[Chem. Pharm. Bull. 30(3) 922—926 (1982)]

Asymmetric Synthesis by Using the Chirality of *l*-Ephedrine. III.[1] Reaction of *N*-(Arylmethylideneamino)ephedrine with Benzylmagnesium Chloride and Phenyllithium

HIROSHI TAKAHASHI* and HIDEKAZU INAGAKI

Hoshi Institute of Pharmaceutical Sciences, 2-4-41, Ebara, Shinagawa-ku, Tokyo 142, Japan

(Received August 26, 1981)

Reaction of *N*-(benzylideneamino)ephedrine (II) with benzylmagnesium chloride gave *N*-(1,2-dimethylethylamino)ephedrine (a mixture of III and IV). On the other hand, reaction of *N*-[(2-phenylethylidene)amino]ephedrine (VII) with phenyllithium gave IV. Hydrogenolysis of these products gave 1,2-diphenylethylamine with 40% (*S*) and 91% (*R*) optical purity, respectively, and *l*-ephedrine used as a chiral auxiliary reagent was recovered.

Reactions of *N*-(arylmethylideneamino)ephedrines (VIII and IX) with benzylmagnesium chloride gave chiral hydrazines (X and XI), and reactions with phenyllithium gave XII and XIII.

Keywords——asymmetric synthesis; chiral hydrazine; chiral hydrazone; 1,2-diphenylethylamine; *l*-ephedrine *N*-amine; Grignard reagent; phenyllithium

In the previous paper,[1] we reported that the reaction of *N*-(benzylideneamino)ephedrine with methylmagnesium bromide gave only one diastereomer of *N*-(α-phenylethylamino)-ephedrine, and (*R*)-α-phenylethylamine was synthesized in 97% optical yield by the hydrogenolysis of this chiral hydrazine. We now describe the reaction of *N*-(arylmethylideneamino)-ephedrine with benzylmagnesium chloride and phenyllithium.

Reaction of *N*-(Benzylideneamino)ephedrine

Chiral hydrazone, *N*-(benzylideneamino)ephedrine (II), was reacted with benzyl magnesium chloride in tetrahydrofuran (THF) to give *N*-(1,2-diphenylethylamino)ephedrine (a mixture of III and IV) in good yield. The crude product of this reaction showed two spots on thin layer chromatography (TLC); and the nuclear magnetic resonance (NMR) spectrum of this product clearly showed the patterns of peaks of two isomers. It is considered that a mixture of two diasteromeric isomers may have been obtained because a new chiral center had been produced by the addition of a benzyl group. The ratio of the maior to the minor product was estimated to be 72: 28% by comparison of the areas under the NMR spectral peaks.

Hydrogenolysis of this mixture with a palladium carbon catalyst under a hydrogen atmosphere in ethanol containing a small amount of hydrochloric acid produced 1,2-diphenylethylamine (mixture of V and VI) and *l*-ephedrine in good yields. The physical and spectral properties of these compounds were identical with those of the corresponding authentic compounds. The former compound was derived to *N*-salicylidene-1,2-diphenylethylamine by condensation with salicylaldehyde in order to elucidate the chiral properties of the original amine. Comparison of the molecular ellipticity of this compound in the circular dichroism (CD) spectrum at 265 nm with that of optically pure (+)-(*S*)-*N*-salicylidene-1,2-diphenylethylamine[2] indicated that the configuration and optical purity of 1,2-diphenylethylamine were (*S*) and 40%, respectively. The *l*-ephedrine used as a chiral auxiliary reagent was recovered without any loss of optical purity.

