was made relative to perfluorokerosene as a reference. All analytical studies were performed with a Shimadzu-DuPont 830 liquid chromatograph, equipped with a UV-202 spectrophotometer. Operating conditions for HPLC are as follows: column, μ-Porasil (30 × 0.4 cm); pressure, 20 kg/cm²; temperature, ambient; detector, UV at 254 nm; mobile phase, 12% diethyl ether in *n*-hexane. Irradiation was carried out as follows: *ca.* 0.1% solution of 9-*cis*-retro-γ-retinal in each solvent was stirred in a flask and exposed to light from a 43 cm long fluorescent lamp (30 W) at a distance of 15 cm.

9,13-Di-*cis*-retro-γ-retinal (III)——MS *m/e*: 284.212 (M^+, $C_{20}H_{28}O$ requires 284.214); UV λ_{max}^{EtOH} 335 nm; NMR δ ($CDCl_3$, 200 MHz), 1.03 (6H, s, *gem*.CH_3), 1.85 (3H, s, C-9-CH_3), 2.10 (3H, s, C-13-CH_3), 3.12 (2H, d, J=7.3 Hz, C-8-H_2), 4.62 (1H, d, J=2.8 Hz, *exo*CH_2), 5.06 (1H, m, *exo*CH_2), 5.14 (1H, t, J=7.3 Hz, C-7-H), 5.81 (1H, d, J=8.1 Hz, C-14-H), 6.00 (1H, d, J=11 Hz, C-10-H), 6.91 (1H, dd, J=11, 15 Hz, C-11-H), 7.15 (1H, d, J=15 Hz, C-12-H), 10.18 (1H, d, J=8.1 Hz, C-15-H).

UV data for retro-γ-retinal isomers

isomer	λ_{max}^{EtOH} nm[8]	ε	$\lambda_{max}^{n\text{-hexane}}$	ε
all-*trans*	340	24300	320	36500
9-*cis*	339	23400	320	35100
11-*cis*	339	13900	321	20800
	228	8900	225	10800
9,13-di-*cis*	335	18100	317	27200

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8) The published[1] UV data for the retro-γ-retinals should have given the λ_{max}^{EtOH} values of the isomers as in this table.

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Asymmetric Synthesis by Using the Chirality of *l*-Ephedrine. II.[1] Synthesis of (*R*)-α-Phenylethylamine

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The chiral hydrazone (II), obtained by the condensation of *N*-aminoephedrine with benzaldehyde, was reacted with Grignard reagent to give the chiral hydrazine (IVa) in almost 100% diastereomeric excess. On the other hand, the chiral hydrazone (III) was reduced by lithium aluminium hydride to give the chiral hydrazine (IV).

Hydrogenolysis of the chiral hydrazine (IVa) gave (*R*)-α-phenylethylamine (Va) with more than 97% optical purity, and *l*-ephedrine used as a chiral auxiliary reagent was

recovered.

Keywords——asymmetric synthesis; phenylethylamine; Grignard reagent; *l*-ephedrine *N*-amine; lithium aluminium hydride; chiral hydrazine; chiral hydrazone

Recently we reported that a new chiral reagent, *N*-aminoephedrine, easily obtainable from commercially available *l*-ephedrine hydrochloride, was very effective in the asymmetric synthesis of (*R*)-α-phenylalkylamines by reduction of chiral hydrazones derived from various arylaldehydes.[2)]

In this paper, we describe the asymmetric synthesis of α-phenylethylamine from benzaldehyde and acetophenone by using *N*-aminoephedrine as a chiral auxiliary reagent.

1) *N*-(Benzylideneamino)ephedrine (II) and *N*-[(α-Phenylethylidene)amino]ephedrine (III)

Condensation of *N*-aminoephedrine (I) with benzaldehyde was carried out in stirred benzene to give *N*-(benzylideneamino)ephedrine (II) in almost quantitative yield. This crude product showed only one spot in thin-layer chromatography (TLC) and only one peak in gas chromatography (GC). The nuclear magnetic resonance (NMR) spectrum showed that this product contained only one isomer.

On the other hand, an isomeric mixture of *N*-[(α-phenylethylidene)amino]ephedrine (IIIa and IIIb) was obtained by the condensation of *N*-aminoephedrine (I) with acetophenone. This product showed two spots in TLC and two peaks in GC. The NMR spectrum of this product showed clearly the patterns of peaks of two isomers.

