Lithium Aluminium Hydride Reduction of Chiral Benzoylformamides Derived from Chiral Amino Alcohols

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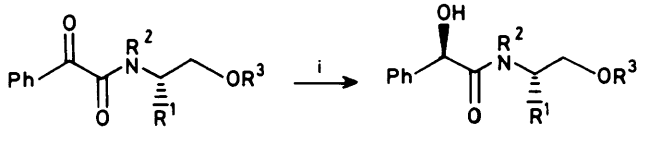
The reduction of benzoylformamides derived from various *N*- and *O*-substituted (*S*)-amino alcohols using lithium aluminium hydride was carried out. Diastereoisomeric excesses could be determined by chromatographic separation of the resulting diastereoisomeric mandelamides. In all cases, the (*S,S*)-diastereoisomer was obtained as the major product (1—72% d.e.), and the degree of asymmetric induction depended largely on the *N*- and *O*-substituents of the amino alcohol moiety. A d.e. of up to 72% was obtained for the benzoylformamide (**4**) derived from *N*-methylvalinol.

There has been considerable success in the asymmetric reduction of prochiral substrates using optically active amino alcohol-modified metal hydride complexes.[1] The reduction of chiral keto esters has been extensively investigated,[2] while that of chiral α-keto-amides has not received much attention, and for other than a few cases only poor to moderate asymmetric yields have been observed.[3] In relation to the amino alcohol-modified metal hydride complex reductions, the reductions of benzoylformamides derived from chiral amino alcohols was studied, and in particular the effect of *N*- and *O*-substituents of the amino alcohol moiety was examined.

Results and Discussion

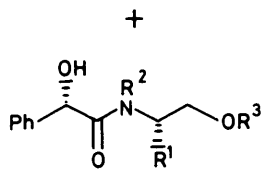
Benzoylformamides (1)—(6) were prepared by the reaction of benzoylformyl chloride and the corresponding amino alcohols prepared from L-amino acids. The reductions were carried out by the reaction of the benzoylformamides with an equimolar amount of lithium aluminium hydride in tetrahydrofuran (THF) under argon atmosphere at −78 °C for 1 h, followed by reaction at room temperature for 12 h (Scheme). After the usual work-up, the corresponding mandelamides (7)—(12) were obtained in the yields summarized in Table 1.



(1) — (6) (7a) — (12a)

(1), (7) R^1 = Me, R^2 = R^3 = H
(2), (8) R^1 = CH_2Ph, R^2 = R^3 = H
(3), (9) R^1 = Pr^i, R^2 = R^3 = H
(4), (10) R^1 = Pr^i, R^2 = Me, R^3 = H
(5), (11) R^1 = Pr^i, R^2 = H, R^3 = Me
(6), (12) R^1 = Pr^i, R^2 = R^3 = Me

+



(7b) — (12)

Scheme. *Reagents and conditions:* i, $LiAlH_4$, THF, −78 °C ⟶ room temp., Ar

Chiral 2-amino alcohols have been successfully applied as chiral derivatizing agents in the chromatographic separation of enantiomeric acids and aldehydes.[4] The separation of diastereoisomeric amides, derived from hydroxy acids and chiral amino alcohols, on silica gel has been reported by Helmchen,[5] and the diastereoisomeric mandelamides (7)—(12) obtained in the reduction above were also expected to show large chromatographic separations. The separability factor (α), the configuration of the first eluted diastereoisomer, and the solvent used in the liquid chromatographic separations of the diastereoisomeric mandelamides (7)—(12) are as listed in Table 2. All diastereoisomers showed large separations and, especially in the case of mandelamides (**8**), (**9**), and (11), the diastereoisomers could be separated by preparative-scale silica gel column chromatography. Although mandelamides (7) and (**10**) showed separability factors of the same order, the diastereoisomers of these two compounds could not be separated by preparative-scale silica gel chromatography under the same conditions. An increase in separability was observed on increasing the bulk of the substituent R^1 of the amino alcohol moiety in the order of methyl < benzyl < isopropyl. Furthermore, on the introduction of a methyl group on the nitrogen atom, the order of elution was reversed, and the (*S,S*)-isomer was eluted first. It has been stated by Helmchen that the NH–silica interaction is important in controlling the elution of diastereoisomeric amides. The reversed order of elution of the diastereoisomeric mandelamides could be explained by postulating a different form of intramolecular

Table 1. H.p.l.c. separations of diastereoisomeric mandelamides (7)—(12)

	R^1	R^2	R^3	First eluted	Eluant	α[a]
(7)	Me	H	H	(*R,S*)	CH_2Cl_2–MeCN (1:1)	1.82
(8)	CH_2Ph	H	H	(*R,S*)	CH_2Cl_2–MeCN (1:1)	2.13
(9)	Pr^i	H	H	(*R,S*)	CH_2Cl_2–MeCN (1:1)	2.47
(10)	Pr^i	Me	H	(*S,S*)	n-Hexane–THF (7:4)	2.15
(11)	Pr^i	H	Me	(*R,S*)	n-Hexane–THF (2:1)	2.33
(12)	Pr^i	Me	Me	(*S,S*)	n-Hexane–THF (6:1)	1.29

[a] Separability factor.