It may be concluded that the introduction of a benzyl group occurs predominantly from the pro-*S* face at the 5-position of II, whereas the attack of a methyl group occures preferentially from the pro-*R* face, as shown in the figure.[1]

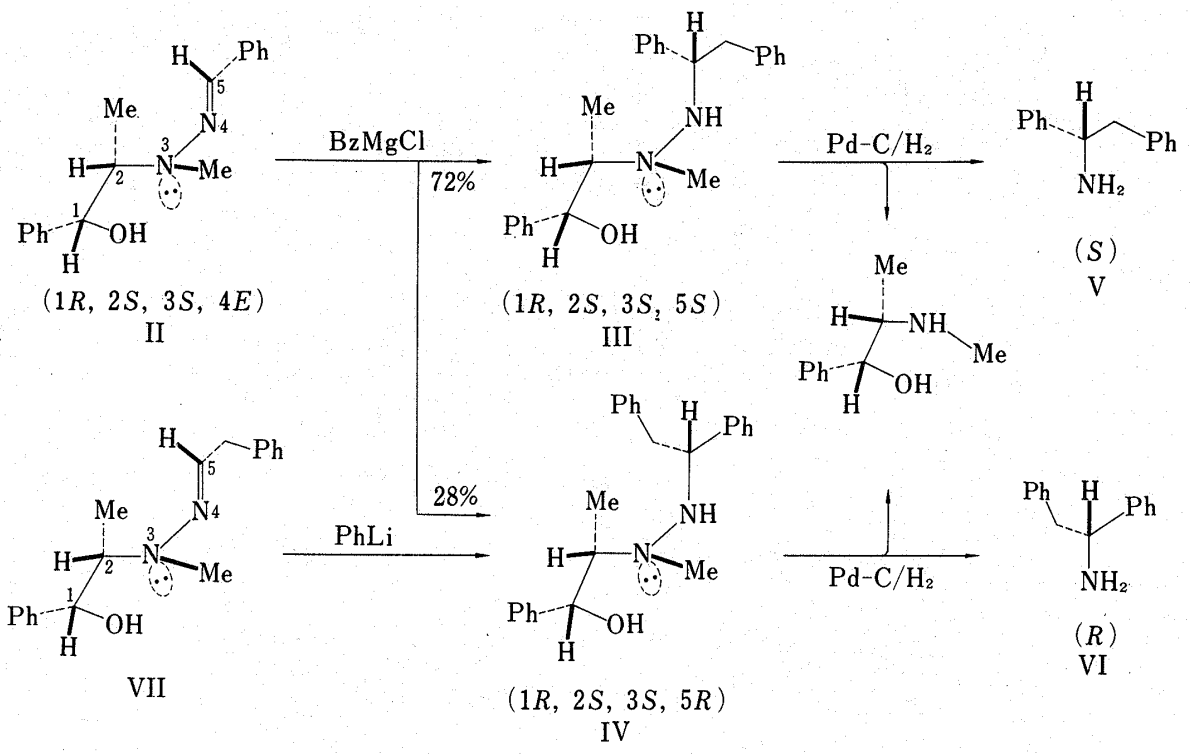


Chart 1

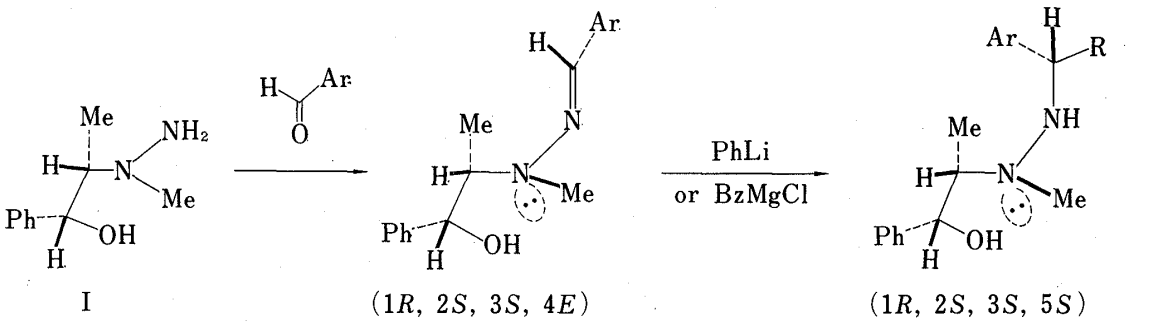
On the other hand, condensation of *N*-aminoephedrine with phenylacetaldehyde gave *N*-[(2-phenylethylidene)amino]ephedrine (VII), which showed only one isomer on TLC and gas chromatography (GC). This compound was reacted with phenyllithium in ether and gave *N*-(1,2-diphenylethylamino)ephedrine (IV) in good yield. This crude product showed only one spot on TLC, and the NMR spectrum also indicated a single compound; this compound was identical with the minor product obtained by condensation of *N*-(benzylideneamino)-ephedrine with benzylmagnesium chloride.

