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Synthesis and Absolute Configuration of Optically Pure (*S*)- and (*R*)-Diarylmethylamines

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Optically pure (1*S*, 1′*S*)-1-aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (**2a**—**c**) were synthesized by the asymmetric reaction of (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**1a**—**c**) with phenyllithium. On the other hand, optically pure (1*R*, 1′*S*)-configuration compounds (**4a**—**c**) were synthesized from (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)phenylmethylideneamine (**3**) and aryllithiums. Other optically pure compounds, (1*R*, 1′*R*)- and (1*S*, 1′*R*)-amines (**2b** and **4b**), were also synthesized.

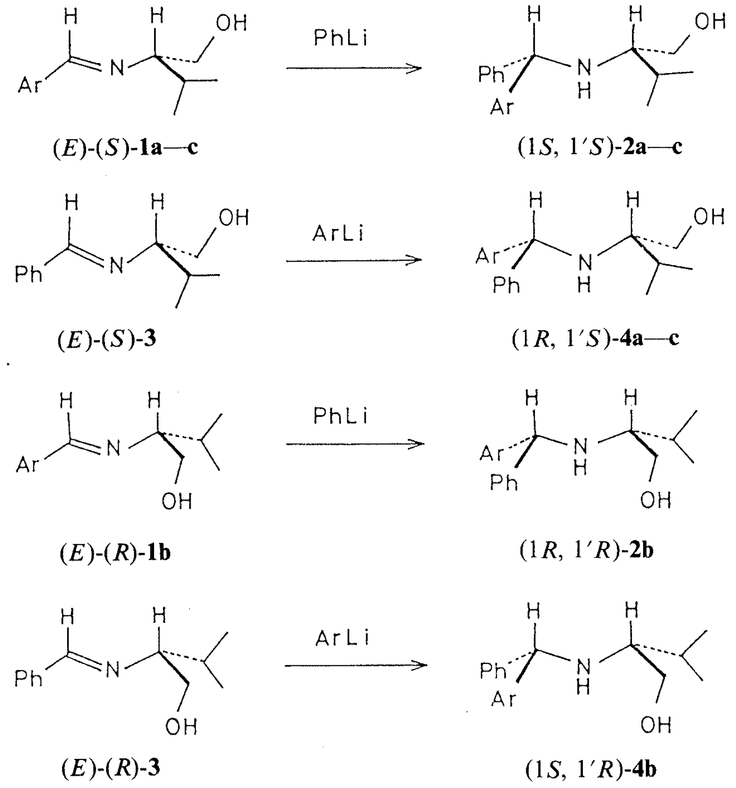
The absolute configurations of these chiral amines were determined by using circular dichroism spectroscopy and X-ray analysis.

Keywords——absolute configuration; aryllithium; asymmetric reaction; chiral azomethine; Cotton effect; diarylmethylamine; optically pure amine; (*S*)-valinol; (*R*)-valinol; X-ray analysis

The diarylmethyl moiety is extremely important in medicinal agents,[1] *e.g.*, in chlorpheniramine, clemastine, homochlorcyclizine, and meclozine. When one aryl group differs from the other in the diarylmethyl compounds, two optical isomers can exist. However, it is very difficult to obtain a compound with 100% optical purity by means of optical resolution because the two aryl groups are similar in steric bulkiness.[2] The chiral reactions of diarylmethyl compounds occur with poor stereoselectivity, and the synthesis of such compounds in optically pure form has not been reported.[3] Evaluation of the optical purity of chiral diarylmethyl compounds and determination of the absolute configuration at the newly created asymmetric carbon atom are very important, but are difficult because the two aryl groups are similar to each other.

We describe here the synthesis of optically pure (1*S*, 1′*S*), (1*R*, 1′*S*), (1*R*, 1′*R*), and (1*S*, 1′*R*)-1,1-diaryl-*N*-2′-hydroxy-1′-isopropylethyl-methylamines as diarylmethyl compounds, and the determination of the absolute configurations of these chiral amines.

