Synthesis and Biological Activities of Optical Isomers of 2-(4-Diphenylmethyl-1-piperazinyl)ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (Manidipine[1]) Dihydrochloride

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Enantiomeric (+)- and (−)-manidipine (1) dihydrochlorides were synthesized by the esterification of the optically active monocarboxylic acids (−)-6 and (+)-6, respectively. The absolute configurations, (*S*)-(+)-1 and (*R*)-(−)-1, were unambiguously determined by X-ray crystallographic analysis of (+)-7 derived from (−)-6. The (*S*)-(+)-1 was about 30 and 80 times as potent as the (*R*)-(−)-isomer in antihypertensive activity in spontaneously hypertensive rats (SHR), and in the radioligand binding assay using [^{3}H]nitrendipine, respectively.

Keywords 1,4-dihydropyridine; optical resolution; hypotensive activity; radioligand binding assay; calcium antagonist; manidipine

The dihydropyridine derivative 2-(4-diphenylmethyl-1-piperazinyl)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (manidipine[1]) dihydrochloride [(±)-**1** (2HCl)] has been selected as a potent and long-acting antihypertensive drug from a series of analogues with piperazinylalkyl ester side chains.[2] This compound has an asymmetric carbon at the 4-position of the dihydropyridine ring and therefore has two enantiomeric forms. The optical isomers of some dihydropyridine derivatives such as nicardipine,[3] nimodipine,[4] and others[5,6] have been synthesized and 3- to 100-fold differences in the biological activities of the isomers have been reported. These observations prompted us to report our results on the synthesis and biological activities of the optical isomers of **1**.

Synthesis The key intermediates, (−)- and (+)-monocarboxylic acids (**6**), were prepared as shown in Chart 1 following the method previously reported by Shibanuma *et al.*,[7] though their absolute configurations have not been assigned.

The (±)-**2** was resolved to (−)- and (+)-**5** through the cinchonidine and cinchonine salts **3** and **4** by the reported procedure.[7] The optical purities of (−)-**5** and (+)-**5** appeared to be 99.9% and 99.2% ee, respectively, as determined by high-performance liquid chromatography (HPLC) of their diphenylmethyl esters using a chiral stationary phase column (Chiralcel OD®, Daicel Chemical Industries, Tokyo, Japan). Deprotection of (−)- and (+)-**5** gave (−)- and (+)-**6**, respectively.

The enantiomeric monocarboxylic acids (−)-**6** and (+)-**6** were then converted to (+)-**1** and (−)-**1**, respectively, by reaction with phosphorus pentachloride or thionyl chloride followed by reaction with 4-diphenylmethyl-1-piperazineethanol (Chart 2). Treatment of the free bases with methanolic hydrogen chloride afforded the crystalline dihydrochlorides, (+)-**1** (2HCl), mp 198—203 °C, $[\alpha]_D^{23}$ +64.9° (c=1.02, dimethylformamide (DMF)) and (−)-**1** (2HCl), mp 197—203 °C, $[\alpha]_D^{24}$ −64.7° (c=1.04, DMF). The optical purities of the enantiomers thus prepared were 100% based on HPLC with a chiral stationary phase column (Chiralcel OJ®, Daicel Chemical Industries, Tokyo, Japan), as shown in Fig. 1.

The absolute configurations of the above optically active compounds were determined as follows. The isopropyl ester (+)-**8** synthesized from (+)-**6** had mp 134—135 °C and $[\alpha]_D^{24}$ +22.6° (c=0.235, EtOH) in good agreement with the values reported for the (*R*)-(+)-isomer[5] [mp 136 °C, $[\alpha]_D^{20}$ +24.97° (c=0.93, EtOH)], suggesting that the starting (+)-

