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Asymmetric α-Substituted Phenethylamines. I. Synthesis of Optically Pure 1-Aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines

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Optically pure 1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines (**3a**—**c**) were synthesized by the reactions of *N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**2a**—**c**) with benzylmagnesium chloride. The diastereomers (**5a**—**c**) were prepared from *N*-(2-hydroxy-1-isopropylethyl)phenylethylideneamine (**4**) and aryllithium compounds.

The optical purity of **3a** was elucidated and the absolute configuration was determined by synthesis *via* an alternative route. The characteristic methyl signals in the nuclear magnetic resonance (NMR) spectra suggested the configurations of the chiral amines (**3a**—**c** and **5a**—**c**).

Keywords——absolute configuration; asymmetric synthesis; azomethine chiral; chirality determination; 1,2-diphenylethylamine; Grignard reaction; optically pure amine; phenethylamine moiety; phenyllithium; (*S*)-valinol

Chiral amines containing the phenylethylamine moiety are extremely important as medicinal agents. For instance, some phenylethylamines having an asymmetric carbon at the α-position with respect to the nitrogen atom potent analgesics, *e.g.*, (*R*)-(−)-morphine, (*R*)-(−)-pentazocine, (*R*)-(−)-*N*,*N*-dimethyl-1,2-diphenylethylamine, (*S*)-(−)-methamphetamine, *etc.* We are interested in the synthesis of these pharmacologically active chiral amines.

In a previous paper,[1)] we described the asymmetric synthesis of (*S*)- and (*R*)-1-aryl-2-phenylethylamines by taking advantage of the chirality of *l*-ephedrine. We mow describe the synthesis of new optically pure phenylethylamines, (1*S*, 1′*S*)-(+)-1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines, and the determination of the absolute configuration of these chiral compounds.

Synthesis of Phenylethylamines

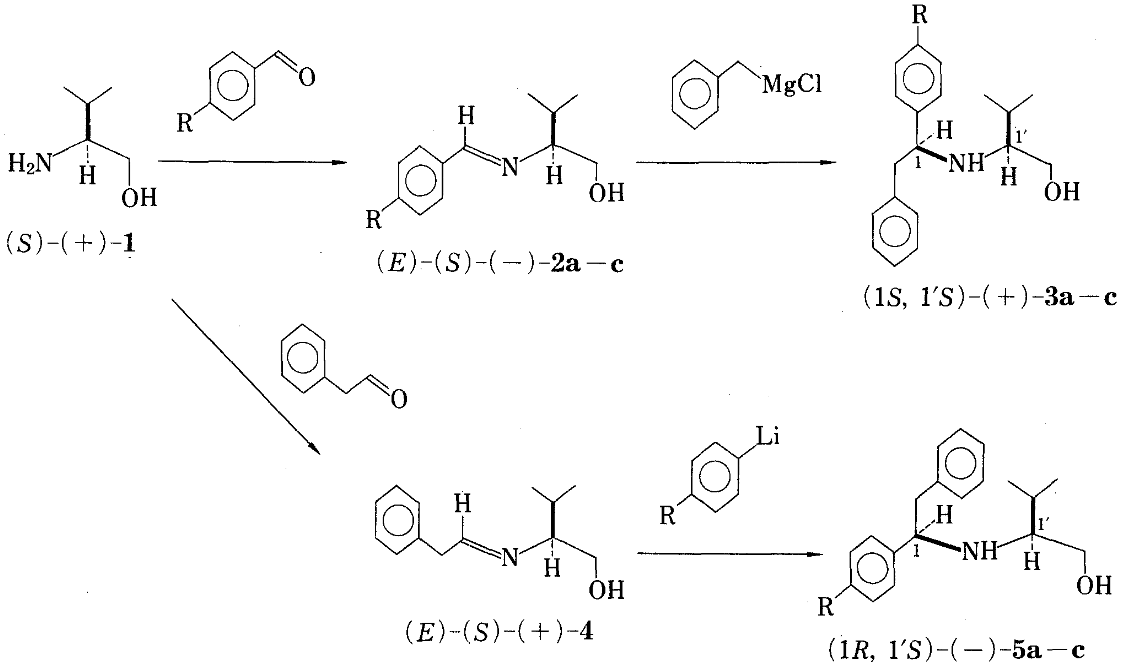
The chiral azomethine compounds, (*E*)-(*S*)-(−)-*N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**2a**—**c**), were synthesized by condensation of (*S*)-valinol (**1**) with benzaldehyde, *p*-methylbenzaldehyde and *p*-anisaldehyde, respectively. The products of these reactions consisted solely of the *E* isomers due to the difference of bulkiness between the hydrogen atom and aryl group.[2,3)]

The reaction of these chiral azomethines (**2a**—**c**) with benzylmagnesium chloride was carried out in tetrahydrofuran (THF) under a nitrogen atmosphere at 40—50 °C for 3—5 h to give 1-aryl-*N*-(2′-hydroxyl-1′-isopropylethyl)-2-phenylethylamines (**3a**—**c**) in good yields. No other diastereomer was detected by thin-layer chromatography (TLC), gas chromatography (GC) and nuclear magnetic resonance (NMR) spectroscopy in any reaction.

