[Chem. Pharm. Bull. 32(11)4323—4327(1984)]

Stereoselective Reaction of Chiral Mannich Bases. 1,5-Asymmetric Inductions of (*S*)-3-4′-Isopropyl-1′,3′-oxazolidino-1-arylpropan-1-ones

HIROSHI TAKAHASHI,* KOJI TANAHASHI, and KIMIO HIGASHIYAMA

Institute of Medicinal Chemistry, Hoshi University, Ebara, Shinagawa, Tokyo 142, Japan

(Received March 6, 1984)

Chiral Mannich bases, (*S*)-3-oxazolidino-1-arylpropan-1-ones (**3a**, **3b**), were obtained from acetophenone, (*S*)-valinol, and paraformaldehyde. The reaction of these 1-arylpropan-1-ones with organometallic reagents gave 3-oxazolidino- and 3-hydroxyethylamino-1-arylpropan-1-ols (**5a**, **5b**, **6a**—**f**) in good yields.

These 1-arylpropan-1-ols consisted of two diastereomers and the ratios of major to minor products were estimated by proton nuclear magnetic resonance spectroscopy. The 1,5-asymmetric induction of the chiral Mannich bases showed low stereoselectivity.

Keywords——absolute configuration; 3-amino-1-arylpropan-1-ol; 3-amino-1-arylpropan-1-one; 1,5-asymmetric induction; chiral Mannich base; Grignard reaction; organolithium reagent; 1,3-oxazolidine chiral; stereoselective reaction; (*S*)-valinol

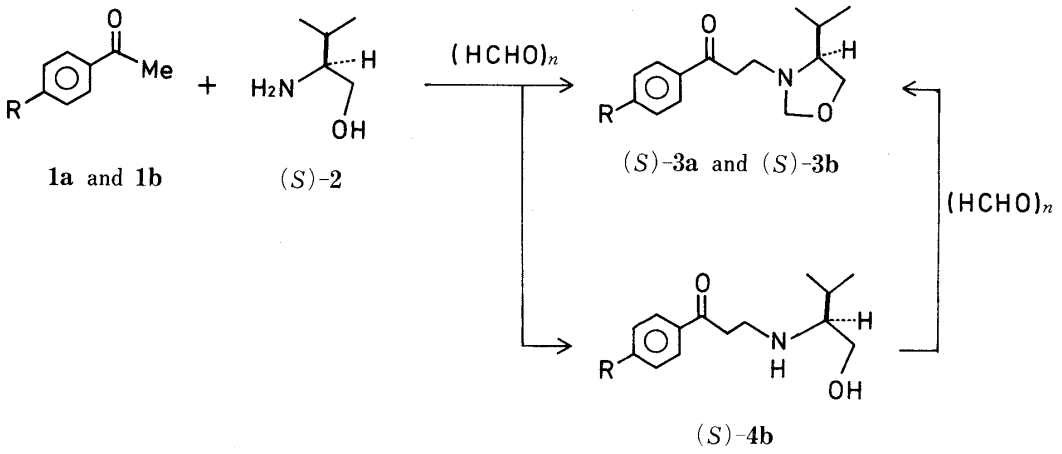
A number of studies[1] have been devoted to the stereochemistry of the reaction of aminocarbonyl compounds with organometallic reagents. Mannich bases such as 3-amino-1-arylpropanones are important intermediates for the synthesis of medicinal agents, and the stereoselective synthesis of 3-amino-1-arylpropanols is of great importance in pharmacological research.[2] We have reported that the 4-isopropyl-1,3-oxazolidino moiety shows high stereo-differentiation owing to the steric effect of the isopropyl group.[3]

In this paper, we deal with 3-amino-1-arylpropan-1-ones having the 4-isopropyl-1,3-oxazolidino group as the amine moiety of the Mannich bases, and describe the stereoselective reactions of these Mannich bases by means of 1,5-asymmetric induction.

(*S*)-3-4′-Isopropyl-1′,3′-oxazolidino-1-arylpropan-1-ones (**3a**, **3b**) were obtained from acetophenones (**1a**, **1b**), (*S*)-valinol (**2**), and paraformaldehyde by Mannich reaction. In the reaction of 4-methoxyacetophenone (**1b**), (*S*)-3-1′-isopropyl-2′-hydroxyethylamino-1-(4-methoxyphenyl)propan-1-one (**4b**) was obtained together with **3b** and **4b** was converted to **3b** by condensation with paraformaldehyde. The structures of these compounds were confirmed by mass, infrared (IR), and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopies.