The (1*S*, 1′*S*)-1,1-diaryl-*N*-2′-hydroxy-1′-isopropylethyl-methylamines (**2a**—**c**) having phenyl, 4-tolyl, 4-chlorophenyl, or 4-methoxyphenyl as the aryl group were synthesized from (*E*)-(*S*)-*N*-2′-hydroxy-1′-isopropylethyl-arylmethylideneamines (**1a**—**c**) and phenyllithium in ether at room temperature. These reactions were achieved by asymmetric induction of the 2-



Ar: **a** = 4-tolyl; **b** = 4-Cl–C_6H_4–; **c** = 4-MeO–C_6H_4–

Chart 1

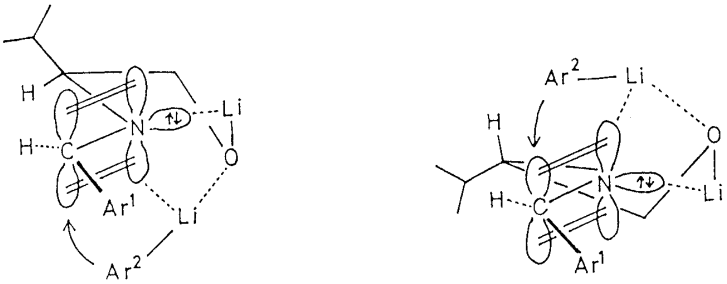
hydroxy-1-isopropylethylamine moiety, and gave asymmetric amines having two different aryl groups. We have previously reported that (1*S*, 1′*S*)-1-aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines are synthesized by the reaction of chiral azomethines (**1a** and **1c**) with benzylmagnesium chloride.[4,5] A new azomethine compound (**1b**) has now been synthesized.

We also attempted to synthesize the diastereomers of **2a—c** in order to confirm whether these amines are optically pure or not by a comparison of the two diastereomers. (1*R*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (**4a—c**) were obtained by the treatment of (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)benzylideneamine (**3**) with aryllithium in ether at room temperature.

On the other hand, (*E*)-(*R*)-*N*-(2-hydroxy-1-isopropylethyl)-(4-chlorophenyl)methylideneamine (**1b**) was treated with phenyllithium to yield (1*R*, 1′*R*)-1-(4-chlorophenyl)-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamine (**2b**). The diastereomer (**4b**) with the (1*S*, 1′*R*)-configuration was obtained by the reaction of (*E*)-(*R*)-*N*-(2-hydroxy-1-isopropylethyl)benzylideneamine (**3**) with 4-chlorophenyllithium.

The mechanism of this asymmetric reaction may be as follows, as in the case of the reaction of benzylmagnesium chloride: The lithium atom of the aryllithium reagent becomes associated with the hydroxyl group and the lone pair electrons of the nitrogen atom, while the aryl anion of another aryllithium molecule attacks the carbon of the C = N bond. The attack of the aryl group on the (*E*)-(*S*)-chiral azomethines (**1a—c** and **3**) occurs from the *si–si* face of the C = N bond, whereas the attack on the (*E*)-(*R*)-configuration compounds occurs from the *re–re* face, as shown in Fig. 1.

The proton nuclear magnetic resonance (^{1}H-NMR) spectra showed that all these compounds (**2a—c** and **4a—c**) consisted of one isomer, without any contamination by the other diastereomer. The values of the chemical shifts for **2a—c** differed from these of the



attack from *si–si* face
(*E*)-(*S*)-compd.

attack from *re–re* face
(*E*)-(*R*)-compd.

Fig. 1

Table I. 1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (**2a**—**c**, **4a**—**c**, and **5**)