These free bases (**3a**—**c**) were converted to the hydrochlorides, the specific rotations of **3a**—**c** hydrochlorides were +93.1°, +117.0° and +110.9°, respectively.

On the other hand, (*E*)-(*S*)-(+)-*N*-(2-hydroxy-1-isopropylethyl)phenylethylideneamine (**4**) was synthesized by condensation of (*S*)-valinol (**1**) with phenylacetaldehyde in a good yield. No other isomer was detected by GC or NMR spectroscopy.

The reaction of this chiral azomethine (**4**) with aryllithium was carried out in ether under a nitrogen atmosphere at room temperature for 20—23 h. After purification by column



a : R=H, **b** : R=Me, **c** : R=MeO

Chart 1

chromatography, 1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines (**5a**—**c**) were obtained. Mass spectra (MS) showed that the relationships between **5a**—**c** and **3a**—**c** were diastereomeric. The retention times in GC of **3a**—**c** were faster than those of the corresponding **5a**—**c**, and the NMR spectra showed that the former compounds were different from the latter. The free bases of **5a**—**c** were converted to colorless crystals of the hydrochlorides. The specific rotation values of the hydrochlorides of **5a**—**c** were −59.5°, −54.7° and −58.9°, respectively.

It was confirmed that both of the chiral amines (**3a**—**c** and **5a**—**c**) are diastereomeric due to the different configurations of the newly created chiral center at the 1-position, and the diastereomeric excess is more than 98 %, because the other diastereomer was not detectable in the NMR spectrum of the chiral amine in any case.

It seems that these asymmetric reactions include two important stereoselective steps; (1) condensation of (*S*)-valinol with aryl aldehydes leads to the *E* isomer at the C=N bond, (2) complexation of the chiral azomethines (**2a**—**c**) with the magnesium or lithium of the reagents leads to a highly stereoselective attack.

Determination of Chirality

The configuration of the newly created chiral center in *N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (**3a**) was elucidated by synthesis *via* an alternative route using material of known absolute configuration.

(*S*)-(+)-1,2-Diphenylethylamine (**6**)[4] was condensed with *dl*-2-bromo-3-methyl-1-butanol (**7**) prepared from *dl*-2-bromo-3-methyl-1-butyric acid.[5] The product was fractionated by column chromatography over silica gel to give *N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine. GC and NMR spectroscopy indicated that the product contained only one isomer. This compound was identical with **3a** as determined from the NMR spectrum and the optical rotation.

It is considered that the configuration of the chiral amine obtained by the introduction of the 1,2-diphenylethyl group into (*S*)-valinol is either (1*R*, 1′*S*) or (1*S*, 1′*S*), because the configuration at the 1′-position came from (*S*)-valinol. On the other hand, the configuration

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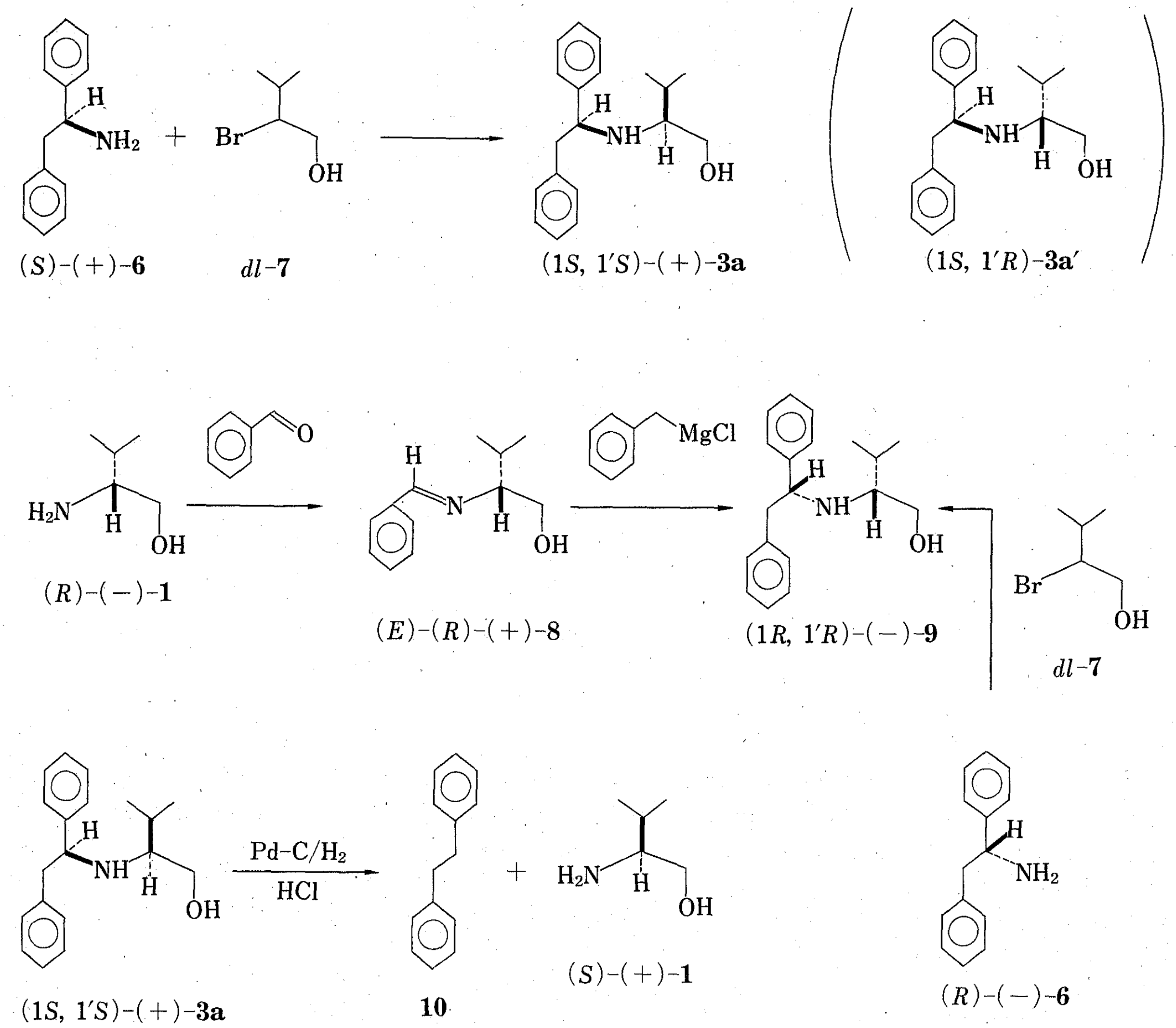

