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Synthesis and resolution of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide by preferential crystallization

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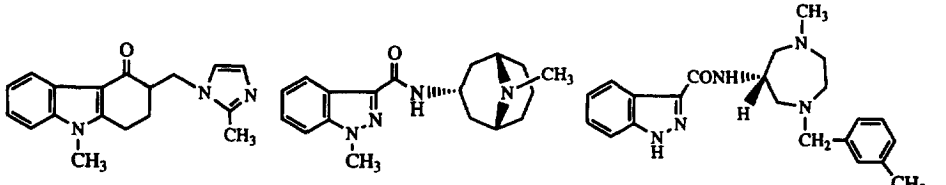
Abstract: (±)-*N*-[1-Methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-**1** was prepared from *N*-methyl-*N'*-(3-methylbenzyl)-ethylenediamine **5** and 2-(1-benzyloxycarbonyl-1*H*-indazole-3-carbonylamino)propenal **4** and was found to exist as a racemic mixture based on the melting point, solubility, infrared spectrum, and X-ray diffraction pattern. Resolution by a preferential crystallization of (±)-**1** and successive recrystallization from acetone gave the enantiomerically pure (*R*)-isomer, which showed a potent and selective 5-HT_3 receptor antagonistic activity. © 1997 Elsevier Science Ltd

In the last decade, the discovery of multiple serotonin (5-HT) receptor subtypes has been reported. 5-HT receptors are currently classified into four types; 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4 receptors.[1] Recently, a number of potent 5-HT_3 receptor antagonists such as ondansetron and granisetron have been reported.[2] These compounds have been shown to be clinically highly effective for the blockade of chemotherapy-induced nausea and emesis,[3] and ondansetron and granisetron are on the market as antiemetics. In addition, several 5-HT_3 receptor antagonists are currently being investigated in man for the treatment of gastrointestinal motility disorders[4] such as irritable bowel syndrome or various centrally mediated disorders[5] such as anxiety and schizophrenia. Previously, we reported that the structurally novel compound (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-**1** showed the most potent 5-HT_3 receptor antagonistic activity in a hexahydro-1*H*-1,4-diazepinylcarboxamide series. The difference in potency of (*R*)-(−)-**1** vs. (*S*)-(+)-**1** made it desirable to use the enantiomerically pure antagonist. Thus, the enantiomerically active (*R*)-(−)-**1** (DAT-582 as its dihydrochloride) was selected as a promising candidate for a clinical trial.[6]



(*R*)-(−)-**1** was prepared via resolution of (±)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine (±)-**2**; the Mosher's amides (*S,R*)-**3** and (*S,S*)-**3** of the amine (±)-**2** were successfully separated into each diastereomer by silica gel column chromatography, and (*S,R*)-**3** was hydrolyzed to give the desired enantiomerically active amine (*R*)-**2** (Scheme 1).[7] However, this procedure is not practical because of the low yield of the required product and the use of the expensive Mosher's acid. This prompted us to find more practical methods applicable to large scale preparation of (*R*)-(−)-**1**. The melting point of the racemate **1** was lower than that of the enantiomerically active **1**, and the solubility of the racemate **1** in acetone was more than that of the enantiomerically active **1**. Furthermore, the

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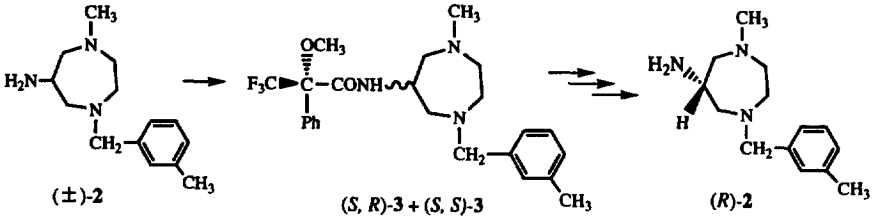
infrared (IR) spectra and the X-ray diffraction patterns of the racemate 1 and the enantiomerically active **1** were completely identical (Table 1). In racemic mixtures, in general, both X-ray diffraction patterns and the solid state IR spectra of respective enantiomers are identical with the corresponding racemate, and the melting point of the enantiomer is higher than that of the racemate.