Hydrogenolysis of this compound in a similar manner produced 1,2-diphenylethylamine (VI) and *l*-ephedrine. The former was converted to *N*-salicylidene-1,2-diphenylamine, and the configuration and optical purity of the original amine were determined to be (*R*) and 91%, respectively, by comparison with those of optically pure (+)-(*S*)-*N*-salicylidene-1,2-diphenyl-ethylamine.[2] Consequently, it was found that the attack of the phenyl group of the reagent occurred preferentially from the pro-*S* face at the 5-position of VII as shown in the figure.

Reaction of *N*-(Arylmethylideneamino)ephedrines

N-(Benzylideneamino)ephedrine (II) has been synthesized by condensation of *N*-amino-ephedrine with benzaldehyde.[3] The syntheses of *N*-(*p*-methylbenzylideneamino)- (VIII) and *N*-(*p*-methoxybenzylideneamino)ephedrine (IX) were carried out by condensation of *N*-aminoephedrine with *p*-methylbenzaldehyde and *p*-anisaldehyde, respectively, in almost quantitative yields. The crude products of these reactions showed only one spot on TLC, and the NMR spectra showed that these products contained only one isomer. It was considered that these compounds consisted solely of the *E* isomer at the C=N bond due to the difference of bulkiness between the hydrogen atom and aryl group. Moreover, the configuration of the amino nitrogen at the 3-position may be expressed as (*S*) if the lone pair electrons of nitrogen are assumed to be a "phantom" atom[1] as shown in Chart 2.

The reaction of these hydrazones (VIII and IX) with benzylmagnesium chloride gave *N*-[2-phenyl-1-(*p*-tolyl)ethylamino]- (X) and *N*-[1-(*p*-methoxyphenyl)-2-phenylethylamino]-ephedrine (XI), respectively. The crude products of these reactions each showed two spots



VIII : Ar=*p*-Tolyl
IX : Ar=*p*-MeO-C_6H_4-

X : Ar=*p*-Tolyl, R=benzyl
XI : Ar=*p*-MeO-C_6H_4-, R=benzyl
XII : Ar=*p*-Tolyl, R=phenyl
XIII : Ar=*p*-MeO-C_6H_4-, R=phenyl

Chart 2

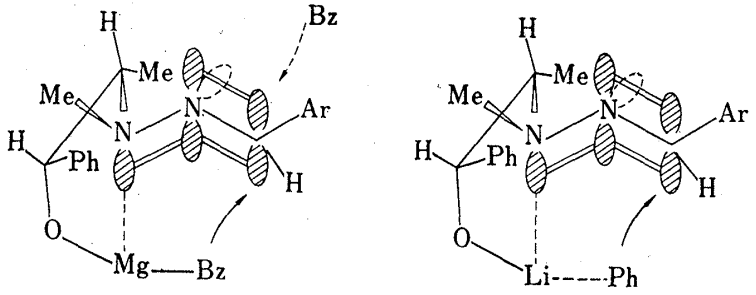


Fig.

on TLC, and the NMR spectra of these products showed the patterns of peaks of two isomers. The ratios of the major to the minor product were estimated to be 70: 30 and 83: 17, respectively, by comparison of the areas under the NMR spectral peaks.

On the other hand, the reaction of VIII and IX with phenyl lithium in ether gave *N*-[phenyl-(*p*-tolyl)methylamino]-(XII) and *N*-[(*p*-methoxyphenyl)-phenylmethylamino]ephedrine (XIII), respectively. The crude products of these reactions showed only one spot on TLC, and the NMR spectra showed that these products contained only one isomer.

It may be concluded that: (1) magnesium and lithium of the reagents approached the hydroxyl group and two nitrogens of the N-N linkage, respectively, then the attack of benzyl and phenyl groups occurred; (2) the benzyl group of the Grignard reagent predominantly attacked from the pro-*S* face at the C=N bond carbon of the chiral hydrazones, whereas methyl, ethyl and isopropyl groups attacked from the pro-*R* face;[4] (3) the phenyl group of phenyllithium attacked from the pro-*S* face at the C=N bond carbon as shown in the figure.