Table 2. Lithium aluminium hydride reductions of benzoylformamides (1)—(6)

	R^1	R^2	R^3	Product	Yield (%)	Config.	D.e. (%)
(1)	Me	H	H	(7)	88	(*S,R*)	25[a]
(2)	CH_2Ph	H	H	(8)	67	(*S,R*)	4[b]
(3)	Pr^i	H	H	(9)	40	(*S,R*)	41[b]
(4)	Pr^i	Me	H	(10)	20	(*S,R*)	72[c]
(5)	Pr^i	H	Me	(11)	74	(*S,R*)	1[b]
(6)	Pr^i	Me	Me	(12)	94	(*S,R*)	22[c]

[a] Elucidated by h.p.l.c. and by hydrolysis to mandelic acid. [b] Elucidated by preparative-scale column chromatography. [c] Elucidated by h.p.l.c.

hydrogen bonding in mandelamides (**7**), (**8**), (**9**), and (**11**) compared with that in *N*-methylmandelamides (**10**) and (**12**), which may explain the peculiar behaviour observed in the ^1H n.m.r. and ^{13}C n.m.r. spectra of the (*S*,*S*)-isomers of mandelamides (**10**) and (**12**); namely, in the ^1H and ^{13}C n.m.r. spectra of (*S*,*S*)-mandelamides (**10b**) and (**12b**), an extremely large upfield shift of the isopropyl group, and coupling of the hydroxy proton of the mandelic acid moiety in the ^1H n.m.r. spectrum, suggesting strong intramolecular hydrogen bonding, were observed. Helmchen has stated that the conformation of amides is the same in the dissolved state and in the adsorbed state.[5] If this is the case, the strong intramolecular hydrogen bonding in the (*S*,*S*)-diastereoisomers of *N*-methylbenzoylformamides (**10**) and (**12**) may have led to a reversal of the magnitude of the attractive interactions of the (*R*,*S*) and (*S*,*S*) isomers with silica gel, which would mean a reversed order of elution. Furthermore, nearly all peaks were observed as pairs, probably due to the hydrogen bonding observed above, which may be attributed to the *cis* and *trans* isomers of the amide bond. Typical examples of the high-pressure liquid chromatography (h.p.l.c.) separations of mandelamides are shown in the Figure. Mandelamides possessing an amide

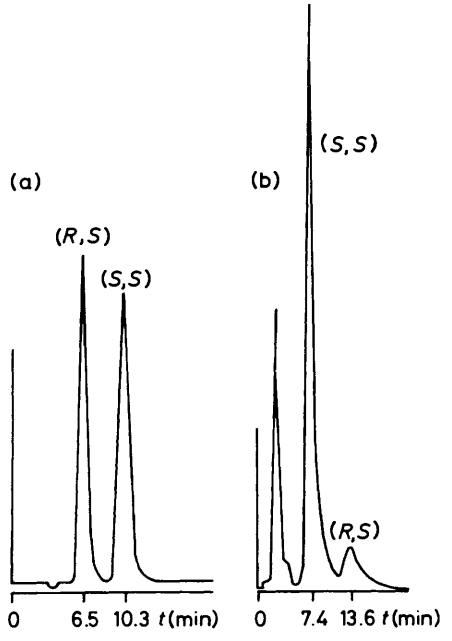


Figure. H.p.l.c. separation of diastereoisomeric mandelamides. (a) Separation of diastereoisomeric mandelamide (**8**). (b) Separation of diastereoisomeric mandelamide (**10**) obtained by lithium aluminium hydride reduction of compound (**4**)

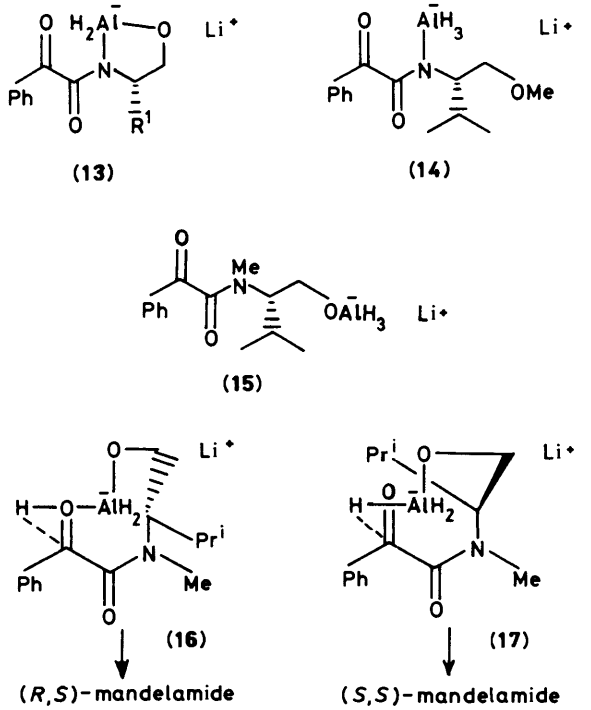
proton, (**7**)—(**9**) and (**11**), showed good baseline separations. On the introduction of an *N*-methyl group, (**10**) and (**12**), a slight broadening of the peaks was observed, however, fairly good separations were obtained.

