The Preparation and Absolute Configuration of the Optically Active Forms of the Diastereoisomers of 2-(1-Phenylethyl)amino-1-phenylethanol and Their Use as Chiral Auxiliaries in the Asymmetric Reduction of Acetophenone with Modified Lithium Aluminium Hydrides

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(1*S*,2*S*)-(−)-2-(1-Phenylethyl)amino-1-phenylethanol† (**4b**) (α-form) and the (1*S*,2*R*)-(+)-diastereoisomer (**4f**) (β-form) were prepared by lithium aluminium hydride reduction of the optically active amides derived from the appropriate mandelic acids and 1-phenylethylamines. The preparative methods give the absolute stereochemistry. The aminoethanols (**4**) were used along with the lower alcohols to prepare chirally modified lithium aluminium hydrides which were in turn used to reduce acetophenone. The optical yields varied, giving at best, under low temperature conditions and use of [LiAlH(OMe)(PhCHOCH$_2$NCH(Me)Ph)] a 25% optical yield.

In recent years there has been extensive investigation into the asymmetric reduction of prochiral ketones using chirally modified metal hydrides.[1–3] In general these reagents have been prepared from simple reducing agents such as lithium aluminium hydride, sodium borohydride, and borane modified by various enantiomeric compounds.[4–6] The types of chiral auxiliary so employed are normally amines, alcohols or amino alcohols, of which many are naturally occurring alkaloids or aminoethanols.[7–9] Although in most cases both enantiomers are available for asymmetric induction, the only diastereoisomeric compounds we have found to be used in such complex reductions are ephedrine and pseudoephedrine.[9] We now report the synthesis and unambiguous absolute configuration of the diastereoisomers of 2-(1-phenylethyl)amino-1-phenylethanol (**4**) and their subsequent use to chirally modify lithium aluminium hydride reductions of acetophenone.

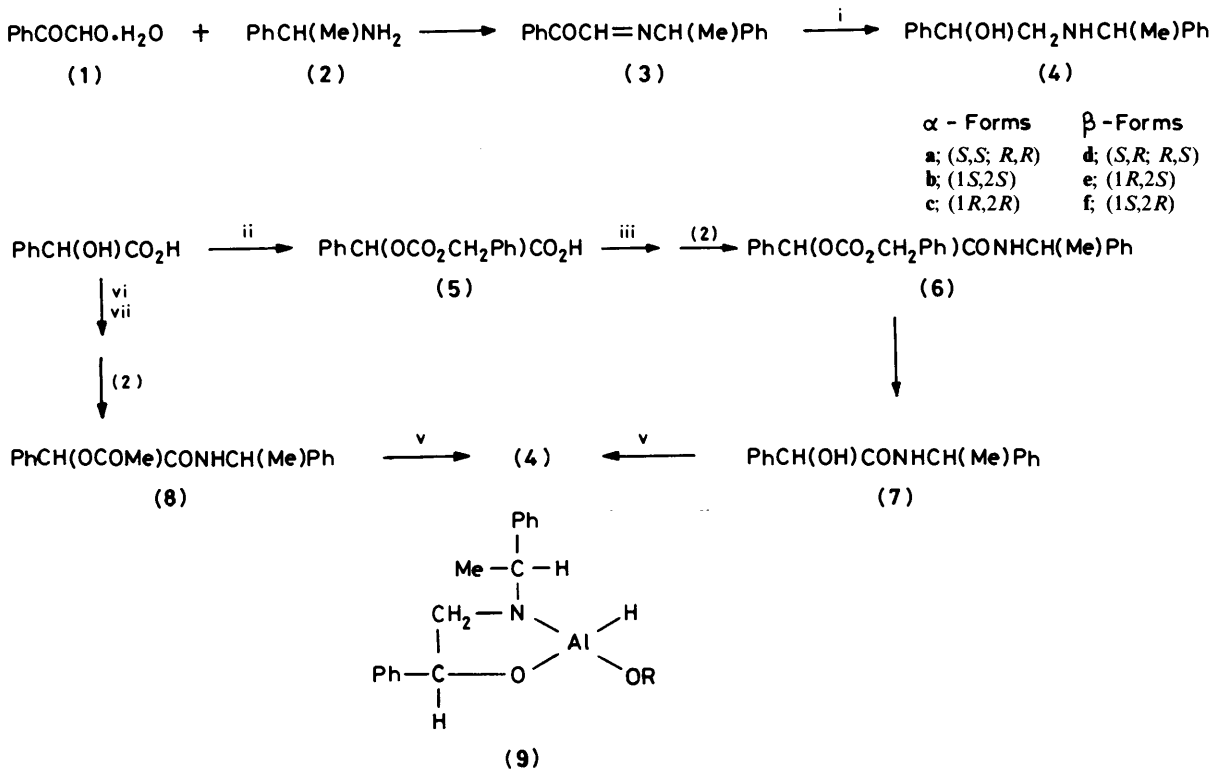
Phenylglyoxal monohydrate (**1**) was condensed with 1-phenylethylamine by the method of Pérez-Ossorio and his co-workers,[10] and then treated with sodium cyanoborohydride[11] to yield 2-(1-phenylethyl)amino-1-phenylethanol (**4**). When the (±)-amine (**2**) was used the ratio of the (±)-diastereoisomers (**4**) (which have been called α- and β-forms[10]) was at best 1:1.17 and varied little whether the imine (**3**) was first isolated then reduced or whether the synthesis was a 'one pot' reaction and the reduction was carried out at pH 4 (carbonyl and imine reduction) or at pH 7 (imine reduction) and subsequently at pH 4 (carbonyl reduction).[11] Temperature changes too had erratic rather than marked effects. These results showing lack of stereoselectivity are in accord with Pérez-Ossorio's work,[10] involving sodium borohydride reduction of related iminoketones—a result not unexpected when the chiral centre influencing the selectivity lies γ to the carbonyl group[12] of compound (**3**). When the *R*-(+)-amine (**2**) was used it was again found possible to isolate an α-form of compound (**4**), $[\alpha]_D$ +47.6° (in MeOH) as a solid, insoluble in hexane, whereas the β-form, (**4**) $[\alpha]_D$ +97.0° (in MeOH) had high solubility in that solvent. The enantiomers of these α- and β-forms were also prepared and had related rotations of opposite sign. One reference to compound (**4**) in its supposed *S,S*-form appears in the patent literature[13] but the quoted rotation, $[\alpha]_D$ −83.3° (MeOH) and a low melting point suggest that these workers did not obtain a pure product. Furthermore we now believe on the basis of our own work (see later) that the wrong configuration has been assigned to this compound in the patent.[13]