NMR studied of configurational isomerism about the C=N double bond have shown that the chemical shift of a methyl group located in *trans* configuration with respect to a lone pair of electrons of nitrogen is observed at lower field than that located in *cis* configuration.[3)] The chemical shift of the methyl group located at the C=N bond of the isomeric mixture of III was observed as two peaks at δ 2.71 and δ 2.48. Consequently, it was considered that the former corresponded to the *trans* configuration while the latter corresponded to the *cis* configuration. The *trans* compound was the predominant isomer of this product, and the ratio of major to minor product was estimated to be 82: 18 by comparison the peak areas. In contrast, compound II, which was obtained by condensation with benzaldehyde, consisted solely of the *trans* isomer due to the difference of bulkiness between the hydrogen atom and phenyl group.

The configuration of amino nitrogen at the 3-position may be expressed as (*S*) for the structure II, while II′ is (*R*), if the lone pair electron of nitrogen is assumed to be a "phantom" atom. However, II′ would be more unstable than II, because the methyl group at the 3-position of II′ is located between the methyl group and the α-hydroxybenzyl group at the 2-position in the Newman projection. The configurations of IIIa and IIIb may be considered in a similar manner.

2) *N*-(α-Phenylethylamino)ephedrine (IV)

Treatment of *N*-(benzylideneamino)ephedrine (II) with methyl magnesium bromide in stirred tetrahydrofuran (THF) under a nitrogen atmosphere afforded the pale yellow oily *N*-(α-phenylethylamino)ephedrine (IVa). The crude product of this reaction showed only one spot in TLC and only one peak in GC. Moreover, the NMR spectrum also indicated only a single compound. Hence, this was a single isomer, in which the newly created chiral center had been produced by the addition of a methyl group.

On the other hand, the reduction of *N*-[(α-phenylethylidene)amino]ephedrine (mixture of IIIa and IIIb) by lithium aluminium hydride treatment produced a diastereomeric mixture of *N*-(α-phenylethylamino)ephedrine (IVa and IVb). This product showed two spots in TLC and two peaks in GC. The NMR spectrum of this product showed the pattern of a mixture of two diastereomers (IVa and IVb). The ratio of the major to the minor product was estimated to be 65: 35 by comparison of the areas under the NMR spectral peaks. The major isomer in this reaction was identical with the product (IVa) obtained by treatment of II with