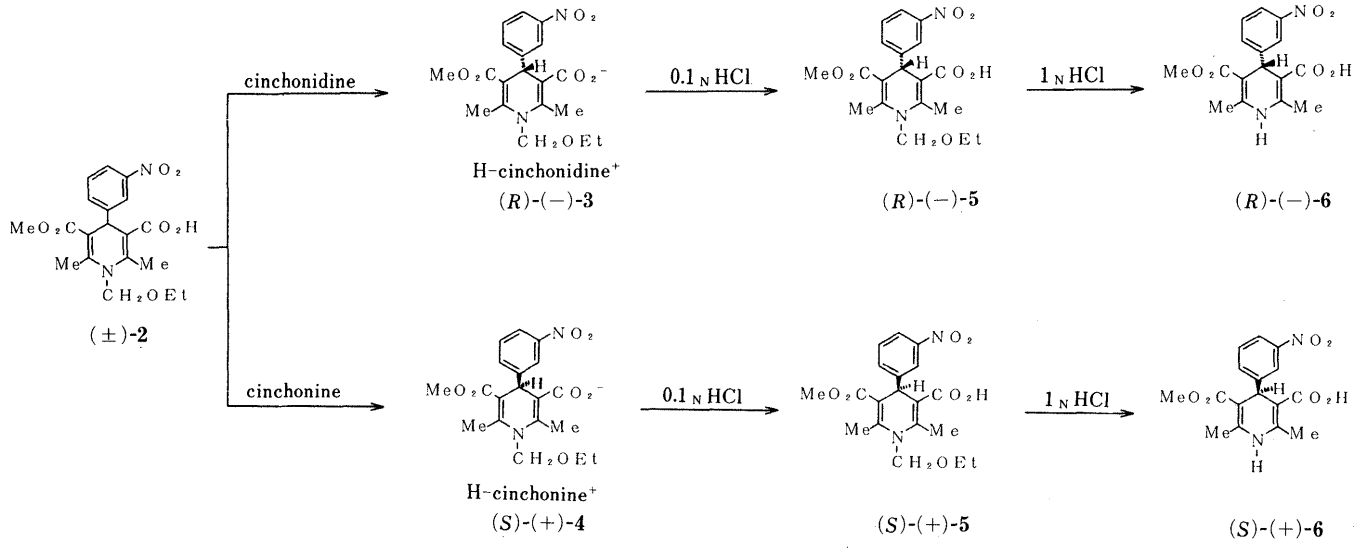

Chart 1

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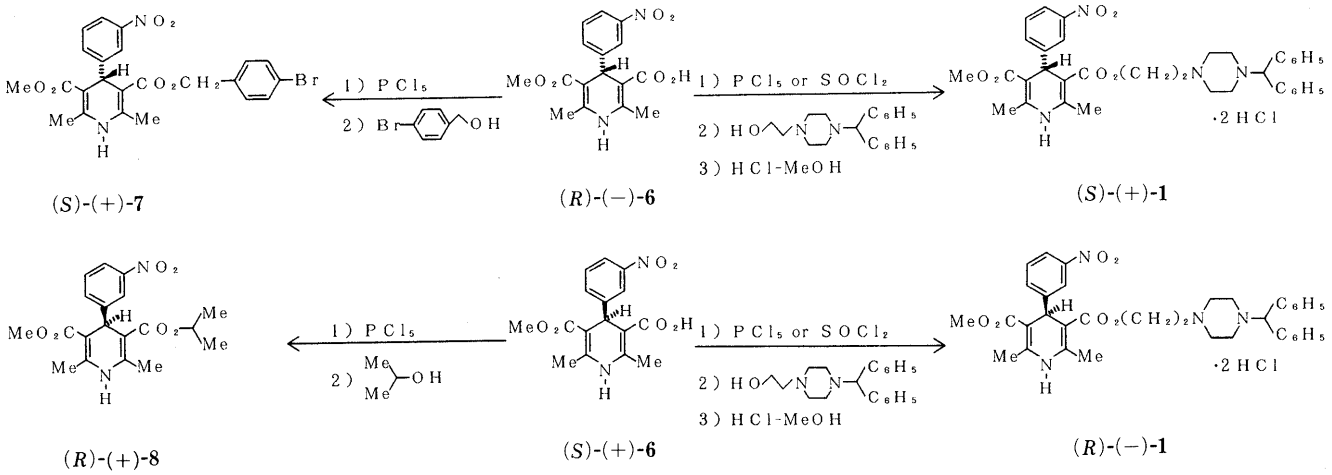