As our above synthesis did not give the configuration of the hydroxy centre of the aminoethanol (**4**), it was decided to prepare compound (**4**) starting from a mandelic acid of known configuration. As the mixed anhydride method had previously been used to prepare mandelamides of type (**6**), this route was investigated as first choice.[14] After protection of the α-hydroxy centre of the mandelic acid with benzyl chloroformate, the mixed anhydride was obtained using ethyl chloroformate and was converted into the protected mandelamide (**6**) by action of the amine (**2**). Subsequent deprotection and lithium aluminium hydride reduction of the mandelamide (**7**) yielded the desired aminoethanol (**4**). The optically active amides (**6**) receive brief mention in the literature from König and Sievers[14] who prepared these reagents as chiral coatings for g.l.c. columns. However, their quoted values[14,15] $[\alpha]_D$ +100.6° ($CHCl_3$), m.p. 85—87 °C and $[\alpha]_D$ +26.6° ($CHCl_3$), m.p. 92—93 °C for the *S,R*‡ and *S,S* forms of compound (**6**) suggest some impurity is present—our own values being $[\alpha]_D$ +103.0° ($CHCl_3$), m.p. 111—113 °C and $[\alpha]_D$ +27.0° ($CHCl_3$), m.p. 113—115 °C respectively. Furthermore, we were able to isolate the deprotected (*S,S*)-amide (**7b**) as a crystalline solid, m.p. 111—112 °C, $[\alpha]_D$ +11.1° ($CHCl_3$) whereas König and Sievers[14,15] report both diastereoisomers (**7**) to be oils. The (*S,R*)-amide (**7a**), as an oil, $[\alpha]_D$ +111.4° ($CHCl_3$) yielded, on reduction the (1*S*,2*R*)-aminoethanol, (β-form) (**4f**) $[\alpha]_D$ +96.0° (MeOH) thus giving unambiguously its absolute configuration. The (1*S*,2*S*)-aminoethanol (α-form) (**4b**) similarly prepared, had $[\alpha]_D$ −46.9° (MeOH). Subsequently it was found that a better route to the aminoethanols (**4**) lay in protecting the optically active mandelic acids by action with acetyl chloride and subsequently treating the acetylated product with (a) thionyl chloride and (b) the amine (**2**) to yield the *O*-acetylamide (**8**). Lithium aluminium hydride was then used to deprotect and reduce the amide (**8**) to the aminoethanol (**4**)—these products agreeing closely in configuration, melting points and rotations with those quoted above (see Experimental section).

