[Chem. Pharm. Bull. 31(12)4295—4299(1983)]

Alkylation of a Chiral Hydrazone by Means of Asymmetric Addition of Grignard Reagents to the Carbon–Nitrogen Double Bond

HIROSHI TAKAHASHI*,[a] and YUJI SUZUKI[b]

Institute of Medicinal Chemistry, Hoshi University,[a] Ebara, Shinagawa, Tokyo 142, Japan and Kaken Pharmaceutical Co., Ltd.,[b] Shinomiya-kawaramachi, Yamashina, Kyoto 607, Japan

(Received April 18, 1983)

A chiral hydrazone, (*E*)-(*S*)-*N'*-benzylidene-*N*,3-dimethyl-2-hydrazinobutanol (**6**), was synthesized from (*S*)-valinol. Compound **6** was reacted with Grignard reagents to give optically pure (2*S*,1'*S*)-*N*,3-dimethyl-*N'*-1'-phenylalkyl-2-hydrazinobutanols (**7a** and **7b**). However, *N'*-2'-aryl-1'-phenylethyl-*N*,3-dimethyl-2-hydrazinobutanols (**7c** and **7d**) were each obtained as a mixture of two diastereomers. Nitrogen–nitrogen bonds of **7a** and **7b** were cleaved by hydrogenolysis to give (*S*)-1-phenylalkylamines (**8a** and **8b**), and their absolute configurations and optical purities were confirmed. These reactions were assumed to proceed *via* the chelated six-membered ring intermediates.

Keywords——absolute configuration; asymmetric reaction; chelated intermediate; chiral hydrazine; chiral hydrazone; conformation control; *l*-ephedrine; Grignard reaction; stereoselectivity; (*S*)-valinol

Synthesis of chiral hydrazines by hydrogenation of the C=N bond of the hydrazones has been reported by Akabori *et al.*[1] and other workers[2-4] as shown in Fig. 1A. On the other hand, alkylations at the carbon atom adjacent to the C=N bond of chiral hydrazones, which were synthesized from aliphatic aldehydes and hydrazine, were reported by Enders *et al.*[5] as shown in Fig. 1B. In contrast, we reported that alkylations of arylmethylidenehydrazino compounds prepared from aromatic aldehydes proceeded as the carbon atom of the C=N bond[6] as shown in Fig. 1C.

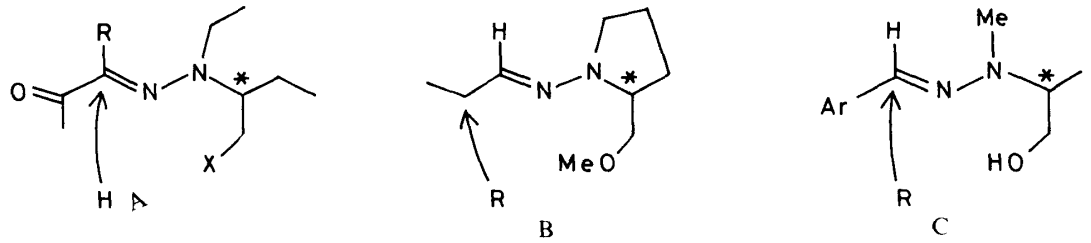

Fig. 1

In this paper, we describe alkylation of a chiral hydrazone derived from L-valinol.

Synthesis and Grignard Reaction of the Chiral Hydrazone 6

(*S*)-*N*,3-Dimethyl-2-hydrazinobutanol (**5**) was obtained by the *N*-nitrosation of (*S*)-*N*,3-dimethyl-2-aminobutanol (**3**) with sodium nitrite and acetic acid, followed by reduction with lithium aluminium hydride. Compound **3** was derived from (*S*)-valinol (**1**) *via* lithium aluminium hydride reduction of (*S*)-*N*-formyl-3-methyl-2-aminobutanol (**2**).

