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Studies on 1,2,3,4-Tetrahydroisoquinolines. VI.[1] Reutilization of the Unwanted (*R*)-Isomer of (*S*)-(—)-5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (TA-073)

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Racemization of the unwanted isomer (*R*-**1**) of (*S*)-(-)-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (TA-073) *via* the imine **6** was examined. Reduction of **6** with $NaBH_4$ followed by hydrogenolysis over 10% Pd-C gave (±)-TA-073 in a good yield. Asymmetric reduction of **6** to *S*-**4**, the precursor of TA-073, by the use of the chiral reducing agent (I), prepared from $NaBH_4$ (1 eq) and (*S*)-*N*-benzyloxycarbonylproline (3 eq), was also investigated. Treatment of **6** with I in a halogenated alkane such as $CHCl_2CH_3$ or $CHCl_2CHCl_2$ at −30°C afforded *S*-**4** in an excellent optical yield (87% e.e.).

Keywords——1,2,3,4-tetrahydroisoquinoline; orally effective bronchodilator; racemization; 1-substituted 3,4-dihydroisoquinoline; asymmetric reduction; cyclic imine; chiral sodium triacyloxyborohydrides

In the preceding paper,[1] we reported that (*S*)-(-)-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-**1**) (TA-073), a positional isomer of trimetoquinol (TMQ) with respect to the hydroxyl groups, is currently under clinical trials as an orally effective bronchodilator. This compound was easily obtained by the optical resolution of racemic TA-073, and its absolute stereochemistry was determined to be *S* by X-ray crystallographic analysis[2] (Chart 1).

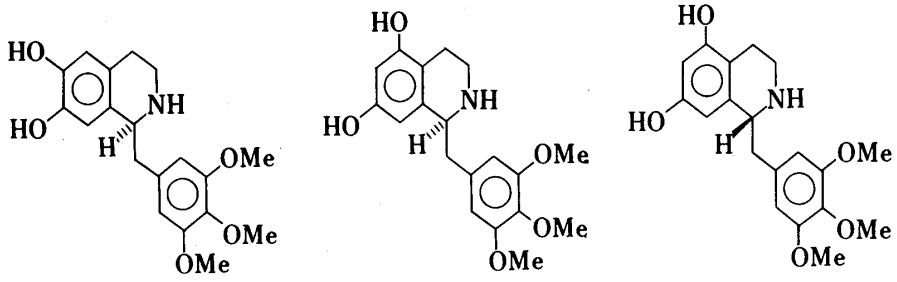


Chart 1

In this paper, we describe the racemization of the unwanted isomer (*R*-**1**) of TA-073 *via* the imine **6**. Direct conversion of *R*-**1** to TA-073 by the asymmetric reduction of **6** was also achieved.

Racemization of *R*-isomer (*R*-1)

Kametani *et al.* reported that (−)-norlaudanosine readily undergoes racemization under catalytic reduction conditions over PtO_2.[3] Yamada showed that the racemization of the unwanted *R*-isomer of TMQ can be effected by heating in ethylene glycol in high yield.[4] However, attempts to racemize (*R*)-**1** by heating or by a catalytic reduction procedure were without success. We then considered the racemization of (*R*)-**1** *via* the 3,4-dihydroisoquinoline(**6**). Whittaker reported that treatment of various 1,2,3,4-tetrahydroisoquinolines with a halogenating agent such as NaOCl or *N*-chlorosuccinimide