The Mannich bases (**3a**, **3b**) were allowed to react with aryllithium in ether to give 3-4′-isopropyl-1′,3′-oxazolidino-1,1-diarylpropan-1-ols (**5a**, **5b**) together with small amounts of 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-arylmethylamino-1,1-diarylpropan-1-ols (**6a**, **6b**), in which two aryl groups are introduced at the 2-position of the 1,3-oxazolidine group and at the carbonyl group. The products (**5a**, **5b**, **6a**, **6b**) were confirmed to consist of two diastereomers by ^{1}H-NMR spectrometric analysis. The 1,3-oxazolidine compound (**5b**) was easily converted to the 2-hydroxyethylamine compound (**6b**) and the major and minor products of **5b** were correlated with those of **6b**, respectively.

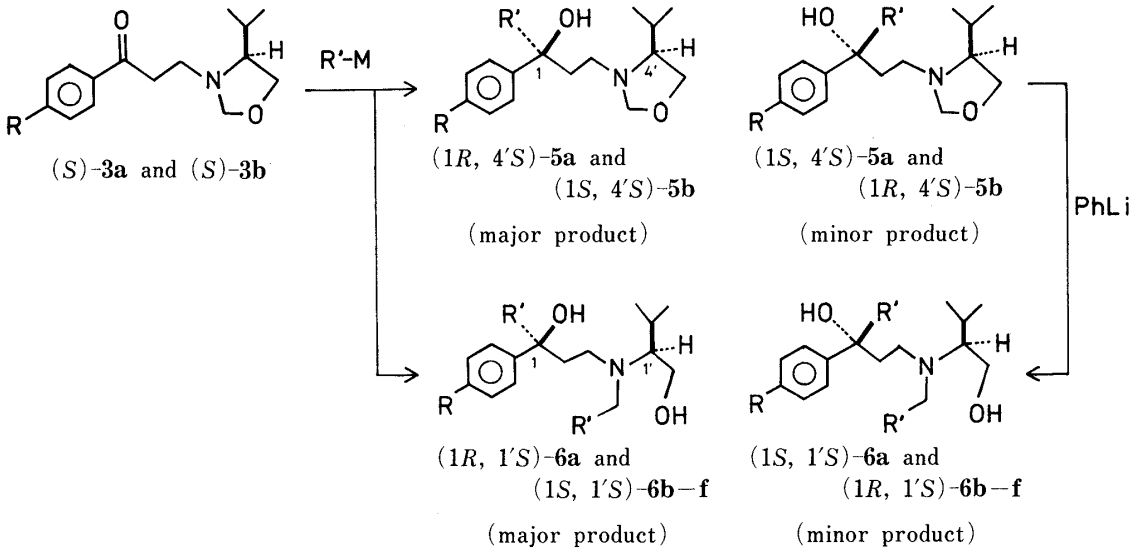
On the other hand, the reaction of Mannich bases with methylmagnesium iodide or benzylmagnesium chloride gave mixtures of (1*S*,1′*S*)- and (1*R*,1′*S*)-1-alkyl-3-*N*-alkyl-*N*-1′-isopropyl-2′-hydroxyethylamino-1-arylpropan-1-ols (**6c**—**f**). No 1-alkyl-3-oxazolidino-1-



1a and **1b** (*S*)-2 (*S*)-**3a** and (*S*)-**3b** (*S*)-**4b**

a: R=H; **b**: R=MeO

Chart 1



(*S*)-**3a** and (*S*)-**3b**

(1*R*, 4'*S*)-**5a** and (1*S*, 4'*S*)-**5b** (major product)

(1*S*, 4'*S*)-**5a** and (1*R*, 4'*S*)-**5b** (minor product)

(1*R*, 1'*S*)-**6a** and (1*S*, 1'*S*)-**6b**–**f** (major product)

(1*S*, 1'*S*)-**6a** and (1*R*, 1'*S*)-**6b**–**f** (minor product)