The diastereoisomeric excesses (d.e.s.) of the resulting diastereoisomeric mandelamides were determined by either isolation of the (*R*,*S*)- and (*S*,*S*)-mandelamides by preparative-scale silica gel chromatography, or by the h.p.l.c. separation mentioned above (Table 2) in the case of compounds (**8**)—(**12**). In the case of compound (**7**), the d.e. was determined by h.p.l.c. separation, by ^1H n.m.r. spectroscopy using europium shift reagents, and by hydrolysis to mandelic acid. The methods above showed fairly good correlations, and asymmetric inductions of 25, 16, and 25% were obtained, respectively, by the methods above.

In the reaction of benzoylformamides derived from (*S*)-alaninol, (*S*)-phenylalaninol, and (*S*)-valinol with lithium aluminium hydride, (*S*,*S*)-mandelamides were obtained in asymmetric yields of up to 41% in the reduction of compound (**3**), derived from (*S*)-valinol. Although compound (**2**), derived from (*S*)-phenylalaninol, was expected to show an increase in asymmetric yield, a low d.e. (4%) was observed. However, an increase in asymmetric yield was observed on increasing the bulk of R^1 from methyl to isopropyl. No clear explanation for the order of asymmetric induction can be presented. In all cases, (*S*)-mandelic acid (*S*)-amide was obtained preferentially.

Interesting results were obtained for the reaction of benzoylformamides derived from various *N*- and *O*-substituted (*S*)-valinol. The reaction of *N*-substituted benzoylformamide (**4**), derived from (*S*)-*N*-methylvalinol, yielded (*S*,*S*)-mandelamide (**10**) in 72% d.e. However, the reduction of *O*-substituted benzoylformamides (**5**) and (**6**), derived from (*S*)-*O*-methylvalinol and (*S*)-*N*,*O*-dimethylvalinol, resulted in a dramatic decrease in d.e. Furthermore, the reaction of various *N*- and *O*-substituted amino alcohols with lithium aluminium hydride was examined, and metallation of both amino and hydroxy groups was observed by the evolution of hydrogen gas. Even in the case of *N*-formylvalinol, both amide and hydroxy protons were metallated.

From these observations, the mechanism of the asymmetric induction of the lithium aluminium hydride reduction of benzoylformamides was speculated upon. When both amide and hydroxy protons exist, (**1**)—(**3**), the benzoylformamide would react with lithium aluminium hydride to yield intermediate (**13**), and hydride attack on the ketone moiety would occur intramolecularly to yield the corresponding mandelamide. However, in the case of benzoylformamide (**5**), lithium aluminium hydride should react first at the amide moiety to form intermediate (**14**). In this case, the attack of the hydride would be less influenced by the chiral centre in the amino alcohol moiety, and indeed practically no asymmetric induction was observed. The highest asymmetric yield was obtained in the case of compound (**4**), derived from *N*-methylvalinol. In this case, lithium aluminium hydride would react first with the hydroxy group to yield an aluminium



alkoxide (**15**). Intramolecular hydride attack would occur preferentially on the *si* face as in intermediate (**17**), and not on the *re* face as in intermediate (**16**), to yield (*S,S*)-mandelamide in excess. The isopropyl group interactions should influence the course of the hydride attack, however, no clear difference in the conformational properties of intermediates (**16**) and (**17**) could be observed using molecular models. The increase in asymmetric yield in the reaction of the benzoylformamide (**4**) as compared with *N,O*-unsubstituted benzoylformamides (**1**)—(**3**) could be explained by the stability of intermediates (**13**) and (**16**) or (**17**). On attack of the hydride, while intermediates (**16**) and (**17**) are stable with the dicarbonyl moiety anticoplanar and the amide planar, intermediate (**13**) can only react with the hydride through a less stable conformation with the two carbonyl groups in a perpendicular state. Reduction of *N,O*-disubstituted benzoylformamide (**6**), where the formation of an adduct with lithium aluminium hydride would be suppressed, a decrease in asymmetric yield was observed, supporting the above speculation.

In conclusion, it was found that on the lithium aluminium hydride reduction of benzoylformamides, (*S,S*)-mandelamides were obtained in 1—72% d.e., and that the extent of asymmetric induction was influenced largely by *N*- and *O*-substituents. Benzoylformamides derived from (*S*)-*N*-methylvalinol showed the highest asymmetric induction (72% d.e.). The asymmetric induction was interpreted by assuming the occurrence of two reaction steps, where the benzoylformamide possessing either a hydroxy or an amide proton would react first with lithium aluminium hydride to form an aluminium alkoxide or an aluminium amide, followed by intramolecular attack of the aluminium hydride on the ketone moiety to yield the corresponding mandelamide.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus, and are uncorrected. I.r. spectra were measured on a Jasco IRA-1 infrared spectrometer. ^{1}H N.m.r. and ^{13}C n.m.r. spectra were recorded using a Hitachi R-24 (60 MHz) and a JEOL-100 (100 MHz) spectrometer, respectively, with tetramethylsilane as internal standard. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyser.