Experimental[5]

Reaction of *N*-(Benzylideneamino)ephedrine (II) with Benzylmagnesium Chloride——Benzylmagnesium chloride (1 M in THF, 50 ml) was added dropwise to a solution of II (1.0 g, 3.7 mmol) in THF (25 ml) under a nitrogen atmosphere. The resulting mixture was stirred at 5—10°C for 8 h, then poured into water, and extracted with ether. The ether–THF solution was dried over anhydrous $MgSO_4$.

After removal of the solvent by evaporation, the residual oily product showed two spots at *Rf* 0.20 (major isomer) and 0.23 (minor isomer) on TLC with CH_2Cl_2, and the NMR spectrum clearly showed the patterns of two diastereomers. The ratio of the major to the minor products was estimated to be 72 : 28% from the peak areas in the NMR spectra.

The residual mixture was fractionated by column chromatography over silica gel using CH_2Cl_2; the first fraction to be eluted was 1,2-diphenylethane and the second fraction gave a pale yellow oil of *N*-(1,2-diphenylethylamino)ephedrine (mixture of III and IV, 1.2 g, 88%). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3300 (OH). MS *m/e*: 360 (M^+, 2%), 253 (M^+−PhCH=OH, 100%). NMR ($CDCl_3$) δ: The major product (III); 0.78 (3H, d, J=6.8

Hz, CH–C<u>H</u>$_3$), 2.53 (3H, s, N–CH$_3$), 2.81 (1H, dq, J=1.7 and 6.8 Hz, CH$_3$–C<u>H</u><), 2.94 (1H, dd, J=9.5 and 12.9 Hz, Ph–CH$_2$), 3.66 (1H, dd, J=4.9 and 12.9 Hz, Ph–CH$_2$), 4.03 (1H, dd, J=4.9 and 9.5 Hz, PhC<u>H</u>–CH$_2$), 5.36 (1H, d, J=1.7 Hz, O–CH<), 7.0—7.6 (aromatic H). The minor product (IV); 0.75 (3H, d, J=6.8 Hz, CH–C<u>H</u>$_3$), 2.34 (3H, s, N–CH$_3$).

Hydrogenolysis of *N*-(1,2-Diphenylethylamino)ephedrine——A solution of the mixture of *N*-(1,2-diphenylethylamino)ephedrines (III: IV=72: 28, 0.9 g) in ethanol (50 ml) was treated with 10% Pd–carbon (0.15 g) and conc. HCl (0.7 ml). The mixture was shaken in a hydrogen atmosphere at 40—50°C for 16 h under a pressure of 5.5 kg/cm^2, 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 using CH_2Cl_2. The first fraction to be eluted was the starting material (0.17 g), the second fraction was 1,2-diphenylethylamine (0.43 g) and the third fraction was ephedrine (0.16 g). These compounds were identified by comparison (TLC, GC and NMR) with the corresponding authentic samples. 1,2-Diphenylethylamine was condensed with an equimolecular amount of salicylaldehyde to give *N*-salicylidene-1,2-diphenylethylamine. This was purified by silica gel column chromatography with CH_2Cl_2 and gave pale yellow needles. CD (c=0.055, ethanol) $[\theta]^{20}$ (nm): −6400 (265) (negative maximum). Comparison of the value of molecular ellipticity with the lit.[2] value for the (*S*)-*N*-salicylidene-1,2-diphenylethylamine, $[\theta]^{20}$ (nm): −16000 (265), indicated an optical purity of 40%. Ephedrine was converted to ephedrine hydrochloride by treatment with methanol–hydrochloric acid; the specific rotation $[\alpha]_D^{20}$ of the originally used *l*-ephedrine hydrochloride had been −34.0°C.