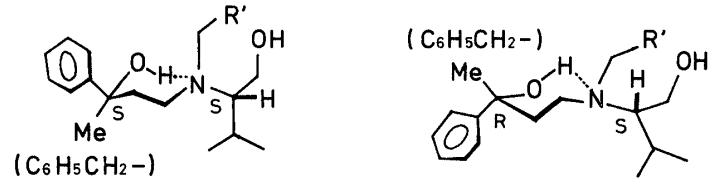
R'-M: 4-$MeOC_6H_4Li$; PhLi; MeMgI; $C_6H_5CH_2MgCl$

Chart 2

TABLE I. Reaction of Mannich Bases [(*S*)-**3a** and (*S*)-**3b**] with Organometallic Reagents at −78 °C in Ether Solution

Compd. No.	R	R'	Yield[a] (%)	Ratio of[b] (1*S*, 1'*S*):(1*R*, 1'*S*)
5a	H	4-$MeOC_6H_4$–	82	34:66
5b	MeO	Ph	89	61:39
6a	H	4-$MeOC_6H_4$–	6	37:63
6b	MeO	Ph	8	64:36
6c	H	Me	93	53:47
6d	MeO	Me	86	54:46
6e	H	$C_6H_5CH_2$–	95	61:39
6f	MeO	$C_6H_5CH_2$–	94	59:41

a) Isolated yield.
b) Estimated from the peak areas in the NMR spectra.



(1*S*, 1′*S*)-form (major product) (1*R*, 1′*S*)-form (minor product)

Fig. 1

arylpropan-1-ol compound was detected in these reactions. It is considered that the Grignard reagents are soft as compared with organolithium reagents and attack without discrimination between the two carbon atoms of the oxazolidine ring and carbonyl group.

The ratios of the two diastereomers of these products (**5a**, **5b**, **6a**—**f**) were estimated from the signal areas in the ^{1}H- and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. These results are summarized in Table I.

Angiolini *et al.* have reported that the hydrogen bond between the hydroxyl group at the 1-position and the nitrogen atom at the 3-position of 3-amino-1-arylpropan-1-ols can be detected by IR spectroscopy.[4] Moreover, they suggested that the methyl group at the 2′-position of the 3-piperidino group should be subject to the anisotropic effect of the aryl group at the 1-position.[5] Hydrogen bonds may also be present in the 3-oxazolidino- and 3-1′-isopropyl-2′-hydroxyethylamino-1-arylpropan-1-ols (**5a**, **5b**, **6a**—**f**), and the anisotropic effects of the aryl group are expected to be observed at the isopropyl group of the (*S*)-valinol moiety.

Actually, the methyl signal of the isopropyl group in the major products of **6c** and **6d** was observed at lower field as compared with that of the minor products because the anisotropic effect of the phenyl group is less in the (1*S*,1′*S*)-series, as shown in Fig. 1.[5] On the other hand, this signal of the major products of **6e** and **6f** was observed at higher field because the anisotropic effect of the benzyl group on the methyl signal is greater, as shown in Fig. 1. Thus, the configuration of major products of **6e** and **6f** was also assumed to be (1*S*,1′*S*).

The methyl signal of the isopropyl group was indistinguishable in the two isomers of **5a**, **5b**, **6a**, and **6b**. However, the signal of the methoxyl group at the benzene ring was distinguishable, and the ratios of the two isomers were estimated from the areas of this peak. The major product of **5a** obtained from **3a** was identical with the minor product of **5b** obtained from **3b**. Similarly, the minor product of **5a** was identical with the major product of **5b**.

These experimental results indicate that the reactions of the Mannich bases, (*S*)-3-4′-isopropyl-1′,3′-oxazolidino-1-arylpropan-1-ones (**3a**, **3b**), with organometallic reagents proceeded in high chemical yield, and the stereoselectivity was 32—36% (d.e.) in 1,5-asymmetric induction of the isopropyl group at the 1,3-oxazolidine ring. Thus, the reactions probably do not occur *via* the chiral chelate intermediate involving the carbonyl group and the oxygen (or nitrogen) atom of 1,3-oxazolidine as a major intermediate.

Experimental

The IR spectra were recorded with a Hitachi 200-10 spectrometer and the ^{1}H-NMR spectra were obtained with a JEOL JNM-FX100 spectrometer (100 MHz for ^{1}H-NMR and 25 MHz for ^{13}C-NMR). The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the EI and the CI (isobutane) methods. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected.