The β-form of the aminoethanol (**4**), $[\alpha]_D$ −83.3° (MeOH), m.p. 82—83 °C has been claimed in patent literature[13] to be the

† The configuration of compound (**4**) at the hydroxy centre is designated (1*S*) or (1*R*), that at the amino centre (2*S*) or (2*R*) as appropriate.

‡ For amides (**6**), (**7**) and (**8**), the configuration (*S,R*) specifies the hydroxy centre to have an *S*- and the amino centre to have an *R*-configuration.



Scheme 1. *Reagents*: i, $NaBH_3CN$, CH_3COOH; ii, $PhCH_2OCOCl$, pyridine; iii, EtOCOCl, Et_3N; iv, H_2, Pd–C; v, $LiAlH_4$; vi, CH_3COCl; vii, $SOCl_2$.

For formulae (**6**), (**7**) and (**8**)

a; *S,R*
b; *S,S*
c; *R,S*

Table. Asymmetric reduction of acetophenone using chiral reducing agents to give (*R*)- or (*S*)-1-phenylethanols.

Run	Chiral ligand	ROH R	Reagent prep.		Reaction conditions *t*/°C	Time/h	Alcohol produced C(Y%); $[\alpha]_D$°;	OY(%)	Config.
1	*S,R*(**4f**)	—	† Reflux	4 h	−10	3	100[a] +2[b]	4	*R*
					r.t.	16			
2	*R,S*(**4e**)	—	* r.t.	1 h	−78	5	91[c] −2.3[b]	5	*S*
3	*S,R*(**4f**)	Et	* r.t.	2 h	−78	5	77[c] +2.3[b]	5	*R*
4	*S,S*(**4b**)	—	* r.t.	2 h	−78	5	97[c] −5.3[d]	12	*S*
5	*S,S*	Et	* r.t.	2 h	−78	6	87[c] −9.6[e]	21	*S*
6	*R,R*(**4c**)	Et	* Reflux	2 h	−78	3	87[a] +8[d]	18	*R*
					r.t.	15			
7	*R,R*	Et	* Reflux	18 h	−78	9	84[a] +9.5[e]	21	*R*
8	*R,R*	Me	* r.t.	1 h	−78	5	97[c] +11.4[d]	25	*R*
9	*R,R*	Pr^i	* r.t.	1 h	−78	4	99[c] +2.3[d]	5	*R*
10	*R,R*	$PhCh_2$	* r.t.	1 h	−78	4	93[c] +2.2[d]	5	*R*

Ratio of acetophenone: amino alcohol: $LiAlH_4$: ROH; 1:2:2:2 When no alcohol added 1:1:1.
* 1M $LiAlH_4$ solution in THF. † 0.1M $LiAlH_4$ solution in THF.
[a] Estimated *via* ^1H n.m.r. [b] Purified *via* p. t.l.c. (dichloromethane). [c] Estimated via g.c. [d] Corrected value for ketone impurity. [e] Purified via preparative g.c.

Optical yields (OY) were evaluated on the basis of the specific rotation: R(+) $PhCHOHCH_3$, $[\alpha]_D$ +45.5° (MeOH) R. Huisgen and C. Ruchardt, *Liebigs Ann. Chem.*, 1956, **601**, 31.

No racemisation of the recovered amino alcohols was observed. No difference is found in the optical yield if the sequence of additions to prepare the chiral reducing agent is varied.