***N*-[(2-Phenylethylidene)amino]ephedrine (VII)**——A mixture of I (0.6 g, 3.3 mmol) and phenylacetaldehyde (0.4 g, 3.3 mmol) in benzene (50 ml) was refluxed for 3 h using a Dean–Stark trap. After removal of the solvent, the residual product was purified by silica gel column chromatography with CH_2Cl_2 to yield a pale yellow oil of VII (0.72 g, 77%). TLC (CH_2Cl_2): Rf 0.26. IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3400 (OH). MS m/e: 282 (M$^+$, 2%), 175 (M$^+$−PhCH=OH, 100%), NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.6 Hz, CH–C<u>H</u>$_3$), 2.69 (3H, s, N–CH$_3$), 3.20 (1H, dq, J=1.6 and 6.6 Hz, CH$_3$–C<u>H</u><), 3.59 (2H, d, J=5.4 Hz, Ph–CH$_2$), 5.29 (1H, d, J=1.6 Hz, O–CH<), 7.0—7.4 (6H, N=CH and aromatic H).

***N*-(1,2-Diphenylethylamino)ephedrine (IV)**——Phenyllithium (1 M in ether, 20 ml) was added dropwise to a solution of VII (0.56 g, 2.0 mmol) in ether (40 ml) under a nitrogen atmosphere, and the mixture was stirred at ambient temperature for 18 h. After being treated with water, the reaction mixture was extracted with ether. Removal of the solvent gave the pale yellow oily product. This product showed one spot at Rf 0.23 on TLC with CH_2Cl_2, and the NMR spectrum indicated that this product consisted of only one isomer.

The residue was fractionated by column chromatography over silica gel using CH_2Cl_2. The first fraction to be eluted was biphenyl and the second fraction gave a pale yellow oil of IV (0.54 g, 70%), which was identical with the minor product obtained by the reaction of II with benzylmagnesium chloride. IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3300 (OH). MS m/e: 360 (M$^+$, 2%), 253 (M$^+$−PhCH=OH, 100%). NMR ($CDCl_3$) δ: 0.75 (3H, d, J=6.8 Hz, CH–C<u>H</u>$_3$), 2.34 (3H, s, N–CH$_3$), 2.65 (1H, dq, J=1.7 and 6.8 Hz, CH$_3$–C<u>H</u><), 2.99 (2H, d, J=7.1 Hz, Ph–C<u>H</u>$_2$), 4.11 (1H, t, J=7.1 Hz, PhC<u>H</u>–CH$_2$), 4.75 (1H, d, J=1.7 Hz, O–CH<), 7.0—7.6 (aromatic H).

***(R)*-1,2-Diphenylethylamine (VI)**——A mixture of IV (0.72 g, 2.0 mmol), 10% Pd–carbon (0.1 g) and conc. HCl (0.5 ml) in ethanol (50 ml) was shaken in a hydrogen atmosphere for 12 h at 45°C under a pressure of 5.5 kg/cm^2, then the catalyst was filtered off and the solvent was removed.

The residue was treated with 14% NH_3 solution, extracted with ether, and fractionated by column chromatography over silica gel using CH_2Cl_2. 1,2-Diphenylethylamine (0.35 g) and ephedrine (0.16 g) were obtained and some starting material (0.11 g) was recovered. 1,2-Diphenylethylamine was converted into *N*-salicylidene-1,2-diphenylethylamine, and purified by silica gel column chromatography with CH_2Cl_2 to give pale yellow needles. CD (c=0.005, ethanol) $[\theta]^{20}$ (nm): +14500 (265) (positive maximum). Comparison of the above value with the lit.[2] value indicated an optical purity of 91%. Ephedrine was converted to ephedrine hydrochloride; its specific rotation $[\alpha]_D^{20}$ was −34.0° (c=0.4, water).

***N*-[(*p*-Methylbenzylidene)amino]ephedrine (VIII)**——A mixture of I (1.00 g, 5.6 mmol) and *p*-methylbenzaldehyde (0.67 g, 5.6 mmol) in benzene (100 ml) was refluxed for 3 h using a Dean–Stark trap. After removal of the solvent, the residual product was purified by silica gel column chromatography using CH_2Cl_2 to yield VIII (1.43 g, 91%). Recrystallization from ethanol gave pale yellow plates of mp 84°C. TLC (CH_2Cl_2): Rf 0.38. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH). MS m/e: 282 (M$^+$, 2%), 175 (M$^+$−PhCH=OH, 100%). NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6.6 Hz, CH–C<u>H</u>$_3$), 2.35 (3H, s, C–CH$_3$), 2.91 (3H, s, N–CH$_3$), 3.36 (1H, dq, J=2.2 and 6.6 Hz, CH$_3$–C<u>H</u><), 5.34 (1H, d, J=2.2 Hz, O—CH<), 7.1—7.5 (6H, N–CH and aromatic H).

