Synthesis and Enantioselectivity of Optically Active 1- and 3-Substituted 4-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols and Related Compounds as Norepinephrine Potentiators

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Optically active 1,2-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (1*R*,4*R*-3a and 1*S*,4*S*-3b, 1*S*,4*R*-4a, and 1*R*,4*S*-4b) and 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines (4*S*-5a and 4*R*-5b) were prepared in order to examine the effects of the 1-, 3-, and 4-substituents of 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (PI-OH) (1) on the enantioselectivity for norepinephrine (NE) potentiating activity. The conformations and absolute configurations of 3—5 were determined from their ^{1}H-NMR and circular dichroism (CD) spectra and by single-crystal X-ray diffractometric analysis. The NE potentiating activity of the optically active 3—5 and previously prepared 3-methyl derivatives (3*R*,4*R*-6a and 3*S*,4*S*-6b) of PI-OH were tested. The results show that compounds 3, 4, and 6 had high enantioselectivity for NE potentiation: the 4*R* series of the enantiomers exhibited activity but not the 4*S*-enantiomers. The activity of the 4-desoxy compound 5 also resided exclusively in the 4*S*-enantiomer. These findings suggest the presence of a specific receptor for NE uptake, and the enantiomers 3a, 4a, 5a, and 6a may be antagonistic at this NE uptake receptor.

Key words norepinephrine potentiator; antidepressant; enantioselectivity; optically active tetrahydroisoquinoline; optical resolution; norepinephrine uptake mechanism

In the previous papers,[1] we reported the synthesis of 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (PI-OH) (**1**), a compound with a structure similar to that of the antidepressant nomifensine (Chart 1), and related compounds as norepinephrine (NE) potentiators. The potentiating activity of PI-OH (**1**) was found to be due to the inhibition of NE uptake.[2] From a study on the structure–activity relationships of PI-OH (**1**), the 4-(4-chlorophenyl) derivative (**2**) was found to have potent activity and was considered to be a candidate for a new antidepressant.[1c] Since optically active **1** and **2** showed enantioselectivity for NE potentiation,[1c,3] we were interested in examination of the effects of 1-, 3-, and 4-substituents of **1** on this enantioselectivity. Here we report the synthesis of optically active 1,4-*cis*- and 1,4-*trans*-1,2-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (**3a, b** and **4a, b**) and 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolines (**5a, b**), as well as the NE potentiating activity of **3a, b**, **4a, b**, **5a, b**, and optically active 3,4-*trans*-2,3-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (**6a, b**) prepared in the previous study.[1d]

Chemistry

In the previous paper,[1c] we reported the synthesis of 1,2-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol, but its stereochemistry could not be determined. Hence, we reexamined the synthesis of the 1-methyl derivative (**3** and **4**) of PI-OH and the optical resolution of **3** and **4** in this study. Treatment of *N*-(2-iodo-α-methylbenzyl)-phenacylamine (**7**) with *n*-BuLi gave two diastereomers **3** (mp 136—137 °C, 37%) and **4** (oil, 27%). The relative stereochemistry of the 1-methyl and 4-phenyl groups were assigned as *cis* for **3** and *trans* for **4** from the nuclear Overhauser effect (NOE) enhancements (Fig. 1). The *cis* configuration in **3** was supported by observation of long-range coupling between hydrogens at C-1 and C-3 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. These spectral data also suggest that the conformations of **3** and **4** are as shown in Fig. 1. The stereochemistry of **3** was finally determined by single-crystal X-ray diffractometric analysis of the methiodide (**8**) of (+)-**3a** (described below), as shown in Fig. 2. Therefore, the structure of the compound having mp 136—137 °C was concluded to be **3**. Steric total energies of the diastereomers **3** and **4** were calculated to be 53.3 kcal/mol and 55.5 kcal/mol, respectively, by Biograf (Molecular Mechanics Inc.) on an IRIS 4D/320 GTX computer. These energies seem consistent with the chemical yields of **3** (37%) and **4** (27%). The racemic **3** and **4** were resolved by HPLC with a chiral stationary phase (Daicel Chiralcel OJ)[1c,3] using hexane-2-propanol as an eluent to give the enantiomers, (+)-**3a**, $[\alpha]_D$ +75.1° and (−)-**3b**, $[\alpha]_D$ −74.7°, and (+)-**4a**, $[\alpha]_D$ +24.1° and (−)-**4b**, $[\alpha]_D$ −19.5°, respectively. The absolute configurations of these optically active compounds were determined by an exciton chirality method.[4] The negative exciton chirality in the circular dichroism (CD) spectrum (Fig. 3) of (+)-**3a** suggests the absolute configuration at C4 to be *R*. The stereochemical relation between the 1-methyl and 4-phenyl groups in **3** is *cis* as noted above. Therefore, the stereochemistry of (+)-**3a** might be 1*R*,4*R*.