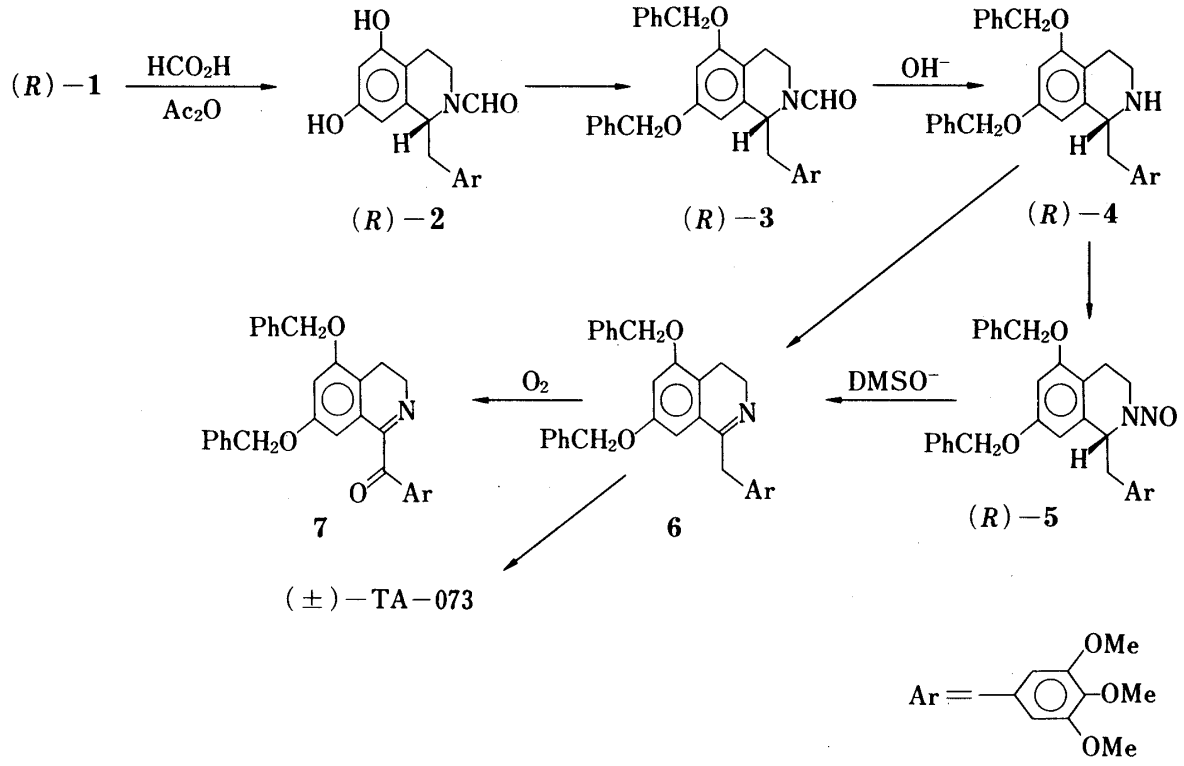


Chart 2

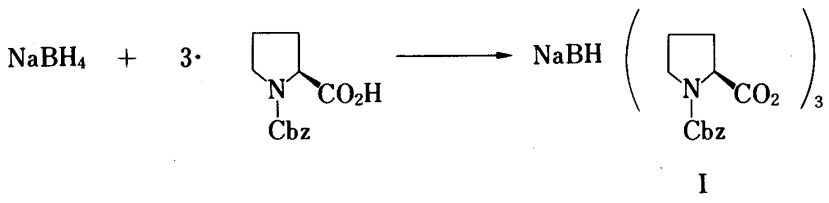
(NCS) followed by base-induced elimination of HCl affords 3,4-dihydroisoquinoline in good yields.[5] Recentry, Imoto *et al.* reported base-induced coversion of *N*-nitroso-1,2,3,4-tetrahydroisoquinolines into 3,4-dihydroisoquinolines.[6] Therefore, we examined the conversion of the amine [(*R*)-**4**], which can be easily prepared from (*R*)-**1** in three steps, into the imine **6** (Chart 2).