Compd. No.	Yield (%)	IR cm$^{-1\,a)}$	MS *m/e*		^{1}H-NMR (CDCl$_3$) δ			Others
		ν_{OH}	M$^+$	PhCH$^+$Ar$^{b)}$	PhC$\underline{H}$–Ar$^{c)}$	CH$_2$–O$^{d)}$	CH(C$\underline{H}_3$)$_2$	
2a	83	3350	283	181	4.95	3.54 (4.4, 10.5) 3.38 (6.3, 10.5)	0.916 (0.69) 0.886 (0.68)	2.31 (3H, s, aromatic CH$_3$)
2b	70	3350	303	201	4.96	3.55 (4.2, 10.7) 3.43 (6.1, 10.7)	0.916 (0.69) 0.889 (0.69)	
2c	73	3400	299	197	4.94	3.54 (4.4, 10.7) 3.39 (6.1, 10.7)	0.916 (0.69) 0.889 (0.69)	3.77 (3H, s, aromatic OCH$_3$)
4a	82	3350	283	181	4.95	3.54 (4.4, 10.7) 3.38 (6.3, 10.7)	0.916 (0.69) 0.884 (0.68)	2.29 (3H, s, aromatic CH$_3$)
4b	73	3350	303	201	4.96	3.56 (4.4, 10.7) 3.41 (6.3, 10.7)	0.916 (0.69) 0.884 (0.69)	
4c	67	3400	299	197	4.94	3.54 (4.4, 10.7) 3.38 (6.4, 10.7)	0.916 (0.69) 0.885 (0.69)	3.76 (3H, s, aromatic OCH$_3$)
5	82	3400	269	167	4.99	3.56 (4.4, 10.7) 3.40 (6.1, 10.7)	0.916 (0.69) 0.884 (0.68)	

a) Liquid film.
b) Observed as base peak.
c) Singlet, one proton.
d) Double doublet; coupling constant (Hz) in parentheses.

corresponding **4a**—**c**. Accordingly, it was concluded that these compounds are optically pure, and the amines (**2a**—**c**) are diastereomeric with respect to the corresponding amines (**4a**—**c**). The chirality of the newly created asymmetric carbon atom is determined by the source of the aryl group, either arylmethylideneamine or aryllithium reagent.

The infrared (IR) spectra showed the absorption band of the OH group at 3300—3400 cm^{-1}, the mass spectra (MS) of these compounds showed the molecular ion peak and the arylphenylmethyl ion peak as the base peak, and their ^{1}H-NMR spectra showed typical peaks of PhCHAr, CH$_2$–OH, CH(CH$_3$)$_2$, *etc.* These results are summarized in Table I.

The free bases of the chiral amines (**2a**—**c** and **4a**—**c**) thus obtained as colorless oils were treated with hydrogen chloride–methanol solution to give colorless crystals of the hydrochlorides. The physical data for these compounds are summarized in Table II.

Determination of Absolute Configuration

The absolute configurations of (+)-chlorpheniramine [(+)-(*S*)-3-(4-chlorophenyl)-3-(2-

TABLE II. Hydrochlorides of 1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (**2a**—**c**, **4a**—**c**, and **5**)

Compd. No.	mp (°C)	Recrystallization Solvent[a]	Appearance[b]	$[\alpha]_D$[c] (*c*, ethanol)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	201—202	E	Pri	+21.0° (0.39)	$C_{19}H_{25}NO \cdot HCl$	71.34	8.19	4.38
						(71.63	8.32	4.18)
2b	199—201	E	Nee	+22.0° (0.43)	$C_{18}H_{22}ClNO \cdot HCl$	63.53	6.81	4.12
						(63.79	6.87	4.14)
2c	170—171	B	Nee	+2.93° (0.41)	$C_{19}H_{25}NO_2 \cdot HCl$	67.94	7.80	4.17
						(68.21	7.89	4.36)
4a	169	B	Nee	+22.5° (0.39)	$C_{19}H_{25}NO \cdot HCl$	71.34	8.19	4.38
						(71.68	8.38	4.27)
4b	165—166	B	Nee	+16.9° (0.43)	$C_{18}H_{22}ClNO \cdot HCl$	63.53	6.81	4.12
						(63.83	6.89	4.29)
4c	157	BE	Nee	+33.9° (0.47)	$C_{19}H_{25}NO_2 \cdot HCl$	67.94	7.80	4.17
						(68.07	7.92	4.12)
5	154—155	E	Pri	+26.5° (0.35)	$C_{18}H_{23}NO \cdot HCl$	70.68	7.58	4.58
						(70.54	7.63	4.55)

a) E = ethanol; B = benzene; BE = benzene–ethanol.
b) Colorless crystals; Nee = needles; Pri = prisms.
c) Temperature, 20—23 °C.