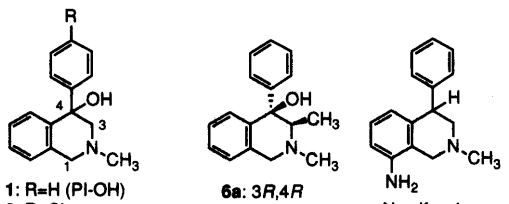

Chart 1

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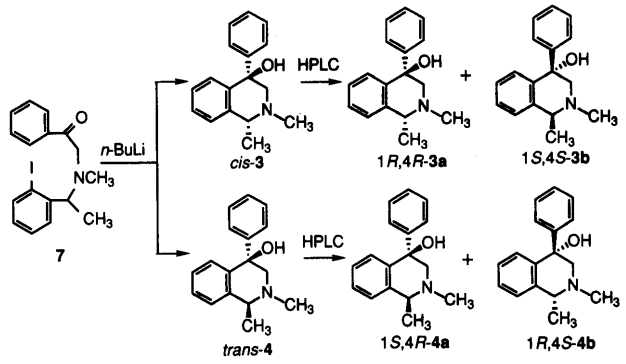

Chart 2

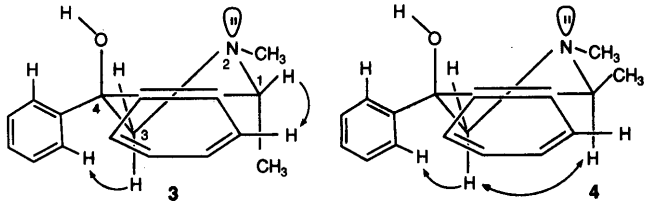

Fig. 1. NOE Enhancements and Conformations of **3** and **4**

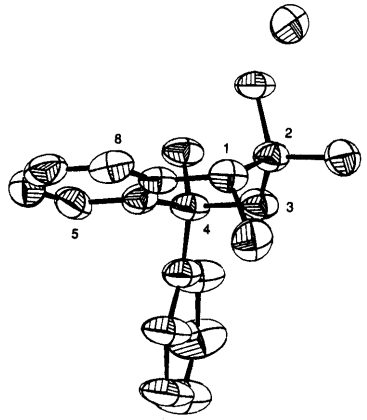

Fig. 2. ORTEP Drawing of **8**

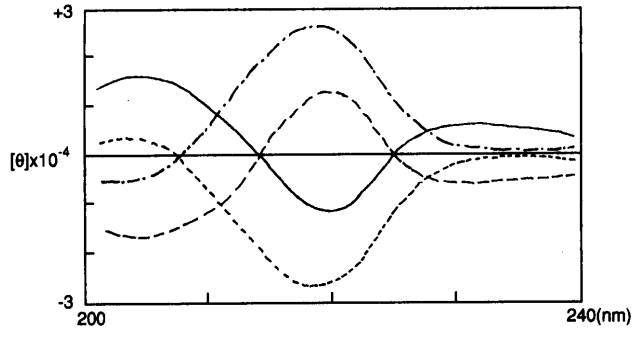

Fig. 3. CD Spectra of (1*R*,4*R*)-**3a**, (1*S*,4*S*)-**3b**, (1*S*,4*R*)-**4a**, and (1*R*,4*S*)-**4b** in MeOH

(——) (1*R*,4*R*)-**3a**; (– – –) (1*S*,4*S*)-**3b**; (------) (1*S*,4*R*)-**4a**; (—·—) (1*R*,4*S*)-**4b**.

