

Enantioselective Synthesis of 1-Substituted 1,2,3,4-Tetrahydroisoquinoline Alkaloids via Asymmetric Reduction

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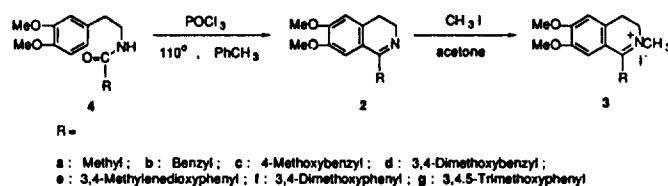
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Enantioselective synthesis of 1-substituted tetrahydroisoquinoline alkaloids (**1**) via asymmetric reduction of 1-substituted 3,4-dihydroisoquinolines (**2**) and the corresponding iminium salts (**3**) with the selected chiral hydride reagents, such as K glucoride (**5**), Itsuno's reagent (**6**), and Mosher's reagent (**7**) were examined. In these reactions, dihydroisoquinolines were not reduced by the hydride reagents, whereas the iminium salts were easily reduced under the same reaction conditions found in successful reduction of ketones. Thus, the reduction of 6,7-dimethoxy-3,4-dihydroisoquinolinium iodide (**3a**) with **5**, **6** and **7** provided the product **1a** with 52.3 % *ee*, 18 % *ee*, and 66.4 % *ee*, respectively. For 1-benzyl derivatives (**3b-3d**), syntheses of **1b-1d** with 0.7-6.2 % *ee*, 5.9-21 % *ee*, and 1.4-2.7 % *ee* were achieved with chiral reducing agents **5**, **6**, and **7**, respectively. For 1-aryl derivatives, use of **5**, **6**, and **7** resulted in optical inductions in the range of 25.2-43 % *ee*, 13-21.1 % *ee*, and 6.3-16 % *ee*, respectively.

Introduction

Since 1-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids (THIQ, **1**) possess important physiological properties¹, a variety of enantioselective synthesis of such compounds have been explored (Figure 1). The synthetic methods include Pictet-Spengler condensation using optically active aldehydes or amino acids as chiral synthons,² diastereoselective alkylation of carbanion derived from chiral amidines,³ cyclization of optically active N-oxaacyliminium salts,⁴ asymmetric catalytic hydrogenation of 1-dehydro derivatives of THIQ,⁵ and diastereoselective reduction of chiral tetrahydroisoquinolinium salts.⁶ However, the methods were only applied to the enantioselective synthesis of 1-alkyl or 1-aralkyl THIQ (**1**, R=alkyl or aralkyl) and there are no examples for the preparation of 1-aryl derivatives (**1**, R=aryl) using these methods.

In recent years, a wide variety of highly effective chiral hydride reagents achieving excellent asymmetric reduction



Scheme 1.

of ketones have been reported.⁷ Therefore, it appeared desirable to develop synthetic methods for preparation of optically active THIQs (**1**) via asymmetric reduction of cyclic imine derivatives, such as 3,4-dihydroisoquinolines (**2**) or 3,4-dihydroisoquinolinium salts (**3**), with these hydride reagents, since the requisite cyclic imine derivatives can be prepared easily by Bishler-Napieralski reaction⁸ and the asymmetric reduction can be applied to enantioselective synthesis of **1** having aryl substituents as well as alkyl or aralkyl groups at C-1 position. For such reduction, only few papers appeared in literature.⁹ Very recently, we reported a short communication on enantioselective synthesis of **1** (R=aryl, R₁=Me) via asymmetric reduction.¹⁰ We described hereby details of this reaction.