Scheme 1.

Furthermore, the solubility of each of the pure enantiomers is less than that of the racemic compound in a suitable solvent for crystallization. The above results suggested that the racemate **1** forms racemic mixture (conglomerate), which could be resolved by a preferential crystallization from a supersaturated solution. The preferential crystallization method[8] is considered to be one of the most useful methods for practical and industrial purposes since it enables the desired enantiomer to crystallize preferentially from a supersaturated solution of the racemate by simple inoculation of the same enantiomer. This method is restricted, however, to racemates existing as racemic mixtures. Unfortunately, this requirement is only rarely met, since about 90% of racemates do in fact form racemic compounds on crystallization. We describe here the preparation of (*R*)-(−)-**1** involving the resolution of the racemate **1** by a preferential crystallization method.

Synthesis of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide

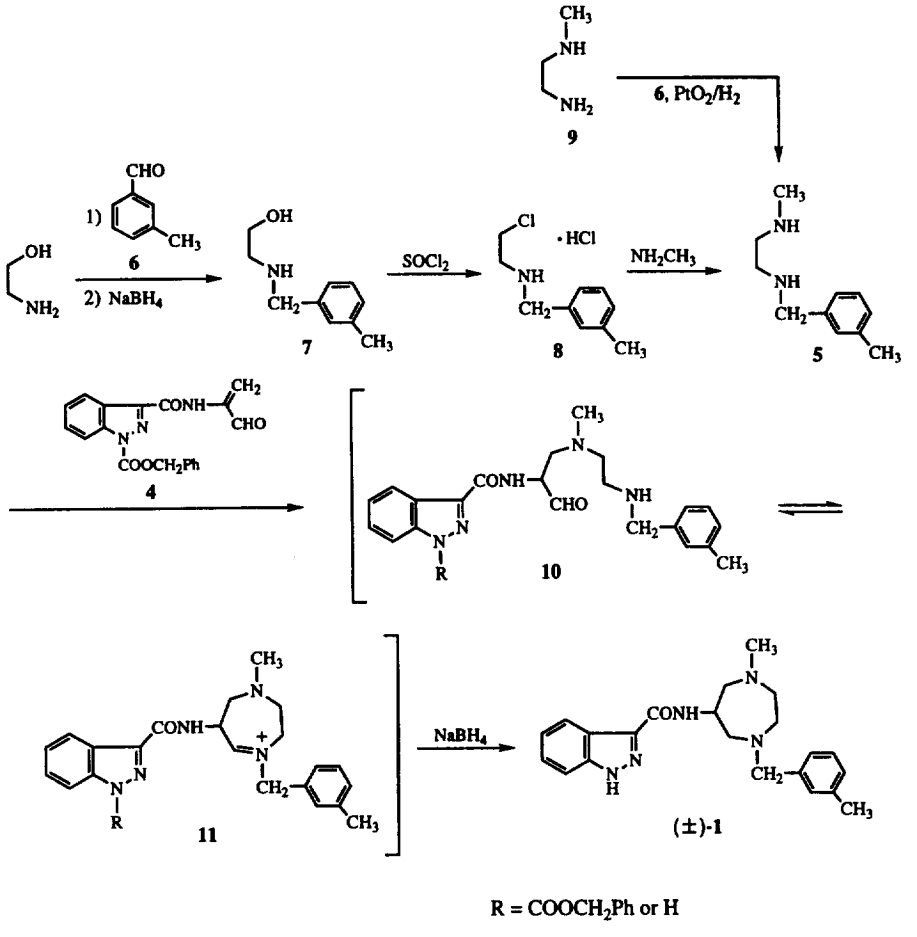
For an efficient and practical method for synthesis of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-**1**, our original formation of a hexahydro-1*H*-1,4-diazepine ring was applied; reaction of 2-(1-benzyloxycarbonyl-1*H*-indazole-3-carbonylamino)propenal **4** with *N*,*N*′-disubstituted ethylenediamines followed by $NaBH_4$ reduction directly gave the corresponding *N*-(hexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamides.[9] The synthesis of the novel *N*-methyl-*N*′-(3-methylbenzyl)ethylenediamine **5** was performed as follows. Treatment of 3-tolualdehyde **6** with 2-aminoethanol followed by reduction of the iminium salt with $NaBH_4$ produced 2-[(3-methylbenzyl)amino]ethanol **7** in 88% yield. Reaction of **7** with thionyl chloride produced *N*-(2-chloroethyl)-*N*-(3-methylbenzyl)amine hydrochloride **8**, which was treated with 40% aqueous CH_3NH_2 solution in EtOH to afford the ethylenediamine **5** in 67% overall yield. Alternatively, **5** was obtained directly by hydrogenation of the iminium salt prepared from the available *N*-methylethylenediamine **9** and **6** in 47% yield. Treatment of **5** thus