***N*-[(*p*-Methoxybenzylidene)amino]ephedrine (IX)**——Condensation of I (1.00 g, 5.6 mmol) with *p*-anisaldehyde (0.76 g, 5.6 mmol) in benzene (100 ml) gave IX (1.42 g, 86%) in the manner described above. The product was recrystallized from ethanol to give pale yellow prisms of mp 63°C. TLC (CH_2Cl_2): Rf 0.34. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH). MS m/e: 298 (M$^+$, 2%), 191 (M$^+$−PhCH=OH, 100%). NMR ($CDCl_3$) δ: 1.01 (3H, d, J=6.7 Hz, CH–C<u>H</u>$_3$), 2.90 (3H, s, N–CH$_3$), 3.81 (3H, s, O–CH$_3$), 3.35 (1H, dq, J=2.1 and 6.7 Hz, CH$_3$–C<u>H</u><), 5.35 (1H, d, J=2.1 Hz, O–CH<), 7.0—7.6 (6H, N=CH and aromatic H).

***N*-[2-Phenyl-1-(*p*-tolyl)ethylamino]ephedrine (X)**——Benzylmagnesium chloride (1 M in THF, 56 ml) was added dropwise to a solution of VIII (1.13 g, 4.0 mmol) in THF (56 ml) under a nitrogen atmosphere,

and the reaction mixture was stirred at 40—45°C for 20 h, then poured into water, and extracted with ether. After removal of the solvent, the residual product showed two spots at *Rf* 0.25 (major isomer) and 0.30 (minor isomer) on TLC with CH_2Cl_2, and the NMR spectrum showed the patterns of two diastereomers. The ratio of the major to the minor products was estimated to be 70: 30 from the peak areas in the NMR spectrum.

The residual mixture was fractionated by column chromatography over silica gel using CH_2Cl_2. The first fraction to be eluted was 1,2-diphenylethane and the second fraction gave a pale yellow oil of X (1.12 g, 75%). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3300 (OH). MS *m/e*: 374 (M^+, 1%), 267 ($M^+-PhCH=OH$, 100%). NMR ($CDCl_3$) δ: The major product; 0.79 (3H, d, $J=6.6$ Hz, CH–C<u>H</u>$_3$), 2.31 (3H, s, C–CH_3), 2.53 (3H, s, N–CH_3), 2.83 (1H, dq, $J=1.7$ and 6.6 Hz, CH_3–C<u>H</u><), 2.94 (1H, dd, $J=9.8$ and 13.2 Hz, Ph–CH_2), 3.67 (1H, dd, $J=4.6$ and 13.2 Hz, Ph–CH_2), 4.01 (1H, dd, $J=4.6$ and 9.8 Hz, PhC<u>H</u>–CH_2), 5.38 (1H, d, $J=1.7$ Hz, O–CH<), 6.9—7.4 (aromatic H). The minor product; 0.75 (3H, d, $J=6.8$ Hz, CH–C<u>H</u>$_3$), 2.31 (3H, s, C–CH_3), 2.33 (3H, s, N–CH_3), 4.78 (1H, d, $J=1.7$ Hz, O–CH<).

***N*-[1-(*p*-Methoxyphenyl)-2-phenylethylamino]ephedrine (XI)**——Reaction of IX (1.19 g, 4.0 mmol) with benzyl magnesium chloride was carried out in a manner similar to that described for the reaction of VIII. The residual product showed two spots at *Rf* 0.22 (major isomer) and 0.26 (minor isomer) on TLC with CH_2Cl_2, and the ratio of the major to the minor products was estimated to be 83: 17 from the peak areas in the NMR spectrum.