In the similar manner, the stereochemistries of (−)-**3b**, (+)-**4a**, and (−)-**4b** were determined to be 1*S*,4*S*, 1*S*,4*R*, and 1*R*,4*S*, respectively.

Attempted resolution of racemic 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**)[1b] was unsuccessful by recrystallization of the diastereomeric salts with di-*p*-toluoyl-D-tartaric acid[5] and 1*S*-(+)-10-camphorsulfonic acid,[6] and by an HPLC method. Thus, the preparation of the optically active **5** was planned *via* optical resolution

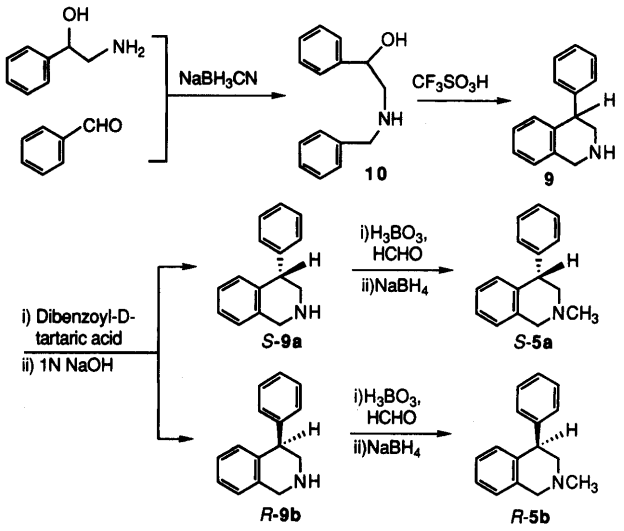

Chart 3

of a secondary amine (**9**), as shown in Chart 3. The isoquinoline (**9**) was prepared in good yield by Friedel–Crafts reaction with trifluoromethanesulfonic acid of *N*-benzyl-*β*-phenylethanolamine (**10**), which was obtained by reductive amination[7] of benzaldehyde with *β*-phenylethanolamine. The diastereomeric salts of **9** with dibenzoyl-D-tartaric acid were recrystallized from EtOH, followed by treatment of the crystals with 1 N NaOH to give (+)-**9b**, $[\alpha]_D$ +11.1°. Similar treatment of the crystals obtained from the mother liquid separated from the salts of (+)-**9b** gave (−)-**9a**, $[\alpha]_D$ −11.1°. The positive exciton chirality in the CD spectrum (see Experimental) of (+)-**9b** indicates the absolute configuration to be *R*. Therefore, the absolute configuration of (−)-**9a** is *S*. The *N*-methylation of *S*-**9a** and *R*-**9b** with formalin and $NaBH_4$ gave the optically active *S*-(+)-**5a**, $[\alpha]_D$ +17.3° and *R*-(−)-**5b**, $[\alpha]_D$ −16.7° in good yields, respectively.