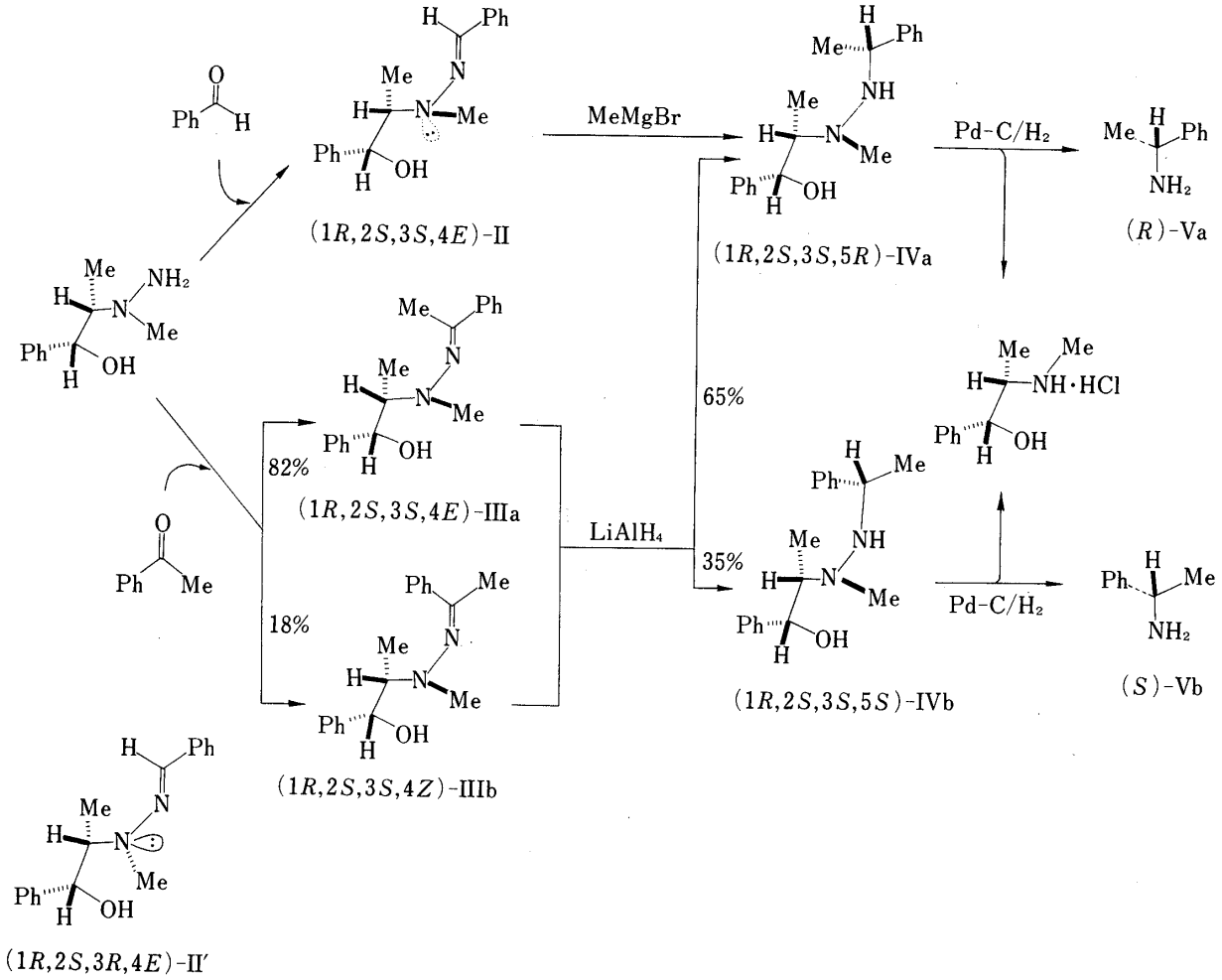

Chart 1

methyl magnesium bromide. Thus, it is possible to calculate the diastereomeric excess of this reaction as 30%.

3) α-Phenylethylamine (V)

Cleavage of the N–N linkage at hydrazine has been reported to proceed by catalytic hydrogenation in an acidic solution.[4] Hydrogenolysis of IVa with a Pd-carbon catalyst under a hydrogen atmosphere in ethanol containing a small amount of hydrochloric acid produced α-phenylethylamine (Va) and *l*-ephedrine in good yields. In this reaction, a small amount of starting material was recovered. The physical and spectral properties of these compounds were identical with those of corresponding authentic compounds.

On the other hand, similar hydrogenolysis of *N*-(α-phenylethylamino)ephedrine, obtained by the reduction of III with lithium aluminum hydride, yielded α-phenylethylamine (mixture of Va and Vb) and *l*-ephedrine, and a small amount of starting material was recovered. These compounds were identical with corresponding authentic samples.

N-Salicylidene-α-phenylethylamine (VIa) was prepared by condensation of Va with salicylaldehyde, in order to elucidate the chiral properties of the original amine. The molecular ellipticity of VIa in the circular dichroism (CD) spectrum at 274, 315, and 405 nm was observed, and the configuration and optical purity of VIa were determined to be (*R*) and more than 97%, respectively, by comparison with those of optically pure (+)-(*S*)-*N*-salicylidene-α-phenylethylamine.[5] On the other hand, the racemic mixture was converted to *N*-salicylidene derivatives having (*R*)-configuration with about 27% optical purity.

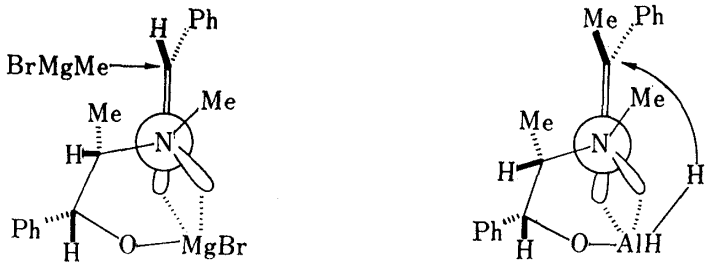

Fig. 1

The *l*-ephedrine used as a chiral auxiliary reagent was recovered in every case in good chemical yield and without any loss of optical purity.

It may be concluded that (1) methylation of II is preferable to reduction of III for the asymmetric synthesis of (*R*)-α-phenylethylamine because the hydroazne II is obtained as a single compound; (2) magnesium and aluminium of the reagents are attached to the hydroxyl group and two nitrogens of the N–N linkage, respectively, and then methylation and hydrogenation occur as shown in the figure; (3) in the reaction of methyl magnesium bromide with *N*-(benzylideneamino)ephedrine, one mol of reagent may be consumed for formation of the chelate compound and another for attack on the hydrazone carbon.