Preparation of Benzoylformamides (**1**)—(**6**).—To an ice–water-bath-cooled THF solution (10 ml) of benzoylformyl chloride (0.84 g, 5 mmol) was added dropwise a solution of the chiral amino alcohol (5 mmol) and triethylamine (10 mmol) in THF (10 ml). The mixture was stirred at 0 °C for 2 h and at room temperature for 12 h. The resulting white precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The resulting oil was dissolved in dichloromethane, washed with water, dried over anhydrous magnesium sulphate, and evaporated under reduced pressure. The oil was purified by silica gel column chromatography (eluant benzene–ethyl acetate). The following amides were thus prepared.

N-(2-Hydroxy-1-methylethyl)benzoylformamide (**1**), 18% yield; $\nu_{max.}$(film) 3 400 (OH), 3 280 (NH), 1 680 (CO), and 1 640 cm^{-1} (CO); δ_H($CDCl_3$) 1.20 (d, 3 H, Me), 3.5—4.0 (m, 3 H, NC*H*C*H*$_2$OH), 7.2—7.9 (m, 3 H, ArH), and 8.1—8.4 (m, 2 H, ArH).

N-(1-Benzyl-2-hydroxyethyl)benzoylformamide (**2**), 28% yield; m.p. 108—109 °C (from benzene–n-hexane) (Found: C, 71.8; H, 6.1; N, 4.9. $C_{17}H_{17}NO_3$ requires C, 72.06; H, 6.04; N, 4.94%); $\nu_{max.}$(KBr) 3 280 (NH, OH) and 1 640 cm^{-1} (CO); δ_H($CDCl_3$) 2.90 (d, *J* 7 Hz, 2 H, PhC*H*$_2$), 3.67 (m, 2 H, C*H*$_2$), 4.3 (m, 1 H, NCH), 7.2—7.6 (m, 8 H, ArH), and 8.0—8.1 (m, 2 H, ArH); δ_C($CDCl_3$) 36.9 (t, Ph*C*H$_2$), 52.8 (d, NCH), 63.3 (t, *C*H$_2$OH), 126.6 (d, Ph), 128.4 (d, Ph), 128.5 (d, Ph), 129.2 (d, Ph), 130.9 (d, Ph), 133.0 (s, Ph), 134.3 (d, Ph), 137.3 (s, Ph), 162.3 (s, CO), and 188.2 (s, CO).

N-(1-Hydroxymethyl-2-methylpropyl)benzoylformamide (**3**), 19% yield; b.p. 145 °C/10^{-4} Torr; $\nu_{max.}$(film) 3 400 (OH), 3 380 (NH), 1 680 (CO), and 1 660 cm^{-1} (CO); δ_H($CDCl_3$) 0.95 (d, *J* 6 Hz, 3 H, MeCH*Me*), 0.98 (d, *J* 6 Hz, 3 H, *Me*CHMe), 3.2 (br s, 1 H, NH), 3.74 (s, 1 H, OH), 4.31 (t, *J* 7 Hz, 1 H, NCH), and 7.1—8.0 (m, 5 H, Ph); δ_C($CDCl_3$) 18.7 (q, MeCH*Me*), 19.6 (q, *Me*CHMe), 29.0 (d, *C*HMe$_2$), 57.1 (d, NCH), 62.9 (t, CH_2OH), 128.4 (d, Ph), 131.0 (d, Ph), 133.2 (s, Ph), 134.3 (d, Ph), 162.6 (s, CO), and 188.2 (s, CO).

N-(1-Hydroxymethyl-2-methylpropyl)-*N*-methylbenzoylformamide (**4**), 6% yield; $\nu_{max.}$(film) 3 380 (OH), 1 685 (CO), and 1 630 cm^{-1} (CO); δ_H($CDCl_3$) 1.04 (d, *J* 7 Hz, 6 H, CH*Me*$_2$), 1.4—2.0 (m, 1 H, C*H*Me$_2$), 2.99 (s, 3 H, NMe), 3.76 (d, *J* 7 Hz, 2 H, C*H*$_2$OH), 4.0—4.4 (m, 1 H, NCH), 7.2—7.8 (m, 3 H, ArH), and 7.9—8.2 (m, 2 H, ArH).