(*S*)-3-4′-Isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-one (3a)——A stirred mixture of (*S*)-valinol (5.67 g, 55 mmol), paraformaldehyde (3.6 g, 120 mmol), and acetophenone (6.0 g, 50 mmol) in ethanol (50 ml) was made acid with saturated hydrogen chloride–ethanol solution (5 ml) and refluxed for 8 h. Two additions of paraformaldehyde (3.6 g, 120 mmol) were made at 2 and 5 h after the beginning of reflux. The reaction mixture was concentrated and the residue was dissolved in 5% hydrochloride solution (200 ml). The neutral components were removed by extraction with *n*-hexane, the whole was made basic with Na_2CO_3 solution then extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was column-chromatographed on silica gel with *n*-hexane–ether (1 : 1) to give (*S*)-3-4′-isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-one (**3a**) as a colorless oil (7.3 g, 59%). IR ($CHCl_3$): 1680 (C=O) cm^{-1}. MS *m/z*: 247 (M^+), 204, 128 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.95 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.9—3.3 (4H, m, CH_2CH_2), 3.40 (1H, dd, J=5.9 and 8.3 Hz, $OC\underline{H}_2CH$), 3.94 (1H, dd, J=7.3 and 8.3 Hz, $OC\underline{H}_2CH$), 4.24 (1H, d, J=5.9 Hz, OCH_2N), 4.35 (1H, d, J=5.9 Hz, OCH_2N).

Mannich Reaction of 4-Methoxyacetophenone (1b) with (*S*)-Valinol (2)——A saturated hydrogen chloride–ethanol solution (4 ml) was added to an ethanol solution (20 ml) of (*S*)-valinol (2.27 g, 22 mmol), paraformaldehyde (1.5 g, 50 mmol), and 4-methoxyacetophenone (3.0 g, 20 mmol), and the reaction mixture was refluxed with stirring for 10 h. Two additions of paraformaldehyde (1.5 g, 50 mmol) were made at 2 and 4 h after the beginning of reflux. After removal of the solvent, the residue was worked-up as described above. The residue was column-chromatographed on silica gel with *n*-hexane–ether (1 : 1) to give (*S*)-3-4′-isopropyl-1′,3′-oxazolidino-1-(4-methoxyphenyl)propan-1-one (**3b**) as a colorless oil (2.9 g, 52%), and (*S*)-3-1′-isopropyl-2′-hydroxyethylamino-1-(4-methoxyphenyl)propan-1-one (**4b**) was obtained as a colorless solid (0.4 g, 8%) from the eluate with ether–methanol–28% aqueous ammonia (97 : 2 : 1).

3b: IR ($CHCl_3$): 1675 (C=O) cm^{-1}. MS *m/z*: 277 (M^+), 234, 135 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.9—3.3 (4H, m, CH_2CH_2), 3.41 (1H, dd, J=5.9 and 8.4 Hz, $OC\underline{H}_2CH$), 3.87 (3H, s, OCH_3), 3.94 (1H, dd, J=7.3 and 8.3 Hz, $OC\underline{H}_2CH$), 4.25 (1H, d, J=5.9 Hz, OCH_2N), 4.36 (1H, d, J=5.9 Hz, OCH_2N).

4b: IR ($CHCl_3$): 3450 (OH), 1675 (C=O) cm^{-1}. MS *m/z*: 266 ($M\cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.00 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.9—3.3 (4H, m, CH_2CH_2), 3.35 (1H, dd, J=7.3 and 10.7 Hz, $OC\underline{H}_2CH$), 3.64 (1H, dd, J=4.4 and 7.3 Hz, $OC\underline{H}_2CH$), 3.87 (3H, s, OCH_3). Recrystallization from *n*-hexane–ether gave colorless plates, mp 44—45 °C. *Anal.* Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 67.62; H, 8.82; N, 5.35.

Reaction of 4b with Paraformaldehyde——An ethereal solution of **4b** (0.27 g, 1 mmol) and paraformaldehyde (0.12 g, 4 mmol) in THF (5 ml) was refluxed in the presence of anhydrous $MgSO_4$ (1 g) for 2 h. The reaction mixture was worked-up as described above to give **3b** (0.24 g, 87%) and unchanged starting material (0.03 g). These compounds were identified by comparison with authentic samples (TLC, gas liquid chromatography (GC), and ^{1}H-NMR spectroscopy).