Results and Discussion

General. 3,4-dihydroisoquinolines (**2**) were prepared by Bishler-Napieralski cyclization of amides (**4**) with phosphorus oxychloride.⁸ Iminium salts (**3**) were prepared by quaternization of **2** with excess of methyl iodide (Scheme 1). K glucoride (**5**),¹¹ Itsuno's reagent (**6**),¹² and Mosher's reagent (**7**)¹³ were chosen as representative chiral hydride reagents, since these hydrides were known to be effective in high optical inductions for asymmetric reduction of imine derivatives.^{12,14} According to the literature procedures, **5** was prepared by the reaction of excess KH with the borinic ester (**8**), which was prepared by the reaction of 9-BBN with 1,2:5,6-di-O-isopropylidene- α -D-glucopyranose (DIPGF).¹¹ The reagent **6** was prepared from the reaction of 2 equiv of BH₃·THF and 1 equiv of (S)-(-)-2-amino-1,1-diphenylbutan-1-ol (**9**) obtained by Grignard reaction of (S)-valine ester.¹² And the reagent **7** was obtained as the precipitated mixed hydride reagent

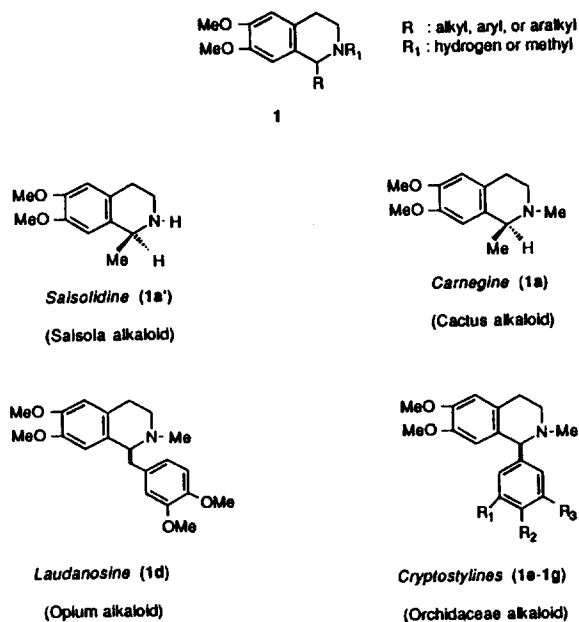
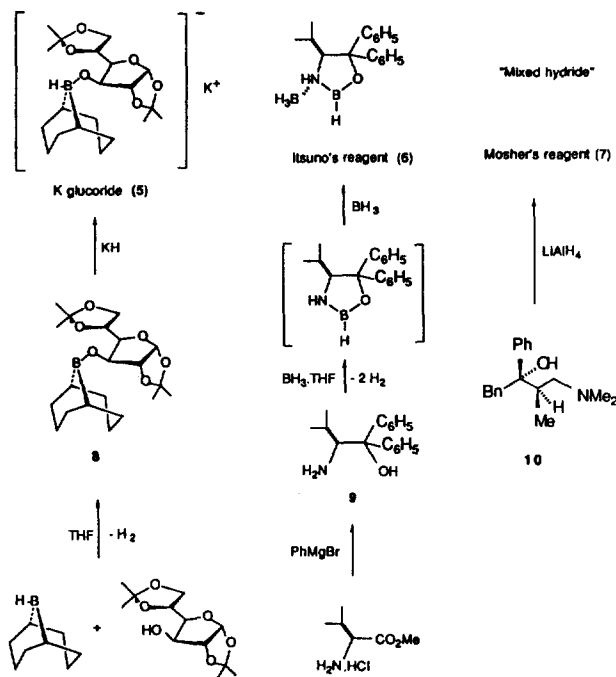


Figure 1.



Scheme 2.

by the reaction of (2S, 3R)-(+)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (**10**) and LiAlH_4 in Et_2O at $0\text{ }^\circ\text{C}^{13}$ (Scheme 2). The reactions were initially carried out under reaction conditions found most successful for reduction of ketones with the reagents, i.e., $-78\text{ }^\circ\text{C}$ with **5**, $30\text{ }^\circ\text{C}$ with **6**, and $0\text{ }^\circ\text{C}$ with **7**.

Asymmetric Reduction of 3,4-dihydroisoquinolines (2) and the Iminium Salts (3). First, asymmetric reduction of **2** with the selected chiral hydride reagents (**5-7**) was carried out. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (**2a**) was chosen as a representative and reacted with the hydrides. However, despite long reaction time (few days), it was found that **2a** was not reduced by these reagents under the reaction conditions adopted in the reduction of ketones with the hydrides. In order to achieve the reduction successfully, several efforts were attempted. For examples, when **2a** was reacted with **5**, the reaction was carried out with excess hydride (4 equiv) and at room temperature. Disappointingly, the reduction underwent still very slowly, (< 10 %, 6 days). In the reduction of **2a** with **6**, the reduction rate was enhanced dramatically by addition of 1 equiv of Lewis acid, AlCl_3 to give **1a'** ($\text{R}_1=\text{H}$) in 90 % yield within 20 h. However, the optical yield obtained was very low (4.7 % ee).