N-(1-Methoxymethyl-2-methylpropyl)benzoylformamide (**5**), 24% yield; $\nu_{max.}$(film) 3 400 (NH), 1 690 (CO), and 1 660 cm^{-1} (CO); δ_H($CDCl_3$) 0.98 (d, *J* 7 Hz, 6 H, CH*Me*$_2$), 1.4—2.2 (m, 1 H, C*H*Me$_2$), 3.40 (s, 3 H, OMe), 3.4—3.6 (m, 2 H, C*H*$_2$OH), 3.8—4.2 (m, 1 H, NCH), 7.2—7.8 (m, 3 H, ArH), and 8.3—8.6 (m, 2 H, ArH); δ_C($CDCl_3$) 18.8 (q, MeCH*Me*), 19.5 (q, *Me*CHMe), 29.5 (d, *C*Me$_2$), 54.4 (d, NCH), 59.0 (q, OMe), 72.3 (t, CH_2O), 128.4 (d, Ph), 131.0 (d, Ph), 133.1 (s, Ph), 134.2 (d, Ph), 162.0 (s, CO), and 188.1 (s, Ph).

N-(1-Methoxymethyl-2-methylpropyl)-*N*-methylbenzoylformamide (**6**), 39% yield; $\nu_{max.}$(film) 1 680 (CO) and 1 640 cm^{-1} (CO); δ_H($CDCl_3$) 0.81 (d, *J* 7 Hz, 3 H, MeCH*Me*), 0.91 (d, *J* 7 Hz, 3H, *Me*CHMe), 1.4—2.1 (m, 1 H, C*H*Me), 2.24 and 2.89 (2 s, 3 H, NMe), 3.10 and 3.31 (2 s, 3 H, OMe), 3.50 (d, 2 H, CH_2O), 4.1—4.6 (m, 1 H, NCH), 7.1—7.6 (m, 3 H, ArH), and 7.7—8.1 (m, 2 H, ArH).

Preparation of Mandelamides (**7**)—(**12**).—(A) (*S*)- or (*R*)-Mandelic acid (5 mmol) was heated under reflux in 1.2M-methanolic hydrochloric acid (10 ml) for 1 h. The reaction mixture was washed successively with saturated aq. sodium hydrogen carbonate and water, and extracted with ether. The extract was dried over anhydrous magnesium sulphate, and evaporated under reduced pressure to yield (*S*)- or (*R*)-methyl mandelate quantitatively. To the resulting methyl mandelate was added a solution of the corresponding 2-amino alcohol in benzene (10 ml), and the mixture was heated under reflux for 24 h, washed with water, and extracted with dichloromethane in the case of (*R,S*)-mandelamides. The (*S,S*)-mandelamides were often insoluble, and were subjected directly to silica gel column chromatography (chloroform–acetone–ethanol).

(B) (*S*)- or (*R*)-Mandelic acid (5 mmol) was dissolved in dry ethyl acetate (15 ml), and the solution was cooled in an ice–water bath. Diethylaminopyridine (4.5 mol) was added and the mixture was stirred for 15 min, then a solution of dicyclohexylcarbodi-imide (5 mmol) in dry ethyl acetate (15 ml) was added and the mixture was stirred for another 30 min. The corresponding amino alcohol (5 mmol) was then added and the resulting mixture was stirred for 36 h, then washed successively with 0.1M-hydrochloric acid, a saturated aq. sodium hydrogen carbonate, and water, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, and evaporated under reduced pressure to yield the corresponding mandelamide.

(C) To a solid CO_2–methanol-cooled suspension of lithium aluminium hydride (1 mmol) in dry THF (10 ml) was added dropwise a solution of benzoylformamide (1 mmol) in THF (5 ml) under argon. The mixture was stirred at −78 °C for 1 h, then for 12 h at room temperature. The reaction was quenched by the addition of ethyl acetate (1 ml) and 1M-sodium hydroxide

(1 ml). The white precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The crude product was dissolved in dichloromethane and the solution was washed with water, dried over anhydrous magnesium sulphate, and evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography to yield the corresponding mandelamide. The fractions containing both (*S,S*)- and (*R,S*)-epimers were collected and subjected to h.p.l.c., or were isolated directly to determine the asymmetric yields.

(D) Mandelamides were prepared by the reaction of racemic mandelic acid and the corresponding amino alcohols according to method A. The resulting diastereoisomeric mandelamides were separated by silica gel column chromatography. The following mandelamides were thus prepared.

(R)-N-[(S)-2-*Hydroxy*-1-*methylethyl*]*mandelamide* (**7a**), 30% yield (method A); m.p. 53.5—54.5 °C (from ethyl acetate–n-hexane) (Found: C, 60.1; H, 7.4; N, 6.3. $C_{11}H_{16}NO_3 \cdot 0.5H_2O$ requires C, 60.55; H, 7.03; N, 6.42%); $\nu_{max.}$(KBr) 3 370 (OH), 3 240 (NH), and 1 660 cm^{-1} (CO); δ_H ($CDCL_3$ + [$^2H_4$]MeOH) 1.15 (d, *J* 7 Hz, 3 H, CH*Me*), 3.47 (d, *J* 5 Hz, 2 H, CH_2OH), 3.7—4.1 (m, 1 H, NCH), 4.34 (s, 3 H, D_2O-exchangeable, NH and OH), 4.98 (s, 1 H, C*H*OH), and 7.0—7.5 (m, 5 H, Ph); δ_C ($CDCl_3$ and [$^2H_4$]MeOH) 16.1 (q, Me), 46.5 (d, NCH), 64.8 (t, CH_2OH), 73.7 (d, CHOH), 126.5 (d, Ph), 127.7 (d, Ph), 128.0 (d, Ph), 139.5 (s, Ph), and 173.0 (s, CO).