1*S*,2*S*-form.‡ These workers[13] prepared compound (**4**) from (*S*)-(−)-α-methylbenzylamine (**2**), *N*-trimethylsilylacetamide, and (*S*)-(−)-phenyloxirane.[13] Their method has been shown to give a high degree of ring opening by attack at the β-carbon of the epoxide and to derive the aminoethanol as its *O*-silyl derivative. Their method[13] is also claimed 'to have no effect on the stereochemistry of its products' but our results would indicate that these workers supposed 1*S*,2*S*-derivative (**4b**) is in fact the impure (1*R*,2*S*)-aminoethanol (**4e**). Indeed the quoted melting point range and rotation (*ca.* 13% lower than ours) suggests

‡ See Note of p. 605

contamination, probably with racemic material. Hence it would appear that the stereochemistry of their reaction is not so unambiguous as proposed.[13]

The aminoethanols (**4**) were used to modify lithium aluminium hydrides [standard solutions in tetrahydrofuran (THF)] at times also in the presence of an alcohol (1M) to form chiral reducing agents. These chirally modified lithium aluminium hydrides (**9**) were then tested on acetophenone to form the well characterised (*R*)- or (*S*)-1-phenylethanols.[16] The Table shows the results obtained. In general the 1*S*,2*S*- and 1*R*,2*R*-diastereoisomers (**4**) gave higher optical yields than the 1*S*,2*R*-species (**4**). Better optical yields (up to 25%) were obtained in general when the chiral reagent was formed from one mole of the aminoethanol (**4**) and one mole of methanol or ethanol per mole of hydride. When more bulky alcohols, *e.g.* t-butyl alcohol or benzyl alcohol, were employed as ligands, although chemical yields were maintained, the optical yields fell markedly in keeping with earlier reports[17,18] that chirally modified hydrides containing bulky alcohol additives tend to disproportionate and hence give lower optical yields. Use of Dreiding models did not show any highly specific reason for the better optical yields with the 1*R*,2*R*- and 1*S*,2*S*- forms of compound (**4**) when used along with lithium aluminium hydride.

Experimental

All m.p.s were obtained using an Electrothermal melting point apparatus and are uncorrected. ^{1}H N.m.r. spectra were run on a Varian EM 360A (60MHz) spectrometer. ^{13}C N.m.r. spectra were run on a Bruker WP60FT instrument resonating at 15.08 MHz.

Phenylglyoxal monohydrate was prepared by a literature method.[19] (*R*)-(+)-1-Phenylethylamine had $[\alpha]_D$ +26° (*c* 0.99 in MeOH);[20] (*S*)-(−)-1-phenylethylamine had $[\alpha]_D$ −28° (*c* 10.0 in EtOH);[20] (*R*)-(−)-mandelic acid had $[\alpha]_D$ −158° [*c* 5.4 in $(Me)_2CO$];[21] (*S*)-(+)-mandelic acid had $[\alpha]_D$ +157° [*c* 5.6 in $(Me)_2CO$].[21]

Preparation of Oxo Imines.[10]—To a stirred suspension of phenylglyoxal monohydrate (0.76 g, 5 mmol) in toluene (30 ml) was added dropwise a solution of (*R*)-(+)-1-phenylethylamine (0.61 g, 5 mmol) in toluene (10 ml). After being stirred at room temperature for 2 h, the reaction mixture was washed several times with water, dried (Na_2SO_4), and concentrated under reduced pressure. The oxo imine (**3a**) was isolated as a light orange oil in almost quantitative yield; $\delta_H(CDCl_3)$ 1.53 (3 H, d, *J* 7 Hz, *Me*CH), 4.43 (1 H, q, *J* 7 Hz, C*H*Me), 7.2 (8 H, m, ArH), 7.96 (1 H, s, C*H*=N), and 8.03 (2 H, m, ArH); $\nu_{max.}$(neat) 1 660 and 1 640 cm^{-1}.

Reductive Amination of Phenylglyoxal.—To a solution of phenylglyoxal monohydrate (0.76 g, 5 mmol) in acetonitrile (20 ml) was added 1-phenylethylamine (0.61 g, 5 mmol) in acetonitrile (5 ml) and stirring was maintained at room temperature for 2 h. Solid $NaBH_3CN$ (0.63 g, 10 mmol) was then added in portions and the solution adjusted to pH 4 with glacial acetic acid, using Bromocresol Green as indicator. After being stirred at room temperature for 3 h, the reaction mixture was worked up as follows: the solvent was evaporated under reduced pressure and the residue cautiously treated with concentrated hydrochloric acid (15 ml). After dilution with water (25 ml), the mixture was extracted with diethyl ether (3 × 50 ml). The aqueous phase was then basified with solid potassium hydroxide, extracted with dichloromethane (4 × 50 ml), and this extract dried (Na_2SO_4) and concentrated. The resulting diastereoisomeric amino-alcohols (**4**) were then separated by refluxing in hexane (20 ml) to give two fractions.