TABLE III. CD and UV Spectral Data for Hydrochlorides of 1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines in 95% Ethanol [CD, Maximum $\Delta\varepsilon$ (nm)[a]; UV, λ_{max} nm ($\varepsilon = 10^{-3}$)[b]]

Compound No.		^1L_a Band	^1L_b Band				
2a	CD	−1.89 (225)	−0.25 (254)	−0.44 (260)	−0.42 (267)		
	UV	224 (14.6)	$254^{b)}$ (0.61)	$259^{b)}$ (0.71)	263 (0.76)	$268^{b)}$ (0.59)	$273^{b)}$ (0.38)
2b	CD	−2.52 (229)	−0.32 (254)	−0.53 (260)	−0.56 (267)		
	UV	226 (24.9)	$255^{b)}$ (1.23)	258 (1.37)	263 (1.32)	$269^{b)}$ (1.15)	$276^{b)}$ (0.57)
2c	CD	−2.38 (234)	−0.97 (254)	−1.16 (260)	−0.82 (267)		
	UV	234 (21.7)	$263^{b)}$ (1.97)	268 (2.15)	$275^{b)}$ (2.20)	281 (1.87)	
4a	CD	+5.62 (224)	+0.31 (254)	+0.53 (260)	+0.51 (267)		
	UV	224 (12.2)	254 (0.71)	260 (0.71)	$269^{b)}$ (0.49)	$272^{b)}$ (0.31)	
4b	CD	+8.02 (228)	+0.31 (254)	+0.39 (260)	+0.40 (267)		
	UV	227 (15.7)	255 (1.75)	260 (1.72)	$268^{b)}$ (1.36)	$275^{b)}$ (0.83)	
4c	CD	+6.71 (234)	+1.26 (254)	+1.50 (260)	+1.10 (267)		
	UV	233 (22.9)	263 (2.29)	279 (2.44)	$274^{b)}$ (2.41)	281 (2.05)	
5	CD	+4.63 (220)	+0.10 (253)	+0.13 (260)	+0.15 (267)		
	UV	220 (18.6)	$253^{b)}$ (0.93)	258 (1.10)	263 (1.08)	269 (0.83)	

a) Concentration, 2.0—4.0 × 10^{-3} M; temperature, 20—25 °C; cell length, 0.1—0.5 cm.
b) Shoulder.

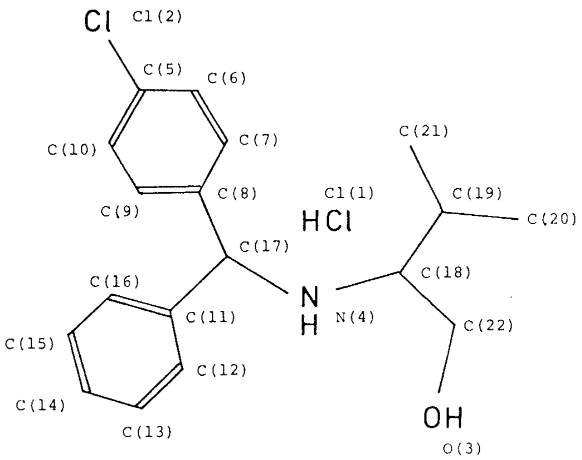


Fig. 2. Atomic Numbering of (1*S*, 1′*S*)-**2b**·HCl

TABLE IV. Crystal Data

Chemical formula	$C_{18}H_{22}ClNO \cdot HCl$
Formula weight	340.30
Crystal system	Orthorhombic
Cell dimensions (Å)	$a = 16.628$ (6)
	$b = 15.186$ (6)
	$c = 7.292$ (5)
Cell volume (Å^3)	181.43 (18)
Space group	$P2_12_12_1$
Z	4
D_c (g cm^{-3})	1.23
μ (Cu*K*α) (cm^{-1})	32.3

pyridyl)-*N*,*N*-dimethylpropylamine]⁶⁾ and (+)-clemastine [(+)-(1*R*)-(4-chlorophenyl)-(1*R*)-phenylethyl-2-(1-methyl-(2*R*)-pyrrolidyl)ethyl ether]⁷⁾ have been determined by X-ray analysis. However, those of other diarylmethyl compounds have not been reported.⁸⁾

We attempted to determine the absolute configuration of the newly created asymmetric carbon atom of the chiral amines here obtained. The Cotton effects in the circular dichroism (CD) spectra of the hydrochlorides of the amines (**2a**—**c**, **4a**—**c**, and **5**) were observed. The results are summarized, along with ultraviolet (UV) spectral data, in Table III.