Chart 2

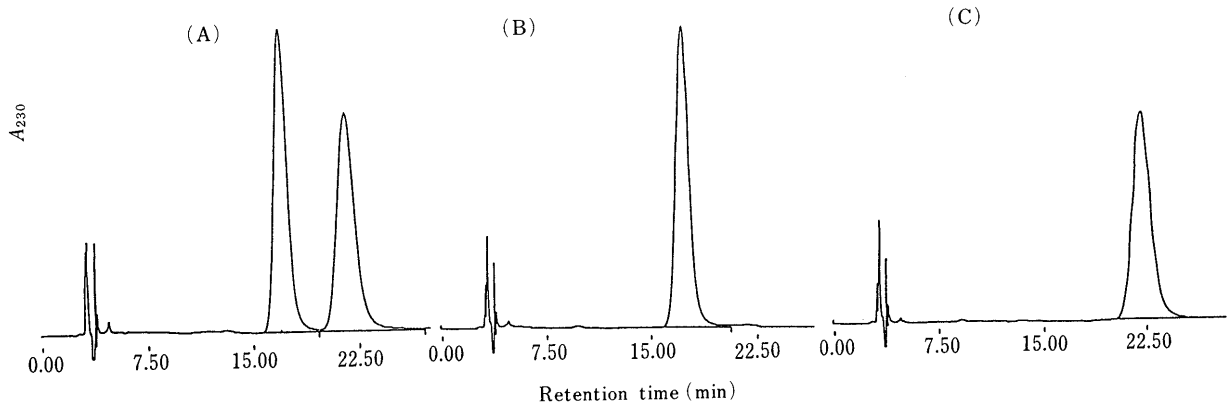

Fig. 1. Chiral Stationary Phase Liquid Chromatograms of: (A) (±)-Manidipine; (B) (*R*)-(−)-Manidipine, and (C) (*S*)-(+)-Manidipine
Column, Chiralcel OJ® 4.6 mm i.d. × 25 cm; mobile phase, hexane–ethanol–methanol (16 : 3 : 1, v/v); flow rate, 1.0 ml/min; temperature, 50 °C; detection, UV 230 nm.

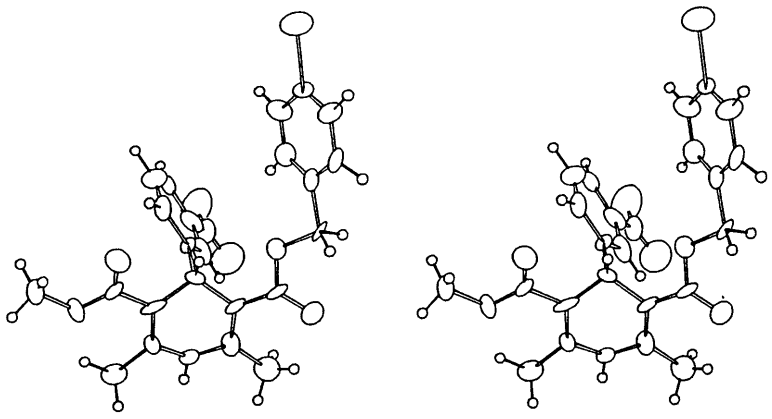

Fig. 2. Stereoscopic Drawing of the Molecule of the *p*-Bromobenzyl Ester (*S*)-(+)-7

6 has (*S*)-configuration.[8] However, it is not clear from the literature how the (*R*)-configuration of (+)-**8** was assigned. Therefore the *p*-bromobenzyl ester (+)-**7** was synthesized from (−)-**6** and subjected to X-ray crystallographic analysis. As shown in Fig. 2, the (*S*)-stereochemistry of (+)-**7** was unambiguously determined. Thus the absolute configurations at C(4) for the isomers of **1** and **3**—**8** are assigned as depicted in Charts 1 and 2. These results also clearly indicate that (+)-nicardipine, which is the pharmacologically more potent enantiomer,[7] has an (*S*)-configuration.