Results and Discussion

The activity of the optically active PI-OH analogues **3a,b**, **4a,b**, **6a,b**, and the related compounds **5a,b** prepared in this study or the previous study[1d] to potentiate the contraction of rat anococcygeus muscle by NE was determined by the methods described in our previous papers.[2,1c] As shown in Table 1, high enantioselectivity for NE potentiation was found: the activity resided exclusively in the 4*R*-series of compounds **3a**, **4a**, and **6a**. These results are consistent with the enantioselectivity of PI-OH (**1**) and the 4-chlorophenyl analogue (**2**) as reported in previous papers.[1c,3] It was also found that the stereochemistry of the substituents at C-1 and C-3 in PI-OH (**1**) influenced the activity as follows. Compound 1*R*,4*R*-**3a** having a quasi-axial methyl group at C-1 (Fig. 1) was almost equipotent with 4*R*-PI-OH (**1a**), but 1*S*,4*R*-**4a** having a quasi-equatorial methyl group was significantly less active than 4*R*-PI-OH (**1a**). Furthermore, 3*R*,4*R*-**6a**[1d] having an equatorial methyl group at C-3 showed a weak activity, being equipotent with 1*S*,4*R*-**4a**. These results suggest that the molecule with an axial substituent such as **3a** provides a good match to the receptor[8] of NE uptake, while the equatorial substituent at C-1 and C-3 interferes greatly with the binding of **4a**

Table 1. Potentiating Activities of Optically Active PI-OH Analogues (3, 4, and 6) and Related Compound (5) on the Response of Rat Anococcygeus Muscle to Norepinephrine

Compound	n[b]	pD_2 value (activity ratio)[a]					
		Concentration (M) of test compound					
		0	10^{-7}	3×10^{-7}	10^{-6}	3×10^{-6}	10^{-5}
4*R*-**1a**	6	6.48±0.08 (1.0)	7.01±0.09 (3.8)	7.26±0.11 (6.0)	7.58±0.11 (12.6)	7.73±0.07 (17.8)	7.69±0.06 (16.2)
1*R*,4*R*-**3a**	6	6.40±0.08 (1.0)	6.61±0.09 (1.6)	6.82±0.07 (2.6)	7.21±0.07 (6.5)	7.44±0.08 (11.0)	7.60±0.08 (15.8)
1*S*,4*S*-**3b**	3	6.39±0.03 (1.0)	6.37±0.08 (1.0)	6.32±0.12 (0.9)	6.26±0.07 (0.7)	6.19±0.12 (0.6)	6.19±0.11 (0.6)
1*S*,4*R*-**4a**	6	6.34±0.04 (1.0)	6.42±0.06 (1.2)	6.45±0.06 (1.3)	6.63±0.05 (1.9)	6.97±0.06 (4.3)	7.14±0.05 (6.3)
1*R*,4*S*-**4b**	3	6.28±0.07 (1.0)	6.36±0.12 (1.2)	6.37±0.13 (1.2)	6.29±0.06 (1.0)	6.33±0.06 (1.1)	6.38±0.11 (1.3)
4*S*-**5a**	6	6.43±0.05 (1.0)	7.34±0.05 (8.1)	7.60±0.06 (14.8)	7.59±0.07 (14.5)	7.45±0.07 (10.5)	7.28±0.12 (7.1)
4*R*-**5b**	4	6.46±0.07 (1.0)	6.45±0.05 (1.0)	6.41±0.06 (0.9)	6.34±0.06 (0.8)	6.20±0.06 (0.5)	6.10±0.07 (0.4)
3*R*,4*R*-**6a**	6	6.34±0.05 (1.0)	6.42±0.07 (1.2)	6.48±0.07 (1.4)	6.77±0.06 (2.7)	7.10±0.05 (5.8)	7.13±0.10 (6.2)
3*S*,4*S*-**6b**	3	6.41±0.07 (1.0)	6.45±0.17 (1.0)	6.34±0.10 (0.9)	6.36±0.11 (0.9)	6.35±0.06 (0.9)	6.38±0.14 (0.9)

a) Activity ratio is calculated as the antilogarithm of the difference between the pD_2 values for NE obtained in the absence and presence of the test compounds. *b*) n is the number of experiments.

and **6a** to the receptor. The 4-desoxy compound **5** also showed high enantioselectivity for NE potentiation (Table 1). The enantiomer 4*S*-**5a**, of which the stereochemistry at C-4 corresponds to those of **3a**, **4a**, and **6a**, exhibited potentiating activity. However, the activity of 4*S*-**5a** was greatly diminished at higher concentrations due to the α_1-antagonistic activity.[1c] Compound 4*R*-**5b** showed no potentiating activity, but rather had weak inhibiting activity. The results in this study indicate that the stereochemistry at C-4 in PI-OH analogues is more important for the NE potentiation than those at C-1 and C-3, and the ethanolamine skeleton with 4*R* configuration may play an important role for selective NE potentiating activity without α_1-antagonistic activity.