The product was fractionated by column chromatography over silica gel using CH_2Cl_2; the first fraction to be eluted was 1,2-diphenylethane and the second fraction gave a pale yellow oil of XI (1.11 g, 71%) IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3300 (OH). MS *m/e*: 390 (M^+, 2%), 298 ($M^+-PhCH=OH$, 100%). NMR ($CDCl_3$) δ: The major product; 0.80 (3H, d, $J=6.8$ Hz, CH–C<u>H</u>$_3$), 2.54 (3H, s, N–CH_3), 2.84 (1H, dq, $J=1.7$ and 6.8 Hz, CH_3–C<u>H</u><), 3.67 (1H, dd, $J=4.9$ and 13.3 Hz, Ph–CH_2), 3.77 (3H, s, OCH_3), 3.98 (1H, dd, $J=4.9$ and 9.8 Hz, Ph–CH_2), 5.38 (1H, d, $J=1.7$ Hz, O—CH<), 6.7—7.4 (aromatic H). The minor product; 0.75 (3H, d, $J=6.6$ Hz, CH–C<u>H</u>$_3$), 2.35 (3H, s, N–CH_3), 3.77 (3H, s, OCH_3), 4.77 (1H, d, $J=1.7$ Hz, O—CH<).

***N*-[Phenyl-(*p*-tolyl)methylamino]ephedrine (XII)**——Phenyllithium (1 M in ether, 30 ml) was added dropwise to a solution of VIII (0.85 g, 3.0 mmol) in ether (30 ml) under a nitrogen atmosphere, and the mixture was stirred at 0—5°C for 2 h, then poured into water, and extracted with ether. After removal of the solvent, residual product showed one spot at *Rf* 0.32 on TLC with CH_2Cl_2, and the NMR spectrum indicated that the product consisted of one isomer. The residue was fractionated by column chromatography over silica gel using CH_2Cl_2 to give a pale yellow oil of XII (0.86 g, 82%). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3300 (OH). MS *m/e*: 360 (M^+, 3%), 253 ($M^+-PhCH=OH$, 78%), 181 (*p*-TolylCHPh$^+$, 98%). NMR ($CDCl_3$) δ: 0.83 (3H, d, $J=6.8$ Hz, CH–C<u>H</u>$_3$), 2.30 (3H, s, C–CH_3), 2.59 (3H, s, N–CH_3), 2.76 (1H, dq, $J=1.7$ and 6.8 Hz, CH_3–C<u>H</u><), 5.04 (1H, d, $J=1.7$ Hz, O–CH<), 5.12 (1H, s, Ph—CH<), 7.1—7.5 (aromatic H).

***N*-[(*p*-Methoxyphenyl)-phenylmethylamino]ephedrine (XIII)**——Reaction of IX (0.75 g, 2.5 mmol) with phenyllithium was carried out as described for the reaction of VIII. This product showed one spot at *Rf* 0.13 on TLC with CH_2Cl_2, and the NMR spectrum indicated that the product consisted of one isomer. IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3350 (OH). MS *m/e*: 376 (M^+, 2%), 269 ($M^+-PhCH=OH$, 33%), 197 (*p*-MeO–C_6H_4–CHPh$^+$, 85%). NMR ($CDCl_3$) δ: 0.83 (3H, d, $J=6.8$ Hz, CH–C<u>H</u>$_3$), 2.59 (3H, s, N–CH_3), 2.76 (1H, dq, $J=1.5$ and 6.8 Hz, CH_3–C<u>H</u><), 3.76 (3H, s, OCH_3), 5.00 (1H, d, $J=1.5$ Hz, O–CH<), 5.11 (1H, s, Ph—CH<), 6.8—7.5 (aromatic H).

References and Notes

1) Part II: H. Takahashi, K. Tomita, and H. Noguchi, *Chem. Pharm. Bull.*, **29**, 3387 (1981).
2) H.E. Smith and T.C. Willis, *Tetrahedron*, **26**, 107 (1970).
3) H. Takahashi, H. Nogichi, K. Tomita, and H. Otomasu, *Yakugaku Zasshi*, **98**, 618 (1978).
4) H. Takahashi, K. Tomita, and H. Otomasu, *Chem. Commun.*, **668** (1979).
5) 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 rotations 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 DC-Alufolien Kieselgel 60 F_{254}, and GC was carried out with a Hitachi 164F gas chromatograph using silicone SE-30.