The chiral hydrazone, (*E*)-(*S*)-*N'*-benzylidene-*N*,3-dimethyl-2-hydrazinobutanol (**6**), was

synthesized by condensation of **5** with benzaldehyde; **6** was established to consist of one isomer by gas chromatography, thin-layer chromatography, and analysis of its proton nuclear magnetic resonance (^{1}H-NMR) spectrum. In the ^{1}H-NMR spectrum, the *N*-methyl protons of the *N*-methylhydrazones show a doublet due to long-range spin–spin coupling to the proton of the CH=N–N bond. The coupling constant is 0.7—0.8 Hz for *E*-configurational isomers and less than 0.4 Hz for *Z* isomers,[7] and the signal of the *N*-methyl protons of **6** was observed as a doublet having the coupling constant of 0.98 Hz. Consequently, it was suggested that the configuration of **6** was *E* form.

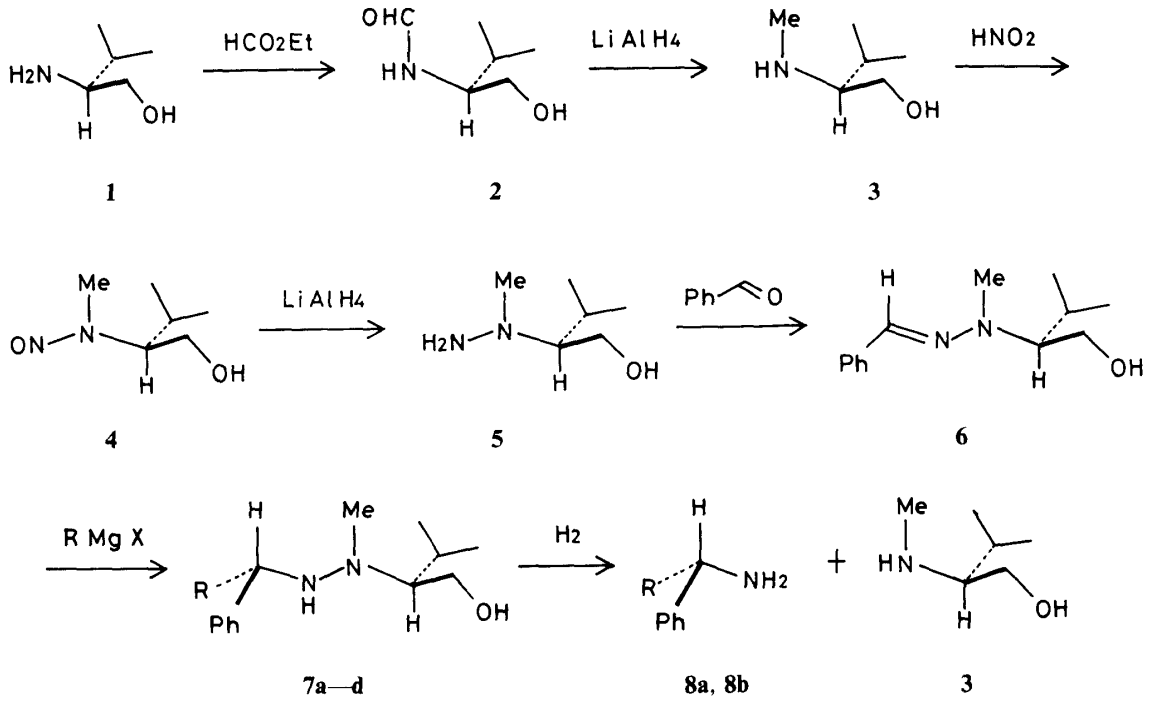

Chart 1

Reactions of the chiral hydrazone (**6**) with Grignard reagents proceeded in ether or tetrahydrofuran (THF) at 40—45 °C for 24 h. The crude reaction mixtures were column-chromatographed on silica gel in order to remove remaining starting material (**6**) and a small amount of by-products. The eluates containing (2*S*, 1′*S*)-*N*,3-dimethyl-*N*′-1′-phenylalkyl-2-hydrazinobutanol (**7a** or **7b**), which was obtained in good yield, were carefully collected, since there was a risk of losing the diastereomer, if formed. This reaction occurred with extremely high stereoselectivity because the other diastereomer could not be detected by analysis of the ^{1}H-NMR signals. On the other hand, reactions of **6** with benzyl- and 4-methoxybenzylmagnesium chloride gave chiral hydrazines (**7c** and **7d**). These compounds were each a mixture of two diastereomers, and the ratios of the major to minor products were estimated as 58 : 42% and 54 : 46% for **7c** and **7d**, respectively. The major products of these reactions were presumed to be (2*S*, 1′*S*)-*N*′-2′-aryl-1′-phenylethyl-*N*,3-dimethyl-2-hydrazinobutanols by analysis of ^{1}H-NMR signals, because the methyl signals at the isopropyl group of (2*S*, 1′*R*)-*N*-2′-aryl-1′-phenylethyl-3-methyl-2-aminobutanols are shifted to higher magnetic field compared with those of the (2*S*, 1′*S*) isomers.[8]