Pharmacology 1. Antihypertensive Activity Methods: Spontaneously hypertensive rats (male, 10 weeks of age) were used. Blood pressure in the tail artery was measured using a tail-pulse pickup method in unanesthetized rats.[9] The animals were previously warmed at 37—38 °C and then placed in a rat holder. The average of three recordings of blood pressure taken at approximately 30-s intervals in the

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TABLE I. Effects of (±)-Manidipine, (*S*)-(+)-Manidipine, and (*R*)-(−)-Manidipine Dihydrochlorides on Blood Pressure of Spontaneously Hypertensive Rats

Treatment	Systolic blood pressure (mmHg)		
	Time after administration (h)		
	0	1	5
Control	197±3	197±3	197±3
(±)-Manidipine·2HCl			
3 mg/kg, *p.o.*	194±1	173±2[a)]	182±3[a)]
10 mg/kg, *p.o.*	194±1	118±1[a)]	134±2[a)]
(*S*)-(+)-Manidipine·2HCl			
3 mg/kg, *p.o.*	192±3	139±5[a)]	173±3[a)]
10mg/kg, *p.o.*	197±3	98±2[a)]	113±2[a)]
(*R*)-(−)-Manidipine·2HCl			
3 mg/kg, *p.o.*	192±3	196±3	196±2
10 mg/kg, *p.o.*	196±2	199±3	201±2
Control	191±2	196±1	195±1
(*R*)-(−)-Manidipine·2HCl			
30 mg/kg, *p.o.*	190±2	185±2[a)]	194±1
100 mg/kg, *p.o.*	191±1	154±2[a)]	168±2[a)]

a) $p<0.05$ *vs.* predrug level (0-time). $n=4$—5.

resting condition was recorded as the systolic blood pressure of the rat. The variation in the three recordings was less than 5%. Test compounds were suspended in 5% arabic gum, and administered orally.

Results: The effects of the dihydrochlorides of (±)-, (*S*)-(+)- and (*R*)-(−)-manidipine (**1**) on blood pressure are shown in Table I. At the doses of 3 and 10 mg/kg (*S*)-(+)-**1** (2HCl) decreased the blood pressure dose-dependently, and the hypotensive action was very potent and long-lasting. In contrast, (*R*)-(−)-**1** (2HCl) showed no hypotensive action in the same doses. The effects of higher doses of (*R*)-(−)-**1** (2HCl) were assessed in a separate experiment. Thirty mg/kg of (*R*)-(−)-**1** (2HCl) decreased blood pressure slightly but significantly only at one hour after the administration, and 100 mg/kg of the compound showed a moderate and long-lasting hypotensive action comparable to 3 mg/kg of (*S*)-(+)-**1** (2HCl). Compound (±)-**1** (2HCl) also showed a marked hypotensive action in the doses of 3 and 10 mg/kg, but its action was less than that of (*S*)-(+)-**1** (2HCl). From these results, it was speculated that (*S*)-(+)-**1** (2HCl) was about 30-fold more potent than (*R*)-(−)-**1** (2HCl), and about 2-fold more potent than (±)-**1** (2HCl).

2. Effect on the Binding of [^{3}H]Nitrendipine Methods: Hearts of Wistar rats (250—300 g) were removed and perfused through the aorta with an ice-cooled saline (0.9%) solution, minced with scissors and homogenized with a Polytron in 50 mM Tris–HCl buffer, pH 7.4, to a final concentration of 100 mg tissue weight/ml buffer. The tissue homogenate was washed five times by centrifugation at 48000 × ***g*** for 10 min followed by resuspension of the pellet in the fresh buffer.The final pellets were resuspended to a concentration of 1 mg/ml buffer. For the binding assay, aliquots (1 ml) of tissue homogenate were incubated with [^{3}H]nitrendipine (87.0 Ci/mmol) and test compounds. Incubations were carried out in the dark for 90 min at 25 °C. Membrane bound [^{3}H]nitrendipine was trapped at the end of the incubation period by rapid vacuum filtration of the incubation mixture over Whatman glass fiber filters (GF/B). The filteres were rinsed with three aliquots (2 ml) of 50 mM Tris–HCl buffer, and trapped radioactivity was measured subsequently by liquid scintillation spectrophotometry. Binding in the presence of 10^{-6} M nifedipine was defined as non-specific.

Results: The binding of [^{3}H]nitrendipine to receptors for calcium channel antagonists was inhibited in a concentration-dependent fashion by (±)-, (*S*)-(+)-, and (*R*)-(−)-**1** (2HCl). The IC_{50} (concentration required for 50% inhibition) values were 0.3, 0.05, and 4.0 nM, respectively. Thus, (*S*)-(+)-**1** (2HCl) shows much higher affinity to the receptors of calcium channel antagonists than (*R*)-(−)-**1** (2HCl). The affinity of (±)-**1** (2HCl) is intermediate between those of the (*S*)-(+)- and (*R*)-(−)-enantiomers.