Table 1. Properties of *N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide **1**

	Racemate	Enantiomerically Active Form
mp (°C)	141—144	163—164
Solubility[a]	37.55	16.16
IR Spectrum	Identical	
X-ray Diffraction Pattern	Identical	

a) mg/ml in acetone at 30 °C.

obtained with the 2-propenal **4**, followed by reduction of the iminium salt **11**, derived from the aldehyde **10**, with $NaBH_4$ gave the racemate **1** in 73% yield (Scheme 2).



Scheme 2.

Resolution of (±)-1 by preferential crystallization

As a preliminary examination of the resolution by a preferential crystallization, (*R*)-(−)-**1**, which was prepared from (*R*)-**2** and 1*H*-indazole-3-carboxylic acid,[10] was seeded with a supersaturated acetone solution of the racemate **1** (1.0 g), and the solution was allowed to stand for *ca.* 1 h at room temperature. The deposited crystals of (*R*)-(−)-**1** (10 mg) showed $[\alpha]_D^{25}$ −58.5 (*c* 0.20, MeOH) as expected, and the enantiomeric excess was 96% ee. To optimize the degree of supersaturation, the resolution of (±)-**1** by a preferential crystallization was first conducted by solutions with *ca.* 279%[11] [A: (±)-**1** (10.0 g) in acetone (90 g)], *ca.* 503%[11] [B: (±)-**1** (10.0 g) in acetone (50 g)], and *ca.* 629%[11] [C: (±)-**1** (10.0 g) in acetone (40 g)] degrees of supersaturation using 0.010 g of (*R*)-(−)-**1** as seed crystals at around 25°C. The results are shown in Figure 1. The enantiomeric excess of the solution gradually increased with resolution time in all cases. The resolution of B gave *ca.* 23% ee of the enantiomeric excess of the solution at about 170 min as the highest degree. On the other hand, in the case of A, the enantiomeric excess at 300 min was *ca.* 14% ee. Thus, we selected supersaturation *ca.* 503% supersaturation of B. In the case of B, effect of the cooling temperature (25°C, 30°C, 35°C, and 40°C) was next examined. As a result, there was not a much differences between the cooling temperature