High enantioselectivity in potentiating the action of NE has not been generally reported.[9] The question as to whether the neuronal uptake pump has absolute stereoselectivity for phenethylamines has not yet been completely resolved.[10] Recently, Cao *et al.*[8] reported the presence of an ATP receptor-mediated uptake in addition to the carrier-mediated neuronal amine uptake. Enantioselectivity of **3**—**6** for NE potentiation found in the present study implies the presence of a specific receptor for NE uptake and the enantiomers **3a**, **4a**, **5a**, and **6a** may be antagonistic at this NE uptake receptor.

Experimental

Chemistry All melting points are given as uncorrected values. The spectrophotometers used were a Perkin–Elmer 1720 infrared Fourier-transform spectrophotometer for IR spectra, a JEOL JMS-D 300 for MS, and JEOL JNM-FX 200 and JNM-GSX 400 spectrometers for ^{1}H-NMR spectra, with tetramethylsilane as an internal standard. Optical rotations were determined with a JASCO DIP-370 polarimeter. CD spectra were recorded on a JASCO J-600 spectropolarimeter. HPLC was run on a Shimadzu LC-6A liquid chromatograph equipped with a chiral stationary phase column (Daicel Chiralcel OJ).

***N*-(2-Iodo-α-methyl)benzyl-*N*-methylphenacylamine (7)** According to the modified method reported by us,[1c] a solution of phenacyl bromide (0.84 g, 4.24 mmol), *N*-methyl-(2-iodo-α-methyl)benzylamine (0.35 g, 0.92 mmol), and propylene oxide (11.2 ml, 26.9 mmol) in dioxane (40 ml) was stirred at room temperature for 25 h. H_2O (30 ml) was added and the mixture was extracted with ether (50 ml × 4). The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a crude product (2.14 g). This was purified by flash chromatography on SiO_2 with hexane–CH_2Cl_2 (1 : 1) to afford **7** as an oil (1.15 g, 72%). The ^{1}H-NMR and IR spectra were identical with those of **7** prepared previously.[1c]

1,4-*cis*- and 1,4-*trans*-1,2-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (3 and 4) *n*-BuLi (4.35 ml of 1.6 M solution in hexane, 6.96 mmol) was added to a solution of **7** (1.32 g, 3.48 mmol) in dry THF (20 ml) under N_2 at −78 °C. The mixture was stirred for 40 min. Work-up in the usual way gave a crude product (1.954 g) as an oil. This was subjected to flash chromatography on SiO_2 with $CHCl_3$–MeOH (49 : 1) to give crude **4** (from first fraction, 456 mg, oil), pure **4** (from second fraction, 51 mg, oil), and **3** [from third fraction, 327 mg (37%), mp 136—137 °C (from EtOH) (lit.[1c] mp 132—133 °C)]. The ^{1}H-NMR and IR spectra of this compound were identical with those of **3** obtained previously.[1c] The crude **4** was further purified by flash chromatography on SiO_2 with CH_2Cl_2–ethyl acetate (9 : 1) to afford pure **4** (188 mg, total yield 239 mg, 27%, oil). IR (film): 2987, 2797, 1448 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.47—7.18 (8H, m, ArH), 6.88 (1H, d, J=7.6 Hz, H-5), 4.14 (1H, br s, OH), 3.58 (1H, q, J=6.4 Hz, H-1), 2.96, 2.87 (each 1H, d, J=11.6 Hz, CH_2-3), 2.54 (3H, s, NCH_3), 1.56 (3H, d, J=6.4 Hz, CH_3-1). MS Calcd for $C_{17}H_{19}NO$ (M^+): 253.1467. Found: 253.1473.