The insoluble fraction was recrystallised from methanol to give clear crystals of the one diastereoisomer (entitled the α-form). When (±)-1-phenylethylamine was used as starting material the product (**4a**) had m.p. 128—130 °C (lit.,[10] m.p. 128—130 °C). (*S*)-(−)-1-Phenylethylamine yielded material (**4b**), m.p. 153—155 °C, $[\alpha]_D$ −47.7° (*c* 0.4 in MeOH); $\delta_C(CD_3OD$; 323K) 23.865 (*Me*CH), 56.042 (CH_2NH), 59.260 (*C*HMe), 73.466 (*C*HOH) and 126.771, 127.569, 127.942, 128.228, 129.138, 129,381, 129,928, 144.316, and 145.713 p.p.m., $\nu_{max.}$(Nujol) 3 280 and 3 080 cm^{-1}. (*R*)-(+)-1-Phenylethylamine yielded material (**4c**), m.p. 153—155 °C, $[\alpha]_D$ +47.6° (*c* 0.4 in MeOH) (Found: C, 79.53; H, 8.0; N, 5.8. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80%).

The soluble fraction was obtained when the decanted hexane was cooled. The precipitated diastereoisomer (β-form) was then recrystallised from dichloromethane–hexane and compound (**4d**) had m.p. 78 °C (lit.,[10] m.p. 78 °C) when (±)-1-phenylethylamine was used, or compound (**4e**) m.p. 92—93 °C, $[\alpha]_D$ −95° (*c* 0.9 in MeOH) when (*S*)-(−)-1-phenylethylamine was the precursor; $\delta_C(CD_3OD$; 323 K) 23.865 (*Me*CH), 55.799 (CH_2NH), 58.531 (*C*HMe), 73.041 (*C*HOH), 126.771, 127.560, 127.942, 128.228, 129.138, 129.381, 129.928, 144.316, and 145.713 p.p.m.

R-(+)-1-Phenylethylamine similarly yielded product (**4f**), m.p. 92—93 °C, $[\alpha]_D$ +97° (*c* 0.9 in MeOH); $\delta_H(CDCl_3)$ 1.37 (3 H, d, *J* 7 Hz, MeCH), 2.36—2.7 (4 H, m, CHO*HCH*$_2$N*H*), 3.37 (1 H, q, *J* 7 Hz, C*H*Me), 4.63 (1 H, dd, C*H*OH), and 7.17 (10 H, s, ArH) (Found: C, 79.65; H, 7.8; N, 5.8. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80%); yield 35% (α-isomer 200 mg; β-isomer 233 mg *i.e.*, an 8% excess of the β-diastereoisomer).

Preformed Oxo Imine.— The oxo imine (**3a**) was prepared in toluene as before using *R*-(+)-1-phenylethylamine (0.61 g, 5 mmol) and the isolated compound dissolved in acetonitrile (25 ml) and reduced with $NaBH_3CN$ (0.63 g, 10 mmol) at pH 4 (glacial acetic acid as buffer) for 3 h. On work-up as before a yield of 28% (α-isomer 168 mg; β-isomer 180 mg, *i.e.* a 4% excess of the β-diastereoisomer) was obtained.

pH *Variant.*—The oxo imine (**3a**) was prepared in acetonitrile as before using (*R*)-(+)-1-phenylethylamine (0.61 g, 5 mmol) and $NaBH_3CN$ (0.31 g, 5 mmol) was added and the solution buffered with glacial acetic acid at pH 7 for 90 mins. The remainder of the $NaBH_3CN$ (0.3 g, 5 mmol) was added and the acidity adjusted to pH 4. After being stirred for a further 90 min the reaction mixture was worked up as before, although purification on a dry silica column [dichloromethane–ethyl acetate (4:1)] was used immediately prior to separation of the diastereoisomers. The yield was 27% (α-isomer 159 mg; β-isomer 166 mg, *i.e.*, a 2% excess of the β-diastereoisomer).

Temperature Variant.—The following reactions were carried out in acetonitrile as before at pH 4 but at the various temperatures and reaction times stated.