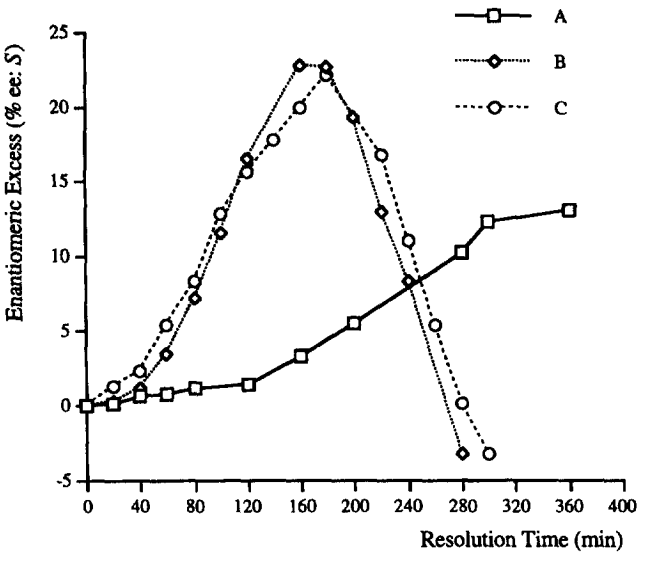


Figure 1. Relationship between enantiomeric excess of solution and resolution time in resolution of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-**1**. Conditions: (±)-**1**, 10.0 g; seed crystals, 0.010 g of (*R*)-(−)-**1**; solvent (acetone), A: 90 g, B: 50 g, C: 40 g; cooling temperature, around 25°C. The enantiomeric excess of the solution was calculated on the basis of the chiral HPLC method.

and the enantiomeric excess of the solution. Therefore, the solution with *ca.* 503% supersaturation was left to stand at 30°C. Table 2 showed the relationship between the amount of deposited crystals (*R*)-(−)-**1** and the enantiomeric excess of the solution in resolution of (±)-**1**. The amount of crystals gradually increased with the enantiomeric excess of the solution, and 2.0 g of (*R*)-(−)-**1** with 95% ee was obtained when the enantiomeric excess of the solution was 22.7% ee (run 4). Based on these results, successive resolution was attempted to obtain (*R*)-(−)-**1** (Table 3). A supersaturated solution of (±)-**1** (10.0 g) in acetone (50 g) was employed as the initial solution. (*R*)-(−)-**1** was seeded, and the solution was left to stand at around 30°C for about 3.5 h, giving 2.0 g of (*R*)-(−)-**1** with 95% ee (the enantiomeric excess of the filtrate was 22.7% ee determined on the basis of chiral HPLC). Alternative seeding of (*S*)-(+)-**1** or (*R*)-(−)-**1** to the supersaturated solution at a similar magnitude gave (*S*)-(+)-**1** or (*R*)-(−)-**1** with high enantiomeric excess (90%–95% ee). Finally, crystals with the (*R*)-configuration were combined and recrystallized from acetone to give highly purified (*R*)-(−)-**1**. The enantiomeric excess of (*R*)-(−)-**1**, thus obtained, was determined to be practically 100% ee on the basis of the chiral HPLC method. This procedure could be applicable to the resolution of 50 g scale of the racemate **1**. While resolution by a preferential crystallization of (±)-**1** provided enantiomerically pure (*R*)-(−)-**1**, the inherent loss of (*S*)-(+)-**1** was a significant drawback. However, attempted racemizations of (*S*)-(+)-**1** were unsuccessful.

In conclusion, (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-**1** was prepared from 2-(1-benzyloxycarbonyl-1*H*-indazole-3-carbonylamino)propenal **4** and *N*-methyl-*N'*-(3-methylbenzyl)ethylenediamine **5** in 73% yield and found to exist as a racemic mixture. The racemate **1** was successively resolved by a preferential crystallization to give a potent and selective 5-HT_3 receptor antagonist (*R*)-(−)-**1** with high optical purity.

Experimental section

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 spectrometer. Chemical ionization mass

Table 2. Relationship between enantiomeric excess of the solution and amount of crystals (*R*)-(−)-**1** in resolution of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide[a]

Run	Enantiomeric Excess[b] of the Solution (% ee)/Rotation	Amount of Crystals (*R*)-(-)-**1** (g)	Enantiomeric Excess (ee %)[b]
1	4.0/+	0.46	95
2	9.1/+	0.91	95
3	17.4/+	1.6	94
4	22.7/+	2.0	95

a) The initial composition of the solution; (±)-**1** (10.0 g) in acetone (50 g). In all runs, 0.010 g of seed (*R*)-(-)-**1** was added. The solution was left to stand at around 30 °C. *b*) The enantiomeric excess was determined on the basis of the chiral HPLC method.

spectra were obtained on a Hitachi M-80B spectrometer. ^{1}H NMR spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard. Optical rotations were measured at 589 nm with a Jasco DIP-4 digital polarimeter. Analytical HPLC was performed with Shimadzu LC-6A and SPD-6A instruments. Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure.