Chart 2

of the chiral amine which was obtained by reaction of (*S*)-1,2-diphenylethylamine (**6**) and *dl*-**7** is presumed to be either (1*S*, 1′*R*) or (1*S*, 1′*S*), because the configuration at the 1-position came from (*S*)-6.

Consequently, the absolute configuration of *N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (**3a**) obtained by reaction of **2a** with benzylmagnesium chloride was determined as (1*S*, 1′*S*). The diastereomer (**5a**) prepared from **4** had the absolute configuration (1*R*, 1′*S*).

On the other hand, condensation of (*R*)-valinol (**1**) with benzaldehyde gave (*E*)-(*R*)-(+)-*N*-(2-hydroxy-1-isopropylethyl)-benzylideneamine (**8**), and this azomethine compound was reacted with benzylmagnesium chloride to give (1*R*, 1′*R*)-(−)-*N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (**9**) in high diastereomeric excess. The structure of this compound was determined by a comparison of GC and the NMR spectrum with those of **3a**. The sign of specific rotation of the hydrochloride of **9** was negative.

This (1*R*, 1′*R*)-compound was also synthesized by reaction of (*R*)-(−)-1,2-diphenylethylamine (**6**) with *dl*-2-bromo-3-methyl-1-butanol (**7**); the product was shown to be identical with **9** by comparison of GC, NMR spectrum and specific rotation of the hydrochloride.

We have attempted to establish the optical purity in order to confirm whether some part of the chiral amines racemized or not under the reaction conditions used. The chiral amine (**3a**) was hydrogenolyzed with a Pd-carbon catalyst containing a small amount of