The ^1L_a and ^1L_b bands, which are attributable to the aromatic ring chromophore,⁹,¹⁰⁾ were observed in the 220—250 and 250—290 nm regions, respectively. The Cotton effects of (*S*)-1,1-diphenyl-*N*-2′-hydroxy-1′-isopropylethyl-methylamine (**5**) were compared with those of **2a**—**c** and **4a**—**c**, and the Cotton effects of the diarylmethyl moiety whose chirality was induced by the 2-hydroxy-1-isopropylethyl group were elucidated. The CD spectra of **2a**—**c** showed negative Cotton effects in both ^1L_a and ^1L_b bands. However, positive Cotton effects were observed for compounds **4a**—**c**. Accordingly, the configuration of the asymmetric carbon at the diarylmethyl moiety of **2a**—**c** was confirmed to be opposite to that of **4a**—**c**.

The Cotton effects of the chiral amines (**2b** and **4b**) obtained from (*R*)-valinol showed the opposite sign as compared with those of (1*S*, 1′*S*)-**2b** and (1*R*, 1′*S*)-**4b**, respectively. However, the absolute configurations of these compounds could not be determined by CD spectroscopy. Thus, the configuration of the hydrochloride of (1*S*, 1′*S*)-**2b** ([α]$_D$ +22.0°) obtained from (*E*)-(*S*)-**1b** and phenyllithium was confirmed by X-ray analysis.

The atomic numbering of **2b** is shown in Fig. 2, and the crystal data are summarized in Table IV. Stereoscopic drawings of the molecular structure are shown in Fig. 3. The positional