Run	Amine (**2**)	*t*/°C	Reaction time/h	Chemical Yield (%)	α-Isomer (mgs)	β-Isomer	Excess (%)
1	*S*-(−)	55	10	32	193	188	1α
2	*S*-(−)	−10	4	62	375	444	8β
3	*R*-(+)	−20	8	47	287	282	1α

Absolute Configuration of the Diastereoisomers of 2-(1-*Phenylethyl*)*amino*-1-*phenylethanol.*—(A) *Mixed anhydride route.* (i) Preparation of *O*-benzyloxycarbonyl-(*S*)-(+)-mandelic acid.[14] Dry pyridine (2.6 g, 33 mmol) was added to a solution of *S*-(+)-mandelic acid (4.6 g, 30 mmol) in anhydrous diethyl ether (100 ml), and the temperature lowered to −20 °C. Benzyl chloroformate (5.6 g, 33 mmol) was added dropwise and stirring was continued in the cold for 3 h and then at room temperature for 16 h. The reaction mixture was washed with dilute hydrochloric acid and then repeatedly extracted with saturated aqueous sodium hydrogencarbonate. These basic extracts were acidified with concentrated hydrochloric acid and extracted with diethyl ether (5 × 50 ml.). The dried (Na_2SO_4) extract was concentrated under reduced pressure and the white crystalline product (**5**) (4.1 g, 47%) was then used without further purification; $\delta_H(CDCl_3)$ 5.1 (2 H, s, CH_2Ph), 5.73 (1 H, s, C*H*Ph), 7.33 (10 H, s, ArH), and 9.43 (1 H, s, COOH).

(ii) Preparation of *O*-benzyloxycarbonyl-*N*-(1-phenylethyl)-mandelamide.[14] To *O*-benzyloxycarbonyl-(*S*)-(+)-mandelic acid (**5**) (1.4 g, 5 mmol) in chloroform (80 ml) at −15 °C, was added dry triethylamine (0.51 g, 5 mmol) with stirring, followed by the slow addition of ethyl chloroformate (0.54 g, 5 mmol). After 15 min 1-phenylethylamine (0.61 g, 5 mmol) in chloroform (10 ml) was added dropwise. Stirring was maintained for 4 h at −15 °C and then for 16 h at room temperature. The reaction mixture was successively washed with dilute hydrochloric acid, (× 3) with water with saturated sodium hydrogencarbonate (× 4), and again with water. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure.

The compound (**5**) from *R*-(+)-1-phenylethylamine gave product (**6a**), m.p. 111—113 °C, $[\alpha]_D$ +103° (*c* 0.84 in $CHCl_3$) from dichloromethane–hexane in 35% yield; $\delta_H(CDCl_3)$ 1.4 (3 H, d, *J* 7 Hz, *Me*CH), 5.1 (3 H, m, CH_2Ph, C*H*Me), 5.93 (1 H, s, CHCON), 6.53 (1 H, s, NH), and 7.26 (15 H, m, ArH); $\nu_{max.}$(Nujol) 3 320, 1 750, 1 660, and 1 530 cm^{-1} (Found: C, 73.5; H, 6.1; N, 3.5. $C_{24}H_{23}NO_4$ requires C, 74.0; H, 5.95; N, 3.6%).

Similarly the compound (**5**) from *S*-(−)-1-phenylethylamine gave product (**6b**), m.p. 113—115 °C, $[\alpha]_D$ +27° (*c* 0.62 in $CHCl_3$) from dichloromethane–hexane in 42% yield; $\delta_H(CDCl_3)$ 1.47 (3 H, d, *J* 7 Hz, *Me*CH), 5.1 (3 H, m, CH_2Ph, C*H*Me), 5.9 (1 H, s, CHCON), 6.6 (1 H, s, NH), and 7.26 (15 H, m, ArH); $\nu_{max.}$(Nujol) 3 350, 1 740, 1 650, and 1 510 cm^{-1} (Found: C, 74.35; H, 6.05; N, 3.6. $C_{24}H_{23}NO_4$ requires C, 74.00; H, 5.95; N, 3.60%).