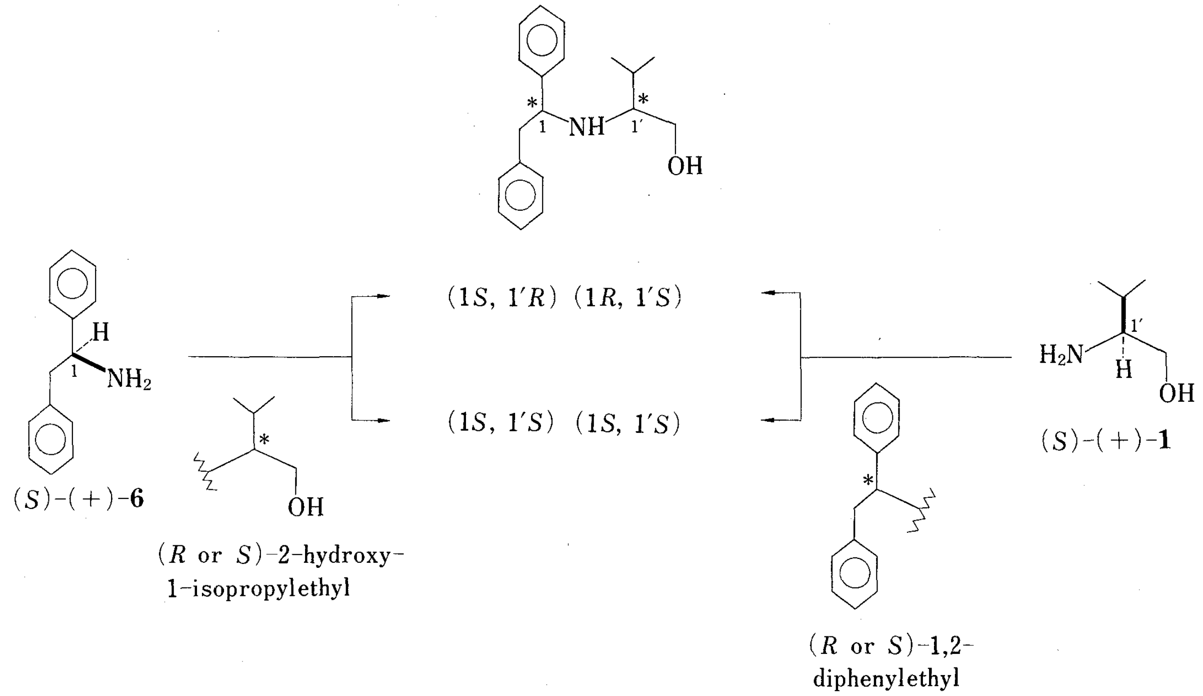

Chart 3

hydrochloric acid under a hydrogen atmosphere, and the reaction mixture was fractionated by chromatography over silica gel to give (*S*)-valinol (**1**) and 1,2-diphenylethane (**10**). The physical and spectral properties of the compounds were identical with those of the corresponding authentic compounds. (*S*)-Valinol thus obtained was converted to the hydrochloride by treatment with hydrogen chloride methanol solution. Judging from the specific rotation, the optical purity of the hydrochloride was 96.5%. Consequently, no racemization took place under the present reaction conditions.

The configurations of *N*-(2′-hydroxy-1′-isopropylethyl)-1-(*p*-tolyl)-2-phenylethylamine (**3b**) and *N*-(2′-hydroxy-1′-isopropylethyl)-1-(*p*-methoxyphenyl)-2-phenylethylamine (**3c**) were investigated by NMR spectroscopy. The characteristic NMR peaks of two pairs of methyl signal doublets due to the isopropyl group of the chiral amines (**3a**—**c** and **5a**—**c**) are summarized in Table I.

Table I. ^{1}H-NMR Characteristics of Diastereomeric 1-Aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines (**3a**—**c** and **5a**—**c**); Chemical Shifts (Hz from TMS) of Two Methyls of the Isopropyl Group in $CDCl_3$[a]

Compound	(1*S*, 1′*S*)-(+)-**3a**—**c**			(1*R*, 1′*S*)-(−)-**5a**—**c**		
	$CH_3(1)$[b]	$CH_3(2)$[b]	Difference[c]	$CH_3(1)$[b]	$CH_3(2)$[b]	Difference[c]
a	80.6 73.8	84.7 77.9	4.1	51.7 44.9	69.1 62.2	17.4
b	80.7 74.0	84.7 78.0	4.0	51.4 44.6	69.3 62.5	17.9
c	81.5 74.7	85.4 78.6	3.9	52.2 45.4	70.1 63.3	17.9

[a] 100 MHz operating frequency, accuracy of ±0.24 Hz.
[b] Doublet signal due to spin-spin coupling with methine proton.
[c] Difference of chemical shifts between the two methyl signals.

The peaks of the two methyl groups of **5a**—**c** were shifted to higher field in comparison with those of **3a**—**c**. Moreover, the differences in chemical shifts between the two methyl

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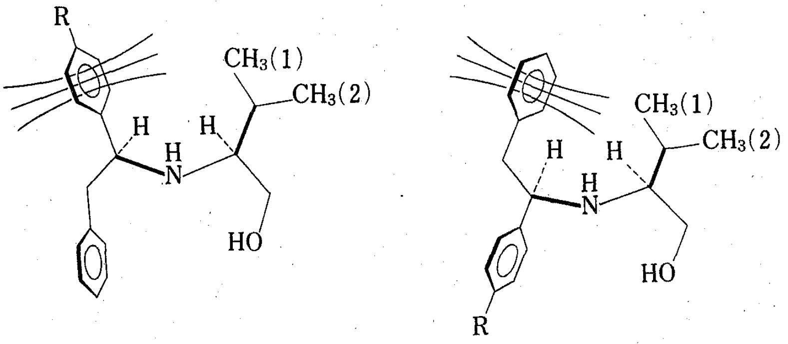
groups of **5a**—**c** were larger than those of **3a**—**c**. It can be presumed that the ring current effect on the two methyl groups of **5a**—**c** is greater than that in **3a**—**c**, and the plane of the aromatic ring of **5a**—**c** is closer to a methyl group than is the case in **3a**—**c**. In addition to the NMR spectral studies described above, consideration of a CPK molecular model suggested that the preferred conformations of these diastereomers (**3a**—**c** and **5a**—**c**) are as shown in Fig. 1.



(1*S*, 1′*S*)-(+)-**3a**—**c** (1*R*, 1′*S*)-(−)-**5a**—**c**

Fig. 1. Preferred Conformations and Ring Current Effects on the Two Methyl Groups of **3a**—**c** and **5a**—**c**

Experimental

The infrared (IR) spectra were recorded with a Hitachi 215, the MS spectra with a JEOL JMS-D300, and the NMR spectra with a JEOLFX100 spectrometer. Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-180 polarimeter. TLC was peformed with Merck DC-Alufolien Kieselgel 60 F_{254}, and GC was carried out with a Hitachi 164F gas chromatograph using silicone SE-30.