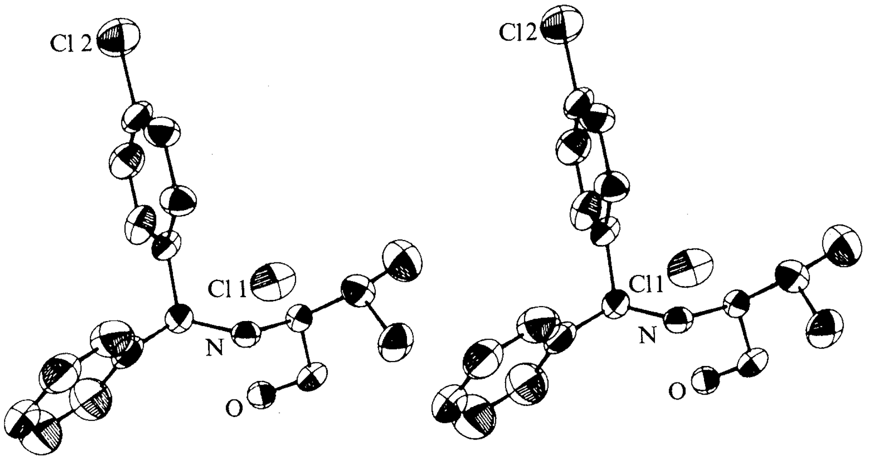


Fig. 3. Stereoscopic Drawings of the Structure of (1*S*, 1′*S*)-**2b**·HCl

Table V. Positional ($\times 10^4$) and Thermal Parameters of(1*S*, 1′*S*)-**2b**·HCl for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	B_{eq} (Å^2)$^{a)}$
Cl (1)	3409 (3)	−3270 (4)	10325 (7)	5.2
Cl (2)	3618 (3)	602 (3)	4537 (7)	6.9
O (3)	2784 (5)	−4689 (5)	2763 (11)	3.6
N (4)	2935 (5)	−3736 (6)	6306 (13)	2.8
C (5)	3275 (8)	− 474 (8)	4833 (22)	4.7
C (6)	3379 (8)	− 865 (8)	6503 (19)	4.3
C (7)	3094 (7)	−1747 (9)	6722 (18)	4.0
C (8)	2724 (7)	−2167 (7)	5260 (18)	3.3
C (9)	2622 (7)	−1732 (10)	3602 (19)	4.9
C (10)	2907 (10)	− 872 (9)	3370 (20)	5.0
C (11)	1580 (9)	−3102 (7)	6515 (21)	4.7
C (12)	882 (9)	−3393 (11)	5573 (30)	7.3
C (13)	143 (10)	−3417 (14)	6415 (34)	9.3
C (14)	72 (10)	−3092 (9)	8193 (35)	8.5
C (15)	757 (9)	−2846 (9)	9177 (28)	6.8
C (16)	1503 (10)	−2825 (10)	8319 (22)	5.9
C (17)	2362 (7)	−3106 (7)	5420 (19)	3.5
C (18)	3645 (7)	−3974 (7)	5043 (15)	3.1
C (19)	4424 (8)	−4043 (9)	6188 (19)	4.4
C (20)	4399 (9)	−4878 (10)	7467 (21)	5.4
C (21)	5168 (9)	−4068 (12)	4938 (26)	6.6
C (22)	3439 (8)	−4804 (8)	3947 (16)	3.8

a) $B_{eq}=(4/3)\ \Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

and thermal parameters with their standard deviations are listed in Table V. The intramolecular bond distances and bond angles for nonhydrogen atoms are givne in Table VI.

Consequently, the structure of **2b** hydrochloride was determined as (1*S*, 1′*S*)-1-(4-chlorophenyl)-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamine, and it was concluded that the absolute configurations of **2a** and **2c** are (1*S*, 1′*S*), while **4a**—**c** have the (1*R*, 1′*S*)-configuration.

Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer; the MS, with a JEOL JMS-D300

Table VI. Bond Distances (Å) and Bond Angles (°) of (1*S*, 1′*S*)-**2b**·HCl for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Cl (2)–C (5)	1.745 (12)	C (11)–C (12)	1.419 (22)
O (3)–C (22)	1.400 (15)	C (11)–C (16)	1.387 (22)
N (4)–C (17)	1.497 (15)	C (11)–C (17)	1.526 (19)
N (4)–C (18)	1.540 (15)	C (12)–C (13)	1.373 (25)
C (5)–C (6)	1.366 (20)	C (13)–C (14)	1.392 (34)
C (5)–C (10)	1.370 (21)	C (14)–C (15)	1.397 (25)
C (6)–C (7)	1.430 (19)	C (15)–C (16)	1.391 (23)
C (7)–C (8)	1.386 (18)	C (18)–C (19)	1.546 (18)
C (8)–C (9)	1.389 (19)	C (18)–C (22)	1.531 (16)
C (8)–C (17)	1.553 (15)	C (19)–C (20)	1.574 (20)
C (9)–C (10)	1.399 (20)	C (19)–C (21)	1.537 (21)

C (17)–N (4)–C (18)	112.3 (9)	C (12)–C (13)–C (14)	118.9 (18)
Cl (2)–C (5)–C (6)	118.4 (11)	C (13)–C (14)–C (15)	120.2 (17)
Cl (2)–C (5)–C (10)	117.6 (11)	C (14)–C (15)–C (16)	120.2 (18)
C (6)–C (5)–C (10)	124.0 (12)	C (11)–C (16)–C (15)	120.1 (15)
C (5)–C (6)–C (7)	117.7 (12)	N (4)–C (17)–C (8)	111.8 (9)
C (6)–C (7)–C (8)	119.5 (12)	N (4)–C (17)–C (11)	108.7 (10)
C (7)–C (8)–C (9)	120.4 (11)	C (8)–C (17)–C (11)	111.5 (9)
C (7)–C (8)–C (17)	122.5 (11)	N (4)–C (18)–C (19)	109.6 (9)
C (9)–C (8)–C (17)	117.0 (11)	N (4)–C (18)–C (22)	109.6 (9)
C (8)–C (9)–C (10)	120.5 (13)	C (19)–C (18)–C (22)	114.4 (10)
C (5)–C (10)–C (9)	118.0 (13)	C (18)–C (19)–C (20)	110.6 (11)
C (12)–C (11)–C (16)	118.6 (15)	C (18)–C (19)–C (21)	110.9 (12)
C (12)–C (11)–C (17)	116.2 (14)	C (20)–C (19)–C (21)	110.7 (12)
C (16)–C (11)–C (17)	125.2 (13)	O (3)–C (22)–C (18)	113.1 (10)
C (11)–C (12)–C (13)	121.5 (19)		