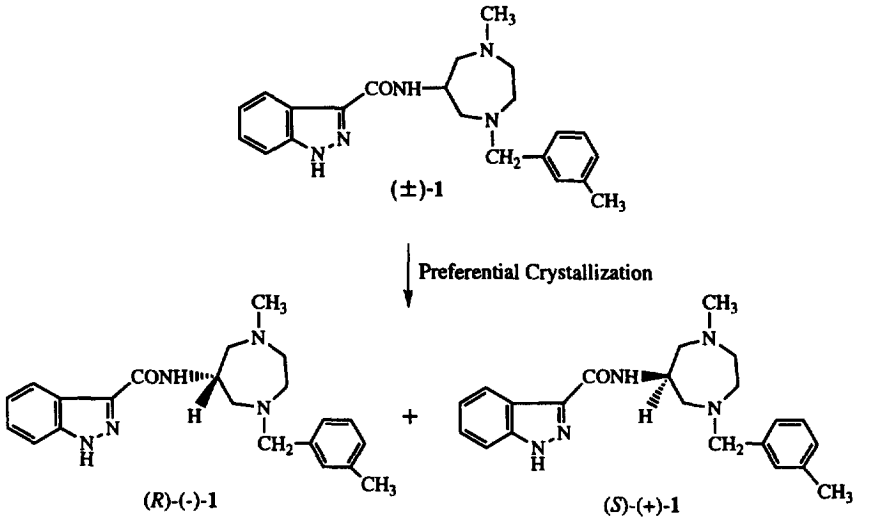
2-[(3-Methylbenzyl)amino]ethanol **7**

A mixture of 3-tolualdehyde (**6**, 808 g, 6.7 mol), 2-aminoethanol (493 g, 8.1 mol), $NaHCO_3$ (848 g, 10 mol), and MeOH (7500 ml) was heated to reflux for 4 h and then cooled to room temperature. To the reaction mixture was added portionwise $NaBH_4$ (305 g, 8.1 mol) kept at *ca.* 10°C. The mixture was stirred at room temperature for 2 h, and then the solvent was evaporated to leave a residue, which was taken up in $CHCl_3$ and water. The organic layer was separated and washed with brine. The solvent was evaporated to give an oily residue, which was distilled to afford 970 g (88%) of **7** as a colorless oil, bp 119–121°C/2–3 mmHg. ^{1}H NMR ($CDCl_3$); δ 2.34 (3H, s, CH_3), 2.4 (2H, br s, OH, NH), 2.77 (2H, t, *J*=7 Hz, CH_2NH), 3.64 (2H, t, *J*=7 Hz, CH_2OH), 3.75 (2H, s, CH_2Ar), 7.02–7.28 (4H, m, ArH). IR (neat) ν cm^{-1}: 3270, 3280, 2920, 1440, 1040. MS *m/z*: 166 (MH^+). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.48; H, 9.42; N, 8.58.

N-*(2-Chloroethyl)*-N-*(3-methylbenzyl)amine hydrochloride* **8**

The method of Brook and Ramage[12] was applied. Thionyl chloride (1000 ml, 13.7 mol) was added dropwise to a solution of **7** (1000 g, 6.1 mol) in $CHCl_3$ (5000 ml) at 0–5°C. The mixture was heated to reflux for 6 h and then cooled to *ca.* 10°C. After addition of Et_2O (7000 ml), the solution was left overnight at room temperature. The resulting precipitates were collected by filtration, washed with Et_2O (1000 ml), and dried to give 1240 g (93%) of **8** as a pale brown powder, which was used in the next step without further purification. An analytical sample was obtained by recrystallization from EtOH, mp 190–192°C. ^{1}H NMR (DMSO-d_6); δ 2.32 (3H, s, CH_3), 3.26 (2H, t, *J*=7 Hz, CH_2CH_2), 3.93 (2H, t, *J*=7 Hz, CH_2CH_2), 4.14 (2H, s, CH_2Ar), 7.19–7.41 (4H, m, ArH). MS *m/z*: 183 (MH^+). Anal. Calcd for $C_{10}H_{15}Cl_2N$: C, 54.56; H, 6.87; Cl, 32.21; N, 6.36. Found: C, 54.70; H, 6.73; Cl, 32.05; N, 6.36.