(*E*)-(*S*)-(−)-*N*-(2-Hydroxy-1-isopropylethyl)benzylideneamine (2a)——A mixture of (*S*)-(+)-**1** (4.2 g, 40.7 mmol) and benzaldehyde (4.4 g, 41.0 mmol) in benzene (100 ml) was refluxed for 3 h using a Dean-Stark trap. The mixture was concentrated under reduced pressure. The residue was allowed to stand at room temperature to give crystals of **2a**. Recrystallization from *n*-pentane gave colorless prisms of mp 71—72°C. Yield 6.8 g (89%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3350 (OH), 1640 (C=N). MS *m*/*e*: 191 (M^+). NMR ($CDCl_3$) δ: 0.87 (3H, d, $J=6.7$ Hz, CH–C$\underline{H}_3$), 0.95 (3H, d, $J=6.7$ Hz, CH–C$\underline{H}_3$), 7.2—7.8 (5H, aromatic H), 8.26 (1H, s, N=CH). $[\alpha]_D^{20}$ −56.2° ($c=0.55$, ethanol).

(*E*)-(*S*)-(−)-*N*-(2-Hydroxy-1-isopropylethyl)-*p*-tolylmethylideneamine (2b)——A mixture of (*S*)-(+)-**1** (3.1 g, 30 mmol) and *p*-methylbenzaldehyde (3.7 g, 31 mmol) in benzene (100 ml) was refluxed for 4 h as described above. After removal of the solvent, **2b** was obtained as a colorless oily product. The product was distilled under reduced pressure. Yield 4.7 g (76%). bp 164—166°C/10 mmHg. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3350 (OH), 1640 (C=N). MS *m*/*e*: 205 (M^+). NMR ($CDCl_3$) δ: 0.95 (3H, d, $J=6.6$ Hz, CH–C$\underline{H}_3$), 1.04 (3H, d, $J=6.6$ Hz, CH–C$\underline{H}_3$), 2.47 (3H, s, aromatic CH_3), 7.28 (2H, d, $J=8.1$ Hz, aromatic H), 7.69 (2H, d, $J=8.1$ Hz, aromatic H), 8.27 (1H, s, N=CH). $[\alpha]_D^{20}$ −53.4° ($c=0.65$, ethanol).

(*E*)-(*S*)-(−)-*N*-(2-Hydroxy-1-isopropylethyl)-*p*-methoxyphenylmethylideneamine (2c)——A mixture of (*S*)-(+)-**1** (5.2 g, 50 mmol) and *p*-anisaldehyde (7.0 g, 52 mmol) in benzene (140 ml) was refluxed for 4 h in the manner described above. After removal of the solvent, the residue was allowed to stand overnight in a refrigerator, and crystals of **2c** were obtained. Recrystallization from *n*-pentane gave colorless needles of mp 38—39°C. Yield 8.2 g (74%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3350 (OH), 1635 (C=N). MS *m*/*e*: 221 (M^+). NMR ($CDCl_3$) δ: 0.85 (3H, d, $J=6.6$ Hz, CH–C$\underline{H}_3$), 0.94 (3H, d, $J=6.6$ Hz, CH–C$\underline{H}_3$), 3.83 (3H, s, OCH_3), 6.88 (2H, d, $J=8.8$ Hz, aromatic H), 7.61 (2H, d, $J=8.8$ Hz, aromatic H), 8.10 (1H, s, N=CH). $[\alpha]_D^{20}$ −57.6° ($c=0.50$, ethanol).

(1*S*,1′*S*)-(+)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (3a)——Benzylmagnesium chloride (1 M in THF, 100 ml) was added dropwise to a solution of **2a** (3.8 g, 20 mmol) in THF (50 ml) under a nitrogen atmosphere. The resulting mixture was stirred at 45—50°C for 3 h, then poured into water, and the extract was dried over anhydrous $MgSO_4$. After removal of the solvent by evaporation, the oily residue was fractionated by column chromatography over silica gel using CH_2Cl_2. 1,2-Diphenylethane was eluted first, and then **3a** was obtained as a colorless oil. Yield 6.2 g (73%). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3350 (OH). MS *m*/*e*: 283 (M^+). NMR ($CDCl_3$) δ: 0.77 (3H, d, $J=6.8$ Hz, CH–C$\underline{H}_3$), 0.82 (3H, d, $J=6.8$ Hz, CH–C$\underline{H}_3$), 2.93 (2H, d,

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J=7.1 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 3.27 (1H, dd, J=4.4 and 11.0 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.49 (1H, dd, J=4.2 and 11.0 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.87 (1H, t, J=7.1 Hz, $\mathrm{PhC\underline{H}}$–$\mathrm{CH_2}$), 7.0—7.4 (10H, aromatic H).

This compound was treated with hydrogen chloride methanol solution to give the hydrochloride of **3a**. Recrystallization from ethanol gave colorless plates of mp 234—235°C. *Anal.* Calcd for $\mathrm{C_{19}H_{25}NO \cdot HCl}$: C, 71.31; H, 8.91; N, 4.38. Found: C, 71.53; H, 8.75; N, 4.29. $[\alpha]_{\mathrm{D}}^{20}$ +93.1° (c=0.41, ethanol).