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-260-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in the solvent indicated. Chemical shifts are given in ppm relative to Me_4Si as the internal standard. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Optical rotations were measured on a JASCO DIP-181 digital polarimeter (Japan Spectroscopic Co., Ltd.). Column chromatography was performed on E. Merck 70—230 mesh silica gel. Evaporation was carried out *in vacuo* on a rotary evaporator.

The following compounds were prepared by following the methods reported by Shibanuma *et al.*[7)]

(4*R*)-1-Ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid Cinchonidine Salt [(*R*)-(−)-3] Yield 18.6%, mp 193—194 °C (lit.[7)] mp 197—199 °C) $[\alpha]_D^{24}$ −40.3° (c = 0.70, DMF). IR (Nujol): 1710, 1695 cm^{-1}. *Anal.* Calcd for $C_{38}N_{44}N_4O_8$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.43; H, 6.46; N, 8.34.

(4*S*)-1-Ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid Cinchonine Salt [(*S*)-(+)-4] Yield 22.1%, mp 202—203 °C (lit.[7)] mp 209—212 °C) $[\alpha]_D^{24}$ +70.6° (c=0.87, DMF). IR (Nujol): 1690 cm^{-1}. *Anal.* Calcd for $C_{38}H_{44}N_4O_8$:C, 66.65; H, 6.48; N, 8.18. Found: C, 66.63; H, 6.52; N, 8.18.

(4*R*)-1-Ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid [(*R*)-(−)-5] Yield 87.7%, mp 136—137 °C (iso-Pr_2O), $[\alpha]_D^{24}$ −21.3° (c=0.99, acetone) [lit.[7)] mp 134—135 °C, $[\alpha]_D^{22}$ −16.0° (c=1.78, acetone)]. *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.68; N, 7.18. Found: C, 58.50; H, 5.76; N, 7.14.

(4*S*)-1-Ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid [(*S*)-(+)-5] Yield 85.3%, mp 137—138 °C (iso-Pr_2O), $[\alpha]_D^{24}$ +21.5° (c=1.02, acetone) [lit.[7)] mp 133—134 °C, $[\alpha]_D^{22}$ +15.3° (c=1.90, acetone)]. *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.68; N, 7.18. Found: C, 58.53; H, 5.75; N, 7.14.

Diphenylmethyl Methyl 1-Ethoxymethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate About 50% diazodiphenylmethane (1.5 g) was added portionwise to a stirred solution of (±)-**5** (1.0 g, 2.5 mmol) in MeOH (30 ml)–$CHCl_3$ (20 ml) at room temperature. The reaction mixture was stirred for 2 h, quenched with AcOH, diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried (anhydrous $MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g) using hexane–AcOEt (3:2, v/v) as an eluant. Recrystallization of the product from iso-Pr_2O gave the title compound as yellow prisms (1.0 g, 71%), mp 103—104 °C. IR (Nujol): 1700, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.2 Hz), 2.51 (3H, s), 2.54 (3H, s), 3.44 (2H, q, J=7.2 Hz), 3.69 (3H, s), 4.83 (2H, s), 5.30 (1H, s), 6.83—7.56 (12H, m), 7.87—8.05 (2H, m). *Anal.* Calcd for $C_{32}H_{32}N_2O_7$: C, 69.05; H, 5.79; N, 5.03. Found: C, 68.92; H, 5.80; N, 4.80.

Determination of the Optical Purities of (+)- and (−)-5 Compounds (*R*)-(−)- and (*S*)-(+)-**5** were each (15 mg) treated with diazodiphenylmethane as in the procedure used for (±)-**5**. The crude residues were subjected to HPLC [column, Chiralcel OD® of 4.6 mm i.d. × 25 cm (Daicel Chemical Industries, Tokyo, Japan); mobile phase, hexane–2-propanol (17:3, v/v); flow rate, 1.0 ml/min; detection, ultraviolet (UV) at 280 nm]. The optical purities were determined to be as follows: (*R*)-(−)-**5**, 99.9% ee (t_R: 8.7 min); (*S*)-(+)-**5**, 99.2% ee (t_R: 15.7 min).