Absolute configurations of the newly created asymmetric carbon atom were determined by conversion of the products to known compounds. The N–N bond in **7a** and **7b** was cleaved by hydrogenolysis with Pd-carbon catalyst in hydrochloric acid solution to give **3** and (*S*)-1-

phenylalkylamine (**8a** and **8b**), respectively. Then, **8a** and **8b** were converted to *N*-salicylideneamines (**9a** and **9b**). The absolute configurations and optical purities of **9a** and **9b** were confirmed by comparison of the circular dichroism data with the values in the literature.[9] It was found that the configurations at the 1′-position of **8a** and **8b** were *S*, and their optical purities were estimated as 99 and 100%, respectively.

N,3-Dimethyl-2-aminobutanol (**3**), obtained along with **8a** and **8b**, was converted to the hydrochloride. No loss of optical purity occurred, based on a comparison of the specific rotation of recovered **3** with that of the originally used material (**3**).

Discussion

The reactions of the chiral hydrazone (**6**) with alkylmagnesium halides occurred with extremely high stereoselectivity, as was the case with a chiral hydrazone derived from *l*-ephedrine.[6a] These reactions were presumed to proceed *via* the magnesium chelated intermediates,[10] involving the hydroxyl group and nitrogen atom of the hydrazones.

This chelated intermediate is a six-membered ring and the isopropyl group is located equatorially since this is the energetically favorable conformation. Thus, the bulkiness of the isopropyl group may have little effect on the stereoselectivity. Consequently, it may be suggested that the second Grignard reagent approaches the lone pair electrons of the oxygen atom, and the alkyl anion attacks from the *re-si* face of the C=N bond under the control of the conformation of the chelated intermediate as shown in Fig. 2A.

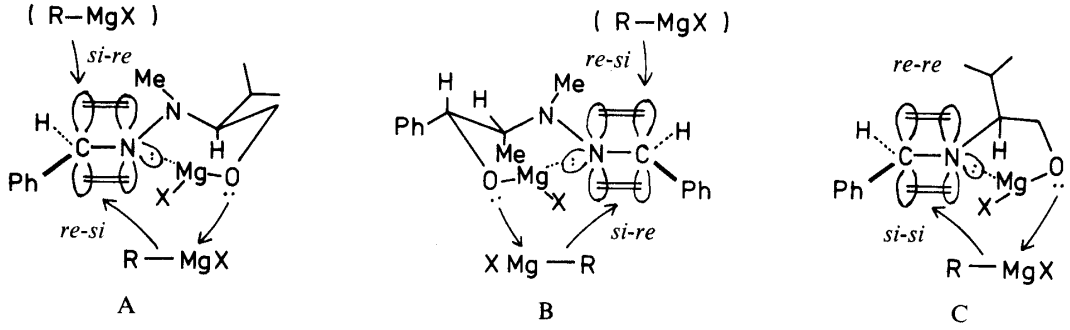

Fig. 2

However, in the case of the aralkylmagnesium halides, the reactions occurred in poor optical yields. It seems that relatively bulky reagents were hindered from approaching the lone pair electrons of the oxygen. Interestingly, in the case of the hydrazones derived from *l*-ephedrine, the chirality of the major products derived from aralkylmagnesium chloride was opposite to that of the products derived from alkylmagnesium halides.[6c] It was presumed that approach of the reagents was hindered by the axial methyl group of the chelated intermediate as shown in Fig. 2B.

On the other hand, the reaction of chiral azomethines with organometallic reagents proceeded *via* a chelated intermediate in which the metal was fixed between the hydroxyl group and the nitrogen atom of the C=N bond.[11] These intermediates were assumed to have a five-membered ring as shown in Fig. 2C, and it was found that aralkylmagnesium reagents were more stereoselective than alkylmagnesium reagents[12] in contrast to the case of the hydrazone (**6**). It was considered that steric factors in the five-membered ring differed from those in the six-membered ring, and the bulkiness of the isopropyl group had a significant effect in determining the stereoselectivity of the chiral reactions.