(1*S*,1′*S*)-(+)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1-(*p*-tolyl)-2-phenylethylamine (3b)——Benzylmagnesium chloride (1 M in THF, 50 ml) was added dropwise to a solution of **2b** (2.1 g, 10 mmol) in THF (50 ml) at 40°C under a nitrogen atmosphere, and stirring was continued for 4 h. The reaction mixture was worked up as described above, and **3b** was obtained as a colorless oil. Yield 2.2 g (74%). IR $\nu_{\max}^{\text{film}}$ $\mathrm{cm^{-1}}$: 3350 (OH). MS m/e: 297 ($\mathrm{M^+}$). NMR ($\mathrm{CDCl_3}$) δ: 0.78 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 0.82 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 2.33 (3H, s, aromatic $\mathrm{CH_3}$), 2.91 (2H, d, J=7.1 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 3.26 (1H, dd, J=4.4 and 11.0 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.48 (1H, dd, J=4.2 and 11.0 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.83 (1H, t, J=7.1 Hz, $\mathrm{PhC\underline{H}}$–$\mathrm{CH_2}$), 7.0—7.4 (9H, aromatic H).

The hydrochloride of **3b** was recrystallized from ethanol to yield colorless columns of mp 209—210°C. *Anal.* Calcd for $\mathrm{C_{20}H_{27}NO \cdot HCl}$: C, 71.94; H, 8.45; N, 4.20. Found: C, 71.80; H, 8.32; N, 4.21. $[\alpha]_{\mathrm{D}}^{20}$ +117.0° (c=0.50, ethanol).

(1*S*,1′*S*)-(+)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1-(*p*-methoxyphenyl)-2-phenylethylamine (3c)——Benzylmagnesium chloride (1 M in THF, 100 ml) was added dropwise to a solution of **2c** (4.4 g, 20 mmol) in THF (50 ml). The resulting mixture was stirred under a nitrogen atmosphere at 40—45°C for 5 h. After treatment as described above, **3c** was obtained as a colorless oil. Yield 3.8 g (61%). IR $\nu_{\max}^{\text{film}}$ $\mathrm{cm^{-1}}$: 3400 (OH). MS m/e: 313 ($\mathrm{M^+}$). NMR ($\mathrm{CDCl_3}$) δ: 0.79 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 0.82 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 2.91 (2H, d, J=7.1 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 3.27 (1H, dd, J=4.5 and 10.8 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.50 (1H, dd, J=4.2 and 10.8 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.79 (3H, s, $\mathrm{OCH_3}$), 3.83 (1H, t, J=7.1 Hz, $\mathrm{PhC\underline{H}}$–$\mathrm{CH_2}$), 6.8—7.4 (9H, aromatic H).

The hydrochloride of **3c** was recrystallized from ethanol to give colorless columns of mp 205—206°C. *Anal.* Calcd for $\mathrm{C_{20}H_{27}NO_2 \cdot HCl}$: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.68; H, 8.20; N, 3.94. $[\alpha]_{\mathrm{D}}^{20}$ +110.9° (c=0.42, ethanol).

(*E*)-(*S*)-(+)-*N*-(2-Hydroxy-1-isopropylethyl)phenylethylideneamine (4)——A mixture of (*S*)-(+)-**1** (3.1 g, 30 mmol) and phenylacetaldehyde (3.6 g, 30 mmol) in ether (50 ml) was stirred at room temperature for 1 h. The reaction mixture was dried over anhydrous $\mathrm{MgSO_4}$ and the solvent was evaporated off to yield a colorless oil (5.5 g, 89%), which showed one peak in GC. The product was distilled under reduced pressure. bp 136—140°C/1 mmHg. IR $\nu_{\max}^{\text{film}}$ $\mathrm{cm^{-1}}$: 3340 (OH), 1635 (C=N). MS m/e: 205 ($\mathrm{M^+}$). NMR ($\mathrm{CDCl_3}$) δ: 0.84 (3H, d, J=6.6 Hz, CH–$\mathrm{C\underline{H}_3}$), 0.97 (3H, d, J=6.6 Hz, CH–$\mathrm{C\underline{H}_3}$), 7.2—7.4 (6H, N=CH and aromatic H). $[\alpha]_{\mathrm{D}}^{20}$ +14.6° (c=1.1, ethanol).