Unlike **2**, iminium salts (**3**) were reduced smoothly by the hydrides to the corresponding amines in good yields. When 6,7-dimethoxy-1,2-dimethyl-3,4-dihydroisoquinolinium iodide (**3a**) dissolved in dry CH_2Cl_2 precooled to $-78\text{ }^\circ\text{C}$ was added to 1.1 equiv of **5** in THF at $-78\text{ }^\circ\text{C}$, the reduction was complete in 3 h. After quenching with $\text{Et}_2\text{O}\cdot\text{HCl}$ at $-78\text{ }^\circ\text{C}$, the reaction mixture was hydrolyzed with $d\text{-HCl}$ at room temperature. The solvent was pumped off *in vacuo* and then the residue was basified with $c\text{-NH}_4\text{OH}$, followed by extraction with CH_2Cl_2 . The extract was dried over anhydrous K_2CO_3 and evaporated to obtain 6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**1a**) (*cactus alkaloid, carnegine*)

Table 1. Asymmetric Reduction of **3** with K Glucuronide (**5**) at $-78\text{ }^\circ\text{C}^a$

cpds.	Time (h)	Yield ^b (%)	1 ($\text{R}_1=\text{Me}$)		abs. config.
			$[\alpha]_D^{22}$, deg.	% ee	
3a	3	76	25.63(c 1.03, PhH)	52.3 ^c	R ^{2c}
3b	3	73	-4.62(c 1.15, MeOH)	4 ^d	R ^e
3c	3	67	-0.57(c 2.1, CHCl_3)	0.7 ^e	R ¹⁷
3d	3	84	-6.12(c 0.47, EtOH)	6.3 ^f	R ²⁰
3e	6	84	20.64(c 2.75, CHCl_3)	37 ^g	S ¹⁹
3f	4	80	25.67(c 0.26, CHCl_3)	43 ^h	S ¹⁹
3g	4	86	-19.62(c 0.32, CHCl_3)	25.2 ⁱ	R ¹⁹

^a Solvent : $\text{CH}_2\text{Cl}_2\text{-THF}$ (1 : 1), [reagent/cpd.] = 1.1. [cpd.] = 0.2 M.

^b Isolated yields after column chromatography. ^c Based on calculated max. value : $[\alpha]_D^{23} -49.0$ (c 1.05, PhH), S(-); ref. 2c. ^d Based on $[\alpha]_D^{22} -116.3$ (c 1.16, MeOH); ref. 16. ^e Based on $[\alpha]_D -84.5$ (c 2.0, CHCl_3), R(-); ref. 17. ^f Based on $[\alpha]_D^{25} 96.6$ (c 0.41, EtOH), S(+); ref. 21. ^g Based on $[\alpha]_D^{20} 56$ (c 2.7, CHCl_3), (S)(+); ref. 19. ^h Based on $[\alpha]_D 59$ (CHCl_3), R(-); ref. 19. ⁱ Based on $[\alpha]_D 78.0$ (CHCl_3), (S)(+); ref. 19. ^j Absolute configuration is not reported, but presumably R, based on (-) sign of optical rotations reported in the benzyl analogues; ref. 17 and 20.