(iii) Preparation of *N*-1-phenylethylmandelamide.[14] *O*-Benzyloxycarbonyl-*N*-(1-phenylethyl)mandelamide (2 g, 5.1 mmol) was dissolved in ethyl acetate (60 ml) and 5% Pd–C catalyst (2 g) was added for atmospheric hydrogenation: the reaction was stopped when the desired volume of hydrogen (115 ml) had been consumed. After filtration through Celite the solution was evaporated and the residue taken up in dichloromethane, dried (Na_2SO_4), and concentrated under reduced pressure. *N*-(*R*)-1-Phenylethyl-(*S*)-mandelamide (**7a**), obtained as in oil in quantitative yield and purified *via* preparative t.l.c. [Light petroleum (b.p. 40—60 °C)–ethyl acetate (3:2)] had $[\alpha]_D$ +111.4° (*c* 1.2 in $CHCl_3$); $\delta_H(CDCl_3)$ 1.3 (3 H, d, *J* 7 Hz, *Me*CH), 4.76—4.9 (3 H, m, C*H*Me, C*H*OH), and 7.13 (11 H, m, ArH, N*H*). *N*-(*S*)-1-Phenylethyl-(*S*)-mandelamide (**7b**), obtained in quantitative yield had m.p. 111.5—112.5 °C, $[\alpha]_D$ +11.1° (*c* 0.64 in $CHCl_3$); $\delta_H(CDCl_3)$ 1.33 (3 H, d, *J* 7 Hz, *Me*CH), 3.9 (1 H, s, OH), 4.76 (1 H, s, C*H*OH) 4.93 (1 H, q, *J* 7 Hz, C*H*CH_3), 6.67 (1 H, s, NH), and 7.2 (10 H, m, ArH); $\nu_{max.}$ (Nujol) 3 380, 3 180, 1 650, and 1 520 cm^{-1} (Found: C, 75.65; H, 6.8; N, 5.5. $C_{16}H_{17}NO_2$ requires C, 75.25; H, 6.71; N, 5.49%).

(iv) Preparation of 2-(1-phenylethyl)amino-1-phenylethanol. To a solution of $LiAlH_4$ in THF was added the required α-hydroxy amide (**7**) in dry THF, and the reaction mixture refluxed under nitrogen for 48 h. It was then quenched with wet THF, filtered, and evaporated under reduced pressure. The residue was then taken up in dichloromethane, washed with water, and dried (Na_2SO_4). Concentration of the solvent yielded the corresponding amino alcohol.

(1*S*,2*R*)-(+)-2-(1-Phenylethyl)amino-1-phenylethanol (**4f**) was obtained in 46% yield from compound (**7a**) and had m.p. 92—93 °C, $[\alpha]_D$ +96° (*c* 0.92 in MeOH) when recrystallised from dichloromethane–hexane. Similarly (1*S*,2*S*)-(−)-2-(1-Phenylethyl)amino-1-phenylethanol (**4b**) was obtained in 48% yield from compound (**7b**) and had m.p. 153—155 °C, $[\alpha]_D$ −46.9° (*c* 0.39 in MeOH) when recrystallised from methanol. Both these results being in good agreement with those quoted above.

(B) *Acid chloride route.*[22] (i) Preparation of *O*-Acetyl-*N*-(1-phenylethyl)mandelamide. Acetyl chloride (8 g, 100 mmol) was added dropwise to (*S*)-(+)-mandelic acid (1.5 g, 9.8 mmol) and after the solid had dissolved, the solution was stirred for 30 min. An excess of acetyl chloride was removed under reduced pressure, the residue treated with thionyl chloride (4.7 g, 39 mmol), and the mixture then gently refluxed for 35 min. An excess of thionyl chloride was removed under reduced pressure and the residue dissolved in dry chloroform (20 ml). This solution was then added to an ice cooled solution of triethylamine (1.01 g, 10 mmol) and (*S*)-(−)-1-phenylethylamine (1.21 g, 10 mmol) in chloroform (30 ml). Stirring was maintained at 0 °C for 3 h and then at room temperature for 16 h. The organic phase was then washed with dilute hydrochloric acid (× 3), with saturated sodium hydrogencarbonate (× 5), with water (× 3) and finally dried (Na_2SO_4). Concentration under reduced pressure yielded the crude product (**8b**) (2.8 g, 96%) which had m.p. 149—151 °C, $[\alpha]_D$ +10.4° (*c* 1.5 in MeOH) on recrystallisation from dichloromethane–hexane; $\delta_H(CDCl_3)$ 1.47 (3 H, d, *J* 7 Hz, *Me*CH), 2.1 (3 H, s, MeCO), 5.07 (1 H, q, *J* 7 Hz, C*H*Me), 6.0 (1 H, s, PhC*H*CO), 6.33 (1 H, s, NH), and 7.26 (10 H, m, ArH); $\nu_{max.}$(Nujol) 3 320, 1 730, 1 650, and 1 535 cm^{-1} (Found: C, 72.9; H, 6.6; N, 4.6. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%).