(1*R*,1′*S*)-(−)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (5a)——A nethereal solution (12 ml) of bromobenzene (3.93 g, 25 mmol) was added dropwise to a suspension of lithium wire (0.37 g, 53 mmol) in ether (7 ml) under a nitrogen atmosphere with vigorous stirring. The phenyllithium solution was added dropwise to a solution of **4** (1.03 g, 5 mmol) in ether (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 20 h, then a small amount of water was added to the reaction mixture. The resulting white precipitate was filtered off and the mixture was extracted with ether. The ethereal solution was dried over anhydrous $\mathrm{MgSO_4}$ and concentrated under reduced pressure. The residue was chromatographed over silica gel using $\mathrm{CH_2Cl_2}$, and **5a** (0.5 g) was obtained as a colorless oil. IR $\nu_{\max}^{\text{film}}$ $\mathrm{cm^{-1}}$: 3400 (OH). MS m/e: 283 ($\mathrm{M^+}$). NMR ($\mathrm{CDCl_3}$) δ: 0.49 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 0.66 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 2.79 (1H, dd, J=9.4 and 13.4 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 2.96 (1H, dd, J=4.9 and 13.4 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 3.07 (1H, dd, J=8.1 and 10.5 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.23 (1H, dd, J=4.9 and 10.5 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.96 (1H, dd, J=4.9 and 9.4 Hz, $\mathrm{PhC\underline{H}}$–$\mathrm{CH_2}$), 7.2—7.4 (10H, aromatic H).

This compound was treated with hydrogen chloride methanol solution to give the hydrochloride of **5a**. Recrystallization from cyclohexane gave colorless prisms of mp 173—174°C. $[\alpha]_{\mathrm{D}}^{20}$ −59.5° (c=0.44, ethanol).

(1*R*,1′*S*)-(−)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1-(*p*-tolyl)-2-phenylethylamine (5b)——*p*-Tolyllithium ethereal solution [prepared from lithium wire (0.37 g, 53 mmol) and *p*-bromotoluene (4.28 g, 25 mmol) in ether (19 ml)], was added dropwise to a solution of **4** (1.03 g, 5 mmol) in ether (10 ml) under a nitrogen atmosphere. After being stirred at room temperature for 20 h, the reaction mixture was worked up as described above, and **5b** (0.6 g) was obtained as a colorless oil. IR $\nu_{\max}^{\text{film}}$ $\mathrm{cm^{-1}}$: 3400 (OH). MS m/e: 297 ($\mathrm{M^+}$). NMR ($\mathrm{CDCl_3}$) δ: 0.48 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 0.66 (3H, d, J=6.8 Hz, CH–$\mathrm{C\underline{H}_3}$), 2.33 (3H, s, aromatic $\mathrm{CH_3}$), 2.79 (1H, dd, J=9.5 and 13.4 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 2.96 (1H, dd, J=5.1 and 13.4 Hz, $\mathrm{PhC\underline{H}_2}$–CH), 3.07 (1H, dd, J=8.1 and 10.3 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.23 (1H, dd, J=4.6 and 10.3 Hz, CH–$\mathrm{C\underline{H}_2OH}$), 3.94 (1H, dd, J=5.1 and 9.5 Hz, $\mathrm{PhC\underline{H}}$–$\mathrm{CH_2}$), 7.2—7.4 (9H, aromatic H).

The hydrochloride of **5b** was recrystallized from cyclohexane to give colorless prisms of mp 164—165°C. $[\alpha]_{\mathrm{D}}^{20}$ −54.7° (c=0.44, ethanol).

(1*R*,1′*S*)-(−)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1-(*p*-methoxyphenyl)-2-phenylethylamine (5c)——A hexane solution of *n*-butyllithium (*ca.* 15%, 24 ml) was added to an ethereal solution (20 ml) of *p*-iodoanisole (9 g, 38.5 mmol), and the mixture was stirred overnight at room temperature. The *p*-methoxyphenyllithium solution was added to an ethereal solution (20 ml) of **4** (1.03 g, 5 mmol) and stirred at room temperature

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for 23 h. The reaction mixture was worked up as described above to yield **5c** (0.5 g) as a colorless oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 3400 (OH). MS *m/e*: 313 (M$^+$). NMR ($CDCl_3$) δ: 0.49 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 0.66 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 2.78 (1H, dd, J=9.3 and 12.8 Hz, PhC$\underline{H}_2$–CH), 2.94 (1H, dd, J=4.9 and 12.8 Hz, PhC$\underline{H}_2$–CH), 3.06 (1H, dd, J=8.1 and 10.5 Hz, CH–C$\underline{H}_2$OH), 3.23 (1H, dd, J=4.6 and 10.5 Hz, CH–C$\underline{H}_2$OH), 3.79 (3H, s, OCH_3), 3.92 (1H, dd, J=4.9 and 9.3 Hz, PhC$\underline{H}$–CH_2), 6.8—7.4 (9H, aromatic H).

The hydrochloride of **5c** was recrystallized from cyclohexane to give colorless prisms of mp 145—148°C. $[\alpha]_D^{20}$ −58.9° (c=0.35, ethanol).

***dl*-Ethyl 2-Bromo-3-methylbutyrate**——An ethanol solution (70 ml) of *dl*-2-bromo-3-methylbutyric acid (9.7 g, 50 mmol) and conc. H_2SO_4 (0.5 ml) was refluxed for 2 h. After removal of the solvent, the residue was distilled under reduced pressure. Yield 8.5 g (81%). bp 64—67°C/2 mmHg. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1740 (C=O). MS *m/e*: 208 (M$^+$). NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6.7 Hz, CH–C$\underline{H}_3$), 1.10 (3H, d, J=6.7 Hz, CH–C$\underline{H}_3$), 1.30 (3H, t, J=7.1 Hz, CH_2C$\underline{H}_3$), 2.24 (1H, double septet, J=6.7 and 8.1 Hz, CH–C$\underline{H}$–$(CH_3)_2$), 4.03 (1H, d, J=8.1 Hz, CH–C$\underline{H}$Br–CO_2), 4.23 (2H, q, J=7.1 Hz, C$\underline{H}_2$$CH_3$).