(S)-N-[(S)-2-*Hydroxy*-1-*methylethyl*]*mandelamide* (**7b**), 42% yield (method B); m.p. 147—148 °C (from benzene) (Found: C, 63.05; H, 7.2; N, 6.5. $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.20; N, 6.54%); $\nu_{max.}$(KBr) 3 350 (NH or OH), 3 240 (OH or NH), and 1 660 (CO) cm^{-1}; δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 1.15 (d, *J* 6 Hz, 3 H, CH*Me*), 3.50 (m, 2 H, CH_2OH), 4.00 (m, 1 H, NCH), 4.60 (s, 3 H, D_2O-exchangeable, NH and OH), 5.02 (s, 1 H, C*H*OH), and 7.2—7.6 (m, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 16.0 (q, Me), 46.3 (d, NCH), 64.5 (t, CH_2OH), 73.6 (d, CHOH), 126.2 (d, Ph), 127.5 (d, Ph), 127.8 (d, Ph), 139.3 (s, Ph), and 173.0 (s, CO).

(R)-N-[(S)-1-*Benzyl*-2-*hydroxyethyl*]*mandelamide* (**8a**), 49% yield (method D); m.p. 96—98 °C (from benzene–n-hexane) (Found: C, 71.6; H, 6.7; N, 4.9. $C_{17}H_{19}NO_3$ requires C, 71.55; H, 6.71; N, 4.90%); $\nu_{max.}$(KBr) 3 350 (OH), 3 300 (NH), and 1 640 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 2.70 (d, *J* 7 Hz, 2 H, PhCH_2), 3.46 (br s, 2 H, CH_2OH), 4.06 (m, 1 H, NCH), 4.49 (br s, 1 H, NH or OH), 4.85 (s, 1 H, C*H*OH), and 6.7—7.3 (m, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 36.7 (t, PhCH_2), 52.8 (d, NCH), 63.5 (t, CH_2OH), 74.0 (d, CHOH), 126.5 (d, Ph), 126.8 (d, Ph), 128.5 (2 d, Ph), 128.6 (d, Ph), 129.1 (d, Ph), 137.1 (s, Ph), 139.2 (s, Ph), and 172.9 (s, CO).

(S)-N-[(S)-1-*Benzyl*-2-*hydroxyethyl*]*mandelamide* (**8b**), 22% yield (method D); m.p. 140—141 °C (from benzene) (Found: C, 71.3; H, 6.7; N, 4.9%); $\nu_{max.}$(KBr) 3 400 (OH), 3 320 (NH), and 1 650 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 2.5—3.1 (m, 2 H, PhCH_2), 3.59 (d, *J* 4 Hz, 2 H, CH_2OH), 4.1—4.3 (m, 1 H, NCH), 4.53 (s, 3 H, D_2O-exchangeable, NH and OH), 4.96 (s, 1 H, C*H*OH), and 7.20 (s, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 37.2 (t, PhCH_2), 52.4 (d, NCH), 63.5 (t, CH_2OH), 74.7 (d, CHOH), 126.7 (d, Ph), 127.2 (d, Ph), 128.3 (d, Ph), 128.6 (2 d, Ph), 129.5 (d, Ph), 138.1 (s, Ph), 140.0 (s, Ph), and 173.9 (s, CO).

(R)-N-[(S)-1-*Hydroxymethyl*-2-*methylpropyl*]*mandelamide* (**9a**), 19% yield (method D); m.p. 91.0—91.5 °C (from ethyl acetate–n-hexane) (Found: C, 65.7; H, 8.0; N, 5.7. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); $\nu_{max.}$(KBr) 3 380 (OH), 3 350 (NH), and 1 660 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 0.72 (d, *J* 7 Hz, 3 H, MeCH*Me*), 0.80 (d, *J* 7 Hz, 3H, *Me*CHMe), 1.5—1.9 (m, 1 H, C*H*Me_2), 3.48 (s, 2 H, CH_2OH), 3.2—3.9 (m, 1 H, NCH), 4.93 (s, 1 H, C*H*OH), and 7.29 (s, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH$_4$) 18.3 (q, MeCH*Me*), 19.4 (q, *Me*CHMe), 28.8 (d, CHMe_2), 57.0 (d, NCH), 62.9 (t, CH_2OH), 74.0 (d, CHOH), 126.8 (d, Ph), 128.6 (2 d, Ph), 139.6 (s, Ph), and 173.3 (s, CO).

