21}F_2N_3O \cdot C_2H_2O_4$	105–110	THF	−18.8	(2, $CHCl_3$)	73
12	7S,10R	$C_{24}H_{23}F_2N_3O \cdot C_2H_2O_4$[c]	92–97	THF–Et_2O	+13.8	(2, $CHCl_3$)	79
12	7R,10S	$C_{24}H_{25}F_2N_3O \cdot C_2H_2O_4$[c]	83–87	THF–Et_2O	−15.5	(2, $CHCl_3$)	70

[a] $C_2H_2O_4$ represents oxalic acid. All new compounds analyzed correctly (±0.4%) for C, H, N. [b] Monohydrate. [c] Hemihydrate. [d] All rotations are of free bases unless otherwise specified. [f] Oxalate salt. [g] Yield refers to the alkylation step depicted in Scheme I (b).

Table IV. Cell Parameters and Experimental Details of the X-ray Analysis of (+)-7 D-Tartrate

Crystal Data	
empirical formula	$C_{17}H_{19}FN_2O_6$
formula weight	366.35
crystal color, habit	colorless, plate
crystal dimensions (mm)	0.400 × 0.200 × 0.100
no. of reflections used for unit cell determination	
(2θ range)	25 (79.3–79.9°)
ω scan peak width at half-height	0.26
lattice parameters	a = 7.7466(8) Å
	b = 8.3872(9) Å
	c = 13.2216(6) Å
	b = 101.285(6)°
	V = 842.4(1) Å^3
space group	$P2_1$
Z value	2
D_{calc}	1.444 g/cm^3
$F000$	384
Intensity Measurements	
$\mu_{CuK\alpha}$	9.58 cm^{-1}
diffractometer	Rigaku AFC5R
radiation	Cu Kα (λ = 1.54178 Å)
temperature	23 °C
take-off angle	6.0°
detector aperture	6.0 mm horizontal
	6.0 mm vertical
crystal to detector distance	40 cm
scan type	$w - 2\theta$
scan rate	16.0°/min (in ω)
	(four rescans)
scan width	(1.37 + 0.35 tan θ)°
$2\theta_{max}$	119.0°
no. of reflections	2881

(7R,10S)-11 (D_2/5-HT_2 = 278). Furthermore, (7S,10R)-11 was observed to have 5-HT_2 and D_2 receptor affinities very similar to those of clozapine, consequently resulting in comparable affinity ratios (i.e. D_2/5-HT_2 = 46 vs 55).

As noted from the data presented in Tables I and II, the length of the side-chain spacer and absolute configuration at stereocenters C-7 and C-10 in the γ-carboline nucleus play a crucial role in contributing to the high 5-HT_2 selectivity of (7R,10S)-8 and (7R,10S)-11. The D_2 receptor is much more sensitive to both of these structural variables than is the 5-HT_2 receptor. Thus, affinity for the D_2 receptor was reduced to a far greater extent than for the 5-HT_2 receptor when the side chains contained only 3 methylene units and the γ-carboline nucleus possessed the less favored 7R,10S absolute configuration. As a result, highly selective 5-HT_2 ligands were afforded by not optimizing either of these structural features with respect to the D_2 receptor. High affinity for the D_2 receptor was achieved when the γ-carboline, concomitantly tethered to benzoyl or benzisoxazole moieties by a four-carbon linkage as noted in our earlier report,[10] had the 7S,10R absolute stereochemistry. As a result, the eutomers (7S,10R)-9 and (7S,10R)-10 had very similar affinities for both the D_2 and 5-HT_2 receptors. In the benzisoxazole series, a dramatic effect was noticed when the side chain spacer of (7S,10R)-11 was increased by one methylene unit [i.e. (7S,10R)-12]. This change, while having only little effect on 5-HT_2 receptor affinity, resulted in a 328-fold increase in affinity for the D_2 receptor. Consequently a reverse selectivity, similar to typical neuroleptics, was observed for (7S,10R)-12 (D_2/5-HT_2 = 0.12).

The enantioselective affinity ratio (eudismic ratio) was consistently observed to be higher at the D_2 receptor versus the 5-HT_2 receptor. Eudismic ratios at the 5-HT_2 receptor varied from 1.6 to 58, whereas the eudismic ratio with respect to the D_2 receptor ranged from 14.5 to 3352, with the four-methylene unit tether exhibiting much higher enantioselectivities than the shorter side-chain analogues.