as an oil. The crude **1a** was purified with silica gel column chromatography using $\text{AcOEt}\text{-Et}_3\text{N}$ (9 : 1). Similarly, asymmetric reductions of 6,7-dimethoxy-1-benzyl-2-methyl-3,4-dihydroisoquinolinium iodide (**3b**), 6,7-dimethoxy-1-(4-methoxybenzyl)-2-methyl-3,4-dihydroisoquinolinium iodide (**3c**), 6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl-3,4-dihydroisoquinolinium iodide (**3d**), 6,7-dimethoxy-1-(3',4'-methylenedioxyphenyl)-2-methyl-3,4-dihydroisoquinolinium iodide (**3e**), 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-2-methyl-3,4-dihydroisoquinolinium iodide (**3f**), and 6,7-di-methoxy-1-(3',4',5'-trimethoxyphenyl)-2-methyl-3,4-dihydroisoquinolinium iodide (**3g**) with **5** were carried out under the same reaction conditions. The reductions were complete in 3-6 h to give the optically active THIQs (**1a-1g**, $\text{R}_1=\text{Me}$) in the yields of 67-86 %. In the reduction of **3a**, carnegine (**1a**) with optical purity of 52.3 % ee was obtained, however, very low optical inductions (0.7-6.2 % ee) are given for 1-benzyl derivatives (**3a-3d**). The reduction of 1-aryl dihydroisoquinolinium salts (**3e-3g**) provided *Orchidaceae alkaloids, cryptostylinines* (**1e-1g**) as optically active forms. The optical purities of the alkaloids obtained were 37 % ee for **1e**, 43 % ee for **1f**, and 25.2 % ee for **1g**.

Both of the optically active 1-methyl and 1-benzyl THIQs (**1a-1d**, $\text{R}_1=\text{Me}$) obtained are enriched with the R enantiomers, which are produced by *si* face addition of hydride. In contrast, 1-aryl THIQs (**1e-1g**) obtained are enriched with *re* face addition products. The results and the physical and spectra data of products (**1**) were summarized in Table 1 and 2, respectively. Reduction of the iminium salts **3** with the chiral hydride reagents, **6** and **7** was also carried out. As shown in Table 3 and 4, only low optical inductions except one case (entry 1 in Table 4) were realized, although the reactions underwent smoothly to form the corresponding amines. It is noteworthy that **7** provided the optical induction of 66.4 % ee for **3a**. Finally we examined asymmetric

Table 2. Physical and Spectra Data of **1** (R₁=Me)

cpds	Mp. (°C)	¹ H-NMR (δ CDCl ₃)	IR (cm ⁻¹) (neat or KBr)
1a	oil ¹⁵	6.60(s, 2H), 3.83(s, 6H), 3.57(q, 1H), 3.10-2.73(m, 4H), 2.47(s, 3H), 1.38(d, 3H)	2930, 2782, 1627, 1510, 1255, 1220.
1b	oil ¹⁶	7.41-7.04(m, 5H), 6.63(s, 1H), 6.07(s, 1H), 2.63-3.30(m, 7H), 2.59(s, 3H)	3011, 2836, 1602, 1515, 1269, 1222.
1c	61-62(EtOH) (lit. ¹⁷ 63-64)	7.13-6.24(m, 6H), 3.79(s, 6H), 3.59(s, 3H), 2.59-3.21(m, 7H), 2.49(s, 3H)	3106, 2951, 1603, 1522, 1260, 1132.
1d	86-87(EtOH) (lit. ¹⁸ 89)	6.73-6.40(m, 4H), 6.07, 3.81(s, 3H), 3.78(s, 3H), 3.61(s, 3H), 2.70-3.33(m, 7H)	2990, 2831, 1604, 1514, 1288, 1223, 1152.
1e	99-101(Et ₂ O) (lit. ¹⁹ 101-102)	6.77(s, 3H), 6.60(s, 1H), 5.93(s, 2H), 4.12(s, 1H), 3.87(s, 3H), 3.64(s, 3H), 3.20-2.60(m, 4H), 2.25(s, 3H)	2978, 2832, 1608, 1513, 1254, 1215, 1137.
1f	115-117(Et ₂ O) (lit. ¹⁹ 117-118)	6.83-6.78(m, 3H), 6.63(s, 1H), 6.17(s, 1H), 4.11(s, 1H), 3.90(s, 3H), 3.86(s, 3H), 3.83(s, 3H), 3.60(s, 3H), 3.24-2.33(m, 4H), 2.23(s, 3H)	2951, 2824, 1608, 1511, 1254, 1145.
1g	140-141(Et ₂ O) (lit. ¹⁹ 141-142)	6.63(s, 1H), 6.53(s, 2H), 6.33(s, 1H), 5.01(s, 1H), 3.90-3.77(12H), 3.67(s, 3H), 3.33-2.67 (m, 4H), 1.97(s, 3H)	2949, 2823, 1603, 1514, 1206 1158.