The free base **4** was converted to the hydrochloride, colorless needles (from acetone), mp 155—157 °C. *Anal.* Calcd for $C_{17}H_{19}NO\cdot HCl\cdot 0.75H_2O$: C, 67.31; H, 7.15; N, 4.62. Found: C, 67.65; H, 6.88; N, 4.56.

Resolution of (±)-1,4-*cis*-1,2-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (3) (±)-**3** (115 mg) was submitted to semi-preparative HPLC with a hexane–2-propanol (20 : 1) mixture at a flow rate of 4 ml/min to give two fractions (detected at 220 nm). The first fraction at 10.9 min retention time afforded the (+)-enantiomer **3a** as a pale brown oil (49 mg), $[\alpha]_D^{24}$ +75.1° (c=1.00, methanol). CD (c=0.00144, methanol) $[\theta]^{23}$ (nm): +5633 (230), 0 (225), −11420 (220) (negative maximum), 0 (214), +13710 (207) (positive maximum).

The second fraction at 17 min retention time gave the (−)-enantiomer **3b** as a pale brown oil (40 mg), $[\alpha]_D^{24}$ −74.7° (c=0.99, methanol). CD (c=0.00146, methanol) $[\theta]^{23}$ (nm): −5703 (230), 0 (225), +11930 (220) (positive maximum, 0 (214), −13960 (207) (negative maximum). The ^{1}H-NMR spectrum of (−)-**3b** was identical with those of (+)-**3a** and (±)-**3**.

Resolution of (±)-1,4-*trans*-1,2-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (4) (±)-**4** (50 mg) was resolved by HPLC with hexane–

2-propanol (200:1) in the same way as described for (±)-**3**. The first fraction at 24.3 min retention time afforded the (+)-enantiomer **4a** as a pale brown oil (20 mg), $[\alpha]_D^{19}$ +24.1° (c=0.407, methanol). CD (c=0.00116, methanol) $[\theta]^{23}$ (nm): −5135 (227), −25620 (218.6) (negative maximum, 0 (208)).

The second fraction at 30.8 min retention time gave the (−)-enantiomer **4b** (12 mg) as a pale brown oil, $[\alpha]_D^{20}$ −19.5° (c=0.409, methanol). CD (c=0.00115, methanol) $[\theta]^{23}$ (nm): +5790 (227), +25580 (218.6) (positive maximum), 0 (208). The ^{1}H-NMR spectrum of (−)-**4b** was identical with those of (+)-**4a** and (±)-**4**.

(+)-1,4-*cis*-4-Hydroxy-1,2,2-trimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (8) A solution of **3a** (33 mg, 0.13 mmol) and methyl iodide (1 ml, 16.1 mmol) in MeOH (4 ml) was refluxed for 55 min. The mixture was evaporated to give pale brown crystals. These were recrystallized from EtOH to afford **8** as colorless plates (35 mg, 79%), mp >300 °C. IR (KBr): 3295, 3015, 2926, 1446 cm^{-1}. *Anal.* Calcd for $C_{17}H_{19}NO \cdot CH_3I$: C, 54.69; H, 5.61; N, 3.54. Found: C, 54.34; H, 5.61; N, 3.29.