(S)-N-[(S)-1-*Hydroxymethyl*-2-*methylpropyl*]*mandelamide* (**9b**), 12% yield (method D); m.p. 137.5—138.0 °C (from benzene) (Found: C, 65.7; H, 8.1; N, 5.9%); $\nu_{max.}$(KBr) 3 400 (OH), 3 300 (NH), and 1 660 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 0.86 (d, *J* 17 Hz, 3 H, MeCH*Me*), 0.91 (d, 3 H, *J* 7 Hz, 3 H, *Me*CHMe), 1.7—2.1 (m, 1 H, C*H*Me_2), 3.63 (s, 2 H, CH_2OH), 3.3—3.7 (m, 1 H, NCH), 4.30 (br s, 1 H, D_2O-exchangeable, NH or OH), 5.04 (s, 1 H, C*H*OH), and 7.1—7.5 (m, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 18.9 (q, MeCH*Me*), 20.0 (q, *Me*CHMe), 29.6 (d, CHMe_2), 56.9 (d, NCH), 63.1 (t, CH_2OH), 75.1 (d, CHOH), 127.2 (d, Ph), 128.8 (d, Ph), 129.0 (d, Ph), 140.0 (s, Ph), and 174.7 (s, CO).

(R)-N-[(S)-1-*Hydroxymethyl*-2-*methylpropyl*]-N-*methylmandelamide* (**10a**), 33% yield (method A); m.p. 73.5—74.5 °C (from ethyl acetate–n-hexane) (Found: C, 66.6; H, 8.4; N, 5.5. $C_{14}H_{21}NO_3$ requires C, 66.90; H, 8.42; N, 5.57%); $\nu_{max.}$(KBr) 3 380 (OH) and 1 640 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 0.59 (d, *J* 7 Hz, 3 H, MeCH*Me*), 0.91 (d, *J* 7 Hz, 3 H, *Me*CHMe), 1.4—1.9 (m, 1 H, C*H*Me_2), 2.62 (s, 3 H, NMe), 3.1—3.9 (m, 3 H, D_2O-exchangeable, CH_2OH and OH), 4.1—4.4 (m, 1 H, NCH), 5.00 (d, *J* 6 Hz, 1 H, D_2O-exchangeable, CHO*H*), 5.23 (d, *J* 6 Hz, 1 H, C*H*OH), and 7.33 (s, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH), 19.7 (q, MeCH*Me*), 19.9 (q, *Me*CHMe), 27.0 (d, CHMe_2), 29.5 (q, NMe), 60.9 (t, CH_2OH), 62.8 (d, NCH), 72.0 (d, CHOH), 127.8 (d, Ph), 128.5 (d, Ph), 128.8 (d, Ph), 138.8 (s, Ph), and 174.1 (s, CO).

(S)-N-[(S)-1-*Hydroxymethyl*-2-*methylpropyl*]-N-*methylmandelamide* (**10b**), 29% yield (method A); m.p. 84—85 °C (from benzene) (Found: C, 66.8; H, 8.4; N, 5.5%); $\nu_{max.}$(KBr) 3 400 (OH), 3 320 (OH), and 1 640 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH), 1.2—1.7 and 1.7—2.1 (each m, 0.5 H, together C*H*Me_2), 2.65 and 2.80 (each s, 1.5 H, together NMe), 3.0—4.2 (m, 4 H, NCH and CH_2OH), 4.91 and 5.11 (each d, *J* 6 Hz, 0.5 H, D_2O-exchangeable, together CHO*H*), 5.25 and 5.46 (each d, *J* 6 Hz, 0.5 H, together C*H*OH), and 7.34 (s, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 18.3 (q, MeCH*Me*), 19.9 (q, *Me*CHMe), 26.9 and 27.6 (each d, together CHMe_2), 31.2 (q, NMe), 60.2 (q, CH_2OH), 61.2 (t, CH_2OH), 63.6 and 64.6 (each d, together NCH), 71.7 and 72.2 (each d, together CHOH), 127.6 (d, Ph), 128.0 (d, Ph), 128.5 (d, Ph), 128.9 (2 d, Ph), 138.7 (s, Ph), 139.8 (s, Ph), 173.8 (s, CO), and 174.3 (s, CO).

(R)-N-[(S)-1-*Methoxymethyl*-2-*methylpropyl*]*mandelamide* (**11a**), 27% yield (method B); b.p. 140 °C/10^{-4} Torr (Found: C, 66.7; H, 8.55; N, 5.75%); $\nu_{max.}$(film) 3 440 (NH and OH) and 1 630 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 0.77 (d, *J* 7 Hz, 3 H, MeCH*Me*), 0.85 (d, *J* 7 Hz, 3 H, *Me*CHMe), 1.6—2.0 (m, 1 H, C*H*Me_2), 3.20 (s, 3 H, CH_2OMe), 3.2—3.5 (m, 2 H, CH_2OMe), 3.5—3.9 (m, 1 H, NCH), 4.77 (br s, 1 H, D_2O-exchangeable, NH or OH), 4.91 (s, 1 H, C*H*OH), and 7.31 (s, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 18.6 (q, MeCH*Me*), 19.5 (q, *Me*CHMe), 29.2 (d, CHMe_2), 54.1 (d, NCH), 58.8 (q, OMe), 72.4 (t, CH_2OH), 74.0 (d, CHOH), 126.8 (d, Ph), 128.2 (d, Ph), 128.5 (d, Ph), 140.1 (s, Ph), and 172.3 (s, CO).