Table 3. Asymmetric Reduction of **3** with K Itsuno's Reagent (**6**) in THF at 30 °C^a

cpds.	Time (h)	Yield ^b (%)	1 (R ₁ =Me)		
			[α] _D ²² , deg.	% ee	abs. config.
3a	15	76	8.71(c 1.04, PhH)	17.8 ^c	R ^{2c}
3b	15	58	-24.19(c 1.24, MeOH)	21 ^d	R ⁱ
3c	15	66	4.97(c 2.13, CHCl ₃)	5.9 ^e	S ¹⁷
3d	15	86	12.52(c 0.32, EtOH)	13 ^f	S ²⁰
3e	15	81	-9.22(c 2.82, CHCl ₃)	17 ^g	R ¹⁹
3f	15	71	-7.57(c 0.32, CHCl ₃)	13 ^h	R ¹⁹
3g	15	79	16.44(c 0.18, CHCl ₃)	21.1 ⁱ	S ¹⁹

^{a-i}See the corresponding foot notes in Table 1.

reduction of **3a** with (R^{*}COO)₃BH (R^{*}=(S)-N-Cbz proline moiety), which provided good optical inductions in the reduction of cyclic imines **2**.⁹ However, reduction did not occur even under reflux condition.

In conclusion, the first enantioselective synthesis of 1-substituted 2-methyl tetrahydroisoquinolines (**1**, R₁=Me) via asymmetric reduction of the corresponding 3,4-dihydroisoquinolium salts (**3**) with the chiral hydride reagents, such as K glucoride (**5**), Itsuno's reagent (**6**), and Mosher's reagent (**7**) has been achieved. Of the selected hydrides, **5** and **7** provides the best results for the reduction of 6,7-dimethoxy-1,2-di-methyl-3,4-dihydroisoquinolium iodide (**3a**) to give *cactus alkaloids, carnegine* (**1a**, R₁=Me) with optical purities of 52.3 % ee and 66.2 % ee, respectively. For 1-aryl derivatives (**3e-3g**), **5** gave better results than those given by **6** and **7** to give *orchidaceae alkaloids, cyptostylin* (**1e-1g**, R₁=Me) with optical purities of 25.2 % ee-43 % ee. However, low op-

Table 4. Asymmetric Reduction of **3** with Mosher's Reagent (**7**) in THF at 0 °C^a

cpds.	Time (h)	Yield ^b (%)	1 (R ₁ =Me)		
			[α] _D ²² , deg.	% ee	abs. config.
3a	18	70	-32.8(c 1.06, PhH)	66.4 ^c	S ^{2c}
3c	18	71	2.26(c 2.20, CHCl ₃)	2.7 ^e	S ¹⁷
3d	20	81	1.54(c 0.33, EtOH)	1.5 ^f	S ²⁰
3e	20	71	3.50(c 2.83, CHCl ₃)	6.3 ^g	S ¹⁹
3f	18	74	-9.38(c 0.32, CHCl ₃)	16.0 ^h	R ¹⁹
3g	18	69	8.75(c 0.16, CHCl ₃)	11.2 ⁱ	S ¹⁹

^aSolvent: CH₂Cl₂:Et₂O=1:2; [reagent/cpd]=1.5; [cpd]=0.125 M. ^{b-i}See the corresponding foot notes in Table 1.

tical inductions for 1-benzyl derivatives (**3b-3d**) were given by all the hydrides examined.

Experimental

General. All glasswares were dried at 140 °C overnight, assembled hot, and cooled to room temperature in a stream of nitrogen. All reactions involving air sensitive materials were carried out under static pressure of nitrogen. The liquids were transferred with a double-ended needles.²⁷

Spectra. ¹H-NMR spectra were recorded on a Varian T-60 spectrometer with Me₄Si as an internal standard. IR measurements were conducted on a Shimadzu IR-435 ratio recording spectrometer equipped with a Shimadzu data recorder. Optical rotations were measured on a Rudolph Polarimeter Autopol III. Melting points were determined using a Fisher-Johns melting point apparatus.