***N*-Benzyl-β-phenylethanolamine (10)** A 2.4 N HCl–MeOH solution (16.7 ml, 40 mmol) and benzaldehyde (2.12 g, 20 mmol) were added to a solution of β-phenylethanolamine (8.23 g, 60 mmol) in dry MeOH (20 ml). Then $NaBH_3CN$ (1.26 g, 20 mmol) was added gradually under ice-cooling and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was evaporated. Concentrated HCl (150 ml) and H_2O (250 ml) were added to the residue. The mixture was washed with ether (100 ml × 3). The aqueous layer was made basic with NH_4OH and extracted with CH_2Cl_2 (100 ml × 3). The extract was dried over $MgSO_4$ and evaporated to give a crude product (3.943 g). This was purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (19:1) to afford **10** (2.805 g, 62%), colorless needles, mp 94—95 °C. IR (KBr): 3294, 3062, 1455 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.20—7.40 (10H, m, ArH), 4.73 (1H, dd, J=8.8, 3.8 Hz, CH), 3.83 (2H, s, ArC$\underline{H}_2$N), 2.94 (1H, dd, J=12.2, 3.8 Hz, CH–C$\underline{H}_2$N), 2.75 (1H, dd, J=12.2, 8.8 Hz, CH–C$\underline{H}_2$N), 2.40 (2H, br s, OH and NH). MS Calcd for $C_{15}H_{18}NO$ (M+1): 228.1388. Found: 228.1430. This free base was converted to the hydrochloride, colorless needles (from acetone), mp 187—193 °C. *Anal.* Calcd for $C_{15}H_{17}NO \cdot HCl$: C, 68.30; H, 6.89; N, 5.31. Found: C, 67.94; H, 6.97; N, 5.23.

4-Phenyl-1,2,3,4-tetrahydroisoquinoline (9) The ethanolamine **10** (1.95 g, 8.58 mmol) was added to trifluoromethanesulfonic acid (4.56 ml, 51.5 mmol) under ice-cooling. The mixture was stirred at room temperature for 3 h. H_2O (20 ml) was added and the whole was made basic with NH_4OH, then extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give a pale brown oil (1.86 g). This was purified by flash chromatography on SiO_2 with CH_2Cl_2–MeOH (24:1) to afford **9** as an oil (1.55 g, 86%). IR (film): 3220, 2800, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.07 (8H, m, ArH), 6.90 (1H, d, J=7.1 Hz, H-5), 4.22—4.02 (3H, m, CH_2-1 and H-4), 3.41 (1H, dd, J=12.8, 5.3 Hz, CH_2-3), 3.10 (1H, dd, J=12.8, 6.5 Hz, CH_2-3), 1.88 (1H, br s, NH). MS Calcd for $C_{15}H_{15}NO$ (M^+): 209.1203. Found: 209.1180.

Resolution of (±)-9 (±)-**9** (500 mg, 2.39 mmol) and dibenzoyl-D-tartaric acid (856 mg, 2.39 mmol) were dissolved in EtOH (3 ml) and the mixture was allowed to stand at 4 °C for 7 d. The crude diastereomeric salt of **9** was recrystallized as white cubes (510 mg, mp 164—167 °C). This salt was separated and recrystallized from EtOH to give white cubes (341 mg, mp 168—173 °C).

Further recrystallization from EtOH–MeOH (1:1) gave colorless needles (199 mg, mp 170—172 °C), whose optical purity (100% ee) was determined by analytical HPLC of the free base. The salt (199 mg) thus obtained was dissolved in H_2O (40 ml) and the solution was made basic with 1 N NaOH. The mixture was extacted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give 4*R*-(+)-**9b** as an oil (36.5 mg). $[\alpha]_D^{22}$ +11.1° (c=0.73, methanol). CD (c=0.00148, methanol) $[\theta]^{23}$ (nm): +1559 (236), +25090 (219) (positive maximum), +13670 (208).

The mother liquid separated from the salt (mp 164—167 °C) gave white cubes (506 mg, mp 149—153 °C). This salt was recrystallized from EtOH to give white cubes (183 mg, mp 151—153 °C); this product was determined to be the pure diastereomeric salt by analytical HPLC of the free base. In a similar manner, the salt (183 mg) was converted to the free base 4*S*-(−)-**9a** as an oil (43 mg). $[\alpha]_D^{20}$ −11.1° (c=0.85, methanol). CD (c=0.00150, methanol) $[\theta]^{23}$ (nm): −1692 (236), −27440 (219) (negative maximum), −16630 (208). The ^{1}H-NMR spectrum of 4*S*-(−)-**9a** was identical with those of 4*R*-(+)-**9b** and (±)-**9**.