Treatment of (*R*)-**1** with HCO_2Ac in tetrahydrofuran (THF) followed by alkylaton with benzyl chloride gave the amide [(*R*)-**3**] in 77% yield. Alkaline hydrolysis of (*R*)-**3** with 10% aqueous NaOH in EtOH afforded the amine [(*R*)-**4**] in 82% yield. Treatment of (*R*)-**4** with 9.7% aqueous NaOCl (1.3 eq) in MeOH–THF gave the imine **6** in 85% yield. Compound **6** was also obtained in 59% yield by the reaction of (*R*)-**4** with NCS (1.1 eq) in EtOH followed by treatment with ethanolic KOH. The *N*-nitroso derivative [(*R*)-**5**], which can be easily prepared from (*R*)-**4**, failed to give the imine (**6**) by Imoto's procedure (20% aqueous NaOH in EtOH). Reaction of (*R*)-**5** with dimsyl anion in DMSO at 20—22°C for 10 min, however, proceeded smoothly to afford **6** in 68% yield. The imine **6** thus obtained was reduced with $NaBH_4$ in MeOH to give the racemic amine (**4**) in 94% yield. Finally, hydrogenolysis of (±)-**4** over 10% Pd-C afforded racemic TA-073 in 87% yield.

Asymmetric Reduction of the Imine 6

Previously, we reported the convenient and highly effective asymmetric reduction of cyclic imines by the use of chiral sodium triacyloxyborohydrides.[7] In particular, the reducing agent (I), isolated from the reaction of $NaBH_4$ (1 eq) and (*S*)-*N*-benzyloxycarbonylproline (3 eq) (Equation 1), was found to reduce various 1-substituted 3,4-dihydroisoquinolines to the corresponding alkaloids (*S*-configuration) in excellent optical yields.
Asymmetic reduction of the imine **6** to (*S*)-**4**, the precursor of TA-073, by the use of this new reducing agent (I) was, therefore, examined (Table I).

As can be seen from Table I, an excellent optical yield of *S*-**4** (87% e.e.) was achieved by the use of a halogenated alkane solvent such as $CHCl_2CH_3$ or $CHCl_2CHCl_2$, and this solvent effect parallels our previous observation. Thus, the unwanted *R*-isomer of TA-073 could be directly converted into TA-073.



I

Chart 3

TABLE I. Solvent Effect in the Asymmetric Reduction of **6** with Reducing Agent (I)

Solvent	Temp. (°C)	Time (h)	Chemical yield (%)	$[\alpha]_D^{20}$ ($c=1$, MeOH)	Optical yield[a] (% e.e.)
THF	−30	5	73	+ 9.0°	60
$PhCH_3$	−30	4	63	+11.0°	73
CH_2Cl_2	−30	4	70	+11.0°	77
$CHCl_3$	−30	4	66	+11.5°	77
CCl_4	−20	4	56	+11.0°	73
CH_2ClCH_2Cl	−20	4.5	76	+11.7°	78
$CHCl_2CH_3$	−30	4	68	+13.0°	87
$CHCl_2CHCl_2$	−30	4	73	+13.0°	87

a) $[\alpha]_D^{20}$ −15.0° ($c=1$, MeOH) was used as the value for optically pure *R*-**4**·HCl.

Interestigly, during the course of our study on this asymmetric reduction, we found that the hydrochlorides of cyclic imines can also be reduced with the reagent (I) in high optical yields. For example, treatment of the hydrochloride of **6** with (I) (1.5 eq) in $CHCl_2CH_3$ at −30°C gave (*S*)-**4** in 85% optical yield (chemical yield 89%). The free bases of 1-benzyl-3,4-dihydroisoquinolines are known to be susceptible to aerial oxidation and to give the corresponding 1-benzoyl derivatives. The imine **6** behaved similarly and readily gave the keto imine **7** in 81% yield on heating in benzene under oxygen. In contrast, the salts of these imines are stable compounds, and are much easier to handle than free bases. Therefore, the use of imine salts as substrates was much more convenient and increased the scope of this asymmetric reduction.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi IR-215 spectrometer, nuclear magnetic resonance (NMR) spectra with a JEOL PMX60 or PS-100 spectrometer with tetramethylsilane as an internal standard, and mass spectra with a Hitachi-RMU-6M spectrometer. Optical rotations were measured with a Union Giken PM-201 polarimeter. Preparative thin-layer chromatogrphy (TLC) and column chromatography were carried out on silica gel 60 GF_{254} (Merck) and 60 (70—230 mesh ASTM) (Merck), respectively.