(4*R*)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-

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pyridinecarboxylic Acid [(*R*)-(−)-6] A mixture of (*R*)-(−)-**5** (1.47 g, 3.77 mmol), 1 N HCl (9 ml) and acetone (45 ml) was stirred at room temperature for 1.5 h. The mixture was concentrated and extracted with AcOEt. The extract was dried (anhydrous $MgSO_4$) and concentrated to give (*R*)-(−)-**6** (0.68 g, 54%), mp 186—187 °C. Recrystallization from MeOH gave pale yellow needles, mp 188—189 °C, $[\alpha]_D^{23}$ −18.8° (*c*=0.825, acetone). [lit.[7] mp 196—197 °C, $[\alpha]_D^{22}$ −19.6° (*c*=0.542, acetone)]. IR (Nujol): 3340, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.28 (6H, s, $C_{2,6}$-Me), 3.54 (3H, s), 4.99 (1H, s, C_4-H), 7.46—7.68 (2H, m), 7.89—8.06 (2H, m), 8.88 (1H, br s). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.86; H, 4.95; N, 8.39.

(4*S*)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid [(*S*)-(+)-6] Hydrolysis of (*S*)-(+)-**5** (2.05 g, 5.3 mmol) with 1 N HCl in a manner similar to that used for (*R*)-(−)-**6** gave (*S*)-(+)-**6** as pale yellow needles (0.84 g, 48%), mp 184—185 °C (MeOH). $[\alpha]_D^{23}$ +19.8° (*c*=0.615, acetone) [lit.[7] mp 194—195 °C, $[\alpha]_D^{22}$ +19.1° (*c*=0.556, acetone)]. *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.73; H, 4.92; N, 8.36.

(4*S*)-2-(4-Diphenylmethyl-1-piperazinyl)ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*S*)-(+)-1] Dihydrochloride Method A: PCl_5 (0.38 g, 1.8 mmol) was added to a stirred and ice-cooled mixture of (*R*)-(−)-**6** (0.50 g, 1.5 mmol) and CH_2Cl_2 (6 ml). Stirring was continued for 1.5 h, then 4-diphenylmethyl-1-piperazineethanol (0.89 g, 3.0 mmol) in CH_2Cl_2 (10 ml) was added at below −20 °C. The temperature was raised to 0 °C and the mixture was stirred for 1.5 h and diluted with water. The CH_2Cl_2 layer was separated and washed first with saturated aqueous $NaHCO_3$, then with water, dried (anhydrous $MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel using $CHCl_3$–MeOH (50 : 1, v/v) as an eluant to give (*S*)-(+)-**1** as a viscous oil (0.70 g, 76%). IR ($CHCl_3$): 3430, 1700, 1685 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 2.23—2.48 (8H, m), 2.36 (6H, s, $C_{2,6}$-Me), 2.57 (2H, t, *J*=6.0 Hz), 3.61 (3H, s), 4.14 (2H, t, *J*=6.0 Hz), 4.18 (1H, s), 5.09 (1H, s, C_4-H), 5.83 (1H, br s, NH), 7.10—8.12 (14H, m). This oil was dissolved in a small amount of MeOH and treated with methanolic hydrogen chloride to afford the dihydrochloride. Recrystallization from MeOH–H_2O gave colorless prisms (0.51 g, 50%), mp 198—203 °C. $[\alpha]_D^{24}$ +64.4° (*c*=0.62, DMF). IR (Nujol): 3340, 1720, 1655 cm^{-1}.^{1}H-NMR (DMSO-d_6) δ: 2.26 (3H, s), 2.33 (3H, s), 2.92—3.73 (10H, m), 3.52 (3H, s), 4.37 (2H, br), 4.97 (1H, s, C_4-H), 5.42 (1H, br), 7.25—7.97 (14H, m), 9.23 (1H, br s, NH). *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl$: C, 61.49; H, 5.90; N, 8.20. Found: C, 61.33; H, 5.90; N, 8.10.