Experimental

The IR spectra were recorded with a Hitachi 215 machine, the mass spectra with a JEOL JMS-D300 machine, and the NMR spectra with a JEOL JNM-FX100. The optical rotation were measured with a Jasco DIP-180 polarimeter, and the CD spectra were taken with a Jasco J-40 machine using a 0.1 cm cell (this instrument was calibrated with D-camphorsulfonic acid).

TLC was performed with Merck Kieselgel 60, and GC was carried out with a Hitachi 164F gas chromatograph using silicone SE-30.

***N*-[(α-Phenylethylidene)amino]ephedrine (III)**——A mixture of *N*-aminoephedrine (900 mg) and acetophenone (600 mg) in anhydrous benzene (*ca.* 10 ml) was stirred for 36 h at ambient temperature. After addition of *n*-hexane (*ca.* 10 ml), the solution was dried over anhydrous $MgSO_4$ and concentrated. The residual oil was purified by Silica gel column chromatography with CH_2Cl_2 to yield a pale yellow oily product. The yield was 1.1 g (79%). IR ν_{max} cm^{-1}: 3370 (OH). MS *m/e*: 282 (M^+).

This product showed two spots at *Rf* 0.21 (major isomer) and 0.32 (minor isomer) on TLC with CH_2Cl_2, and two peaks at 6.0 min (major isomer) and 6.6 min (minor isomer) retention times on GC (column temp.: 190°C). The ratio of major to minor product was estimated to be 82: 18 by comparison of the peak areas in the NMR spectra of the mixture of two isomers. The major isomer (IIIa), δ ($CDCl_3$): 1.03 (3H, d, J= 6.6 Hz, C–CH_3), 2.37 (3H, s, N=C–CH_3), 2.71 (3H, s, N–CH_3), 3.11 (1H, double q, N–CH<), 5.0 (1H, s, OH), 5.41 (1H, d, J=3.0 Hz, O–CH<), 7.2—7.8 (10H, aromatic H). The minor isomer, δ ($CDCl_3$): 0.71 (3H, d, J=6.6 Hz, C–CH_3), 1.54 (3H, s, N=C–CH_3), 2.48 (3H, s, N–CH_3), 2.97 (1H, s, N–CH_3), 2.97 (1H, double q, N–CH<), 4.91 (1H, d, J=3.0 Hz, O–CH<), 7.2—7.8 (10H, aromatic H).

Methylation of II by Methyl Magnesium Bromide: *N*-(α-Phenylethylamino)ephedrine (IVa)——Methyl magnesium bromide (1 M in THF, 80 ml) was added dropwise to a solution of II (2.0 g) in THF (*ca.* 50 ml) under a nitrogen atmosphere. The resulting mixture was stirred at 40°C for 6 h and at ambient temperature for 37 h, then poured into water (*ca.* 150 ml), and extracted with ether (*ca.* 100 ml). The ether–THF solution was dried over anhydrous $MgSO_4$. After removal of the solvent by evaporation, the residual pale yellow oily product (1.7 g) was fractionated by column chromatography over Silica gel using CH_2Cl_2. The first fraction to be eluted was *N*-(α-phenylethylamino)ephedrine (1.66 g, 79%). IR ν_{max} cm^{-1}: 3300 (OH). MS *m/e*: 284 (M^+, 0.4%), 177 (M^+ –  –CH=OH, 68%), 118 ( –C(CH_3)=N$^+$, 96%), 107 (–CH=OH$^+$, 17%), 105 ( –C=O$^+$, 100%). NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, C–CH_3), 1.40 (3H, d, J=6.6 Hz, C–CH_3), 2.56 (3H, s, N–CH_3), 2.68 (1H, double q, N–CH<), 4.08 (1H, q, J=6.6 Hz, C<u>H</u>–CH_3), 4.85 (1H, d, J=1.7 Hz, O–CH<), 7.2—7.4 (10H, aromatic H).

Reduction of III by Lithium Aluminium Hydride——An ethereal solution (20 ml) of lithium aluminium hydride (300 mg) was refluxed for 30 min with gentle stirring. The mixture of *N*-[(α-phenylethylidene)-amino]ephedrine (IIIa: IIIb=82: 18, 1.41 g), obtained by condensation of acetophenone, was dissolved in ether (30 ml) and added dropwise to the $LiAlH_4$–ether mixture over 15 min, and stirring was continued for

3 h. After being treated with water, the reaction mixture was extracted with ether. Removal of this solvent gave the pale yellow oily product (1.1 g, 70%).