(*R*)-*N*-Formyl-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*-2)——(+)-TA-073[2] (11.4 g 30 mmol) was added to a stirred mixture of HCO_2Na (2.04 g, 30 mmol), THF (115 ml), and HCO_2Ac (2 eq) [prepared from 99% HCO_2H (2.76 g, 60 mmol) and Ac_2O (6.12 g, 60 mmol) at 50°C for 15 min], and the whole was stirred at room temperature for 2 h. The reaction mixture was treated with 30% aq. K_2CO_3 (138 ml), and then stirred at room temperature overnight. The mixture was made acidic with conc. HCl (70 ml) and extracted with AcOEt. The AcOEt extracts were washed with sat. brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH–AcOEt to afford *S*-**2**·AcOEt (12.43 g, 90%) as colorless needles, mp 107—110°C, $[\alpha]_D^{20}$ −47.1° ($c=1$, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3390, 3140, 1710 (AcOEt), 1650. Mass Spectra (MS) *m/e*: 373 (M^+), 192 (M^+-181), 181. NMR ($CDCl_3$) δ: 1.17 (3H, t, $J=7$ Hz, $CH_3CO_2CH_2CH_3$), 1.98 (3H, s, $CH_3CO_2CH_2CH_3$), 2.8—3.2 (4H, m), 3.63, 3.70, and 3.75 (9H, 3s, OMe×3), 4.03 (2H, q, $J=7$ Hz, $CH_2CO_2CH_2CH_3$), 6.1—6.3 (3H, m), 6.45 and 6.52 (2H, 2s, ArH×2), 7.55 and 7.98 (1H, 2s, NCHO), 9.00 and 9.20 (2H, br s, OH×2). *Anal.* Calcd for $C_{20}H_{23}NO_6 \cdot AcOEt$: C, 62.45; H, 6.77; N, 3.04. Found: C, 62.68; H, 6.72; N, 3.27.

(*R*)-5,7-Dibenzyloxy-*N*-formyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*-3)——A mixture of *R*-**2** (1.85 g, 4 mmol), benzyl chloride (1.27 g, 10 mmol), NaI (60 mg), and K_2CO_3 (1.66 g, 12 mmol)

in DMSO (30 ml) was stirred at room temperature for 19.5 h, and then at 40°C for 1 h. The reaction mixture was treated with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [AcOEt–hexane (1:1, v/v)] to afford *S*-**3** (1.89 g, 86%) as a colorless oil. $[\alpha]_D^{22}$ −44.2° (*c*=1, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655 (NCHO). MS *m/e*: 553 (M^+), 372 (M^+-181). NMR($CDCl_3$) δ: 3.75 (3H, s, OMe), 3.83 (6H, s, OMe×2), 4.89 and 5.02 (4H, 2s, $-OC\underline{H}_2C_6H_5\times2$), 6.32 (2H, s, ArH×2), 6.1—6.5 (2H, m), 7.38 (10H, s, $-C_6H_5\times2$), 7.75 and 8.13 (1H, 2s, CHO).

(*R*)-5,7-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*-4)———A solution of *R*-**3** (1.38 g, 2.5 mmol) and 10% aq. NaOH (10 g, 25 mmol) in EtOH (30 ml) was heated under reflux for 17.5 h. After removal of the solvent, the residue was diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with 10% ethanolic HCl, and recrystallized from EtOH to afford *R*-**4**·HCl (1.15 g, 82%) as colorless needles, mp 213—214.5°C. $[\alpha]_D^{20}$ −15.0° (*c*=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2450, 1605. MS *m/s*: 524 (M^+-1), 344 (M^+-181). NMR ($CDCl_3$) δ: 3.70 (6H, s, OMe×2), 3.77 (3H, s, OMe), 4.78 and 4.95 (2H, each s, $-OC\underline{H}_2C_6H_5\times2$), 6.04 (1H, br s, ArH), 6.42 (3H, br s, ArH×3), 7.28 and 7.30 (10H, 2s, $-C_6H_5\times2$). *Anal.* Calcd for $C_{33}H_{35}NO_5\cdot HCl$: C, 70.51; H, 6.46; N, 2.49; Cl, 6.31. Found: C, 70.46; H, 6.49; N, 2.69; Cl, 6.14.