Table 3. Successive resolution by preferential crystallization of (±)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide **1**[a)]



Run	(±)-1 added (g)	Seed	Time[b)] (min)	Enantiomeric Excess[c)] of the Solution (% ee)/Rotation	Amount of Crystals (g)	Rotation of Crystals	Enantiomeric Excess[c)] (% ee)
1	–	(*R*)-(-)-1	220	22.7/+	2.0	-	95
2	4.0	(*S*)-(+)-1	210	19.4/-	4.6	+	92
3	4.6	(*R*)-(-)-1	190	21.2/+	3.8	-	95
4	3.8	(*S*)-(+)-1	205	21.0/-	3.9	+	95
5	3.9	(*R*)-(-)-1	210	21.5/+	3.8	-	95
6	3.8	(*S*)-(+)-1	220	16.4/-	5.0	+	90
7	5.0	(*R*)-(-)-1	200	21.3/+	3.4	-	92
8	3.4	(*S*)-(+)-1	215	21.2/-	3.9	+	94
9	3.9	(*R*)-(-)-1	190	22.2/+	4.0	-	93
10	4.0	(*S*)-(+)-1	220	21.4/-	4.0	+	95
11	4.0	(*R*)-(-)-1	200	20.8/+	4.0	-	95

a) The initial composition of the solution; (±)-**1** (10.0 g) in acetone (50 g). In all runs, 0.010 g of seed was added. *b*) The solution was left to stand at around 30 °C. *c*) The enantiomeric excess was determined on the basis of the chiral HPLC method.

N-Methyl-N'-(3-methylbenzyl)ethylenediamine **5**

a) The method of Jucker and Rissi[13] was applied. To a mixture of 40% aqueous CH_3NH_2 solution (3000 ml, 35 mol) and EtOH (3500 ml) was added portionwise **8** (682 g, 3.1 mol) kept at *ca.* 10°C. The mixture was heated at *ca.* 50°C for 16 h and cooled to room temperature. The reaction mixture was concentrated, diluted with a solution of KOH (600 g) in water (500 ml), and extracted with toluene (1000 ml×2, 600 ml×1). The extract was concentrated to dryness to afford a yellow oily residue, which was distilled to give 398 g (72%) of **5** as a colorless oil, bp 104–106°C/2–3 mmHg. ^{1}H NMR ($CDCl_3$); δ 1.61 (2H, s, NH), 2.35 (3H, s), 2.43 (3H, s), 2.65–2.85 (4H, m, CH_2CH_2), 3.77 (2H, s,

CH_2Ar), 7.02–7.24 (4H, m, ArH). IR (neat) ν cm^{-1}: 2830, 2790, 1440. MS *m/z*: 179 (MH$^+$). Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.82; H, 10.14; N, 15.76.

b) A solution of *N*-methylethylenediamine (**9**, 7.4 g, 0.10 mol) and **6** (12.0 g, 0.10 mol) in EtOH (120 ml) was stirred at room temperature in the presence of platinum oxide (0.12 g) under hydrogen. When hydrogen consumption ceased, the platinum oxide was filtered off. The filtrate was concentrated to leave an oily residue, which was distilled to give 8.3 g (47%) of **5**, bp 100–101°C/1–2 mmHg. This compound was identical with the sample obtained above, by comparison of IR and ^{1}H NMR spectra.