***dl*-2-Bromo-3-methyl-1-butanol (7)**——*dl*-Ethyl 2-bromo-3-methylbutyrate (20.9 g, 100 mmol) in ether (150 ml) was added dropwise to an ethereal suspension (200 ml) of lithium aluminium hydride (6.0 g) over 0.5 h, and stirring was continued for 1 h. After being treated with water, the reaction mixture was extracted with ether. The extract was dried over anhydrous $MgSO_4$. After removal of the solvent, the residual oil was distilled under reduced pressure. Yield 11.7 g (80%). bp 63—64°C/12 mmHg. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 3350 (OH). MS *m/e*: 148 (M$^+$−H_2O), 69 ($CH_3CH(CH_3)C{=}CH_2^+$). NMR ($CDCl_3$) δ: 1.01 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 1.05 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 2.03 (1H, double septet, J=4.5 and 6.6 Hz, CH–C$\underline{H}$–$(CH_3)_2$), 2.41 (1H, t, J=6.2 Hz, OH), 3.82 (2H, t, J=6.2 Hz, CH–C$\underline{H}_2$OH), 4.08 (1H, d and t, J=4.5 and 6.2 Hz, CH–C$\underline{H}$Br–CH_2).

Reaction of (*S*)-(+)-1,2-Diphenylethylamine (6) with *dl*-2-Bromo-3-methyl-1-butanol (7)——A mixture of (*S*)-(+)-**6** (2.0 g, 10 mmol), **7** (3.0 g, 20 mmol) and anhydrous Na_2CO_3 (1.5 g) in ethanol (30 ml) was refluxed with gentle stirring for 18 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was fractionated by column chromatography over silica gel using CH_2Cl_2 to give (1*S*,1′*S*)-(+)-*N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (**3a**) (1.9 g, 67%), and a small amount of starting material (**6**, 0.3 g) was recovered. These compounds were shown to be identical with the corresponding authentic samples by comparison of retention time in GC, IR and NMR spectra, and specific rotation.

(*E*)-(*R*)-(+)-*N*-(2-Hydroxy-1-isopropylethyl)benzylideneamine (8)——Condensation of (*R*)-(−)-**1** (1.0 g, 10 mmol) with benzaldehyde (1.3 g, 12 mmol) in benzene gave **8** (1.7 g, 83%) in a manner similar to that described for **2a**. This compound was indistinguishable from **2a** by comparison of the IR and NMR spectra. Specific rotation: $[\alpha]_D^{20}$ +55.8° (c=0.48, ethanol).

(1*R*,1′*R*)-(−)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1,2-diphenylethylamine (9)——i) Reaction of **8** with Benzylmagnesium Chloride: **9** was obtained by reaction of **8** with benzylmagnesium chloride as described for **3a**. The product was indistinguishable from **3a** by comparison of the IR and NMR spectra. The specific rotation of the hydrochloride of **9** was $[\alpha]_D^{20}$ −96.5° (c=0.42, ethanol).

ii) Reaction of (*R*)-1,2-Diphenylethylamine (**6**) with **7**: A mixture of (*R*)-(−)-**6** (1.0 g, 5 mmol) and **7** (1.5 g, 10 mmol) in ethanol (10 ml) was refluxed with gentle stirring for 12 h in the presence of Na_2CO_3 (0.75 g) to give **9** (1.0 g, 71%). This compound was indistinguishable from **3a** by comparison of IR and NMR spectra. The specific rotation of hydrochloride of this compound was $[\alpha]_D^{20}$ −95.8° (c=0.40, ethanol).

Hydrogenolysis of 3a——A solution of **3a** (0.9 g, 3.2 mmol) in methanol (30 ml) was treated with 10% Pd-carbon (0.3 g) and conc. HCl (0.5 ml), and the mixture was shaken in a hydrogen atmosphere at room temperature for 12 h under a pressure of 5.5 kg/cm^2. The catalyst was then filtered off and the filtrate was concentrated by evaporation. The residue was treated with 2 N NaOH, extracted with ether, and fractionated by column chromatography over silica gel using CH_2Cl_2. The first eluted material was 1,2-diphenylethane (0.35 g), the second was the starting material (0.32 g) and the third was valinol (0.13 g). These compounds were identified by comparison of TLC, GC and NMR spectra with those of the corresponding authentic samples. Valinol was treated with hydrogen chloride methanol solution to give valinol hydrochloride. The specific rotation of this compound was $[\alpha]_D^{20}$ +13.8° (c=0.8, methanol). The originally used (*S*)-valinol hydrochloride had $[\alpha]_D^{20}$ +14.3° (c=1.5, methanol).

References and Notes

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