Experimental

The infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer and the ^{1}H-NMR spectra were obtained with a JEOL FX100 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the EI and the CI (CH_4) methods. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-180 polarimeter.

The circuler dichroism (CD) spectra were measured at 18—20 °C with a Jasco J-40 spectropolarimeter; the magnitudes of the bands were calibrated with D-10-camphorsulfonic acid (at 289 nm) and D-pantolactone ((*R*)-4,5-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone) (at 221 nm) as standards.

(*S*)-*N*-Formyl-3-methyl-2-aminobutanol (2)——**1** (20.6 g, 0.2 mol) was dissolved in ethyl formate (100 ml), then the mixture was refluxed for 1 h. After removal of the solvent, the residue was distilled under reduced pressure; bp 153 °C/0.4 mmHg. Yield, 24.1 g (92%). IR (film): 3300 (OH), 1660 (C=O) cm^{-1}. MS *m/e*: 131 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 8.23 (1H, s, CHO).

(*S*)-*N*,3-Dimethyl-2-aminobutanol (3)——A solution of **2** (26.2 g, 0.2 mol) in THF (80 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (11.4 g, 0.3 mol) in THF (400 ml), and the mixture was stirred overnight at room temperature. Then, H_2O (18 ml) and $Na_2SO_4 \cdot 10H_2O$ (30 g) were added to the mixture, and the whole was stirred for 3 h. The solid was filtered off, and the filtrate was concentrated. The residue was distilled under reduced pressure; bp 110 °C/42 mmHg. Yield, 19.2 (82%). IR (film): 3350 (OH) cm^{-1}. MS *m/e*: 117 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.42 (3H, s, NCH_3), 3.33 (1H, dd, J=6.8 and 10.6 Hz, $CHC\underline{H}_2O$), 3.63 (1H, dd, J=4.4 and 10.6 Hz, $CHC\underline{H}_2O$).

(*S*)-*N*,3-Dimethyl-*N*-nitroso-2-aminobutanol (4)——An aqueous solution of $NaNO_2$ (13.8 g in 30 ml of H_2O) was added to a suspension of **3** (11.7 g, 0.1 mol) in H_2O (30 ml) with vigorous stirring on an ice-cold bath, and acetic acid (9 g, 0.15 mol) was added. Then, the mixture was stirred at room temperature for 4 h. The whole was extracted with ether, and the ethereal solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was used for the following reaction without any purification. IR (film): 3350 (OH), 1450 (N=O) cm^{-1}. MS *m/e*: 147 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.07 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.05 (3H, s, NCH_3).

(*S*)-*N*,3-Dimethyl-2-hydrazinobutanol (5)——A solution of crude **4** (15 g) in THF (50 ml) was slowly added to a stirred suspension of $LiAlH_4$ (5.7 g, 0.15 mol) in THF (300 ml). The mixture was stirred at room temperature for 2 h, and refluxed for 1 h. Then, H_2O (9 ml) and $Na_2SO_4 \cdot 10H_2O$ (15 g) were added to the mixture and stirring was continued for 3 h. After the solid had been filtered off, the filtrate was concentrated and the residue was distilled under reduced pressure; bp 80—85 °C/0.9 mmHg. Yield, 9.2 g (70%). IR (film): 3350 (OH) cm^{-1}. MS *m/e*: 133 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.01 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.59 (3H, s, NCH_3).

(*E*)-(*S*)-*N'*-Benzylidene-*N*,3-dimethyl-2-hydrazinobutanol (6)——A mixture of **5** (7.26 g, 55 mmol) and benzaldehyde (5.83 g, 55 mmol) in benzene (80 ml) was refluxed for 1 h using a Dean–Stark trap. The mixture was concentrated and the residue was distilled under reduced pressure; bp 145—150 °C/0.5 mmHg. Yield, 8.3 g (70%). IR (film): 3450 (OH) cm^{-1}. MS *m/e*: 221 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.04 (3H, d, J=0.98 Hz, $CH=NNC\underline{H}_3$).