(*R*)-(−)-Mandelic acid with (*S*)-(−)-1-phenylethylamine gave a corresponding product (**8c**) in 94% yield, which had m.p. 138—139 °C, $[\alpha]_D$ −164.7° (*c* 0.96 in MeOH) on recrystallisation from dichloromethane–hexane; $\delta_H(CDCl_3)$ 1.47 (3 H, d, *J* 7 Hz, *Me*CH), 2.13 (3 H, s, MeCO), 5.1 (1 H, q, *J* 7 Hz, C*H*Me), 5.97 (1 H, s, PhC*H*O), 6.23 (1 H, s, NH), and 7.27 (10 H, m, ArH); $\nu_{max.}$(Nujol) 3 280, 1 730, 1 650, and 1 550 cm^{-1} (Found: C, 71.5; H, 6.3; N, 4.6. $C_{18}H_{19}NO_3 \cdot \frac{1}{4}H_2O$ requires C, 71.6; H, 6.5; N, 4.6%).

(ii) Preparation of 2-(1-phenylethyl)amino-1-phenylethanol. A solution of the (*S*,*S*)-*O*-acetyl amide (**8b**) (3.5 g, 11.8 mmol) in THF (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2 g, 52 mmol) in THF (50 ml) and the mixture refluxed for 40 h. After cautious addition of wet THF to destroy the excess of $LiAlH_4$, the precipitate was filtered off and the filtrate concentrated under reduced pressure, diluted with dichloromethane (100 ml), and dried (Na_2SO_4). Evaporation yielded the crude product which was purified by refluxing in hexane (50 ml) and decanting off the organic phase. The insoluble residue was recrystallised from methanol to yield the product amino alcohol (**4b**) (1.7 g). The hexane phase only yielded more of the product (**4b**) (0.3 g) but none of the racemised diastereoisomer. Compound (**4b**) (2 g, 70%) had m.p. 152—155 °C, $[\alpha]_D$ −47.8° (*c* 0.41 in MeOH).

The diastereomeric compound (**8c**) was similarly reduced in 74% yield with $LiAlH_4$ and on purification by flash chromatography (ethyl acetate) the product (**4e**) had m.p. 91—93 °C, $[\alpha]_D$ −95.8° (*c* 0.83 in MeOH) after recrystallisation from dichloromethane–hexane.

Asymmetric Reductions.—All reactions were carried out under ultra-dry conditions in a nitrogen atmosphere.

General procedure. To a three-necked flask containing the desired aminoalcohol (1.2 g, 5 mmol) a standardised solution of $LiAlH_4$ (1M; 5 ml) in THF was added very slowly. After evolution of hydrogen had ceased, the dropping funnel was washed with a few ml of solvent and the alcohol component (5 mmol) was added if required. The reaction mixture was stirred at either room temperature or reflux for a given time and then cooled to the desired temperature. Acetophenone (0.3 g, 2.5 mmol) in THF (4 ml) was then added dropwise and the temperature maintained (or varied) until quenching. After cautious addition of wet THF, the gelatinous solution was filtered and the liquors concentrated to yield a solid. This residue was refluxed in hexane (40 ml) for 2 h and after cooling, the liquid was decanted from the insoluble amino alcohol (>90%) and concentrated under reduced pressure. Dichloromethane was then added and the solution washed with dilute hydrochloric acid (×5) and with water (×3). After drying (Na_2SO_4), evaporation yielded the product alcohol.

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Note added in proof. Subsequent to the submission of this paper and contrary to the results published in their patent,[3] Weigel and co-workers now report the absolute configuration of the aminoethanol (**4e**) to be (1*R*, 2*S*) and not (1*S*, 2*S*); this is in accord with the results in this paper. (R. K. Atkins, J. Frazier, L. L. Moore, and L. O. Weigel, *Tetrahedron Lett.*, 1986, **27**, 2451).

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