GC Analysis. All GC analyses were carried out with Shimadzu GC-7A gas chromatograph and Hewlett-Packard 5890 capillary gas chromatograph equipped with a Hewlett-Packard 3390A integrator plotter.

Materials. 9-Borabicyclo[3.3.1]nonane (9-BBN), potassium hydride, 1,2 : 5,6-di-*O*-isopropylidene- α -D-glucopyranose (DIPGF, diaceton- α -D-glucose), Darvon alcohol (**10**), (S)-valine methyl ester hydrochloride, and phenyl magnesium bromide (3 M in ether) were purchased from the Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl and stored in an ampule under nitrogen pressure. Methylene chloride was distilled over calcium hydride. According to the literatures, 3,4-dihydroisoquinolines (**2**) and the corresponding iminium salts (**3**) were prepared by cyclization of amides (**4**) (Bischler-Napieralski reaction⁸) and treatment of **2** with excess of methyl iodide, respectively: (compound, yield, mp); **2a**, 78 %, 105-107 °C (lit.²² 105-107 °C); **2b**, 76 %, 80-82 °C (lit.²³ 84-85 °C); **2c**, 83 %, 176-178 °C; **2d**, 82 %, 97-99 °C (lit.⁹ 96-98 °C); **2e**, 83 %, 106-108 °C (lit.²⁴ 109-110 °C); **2f**, 85 %, 166-168 °C (lit.²⁴ 171 °C); **2g**, 85 %, 158-159 °C (lit.²⁴ 159-160 °C); **3a**, 94 %, 173-175 °C; **3b**, 93 %, 105-106 °C (lit.²⁵ 106 °C); **3c**, 95 %, 203-205 °C; **3d**, 91 %, 188-190 °C (lit.²⁶ 191-193 °C); **3e**, 96 %, 206-208 °C (lit.²⁴ 208-209 °C); **3f**, 95 %, 210-212 °C (lit.²⁴ 211-212 °C); **3g**, 95 %, 194-196 °C (lit.²⁴ 193-196 °C). Chiral hydride reagents, **5**¹¹, **6**¹² and **7**¹³, were prepared by the known methods.

Asymmetric Reduction of 3 with 5. The reduction of **3f** is representative. An oven-dried 25 ml, long-necked, round-bottom flask equipped with a septum caped-side arm, a magnetic stirring bar was cooled to room temperature under a stream of nitrogen. The flask was charged with **5** (3.3 mmol) in 7 ml of THF and cooled to -78 °C. To this was added **3f** (3 mmol) in 8 ml of CH₂Cl₂ precooled to -78 °C via a doubled-ended needle. The reaction mixture was stirred at -78 °C. After 3 h, unreacted hydride was quenched by injection of anhydrous HCl in Et₂O precooled to -78 °C. And then the reaction mixture was warmed to room temperature and treated with 5 ml of 6 N HCl for 1 h at 25 °C. After evaporation of the volatiles under reduced pressure, the residue was made alkaline with *c*-NH₄OH and extracted with CH₂Cl₂ (3×10 ml). The extract was dried over anhydrous K₂CO₃ and evaporated. The product **1f** (R₁=Me) was obtained by column chromatography on silica gel using AcOEt-Et₃N (9 : 1) as an eluent. Yield : 80 %; mp. 115-117 °C (lit.¹⁹ 117-118 °C); IR (KBr) : 2951, 2824, 1608, 1511, 1254, 1145 cm⁻¹; ¹H-NMR (δ , CDCl₃) : 6.83-6.78 (m, 3H), 6.63 (s, 1H), 6.17 (s, 1H) 4.11 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.60 (s, 3H), 2.33-3.24 (m, 4H), 2.23 (s, 3H); [α]_D²² 25.67 (c 0.26, CHCl₃), which represents 43 % ee, R, based on [α]_D 59.0 (CHCl₃)¹⁹. The results are summarized with Table 1 and 2.