spectrometer; the UV spectra, with a Hitachi 124 spectrometer; and the ^{1}H-NMR spectra, with a JEOL FX100 spectrometer. 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. Gas chromatography (GC) was carried out with a Hitachi 164F gas chromatograph, using silicone SE-30.

The CD spectra were measured at 20—23 °C using a Jasco J-40 spectropolarimeter; the magnitudes of the bands were calibrated with D-10-camphorsulfonic acid (at 289 nm) and D-pantolactone (3,4-dihydro-3-hydroxy-4,4-dimethylfuran-2(3*H*)-one) (at 221 nm) as standards.

(*E*)-(*S*)-*N*-(2-Hydroxy-1-isopropylethyl)-(4-chlorophenyl)methylideneamine (1b)——A mixture of (*S*)-valinol (3.1 g, 30 mmol) and 4-chlorobenzaldehyde (4.2 g, 30 mmol) in benzene (80 ml) was refluxed for 5 h using a Dean–Stark trap. The mixture was then concentrated under reduced pressure, and the residual oily product was chromatographed on a column of silica gel, using CH_2Cl_2, to give a colorless liquid (5.0 g, 74%); bp 158—160 °C/9 mmHg. IR (film): 3350 (OH), 1635 (C=N) cm^{-1}. MS *m/e*: 225 (M$^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=8.5 Hz, CH–C$\underline{H}_3$), 1.01 (3H, d, J=8.5 Hz, CH–C$\underline{H}_3$), 3.87 (2H, AB_2 pattern, CH_2–O), 7.42 (2H, d, J=8.5 Hz, aromatic H), 7.70 (2H, d, J=8.5 Hz, aromatic H), 8.23 (1H, s, CH=N).

(1*S*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (2a—c)——An ethereal solution (25 ml) of bromobenzene (6.3 g, 40 mmol) was slowly added, drop by drop, to a suspension of lithium wire (0.58 g, 84 mmol) in ether (15 ml) under a nitrogen atmosphere. The phenyllithium solution was added, drop by drop, to a solution of (*E*)-(*S*)-**1a**—**c** (5 mmol) in ether (30 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 5—8 h; then a small amount of water was added to the reaction mixture, and the whole was extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was column-chromatographed over silica gel, using CH_2Cl_2. After the removal of the diphenyl, **2a**—**c** were obtained as colorless oils. The physical data for **2a**—**c** are summarized in Table I.

The free bases were treated with a hydrogen chloride–methanol solution to give the hydrochlorides of **2a**—**c**. The physical data for these compounds are summarized in Table II.

(1*R*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamines (4a—c)——An ethereal solution of *n*-butyllithium (50 mmol, 30 ml) was added, drop by drop, to a solution of a halogen derivative, *i.e.*, 4-iodotoluene (10.9 g, 50 mmol), 4-iodochlorobenzene (11.9 g, 50 mmol), or 4-iodoanisole (11.7 g, 50 mmol), in ether (20 ml) under a nitrogen atmosphere. The aryllithium solution was then added, drop by drop, to a solution of (*E*)-(*S*)-**3** (0.95 g, 5 mmol) in ether (20 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 5—8 h, then a small amount of water was added to the reaction mixture, and the whole was extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was column-chromatographed over silica gel, using CH_2Cl_2. After the removal of the diaryl compounds, **4a**—**c** were obtained as colorless oils. The physical data for these compounds are summarized in Table I.

The free bases were treated with a hydrogen chloride–methanol solution to give the hydrochlorides of **4a**—**c**. The physical data are summarized in Table II.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-isopropylethyl)-(4-chlorophenyl)methylideneamine (1b)——A mixture of (*R*)-valinol (3.1 g, 30 mmol) and 4-chlorobenzaldehyde (3.8 g, 27 mmol) in benzene (80 ml) was refluxed for 4 h using a Dean–Stark trap. The reaction mixture was then worked up as has been described for the *S*-compound to give a colorless oil. This compound was indistinguishable from (*E*)-(*S*)-**1b** by comparison of their IR, MS, and ^{1}H-NMR spectra.