Conclusions

Large differences are often noted in the affinities of enantiomers for receptors. In this paper, we observed a common enantioselectivity of the 5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indoles for the 5-HT_2 and D_2 receptors, with the eutomer possessing the 7S,10R absolute configuration. In contrast, the distomers (7R,10S)-8 and (7R,10S)-11 were more discriminating and therefore exhibited the highest selectivity for the 5-HT_2 receptor. Differences in the eudismic ratios at the 5-HT_2 and D_2 receptors not only led to the identification of selective 5-HT_2 ligands but also resulted in the discovery of ligands retaining various combinations of 5-HT_2 and D_2 affinities.

Examining the enantioselective properties of ligand–receptor interactions versus the 5-HT_2 and D_2 receptors may allow us to discover novel atypical antipsychotics by varying the D_2/5-HT_2 ratio in a structurally predictable fashion. Though chirality is not a requirement for biological activity, an understanding of the processes involved may aid in the design of more active and selective antipsychotics with fewer side effects.

Experimental Section

Chemistry. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a General Electric QE300 spectrometer or Bruker AC 400-MHz spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained on a Beckman FT 1300 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Specific rotation determinations at the sodium D line were obtained on a Perkin-Elmer 241-MC polarimeter at 24 °C. Single-crystal X-ray analysis of (+)-7 was carried out by the Molecular Structure Corp., The Woodlands, TX. Thin-layer chromatography (TLC) was performed using 0.25-mm silica gel fluorescent coated plates (Merck, Kieselgel 60 F-254).

Resolution of (±)-2-Fluoro-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indole [(±)-7]. To a suspension of 2-fluoro-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indole[9] [(±)-7] (8.0

g, 37.0 mmol) in hot ethanol (60 mL) was slowly added a warm solution of l-tartaric acid (5.55 g, 37.0 mmol) in water (20 mL). The mixture, which became homogeneous, was allowed to stand at ambient temperature for 3 h and then placed in a refrigerator. After 2 days the precipitated salt was filtered and washed with ethanol (10 mL), affording light tan crystals: 5.1 g; mp 213–214 °C dec; $[\alpha]^{24}_D$ = −6.92° (c = 1.0, H_2O). The salt was dissolved in a hot 31% solution of water in ethanol (51 mL; 16.5 mL of water and 36.5 mL of ethanol), allowed to stand at ambient temperature for 18 h, and then placed in a refrigerator for 1 day. The salt was filtered, washed (20 mL of ethanol), and dried to afford light tan crystals: 4.04 g; mp 215–216 °C dec; $[\alpha]^{24}_D$ = −7.24° (c = 1.0, H_2O). The salt was again recrystallized from a hot solution of 31% aqueous ethanol (42 mL) by allowing it to stand at ambient temperature for 2 h and then placing it in a refrigerator for another 18 h to afford large light tan crystals: yield, 3.25 g (47.8%); mp 217–218 °C dec; $[\alpha]^{24}_D$ = −8.16° (c = 1.0, H_2O). Anal. ($C_{13}H_{13}N_2F \cdot C_4H_6O_6$) C, H, N. The free base was regenerated by stirring the salt in the presence of aqueous ammonia (100 mL) and methylene chloride (300 mL). After stirring for 1 h, the organic layer was separated, dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford (−)-7 as a white crystalline solid: yield, 1.71 g (43%); >98% ee (HPLC of diastereomeric amides); mp 180–182 °C; $[\alpha]^{24}_D$ = −41.8° (c = 1.0, MeOH). Anal. ($C_{13}H_{13}N_2F$) C, H, N.