Reaction of (*S*)-3a with 4-Methoxyphenyllithium——An ethereal solution of 4-methoxyphenyllithium (20 mmol) in ether (10 ml) was slowly added dropwise to a stirred solution of (*S*)-**3a** (1.24 g, 5 mmol) in ether (10 ml). After being stirred at −78 °C under a nitrogen atmosphere for 6 h, the reaction mixture was treated with H_2O, and the whole was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The oily residue was fractionated by column-chromatography on silica gel with *n*-hexane–ether (1 : 1). The first fraction gave 3-4′-isopropyl-1′,3′-oxazolidino-1-(4-methoxyphenyl)-1-phenylpropan-1-ol (**5a**) (1.45 g, 82%) and the second fraction gave 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-(4-methoxybenzyl)amino-1-(4-methoxyphenyl)-1-phenylpropan-1-ol (**6a**) (0.13 g, 6%). These products were meticulously separated by rechromatography of the boundary fractions between the two compounds. The ratios of the two diastereomers of **5a** and **6a** were estimated by ^{1}H-NMR spectroscopy.

5a: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 356 ($M\cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.82 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.46 (1H, dd, J=5.9 and 8.3 Hz, $OC\underline{H}_2CH$), 3.75 (3H, s, OCH_3), 3.87 (1H, dd, J=7.3 and 8.3 Hz, $OC\underline{H}_2CH$), 4.36 (2H, s, OCH_2O). Minor product; 0.82 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.47 (1H, dd, J=5.9 and 8.3 Hz, $OC\underline{H}_2CH$), 3.78 (3H, s, OCH_3), 3.87 (1H, dd, J=7.3 and 8.3 Hz, $OC\underline{H}_2CH$), 4.36 (2H, s, OCH_2O).

6a: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 464 ($M\cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.79 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3). Minor product; 0.79 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3).

Reaction of (*S*)-3b with Phenyllithium——An ethereal solution of phenyllithium (20 mmol) in ether (10 ml) was added dropwise to a stirred solution of (*S*)-**3b** (1.39 g, 5 mmol) in ether (10 ml). After being stirred at −78 °C under a nitrogen atmosphere for 6 h, the reaction mixture was worked-up as described for (*S*)-**3a**. 3-4′-Isopropyl-1′,3′-oxazolidino-1-(4-methoxyphenyl)-1-phenylpropan-1-ol (**5b**) (1.60 g, 89%) and 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-benzylamino-1-(4-methoxyphenyl)-1-phenylpropan-1-ol (**6b**) (0.20 g, 8%) were obtained.

(1*S*,4′*S*)-**5b** (major product prepared from (*S*)-**3b**) was confirmed to be identical with (1*S*,4′*S*)-**5a** (minor product prepared from (*S*)-**3a**) by mass, IR, and ^{1}H-NMR spectral comparisons. Similarly, (1*R*,4′*S*)-**5b** was identical

with (1*R*, 4′*S*)-**5a**.

6b: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 434 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.80 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.94 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.77 (3H, s, OCH_3). Minor product; 0.80 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.94 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.76 (3H, s, OCH_3).

Conversion of 5b into 6b——A suspension of phenyllithium (1 mmol in 5 ml of ether) was slowly added, drop by drop, to a stirred solution of **5b** (0.36 g, 1 mmol) in ether (5 ml) under a nitrogen atmosphere. After being stirred at room temperature for 12 h, the reaction mixture was worked-up as described above to give **6b** (0.32 g, 74%), which was identified by comparison with an authentic sample (TLC and ^{1}H-NMR spectroscopy).

3-*N*-Ethyl-*N*-1′-isopropyl-2′-hydroxyethyl-1-methyl-1-arylpropan-1-ols (6c, 6d)——A suspension of methylmagnesium iodide (12 mmol in ether 10 ml) was slowly added dropwise to a stirred ethereal solution of Mannich base (**3a**, **3b**, 3 mmol) in ether (10 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 6 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 ^{1}H-NMR spectrum of the oily residue was taken and the ratio of the two diastereomers [(1*S*, 1′*S*): (1*R*, 1′*S*)] was estimated. The crude products were purified by column-chromatography on silica gel with CH_2Cl_2–methanol (95 : 5).