Asymmetric Reduction of 3 with 6. The reduction of **3g** is described as a representative. The experimental set-up was the same as in the previous experiment. Into the flask was introduced **6** (3.3 mmol) in 7 ml of THF. To this was added **3g** (1.498 g, 3 mmol) in 8 ml of CH₂Cl₂ at room temperature. The reaction mixture was stirred at 30 °C for 15 h. And then excess of hydride was destroyed by addition of 3 mmol of 3 N HCl. After solvent was evaporated *in vacuo*, the deposited precipitate was filtered and washed with 5 ml of water. The water layer was basified with *c*-NH₄OH

and extracted with Et₂O. The extract was washed with brine, dried over anhydrous K₂CO₃, and concentrated to obtain product **1g** (R₁=Me). Finally, **1g** (R₁=Me) was purified by column chromatography on silica gel. [Eluent : AcOEt-Et₃N (9 : 1). Yield : 79 %; mp. 140-141 °C (lit.¹⁹ 141-142 °C); IR(KBr) : 2949, 2823, 1603, 1514, 1206, 1158 cm⁻¹; ¹H-NMR (δ , CDCl₃) : 6.63 (s, 1H), 6.53 (s, 2H), 6.33 (s, 1H), 5.01 (s, 1H), 3.90-3.77 (12H), 3.67 (s, 3H), 3.33-2.67 (m, 4H), 1.97 (s, 3H); [δ]_D²² 16.44 (c 0.18, CHCl₃), which represents 21.1 % ee, S, based on [α]_D 78.0 (CHCl₃)¹⁹. The results are summarized in Table 3.

Asymmetric Reduction of 3 with 7. The reduction of **3a** with is illustrated as a representative. The experimental set-up is the same as above. To "insoluble reagent" of **7** (4.5 mmol) in 16 ml of Et₂O reported by Mosher¹³ was added **3a** (3 mmol) in 8 ml of CH₂Cl₂ at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 18 h, and then hydrolyzed by 7 ml of 3 N HCl. After evaporation of solvent, the deposited precipitate was filtered and washed with 5 ml of water. The combined aqua layer was basified with *c*-NH₄OH and extracted with CH₂Cl₂. The extract was washed with brine, dried over anhydrous K₂CO₃, and concentrated to get the product **1a** (R₁=Me). It was further purified by column chromatography on silica gel. [Eluent : AcOEt-Et₃N (9 : 1)]. Yield : 70 % (oil); IR(neat) : 2930, 2782, 1627, 1510, 1255, 1220 cm⁻¹; ¹H-NMR(δ , CDCl₃) : 6.60(s, 2H), 3.83(s, 6H), 3.57(q, 1H), 3.10-2.73(m, 4H), 2.47(s, 3H), 1.38(d, 3H); [α]_D²² -32.08 (c 1.06, PhH), which represents 66.4 % ee, S, based on calculated maximum value, [α]_D²³ -49.0(c 1.05, PhH).^{2c} The results are summarized in Table 4.

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Probe Diffusion in Polymer Solutions by Forced Rayleigh Scattering

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Methyl red diffusion in polymer solutions was studied by a transient holographic method, forced Rayleigh scattering. In semi-dilute solutions of a polystyrene, where no specific interaction with the probe exists, we found within experimental uncertainty that the retardation of diffusion rate of methyl red is independent of the solvents used. This indicates that the hydrodynamic interaction in polymer coils is not affected by the nature of solvents enough to exhibit a detectable change in the diffusion rate of the probe. On the other hand, a substantial reduction of diffusion rate was observed in poly (methyl methacrylate) solutions in toluene. Together with the similar observation reported with poly (vinyl acetate), it is confirmed that hydrogen bond between the probe and the polymer is responsible for the retarded diffusion. The decay-growth-decay profile found in this system reveals a finite difference in diffusion coefficients of *cis* and *trans* isomer of methyl red. We estimate the difference and suggest that the *cis* isomer interacts with the polymer more strongly than the *trans* isomer.

Introduction

The study of probe diffusion in polymer solutions and polymer gels provides basic knowledges regarding the molecular sieving process which constitutes the basis of many applica-

tions in material separation process such as gel filtration, separation membrane etc. The diffusion of probes through mesh like structure of polymer chains are known to be influenced by the size of diffusant and polymer concentration for a given polymer solution system. It is generally believed that a stretched exponential form can describe the diffusion behavior,

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