The combined mother liquors of the above tartrate were evaporated under reduced pressure to remove most of the ethanol. To this aqueous solution was added aqueous ammonia (200 mL) and methylene chloride (300 mL). The mixture was stirred for 1 h, and then the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated to afford 5.67 g (26.3 mmol) of free base. The free base was suspended in hot 25% aqueous ethanol (30 mL), and D-tartaric acid (3.94 g, 26.3 mmol) was added. The mixture, which became homogeneous, was allowed to stand at ambient temperature for 1 day. The salt was isolated and dried: 6.27 g; mp 210–211 °C dec; $[\alpha]^{24}_D$ = +7.17° (c = 1.4, H_2O). The salt was recrystallized from 30% aqueous ethanol (53 mL). After allowing the mixture to stand at +5 °C for 1 day, the precipitated salt was isolated and dried: 4.97 g; mp 215–216 °C dec; $[\alpha]^{24}_D$ = +8.06° (c = 1.3, H_2O). The salt was recrystallized again from 30% aqueous ethanol (50 mL) and isolated after allowing to stand at +5 °C for 1 day: 3.74 g; mp 216–217 °C dec; $[\alpha]^{24}_D$ = +8.29° (c = 1.2, H_2O). Anal. ($C_{13}H_{13}N_2F \cdot C_4H_6O_6$) C, H, N. The free base was regenerated, as described in the L-tartrate procedure, using aqueous ammonia (100 mL) and methylene chloride (300 mL) to afford (+)-7 as an off-white crystalline solid: yield, 1.78 g (44%); >99% ee (HPLC of diastereomeric amides); mp 175–177 °C; $[\alpha]^{24}_D$ = +42.3° (c = 1.2, MeOH). Anal. ($C_{13}H_{13}N_2F$) C, H, N.

General Procedure for *N*-Alkylation. 2-Fluoro-11-[4-(4-fluorophenyl)-4-oxobutyl]-5,6,7,8,9,10-hexahydro-7(*S*),10-(*R*)-iminocyclohept[*b*]indole [(+)-10]. A mixture of 2-fluoro-5,6,7,8,9,10-hexahydro-7(*S*),10(*R*)-iminocyclohept[*b*]indole [(+)-7] (659 mg, 3.04 mmol), 5-bromo-1-(4′-fluorophenyl)-1-pentanone[9] (870 mg, 3.35 mmol), and potassium carbonate (550 mg, 3.98 mmol) in anhydrous dimethylformamide (15 mL) was stirred at room temperature for 12 h. The reaction mixture was dissolved in water (50 mL) and extracted with methylene chloride (2 × 100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum. The product was purified by chromatography (flash silica, MeOH–CH_2Cl_2, 1:20) to afford a pale yellow foam: yield, 1.12 g (93%); ^{1}H NMR ($CDCl_3$) δ 1.53–1.75 (5H, m), 1.90–1.97 (1H, m), 2.28–2.35 (2H, m), 2.40 (1H, d, J = 16.6 Hz), 2.60 (2H, m), 2.93 (2H, t, J = 6.8 Hz), 3.26 (1H, dd, J = 16.6, 4.0 Hz), 3.70 (1H, m), 4.34 (1H, d, J = 4.8 Hz), 6.83 (dt, J = 9.1, 2.4 Hz), 7.07–7.11 (3H, m), 7.17 (1H, m), 7.90–7.95 (2H, m), 8.24 (1H, s); IR ($CHCl_3$) 3471 (s), 1684 (s) cm^{-1}. See Table III for physical data.

HPLC Analysis. Derivatization and Enantiomeric Excess Determination of (+)- or (−)-7.[12] To a mixture of (−)-7 (41 mg, 0.19 mmol), 1-hydroxybenzotriazole hydrate (28 mg, 0.21 mmol), and (*R*)-(−)-α-methoxyphenylacetic acid (35 mg, 0.21 mmol, Aldrich, 99.5 ± 0.5% optically pure) in methylene chloride (3 mL) at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (40 mg, 0.21 mmol). The reaction mixture was stirred for 1 h and quenched by the addition of water (2 mL). The mixture was extracted with methylene chloride (10 mL), the organic layer dried over anhydrous magnesium sulfate and filtered, and the solvent removed under vacuum to afford the crude product mixture. The residue was dissolved in methanol (3 mL) and analyzed by HPLC (reverse phase, C_{18}; 40% acetonitrile–60% water; flow, 1.5 mL/min; UV at 254 nM). (−)-7 was calculated to be >98% ee and (+)-7 was calculated to be >99% ee.

X-Ray Crystallographic Analysis. The absolute configuration of (+)-7 was established by an X-ray analysis of its d-tartrate salt. A colorless plate-shaped crystal of $C_{17}N_{19}FN_2O_6$ having approximate dimensions of 0.400 × 0.200 × 0.100 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated Cu Kα radiation and a 12-kW rotating anode generator. The structure was solved by direct methods.[17] The non-hydrogen atoms were refined either anisotropically or isotropically. The hydrogen atoms were either refined isotropically or included in the structure factor calculation in idealized positions (d_{C-H} = 0.95 Å). The standard deviation of an observation of unit weight was 2.58. The cell parameters and characteristics are given in Table IV.

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