4*S*-2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (5a) Boric acid (51.6 mg, 0.84 mmol) and formalin (0.46 ml, 6.14 mmol) were added to a solution of 4*S*-(−)-**9a** (26.2 mg, 0.125 mmol) in MeOH (9 ml) and the mixture was stirred at room temperature for 10 min. Then $NaBH_4$ (51.4 mg, 1.35 mmol) was added and the mixture was stirred for 2 h. It was made acidic with 1 N HCl and evaporated. H_2O (20 ml) was added to the residue and the mixture was made basic with $NaHCO_3$, then extracted with CH_2Cl_2 (15 ml × 3). The extract was washed with a saturated solution of NaCl, dried over $MgSO_4$, and evaporated to give 4*S*-(+)-**5a** as an oil (22.1 mg, 79%). $[\alpha]_D^{24}$ +17.3° (c=1.15, methanol). CD (c=0.00280, methanol) $[\theta]^{24}$ (nm): +1862 (233.8), 0 (230), −18460 (224.6) (negative maximum), −10730 (212). ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.01 (8H, m, ArH), 6.86 (1H, d, J=7.8 Hz, H-5), 4.27 (1H, dd, J=8.7, 5.6 Hz, H-4), 3.76, 3.61 (each 1H, d, J=14.9 Hz, CH_2-1), 3.03 (1H, dd, J=11.5, 5.6 Hz, CH_2-3), 2.57 (1H, dd, J=11.5, 8.7 Hz, CH_2-3), 2.43 (3H, s, NCH_3).

(4*R*)-2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (5b) In the same way as described for 4*S*-(−)-**9a**, reaction of 4*R*-(+)-**9b** (20.2 mg, 0.097 mmol) with boric acid (39.1 mg, 0.63 mmol), formalin (0.35 ml, 4.67 mmol), and $NaBH_4$ (60 mg, 1.59 mmol) gave 4*R*-(−)-**5b** as an oil (14.6 mg, 68%). $[\alpha]_D^{24}$ −16.7° (c=0.72, methanol). CD (c=0.00210, methanol) $[\theta]^{24}$ (nm): −2403 (233.8), 0 (230), +12270 (224.6) (positive maximum), +7557 (212). The ^{1}H-NMR spectrum of 4*R*-(−)-**5b** was identical with those of 4*S*-(+)-**5a** and (±)-**5** prepared from (±)-**1**.[1b]

Single-Crystal X-Ray Analysis of the Methiodide of (+)-3a Crystal data were measured on an MXC M18X diffractometer and the structure analysis was performed by a Crystan-G system (MAC Science Ltd., Japan) on a Silicon Graphics IRIS 4D/320GTX computer: molecular formula $C_{17}H_{19}NO \cdot CH_3I$, space group $P2_12_12_1$; unit cel a=12.219(8), b=15.191(7), c=9.564(6) Å, D_{calcd}=1.870 Mg m^{-3}; R=0.0435; R_w=0.0476; observed reflections 1597.

Pharmacology The methods used for evaluating the compounds (**1a**, **3a, b**, **4a, b**, **5a, b**, and **6a, b**) were reported in our previous papers.[1c,2,3] The isolated rat anococcygeus muscles were used for the assay of potentiating activity of the optically active PI-OH derivatives on the response to NE, which was evaluated from the shift in the concentration-response curves of NE. The potency of drugs for the potentiation of NE was expressed as the activity ratio, which was determined as the antilogarithm of the difference between the pD_2 values for NE (negative logarithm of the molar concentration of the agonist producing 50% of the maximum response) in the presence and absence of the test compounds.

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