6c: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 280 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.04 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.51 (3H, s, CCH_3). Minor product; 0.80 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.06 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.52 (3H, s, CCH_3). ^{13}C-NMR ($CDCl_3$) δ: Major product; 14.5 (q), 20.0 (q), 22.1 (q), 27.9 (d), 31.8 (q), 40.4 (t), 44.6 (t), 47.1 (t), 59.6 (t), 67.2 (d), 74.9 (s), 124.8 (d), 126.2 (d), 127.9 (d), 148.3 (s). Minor product; 14.6 (q), 19.9 (q), 22.5 (q), 27.1 (d), 31.9 (q), 40.4 (t), 44.5 (t), 47.3 (t), 59.6 (t), 67.4 (d), 74.9 (s), 124.7 (d), 126.2 (d), 128.0 (d), 148.2 (s).

6d: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 310 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.00 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.48 (3H, s, CCH_3), 1.98 (2H, q, J=7.1 Hz, $NC\underline{H}_2CH_3$), 3.38 (1H, dd, J=7.8 and 11.0 Hz, $OC\underline{H}_2CH$), 3.63 (1H, dd, J=4.6 and 11.0 Hz, $OC\underline{H}_2CH$), 3.81 (3H, s, OCH_3). Minor product; 0.81 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.94 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.04 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.48 (3H, s, CCH_3), 1.98 (2H, q, J=7.1 Hz, $NC\underline{H}_2CH_3$), 3.21 (1H, dd, J=8.5 and 11.2 Hz, $OC\underline{H}_2CH$), 3.52 (1H, dd, J=4.2 and 11.2 Hz, $OC\underline{H}_2CH$), 3.81 (3H, s, OCH_3).

1-Benzyl-3-*N*-phenylethyl-*N*-1′-isopropyl-2′-hydroxyethyl-1-arylpropan-1-ols (6e, 6f)——A suspension of benzylmagnesium chloride (20 mmol in ether 10 ml) was slowly added dropwise to a stirred ethereal solution of Mannich base (**3a**, **3b**, 5 mmol) in ether (20 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 6 h, the mixture was worked-up as described for the reaction with methylmagnesium iodide. The diastereomeric mixture was obtained as a colorless solid and the experimental data are summarized in Tabel I.

6e: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 432 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.75 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.84 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$). Minor product; 0.79 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.91 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$).

6f: IR ($CHCl_3$): 3400 (OH) cm^{-1}. MS *m/z*: 462 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.76 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.81 (3H, s, OCH_3). Minor product; 0.79 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.91 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.81 (3H, s, OCH_3).

The major products were isolated by recrystallization of the mixture of two diastereomers from *n*-hexane–ethanol.[6] (1*S*, 1′*S*)-**6e**; Colorless needles, mp 99—100 °C. *Anal.* Calcd for $C_{29}H_{37}NO_2$: C, 80.70; H, 8.64; N, 3.25. Found: C, 80.52; H, 8.54; N, 3.20. (1*S*, 1′*S*)-**6f**; Colorless needles, mp 132 °C. *Anal.* Calcd for $C_{30}H_{39}NO_3$: C, 78.05; H, 8.52; N, 3.03. Found: C, 77.91; H, 8.55; N, 2.99.

References and Notes

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, 1971, pp. 84—159; D. A. Evans, J. V. Nelson, and T. R. Taber, "Topics in Stereochemistry," Vol. 13, ed. by N. L. Allinger, E. L. Eliel, and S. H. Wilen, John Wiley and Sons, 1982, pp. 1—115.
2) R. Andrisano, P. C. Bizzarri, and M. Tramontini, *Tetrahedron*, **26**, 3959 (1970); M. Tramontini, *Synthesis*, **1982**, 605.
3) H. Takahashi, Y. Suzuki, and T. Kametani, *Heterocycles*, **20**, 607 (1983); H. Takahashi, Y. Chida, T. Suzuki, H. Onishi, and S. Yanaura, *Chem. Pharm. Bull.*, **32**, 2714 (1984).
4) R. Andrisano and L. Angiolini, *Tetrahedron*, **26**, 5247 (1970).
5) L. Angiolini, P. C. Bizzarri, G. Scapini, and M. Tramontini, *Tetrahedron*, **37**, 2137 (1981).
6) Each compound was confirmed to be the major component by ^{1}H-NMR spectroscopy.