(2*S*, 1'*S*)-*N*,3-Dimethyl-*N'*-1'-phenylalkyl-2-hydrazinobutanols (7a and 7b)——A solution of **6** (2.2 g, 10 mmol) in THF (10 ml) was slowly added dropwise to a stirred suspension of alkylmagnesium halide (40 mmol in 24 ml of ether) at 0—5 °C under a nitrogen atmosphere. After being stirred at 45 °C for 24 h, the reaction mixture was poured into NH_4Cl solution and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated off. The residue was column-chromatographed on silica gel with hexane–CH_2Cl_2 to give a colorless oil (**7a** and **7b**).

(2*S*, 1'*S*)-*N*,3-Dimethyl-*N'*-1'-phenylethyl-2-hydrazinobutanol (**7a**); Yield, 1.7 g (72%). IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 237 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.84 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.32 (3H, d, J=6.6 Hz, $PhCHC\underline{H}_3$), 2.51 (3H, s, NCH_3), 3.23 (1H, dd, J=8.2 and 11.2 Hz, $CHC\underline{H}_2O$), 3.55 (1H, dd, J=2.9 and 11.2 Hz, $CHC\underline{H}_2O$), 3.99 (1H, q, J=6.6 Hz, $PhC\underline{H}CH_3$).

(2*S*, 1'*S*)-*N*,3-Dimethyl-*N'*-1'-phenylpropyl-2-hydrazinobutanol (**7b**); Yield, 1.7 g (68%). IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 251 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.80 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.82 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.50 (3H, s, NCH_3), 3.21 (1H, dd, J=8.2 and 11.2 Hz, $CHC\underline{H}_2O$), 3.54 (1H, dd, J=2.7 and 11.2 Hz, $CHC\underline{H}_2O$), 3.70 (1H, dd, J=6.4 and 7.8 Hz, $PhC\underline{H}CH_2$).

Reaction of 6 with Arylmethylmagnesium Chloride——A solution of **6** (2.2 g, 10 mmol) in THF (10 ml) was slowly added dropwise to a suspension of arylmethylmagnesium chloride (40 mmol in 24 ml of THF) under a nitrogen atmosphere. After being stirred at 40—45 °C for 24 h, the reaction mixture was worked up as has been described for the alkylmagnesium halide. The residue was column-chromatographed on silica gel and 1,2-diarylethane was removed. The chiral hydrazines (**7c** and **7d**) were each obtained as a colorless oil, and each was confirmed to consist of a mixture of two diastereomers.

Mixture of (2*S*, 1'*S*)- and (2*S*, 1'*R*)-*N*,3-dimethyl-*N'*-1',2'-diphenylethyl-2-hydrazinobutanol (**7c**); Yield, 1.1 g

(35%). Major : minor = 58 : 42%. IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 313 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.82 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.86 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.41 (3H, s, NCH_3). Minor product; 0.61 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.77 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.26 (3H, s, NCH_3).

Mixture of (2*S*, 1′*S*)- and (2*S*, 1′*R*)-*N*′-2′-(4-methoxyphenyl)-1′-phenylethyl-*N*,3-dimethyl-2-hydrazinobutanol (**7d**); Yield, 1.5 g (39%). Major : minor = 54 : 46%. IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 343 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.83 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.42 (3H, s, NCH_3). Minor product; 0.61 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.77 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.26 (3H, s, NCH_3).

Hydrogenolysis of 7a——Conc. HCl (4 ml) and 10% Pd-carbon (0.5 g) were added to a solution of **7a** (2.0 g, 8.5 mmol) in methanol (40 ml). The mixture was shaken in a hydrogen atmosphere for 48 h at room temperature under a pressure of 4.5 kg/cm^2, then the catalyst was filtered off and the solvent was removed by evaporation. The residue was treated with 2 N NaOH solution and extracted with ether. The oily residue was fractionated by column-chromatography on silica gel with CH_2Cl_2–ethanol. The first fraction was the starting material (210 mg), the second fraction was 1-phenylethylamine (**8a**, 300 mg), and the third fraction was **3** (180 mg). These compounds were identical with corresponding authentic samples.