*(±)-N-[1-Methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide (±)-1*

To a suspension of 2-(1-benzyloxycarbonyl-1*H*-indazole-3-carbonylamino)propenal[9] (**4**, 304 g, 0.87 mol) and MeOH (7600 ml) was added dropwise **5** (453 g, 2.5 mol) at room temperature over a period of 1 h. The mixture was stirred at the same temperature for 3 h. $NaBH_4$ (132 g, 3.5 mol) was added portionwise at room temperature, and then the mixture was stirred at the same temperature for 18 h. The solvent was evaporated to leave a residue, which was dissolved in water (2000 ml) and Et_2O (2500 ml). The organic layer was separated, and the aqueous solution was extracted with Et_2O (2500 ml×2). The combined organic layer was washed with brine and concentrated to dryness. The residue was purified by short silica gel column chromatography with $CHCl_3$/MeOH=30/1 to give an amorphous solid, which was crystallized from acetone to afford 319 g (73%) of (±)-**1**, mp 141–144°C. ^{1}H NMR ($CDCl_3$); δ 2.25 (3H, s), 2.55 (3H, s), 2.50–3.80 (8H, m), 3.62 (2H, s, C$H_2C_6H_4$), 4.55 (1H, m, 6-CH), 6.95–7.45 (7H, m, indazole 5-H, 6-H, 7-H, ArH), 8.42 (1H, d, *J*=9 Hz, indazole 4-H), 8.98 (1H, br d, *J*=9 Hz, CONH). IR (KBr) ν cm^{-1}: 3294, 2820, 1649, 1541, 1528. MS *m/z*: 368 (MH$^+$). Anal. Calcd for $C_{22}H_{26}N_5O$: C, 70.00; H, 7.21; N, 18.55. Found: C, 69.70; H, 7.44; N, 18.35.

Resolution of (±)-1 by preferential crystallization (Table 2)

Racemate **1** [(±)-**1**, (10.0 g)] was completely dissolved in an excess of acetone (100 g) at reflux temperature, and the resulting clear solution was concentrated under atmosphere pressure to leave a supersaturated acetone solution (60 g). The hot solution was seeded with (*R*)-(−)-**1** (0.010 g) and left to stand at around 25°C. After HPLC analysis of the solution (4.0% ee, 9.1% ee, 17.4% ee, and 22.7% ee), the crystallized (*R*)-(−)-**1** was collected by filtration, washed successively with a small amount of acetone and Et_2O, and dried at room temperature to give 0.46 g, 0.91 g, 1.6 g, and 2.0 g, respectively. The enantiomeric excesses of the solution and the obtained crystals were calculated on the basis of chiral HPLC [column, Ultron ES-OVM (Shinwa Chemical Industries, Ltd., Japan); 4.6 mm ϕ×150 mm; eluent, 20 mM KH_2PO_4 (pH 4.0)–CH_3CN (9:1); flow rate, 1.2 ml/min; column temperature, 25°C; detection, 220 nm]. The retention times of (*R*)-(−)-**1** and (*S*)-(+)-**1** were 10.7 min and 19.6 min, respectively.

Successive resolution of (±)-1 by preferential crystallization (Table 3)

Racemate **1** [(±)-**1**, (10.0 g)] was completely dissolved in an excess of acetone (100 g) at reflux temperature, and the resulting clear solution was concentrated under atmosphere pressure to leave a supersaturated acetone solution (60 g). The hot solution was seeded with (*R*)-(−)-**1** (0.010 g) and left to stand at around 30°C for about 3.5 h. After HPLC analysis of the solution, white crystals were collected by filtration, washed successively with a small amount of acetone and Et_2O, and dried at room temperature to give 2.0 g of (*R*)-(−)-**1** (The enantiomeric excess was analyzed by chiral HPLC; 95% ee). Successively, (±)-**1** (4.0 g) and acetone (40 g) were added to the filtrate and dissolved under reflux temperature. The solution was similarly concentrated, seeded with (*S*)-(+)-**1** (0.01 g), and allowed to stand at around 30°C for about 3.5 h. Similar treatment of the deposited white crystals gave 4.6 g of (*S*)-(+)-**1** (92% ee). The process was repeated in a similar manner, and the enantiomers (*R*)-(−)-**1** and (*S*)-(+)-**1** were alternatively obtained. The crystals with (*R*)-configuration (runs 1, 3, 5, 7, 9, and 11 in Table 3) were combined and recrystallized twice from acetone to afford 16.0 g of the enantiomerically pure (*R*)-(−)-**1** (>99.5% ee). The enantiomeric excess was analyzed by chiral HPLC.