This sample showed two spots at *Rf* 0.21 (major isomer) and 0.26 (minor isomer) on TLC with CH_2Cl_2, and two peaks at 2.6 min (major isomer) and 3.0 min (minor isomer) retention times on GC (column temp.: 210°C). The major product was identical with IVa as judged by TLC, GC, and NMR comparisons. The ratio of major to minor products was estimated to be 65: 35 from the peak areas in the NMR spectra. The mixture was fractionated by column chromatography over Silica gel using CH_2Cl_2. The first fraction to be eluted was the minor product (IVb) and the second fraction was the major product (IVa). *N*-(α-phenylethylamino)ephedrine (IVb), NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.6 Hz, C-CH_3), 1.50 (3H, d, J=6.6 Hz, C-CH_3), 2.54 (3H, s, N-CH_3), 2.84 (1H, double q, N-CH<), 4.04 (1H, q, J=6.6 Hz, C<u>H</u>-CH_3), 5.32 (1H, d, J=1.5 Hz, O-CH<), 7.2—7.4 (10H, aromatic H).

Hydrogenolysis of IVa: α-Phenylethylamine (IVa)——A solution of IVa (500 mg) in ethanol (40 ml) was treated with 10% Pd-carbon (100 mg) and conc. HCl (0.3 ml). The mixture was shaken in a hydrogen atmosphere at 50—60°C for 8 h under a pressure of 6 kg/cm², then the catalyst was filtered off and the solvent was removed by evaporation.

The residue was treated with 14% NH_3 solution, exctracted with ether, and fractionated by column chromatography over Silica gel (80 g) using CH_2Cl_2–methanol (10: 1). The first fraction to be eluted was the starting material (IVa, 80 mg), the second fraction was α-phenylethylamine (Va, 370 mg), and the third fraction was ephedrine (250 mg). These compounds were identified by comparison (TLC, GC and NMR) with corresponding authentic samples.

α-Phenylethylamine (Va) thus obtained was condensed with an equimolecular amount of salicylaldehyde to give *N*-salicylidene-α-phenylethylamine. This was purified by Silica gel column chromatography with CH_2Cl_2 and gave pale yellow needles, mp 78°C. CD (c=0.4, ethanol) $[\theta]^{20}$ (nm): −1050 (405) (negative maximum); (c=0.04, ethanol) $[\theta]^{20}$ (nm): −17800 (315) (negative maximum), +2950 (274) (positive maximum). Comparison of the above values of molecular ellipticity with the lit.[5] values for the (*S*)-compound, $[\theta]^{20}$ (nm): +1100 (405), +18000 (315), −3000 (274), indicated an optical purity of 97.6% on average.

Ephedrine was converted to ephedrine hydrochloride by treatment with methanol–hydrochloride, and the specific rotation $[\alpha]_D^{20}$ of this compound was −33.5° (c=0.4, H_2O); $[\alpha]_D^{20}$ of the originally used *l*-ephedrine hydrochloride had been −34.0°.

Hydrogenolysis of the Mixture of IV——The mixture of *N*-(α-phenylethylamino)ephedrine (IVa: IVb= 65: 35, 1.0 g), obtained by reduction of III, was dissolved in ethanol (60 ml), and 10% Pd-carbon (200 mg) and conc. HCl (0.5 ml) were added to the solution. The mixture was shaken in a hydrogen atmosphere for 12 h at 45°C under a pressure of 5.5 kg/cm², then the catalyst was filtered off and the solvent was removed by evaporation. The residue was treated with 14% NH_3 solution, extracted with ether, and fractionated by column chromatography over Silica gel (80 g) using CH_2Cl_2–methanol (10: 1).

The first fraction to be eluted was the starting material (*ca.* 100 mg), the second fraction was α-phenylethylamine (300 mg), and the third fraction was ephedrine (410 mg). These compounds were identified by comparison (TLC, GC and NMR) with authentic samples.

α-Phenylethylamine thus obtained was condensed with an equimolecular amount of salicylaldehyde to give *N*-salicylidene-α-phenylethylamine. This was purified by Silica gel column chromatography with CH_2Cl_2 and gave pale yellow needles. CD (c=0.4, ethanol) $[\theta]^{20}$ (nm): −290 (405) (negative maximum), −5000 (315) (negative maximum). Comparison of the above values with lit.[5] values indicated an optical purity of 27.1% on average.

Ephedrine was converted to ephedrine hydrochloride; its specific rotation $[\alpha]_D^{20}$ was −34.0° (c=0.4, H_2O), whereas $[\alpha]_D^{20}$ of the original *l*-ephedrine hydrochloride had been −34.0°.

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