(1*R*, 1′*R*)-1-(4-Chlorophenyl)-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamine (2b)——An ethereal solution (60 ml) of bromobenzene (14.1 g, 90 mmol) was slowly added, drop by drop, to a suspension of lithium wire (1.32 g, 190 mmol) in ether (30 ml) under a nitrogen atmosphere. The phenyllithium solution was then added, drop by drop, to a solution of (*E*)-(*R*)-**1b** (2.3 g, 10 mmol) in ether (40 ml) under a nitrogen atmosphere. After being stirred at room temperature for 6 h, the reaction mixture was worked up as has been described for the *S*-compound. **2b** was thus obtained as a colorless liquid; its IR, MS, and ^{1}H-NMR spectra were indistinguishable from those of (1*S*, 1′*S*)-**2b**.

The free base was converted into colorless needles of the hydrochloride, which was recrystallized from ethanol; mp 203—204°C. The specific rotation of the hydrochloride of (1*R*, 1′*R*)-**2b** was $[\alpha]_D^{20}$ $-21.8°$ ($c=0.42$, ethanol).

(1*S*, 1′*R*)-1-(4-Chlorophenyl)-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamine (4b)——An ethereal solution of *n*-butyllithium (50 mmol, 30 ml) was slowly added, drop by drop, to a solution of 4-iodochlorobenzene (11.0 g, 50 mmol) in ether (20 ml) under a nitrogen atmosphere. The 4-chlorophenyllithium solution was then added, drop by drop, to a solution of (*E*)-(*R*)-**3** (0.95 g, 5 mmol) in ether (20 ml) under a nitrogen atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was worked up as has been described for the *S*-compound. **4b** was thus obtained as a colorless liquid and was indistinguishable from (1*R*, 1′*S*)-**4b** by comparison of their IR, MS, and ^{1}H-NMR spectra.

The free base was converted into colorless needles of the hydrochloride, which was recrystallized from benzene; mp 166—167 °C. The specific rotation of the hydrochloride of (1*S*, 1′*R*)-**4b** was $[\alpha]_D^{20}$ $+16.6°$ ($c=0.42$, ethanol).

(*S*)-*N*-2′-Hydroxy-1′-isopropylethyl-1,1-diphenylmethylamine (5)——Phenyllithium ethereal solution, prepared from bromobenzene (6.3 g, 40 mmol) and lithium wire (0.58 g, 84 mmol) in ether (40 ml), was added, drop by drop, to a solution of (*E*)-(*S*)-**3** (0.95 g, 5 mmol) in ether (30 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h. After treatment as has been described above, **5** was obtained as colorless crystals in a yield of 1.1 g (82%). This compound was recrystallized from *n*-pentane to give colorless columns; mp 53—54 °C. The physical data for this compound are summarized in Table I.

The free base was treated with a hydrogen chloride–methanol solution to give the hydrochloride of **5**. The physical data for this compound are summarized in Table II.

X-Ray Analysis of (+)-(1*S*, 1′*S*)-1-(4-Chlorophenyl)-*N*-2′-hydroxy-1′-isopropylethyl-1-phenylmethylamine Hydrochloride (2b–HCl)——The crystal used in this study was a colorless column with dimensions of 0.3 × 0.3 × 0.4 mm, obtained from ethanol solution. All the measurements were performed on a Rigaku AFC-6 diffractometer using graphite-monochromated Cu*Kα* radiation. The unit cell dimensions were determined by least-squares calculation with 20 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $2\theta > 30°$ and ω scan for $2\theta < 30°$ with an average scan rate of 3°/min. In total, 1940 independent reflections with $2\theta < 135°$ were collected, and 1280 satisfying the condition $F_o \geqq 2\sigma(F)$ were used for calculations.

The structure was solved by the direct method using MULTAN[11] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method with anisotropic temperature factors. The *R* factor value was 0.102 (for nonhydrogen atom).

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