(*R*)-5,7-Dibenzyloxy-*N*-nitroso-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*R*-5)——— $NaNO_2$ (500 mg, 7.12 mmol) was added to a stirred mixture of *R*-**4**·HCl (1.00 g, 1.78 mmol), AcOH (3 ml), and EtOH (20 ml), and the whole was stirred at room temperture for 1.5 h. The reaction mixture was treated with H_2O, and extracted with AcOEt. The AcOEt extracts were washed with aq. $NaHCO_3$ and H_2O, and dried (Na_2SO_4). Removal of the solvent gave *R*-**5** (985 mg, 100%) as a pale brown viscous oil. $[\alpha]_D^{20}$ +0.2° (*c*=1.43, AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600 (sh), 1590, 1490, 1455. Mass (*m/e*): 524 (M^+-NO), 343, 252, 224, 181, 91. NMR ($CDCl_3$) δ: 3.00 and 3.20 (1H each, d, *J*= Hz, C(1)-$C\underline{H}_2$Ar), 3.71 (6H, s, OMe×2), 3.80 (3H, s, OMe), 4.91 and 4.94 (2H, 2s, $-OC\underline{H}_2C_6H_5$), 5.03 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.15 (2H, s, H(2′) and H(6′)), 7.38 (10H, s, $-C_6H_5\times2$).

5,7-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline (6)———i) NaOCl Method: Aq. 9.7% NaOCl (24.5 g, 31.9 mmol) was added to a stirred solution of *R*-**4** (12.7 g, 24.2 mmol) in THF (100 ml) and MeOH (200 ml) under ice-cooling below 15°C under an argon atmosphere. The mixture was stirred at room temperature for 2 h, then treated with 10% aq. HCl and extracted with $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH–Et_2O–H_2O to afford **6**·HCl (11.9 g, 85%) as slightly yellowish needles, mp 202—205°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3220 (br), 1660. MS *m/e*: 523 (M^+), 508, 432, 181, 91. NMR ($CDCl_3$) δ: 3.79 (9H, s, OMe×3), 4.60 (2H, br s, C(1)-$C\underline{H}_2$Ar), 5.05 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.74 (2H, s, H(2′) and H(6′)), 6.89 and 7.19 (1H each, d, *J*=2 Hz, H(6) and H(8)), 7.35 (10H, s, $-C_6H_5\times2$). *Anal.* Calcd for $C_{33}H_{33}NO_5\cdot HCl\cdot H_2O$: C, 68.56; H, 6.10; N, 2.42. Found: C, 68.84; H, 6.25; N, 2.48.

ii) NCS/KOH Method: *N*-Chlorosuccinimide (90 mg, 0.68 mmol) was added to a stirred solution of *R*-**4** (320 mg, 0.61 mmol) in EtOH (6 ml) at 4°C, and the whole was stirred at room temperature for 0.5 h. A 10% ethanolic KOH solution (1 g) was added, and the mixture was stirred at room temperature for an additional 1 h. The reaction mixture was made acidic with 10% aq. HCl, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH–Et_2O–H_2O to afford **6**·HCl (205 mg, 59%) as pale yellow needle, mp 202—205°C (dec.).

iii) From *R*-**5**: A solution of *R*-**5** (554 mg, 1 mmol) in DMSO (5 ml) was added to a stirred solution of excess dimsyl anion in DMSO [prepared from NaH (145 mg of 66.2% mineral oil dispersion, washed with hexane) and DMSO (5 ml) at 70°C for 10 min], and the whole was stirred at 20—22° C for 10 min. The reaction mixture was treated with ice-water, made acidic with 10% aq. HCl, and then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOH–Et_2O–H_2O to afford **6**·HCl (385 mg, 68%) as slightly yellowish needles, mp 202—205°C (dec.).