(*R*)-(−)-**1** thus obtained was identical with the sample prepared in the alternative synthesis,[7] based on comparison TLC behavior and IR and ^{1}H NMR spectra.

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References

1. a) Richardson, B. P.; Engel, G. *Trends Neurosci.*, **1986**, *9*, 424–428; b) Bradley, P. B.; Engel, G.; Feniuk, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, N. D.; Mylecharane, E. J.; Richardson, B. P.; Saxena, P. R. *Neuropharmacology*, **1986**, *25*, 563–576; c) Peroutka, S. J. *Trends Neurosci.*, **1988**, *11*, 496–500; d) Clarke, D. E.; Graig, D. A.; Fozard, J. R. *Trends Pharmacol. Sci.*, **1989**, *10*, 385–386.
2. a) Peroutka, S. J. *Annu. Rev. Neurosci.*, **1988**, *11*, 45–60; b) King, F. D. Structure Activity Relationships of 5-HT_3 Receptor Antagonists. In *5-Hydroxytryptamine-3 Receptor Antagonists*, King, F. D.; Jones, B. J.; Sanger, G. J. Eds., CRC Press Inc., **1994**; pp. 1–43.
3. Plosker, G. L.; Goa, K. L. *Drugs*, **1991**, *42*, 805–824.
4. Miyata, K.; Kamato, T.; Nishida, A.; Ito, H.; Yuki, H.; Yamano, M.; Tsutsumi, R.; Katsuyama, Y.; Honda, K. *J. Pharmacol. Exp. Ther.*, **1992**, *261*, 291–303.
5. a) Cooper, S. J.; Abbott, A. *Trends Pharmacol. Sci.*, **1988**, *9*, 269–271; b) Roca, J.; Artaiz, I.; Del Río, J. *Exp. Opin. Invest. Drugs*, **1995**, *4*, 333–342; c) *5-Hydroxytryptamine-3 Receptor Antagonists*, King, F. D.; Jones, B. J.; Sanger, G. J. Eds., CRC Press Inc., **1994**.
6. Yoshida, N.; Omoya, H.; Kato, S.; Ito, T. *Eur. J. Pharmacol.*, **1992**, *216*, 435–440.
7. Kato, S.; Morie, T.; Ito, T.; Yoshida, N. *Jpn. Kokai Tokkyo Koho* JP 05,230,057 [93,230,57] [*Chem. Abstr.*, **1994**, *120*, 164242*c*].
8. Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.*, **1980**, *80*, 215–230.
9. Harada, H.; Morie, T.; Hirokawa, Y.; Kato, *S. Chem. Pharm. Bull.*, **1996**, *44*, 2205–2212.
10. Yoshida, T.; Matsuura, N.; Yamamoto, K.; Doi, M.; Shimada, K.; Morie, T.; Kato, S. *Heterocycles*, **1996**, *43*, 2701–2712 and references cited therein.
11. The degree of supersaturation (%) was calculated from the equation below, where W is the weight (g) of acetone, d (0.791) is specific gravity of acetone, and S (31.45 mg/ml) is the solubility of the racemate (±)-**1** in acetone at 25°C.

$$\% = \frac{10.0 \times 1000}{\frac{W}{d} \times S} \times 100$$

12. Brook, P. R.; Ramage, G. R. *J. Chem. Soc.*, **1955**, 896–900.
13. Jucker, E.; Rissi, E. *Helv. Chim. Acta*, **1962**, *45*, 2383–2403.

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