8a was condensed with an equimolecular amount of salicylaldehyde to give *N*-salicylidene-1-phenylethylamine (**9a**). **9a** was purified by alumina column-chromatography (Aluminiumoxid 90, Merck) to give pale yellow needles. CD (c=0.09, 95% ethanol) $[\theta]^{20}$ (nm): +1300 (405) (positive maximum), +17000 (315) (positive maximum), −2700 (274) (negative maximum); CD (c=0.009, 95% ethanol) $[\theta]^{20}$ (nm): +32000 (253) (positive maximum). Comparison of the above values with the reported[7] values for (*S*)-*N*-salicylidene-1-phenylethylamine indicated *S*-configuration and an optical purity of 99%.

3 was converted to its hydrochloride by treatment with hydrogen chloride methanol solution. The specific rotation of this compound was $[\alpha]_D^{20}$ +10.8° (c=0.39, 95% ethanol); the hydrochloride of the originally used (*S*)-*N*,3-dimethyl-2-aminobutanol (**3**) showed $[\alpha]_D^{20}$ +11.7° (c=0.4, 95% ethanol).

Hydrogenolysis of 7b——Hydrogenolysis of **7b** (2 g) was carried out as has been described for **7a** to give 1-phenylpropylamine (**8b**, 280 mg), **3** (200 mg), and the starting material (180 mg). These compounds were identical with corresponding authentic samples.

8b was converted to *N*-salicylidene-1-phenylpropylamine (**9b**) in a manner similar to that described above. CD (c=0.08, 95% ethanol) $[\theta]^{20}$ (nm): +1300 (402) (positive maximum), +16000 (317) (positive maximum), −3000 (279) (negative maximum); CD (c=0.008, 95% ethanol) $[\theta]^{20}$ (nm): +28000 (253) (positive maximum). Comparison of the above values with the reported[7] values for (*S*)-*N*-salicylidene-1-phenylpropylamine indicated *S*-configuration and an optical purity of 100%.

3 was converted to its hydrochloride, and the specific rotation was $[\alpha]_D^{20}$ +11.5° (c=0.42, 95% ethanol).

References and Notes

1) S. Akabori and S. Sakurai, *Nippon Kagaku Kaishi*, **78**, 1629 (1957).
2) A. N. Kost, R. S. Sagitullin, and M. A. Yurovskaja, *Chem. Ind.* (London), **1966**, 1496.
3) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970); E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, **92**, 2488 (1970).
4) S. Kiyooka, K. Takeshima, H. Yamamoto, and K. Suzuki, *Bull. Chem. Soc. Jpn.*, **49**, 1897 (1976).
5) E. J. Corey and D. Enders, *Chem. Ber.*, **111**, 1362 (1978); D. Enders and H. Eichenauer, *ibid.*, **112**, 2933 (1979); D. Enders, H. Eichenauer, and R. Pieter, *ibid.*, **112**, 3703 (1979); K. G. Davenport, H. Eichenauer, D. Enders, M. Newcomb, and D. E. Bergbreiter, *J. Am. Chem. Soc.*, **101**, 5654 (1979).
6) *a*) H. Takahashi, K. Tomita, and H. Otomasu, *Chem. Commun.*, **1979**, 668; *b*) H. Takahashi, K. Tomita, and H. Noguchi, *Chem. Pharm. Bull.*, **29**, 3387 (1981); *c*) H. Takahashi and H. Inagaki, *ibid.*, **30**, 922 (1982).
7) G. J. Karabatsos and K. L. Krumel, *Tetrahedron*, **23**, 1097 (1967).
8) H. Takahashi, Y. Suzuki, and H. Inagaki, *Chem. Pharm. Bull.*, **30**, 3160 (1982).
9) H. E. Smith and R. Records, *Tetrahedron*, **22**, 813 (1966).
10) K. Koga, "Asymmetric Reactions and Processes in Chemistry," ed. by E. L. Eliel and S. Otsuka, American Chemical Society, 1982, pp. 73—81; S. Hashimoto, *Yakugaku Zasshi*, **102**, 1103 (1982).
11) H. Takahashi, Y. Suzuki, and T. Hori, *Chem. Pharm. Bull.*, **31**, 2183 (1983).
12) Y. Suzuki and H. Takahashi, *Chem. Pharm. Bull.*, **31**, 2895 (1983).