Method B: $SOCl_2$ (4.60 ml, 0.06 mol) was added dropwise to a stirred and ice-cooled suspension of (*R*)-(−)-**6** (19.94 g, 0.06 mol) in CH_2Cl_2–DMF (4 : 1, v/v, 125 ml). The mixture was stirred at 0 °C for 2 h, and 4-diphenylmethyl-1-piperazineethanol (19.56 g, 0.06 mol) in CH_2Cl_2 (60 ml) was added dropwise thereto. The resulting mixture was stirred for 40 min with ice-cooling, diluted with water (50 ml), basified with 1 N NaOH (160 ml) and extracted with $CHCl_3$. The extract was washed with water, dried (anhydrous $MgSO_4$) and concentrated. The residue was dissolved in MeOH (70 ml) and treated with 4.86 N methanolic hydrogen chloride (35 ml) to give the dihydrochloride (33.6 g, 82%). Recrystallization from MeOH (450 ml)–H_2O (50 ml) gave colorless prisms (31.0 g, 76%), mp 198—203 °C. $[\alpha]_D^{23}$ +64.9° (*c*=1.02, DMF). *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl$: C, 61.49, H, 5.90; N, 8.20. Found: C, 61.57; H, 5.97; N, 8.01.

(4*R*)-2-(4-Diphenylmethyl-1-piperazinyl)ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*R*)-(−)-1] Dihydrochloride (*R*)-(−)-**1** dihydrochloride was similarly prepared from (*S*)-(+)-**6** in 43% and 61% yields by methods A and B, respectively; mp 197—203 °C, $[\alpha]_D^{24}$ −64.7° (*c*=1.04, DMF). *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl$: C, 61.49; H, 5.90; N, 8.20. Found: C, 61.52; H, 5.80; N, 8.06.

(4*S*)-4-Bromobenzyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*S*)-(+)-7] PCl_5 (0.10 g, 0.48 mmol) was added to a stirred and ice-cooled mixture of (*R*)-(−)-**6** (0.15 g, 0.45 mmol) and CH_2Cl_2 (4 ml). Stirring was continued for 1 h, then 4-bromobenzyl alcohol (0.17 g, 0.91 mmol) was added at below −20 °C. The resulting mixture was stirred at 0 °C for 1 h, diluted with water, and extracted with CH_2Cl_2. The extract was washed with water, dried (anhydrous $MgSO_4$) and concentrated. The residue was chromatographed on silica gel (30 g) using hexane–AcOEt (3 : 2, v/v) as an eluant to give (*S*)-(+)-**7** (0.13 g, 57%). Recrystallization from iso-Pr_2O gave colorless needles, mp 165—166 °C. $[\alpha]_D^{24}$ +36.5° (*c*=0.79, CH_2Cl_2). IR ($CHCl_3$): 3445, 1700, 1690 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.35 (3H, s), 3.62 (3H, s), 5.01 (2H, q, *J*=11.4 Hz), 5.09 (1H, s, C_4-H), 5.87 (1H, br s, NH), 6.97—7.62 (6H, m), 7.89—8.09 (2H, m). *Anal.* Calcd for $C_{23}H_{21}BrN_2O_6$: C, 55.10; H, 4.22; N, 5.59. Found: C, 55.19; H, 4.19; N, 5.43.

(4*R*)-Isopropyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*R*)-(+)-8] (*S*)-(+)-**6** (0.17 g, 0.52 mmol) was esterified with 2-propanol in a manner similar to that used for the preparation of (*S*)-(+)-**7** to give (*R*)-(+)-**8** (0.13 g, 66%), mp 129—130 °C (iso-Pr_2O). Recrystallization from iso-Pr_2O gave colorless prisms, mp 134—135 °C. $[\alpha]_D^{24}$ +22.7° (*c*=0.52, EtOH) [lit.[5] mp 136 °C, $[\alpha]_D^{20}$ +24.97° (*c*=0.93, EtOH)]. IR ($CHCl_3$): 3430, 1700, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, *J*=6.6 Hz), 1.25 (3H, d, *J*=6.6 Hz), 2.32 (6H, s), 3.63 (3H, s), 4.96 (1H, t, *J*=6.6 Hz), 5.07 (1H, s), 6.42 (1H, br s), 7.33 (1H, t, *J*=7.5 Hz), 7.55—7.72 (1H, m), 7.89—8.16 (2H, m). *Anal.* Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.75; H, 5.73; N, 7.45.

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