(±)-5,7-Dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-4]———The imine (**6**)·HCl (572 mg, 0.79 mmol) was added to a stirred solution of $NaBH_4$ (114 mg, 3 mmol) in EtOH (15 ml) under ice-cooling, and the whole was stirred at room temperature for 2 h. The mixture was treated with H_2O, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with 10% ethanolic HCl and crystallized from EtOH–Et_2O to afford (±)-**4**·HCl (525 mg, 94%) as colorless needles, mp 212—215.5°C. IR ν_{max}^{Nujol} cm^{-1}: 2800—2450. Mass and NMR spectra of this material were identical with those of *R*-**4**·HCl *Anal.* Calcd for $C_{33}H_{35}NO_5\cdot HCl$: C, 70.51; H, 6.46; N, 2.49; Cl, 6.31. Found: C, 70.32; H, 6.48; N, 2.49; Cl, 6.23.

Hydrogenolysis of (±)-4———A solution of (±)-**4**·HCl (1.09 g, 1.94 mmol) in MeOH (20 ml) was hydrogenated over 10% Pd-C (0.5 g) at 3.3 times atmospheric pressure and at 50°C for 17.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was converted to the sulfate and crystallized from EtOH–H_2O to afford (±)-TA-073·1/2H_2SO_4·EtOH[8] (745 mg, 87%) as colorless prisms, mp 206—209°C (dec.).

5,7-Dibenyloxy-1-(3,4,5-trimethoxybenzoyl)-3,4-dihydroisoquinoline (7)———Oxygen was bubbled into a stirred solution of **6** (90 mg, 0.172 mmol) in benzene (20 ml) at reflux temperature for 45 min. After removal of the solvent, the residue was recrystallized from AcOEt–hexane to afford **7** (75 mg, 81%) as pale yellow needles, mp 142—144°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665, 1600 (sh), 1580. MS *m/e*: 537 (M^+), 535 (M^+-2), 195, 91. NMR ($CDCl_3$) δ: 2.81 (2H, t, J=7 Hz), 3.85 (6H, s, OMe×2), 3.91 (3H, s, OMe), 3.75—4.05 (2H, m), 4.94 and 5.06 (2H each, s, $-OC\underline{H}_2C_6H_5\times2$), 6.59 and 6.70 (1H each, d, J= 2 Hz, H(6) and H(8)), 7.25 (2H, s, H(2′) and H(6′)), 7.29 and 7.36 (5H each, s, $-C_6H_5\times2$). *Anal.* Calcd for $C_{33}H_{31}NO_6$: C, 73.72; H, 5.81; N, 2.61. Found: C, 73.63; H, 5.85; N, 2.94.

Asymmetric Reduction of 6 with (I) (1.5 eq) (Table I)———The use of 1,1-dichloroethane as a solvent is described as a representative example. A solution of **6** (396 mg, 0.758 mmol) in $CHCl_2CH_3$ (8 ml) was added to a stirred solution of (I) (890 mg, 1.14 mmol) in $CHCl_2CH_3$ (7 ml) at −30°C, and whole was stirred at −30°C, for 4 h. The reaction mixture was quenched with 10% aq·HCl. After removal of the solvent, the aqueous residue was made basic with K_2CO_3, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC ($CHCl_3$–MeOH, 30:1 v/v) and treated with 10% ethanolic HCl to afford *S*-**4**·HCl (290 mg, 68%) (from EtOH–Et_2O) as a colorless solid, mp 206—211°C, $[\alpha]_D^{20}$ +13.0° (c=1, MeOH) (87% e.e.). IR ν_{max}^{Nujol} cm^{-1}: 2800—2450. Mass and NMR spectra of this material were identical with those of *R*-**4**·HCl.

Asymmetric Reduction of Imine 6·HCl with (I) (1.5 eq) in $CHCl_2CH_3$———The imine (**6**)·HCl (440 mg, 0.758 mmol) was added to a sirred solution of (I) (890 mg, 1.14 mmol) in $CHCl_2CH_3$ (17 ml), and the whole was stirred at −30°C for 2 h. Work-up as described above gave *S*-**4**·HCl (380 mg, 89%) (from EtOH–Et_2O) as a colorless solid, mp 206—211°C, $[\alpha]_D^{20}$ +12.7° (c=1, MeOH) (85% e.e.).

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