(S)-N-[(S)-1-*Methoxymethyl*-2-*methylpropyl*]*mandelamide* (**11b**), 24% yield (method B); b.p. 140 °C/10^{-4} Torr (Found: C, 66.55; H, 8.5; N, 5.6%); $\nu_{max.}$(film) 3 400 (NH and OH) and 1 630 cm^{-1} (CO); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) 0.82 (d, *J* 7 Hz, 3 H, MeCH*Me*), 0.86 (d, *J* 7 Hz, 3 H, *Me*CHMe), 1.6—2.1 (m, 1 H, C*H*Me_2), 3.20 (s, 3 H, OMe), 3.2—3.5 (m, 2 H, CH_2OH), 3.5—3.9 (m, 1 H, NH), 4.50 br s, 1 H, NCH), 4.96 (s, 1 H, C*H*OH), and 7.1—7.5 (m, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 18.8 (q, MeCH*Me*), 19.5 (q, *Me*CHMe), 29.3 (d, CHMe_2), 54.0 (d, NCH), 58.9 (q, OMe), 72.4 (t, CH_2OMe), 74.2 (d, CHOH), 126.6 (d, Ph), 128.2 (d, Ph), 128.5 (d, Ph), 139.9 (s, Ph), and 172.2 (s, CO).

(RS)-N-[(S)-1-*Methoxymethyl*-2-*methylpropyl*]-N-*methylmandelamide* (**12**), 94% yield (method C); m.p. 77—78 °C (from benzene–n-hexane) (Found: C, 67.8; H, 8.7; N, 5.2. $C_{15}H_{23}NO_3$

requires C, 67.89; H, 8.73; N, 5.27%); δ_H ($CDCl_3$ + [$^2H_4$]MeOH) −0.07, 0.70, 0.87, and 0.98 (each d, *J* 7 Hz, 1.5 H, together $CHMe_2$), 1.6—2.2 (m, 1 H, $CHMe_2$), 2.59 and 2.82 (each s, 1.5 H, together NMe), 3.18 and 3.33 (each s, 1.5 H, together OMe), 3.4—3.8 (m, 2 H, CH_2O), 4.4—4.8 (m, 1 H, NCH), 4.82 and 5.00 (each d, *J* 6 Hz, 0.5 H, D_2O-exchangeable, CHO*H*), 5.21 and 5.29 (each d, *J* 6 Hz, 0.5 H, together C*H*OH), and 7.3—7.6 (m, 5 H, Ph); δ_C ($CDCl_3$ + [$^2H_4$]MeOH) 19.8 (2 q, $CHMe_2$), 26.5 and 27.0 (each d, together $CHMe_2$), 27.9 and 29.8 (each q, together NMe), 58.5 and 59.2 (each q, together OMe), 61.0 and 61.4 (each d, together NCH), 70.9 and 71.3 (each t, together CH_2O), 71.8 (d, CHO), 127.8 (d, Ph), 128.0 (d, Ph), 128.2 (d, Ph), 128.3 (d, Ph), 128.7 (d, Ph), 128.8 (d, Ph), 139.0 (s, Ph), 140.2 (s, Ph), 173.1 (s, CO), and 174.0 (s, CO).

H.p.l.c. Separations of Diastereoisomeric Mandelamides.—The separations were carried out on a Jasco Familic-100N high-pressure liquid chromatograph using a column (10 × 0.05 cm) packed with Nihon Bunko SS-05 (5 μm), and detected at 255 nm using a Jasco UVIDEC-100-II u.v. spectrometer. The eluants are shown in Table 1.

Hydrolysis of Mandelamide (**7**) *to Mandelic Acid.*—The mandelamide (**7**) (300 mg, 1.44 mmol) obtained by lithium aluminium hydride reduction of the benzoylformamide (**1**) in aqueous hydrochloric acid (8 ml) was heated at reflux for 24 h. The mixture was made alkaline with dil. sodium hydroxide, and extracted with dichloromethane to remove the resulting ethanolamine. The aqueous layer was made neutral with 6M-hydrochloric acid, and extracted with ether, and the extract was dried and evaporated. The crude mandelic acid was purified by silica gel column chromatography (eluant: chloroform–acetone–ethanol 100:50:10) (yield 137 mg, 63%), $[\alpha]_D$ +39.4° (*c* 1.07 in H_2O).

Europium Shifts of Mandelamide (**7**).—The diastereoisomeric excess of the mandelamide (**7**) obtained by lithium aluminium hydride reduction of the benzoylformamide (**1**) was determined by ^1H n.m.r. spectroscopy using Eu(fod)$_3$ by observing the methine proton of the mandelic acid moiety (16.3% d.e.).

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