Asymmetric Synthesis of (1*R*,1'*R*)- and (1*S*,1'*S*)-Bis(1-arylethyl)amines by way of a Diastereoselective Addition to Chiral Imines and Oxaxolidines with Organometallic Reagents

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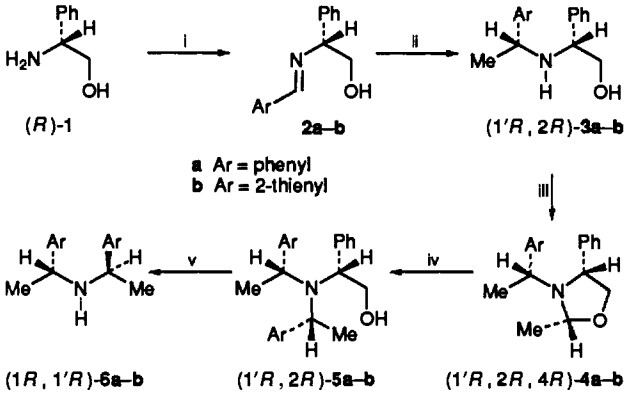
The asymmetric synthesis of the bis(α-methylbenzyl)amines, (1*R*,1'*R*)- and (1*S*,1'*S*)-bis(1-arylethyl)-amines **6**, utilizing a diastereoselective reaction of chiral imines and oxazolidines derived from (*R*)-phenylglycinol with organometallic reagents, is described.

Chiral imines and oxazolidines, which are readily synthesized by the condensation of chiral 2-aminoethanols or their *N*-alkylated counterparts [such as (*R*)-*N*-alkylphenylglycinol] with aldehydes,[1] react with various organometallic reagents in a highly diastereoselective manner, ultimately providing a route to chiral amines in both high chemical and optical yields.[2] We have already reported the application of such reactions to the asymmetric syntheses of two piperidine alkaloids, (*R*)-(−)-coniine and (2*R*,6*R*)-(+)-dihydropinidine,[3] and the indolizidine alkaloid (+)-monomorine I.[4]

As part of a programme aimed at increasing the synthetic utility of this reaction, we have accomplished the asymmetric synthesis of (1*R*,1'*R*)- and (1*S*,1'*S*)-bis(arylethyl)amines, which are useful as both chiral bases and auxiliaries for stereoselective syntheses.[5]

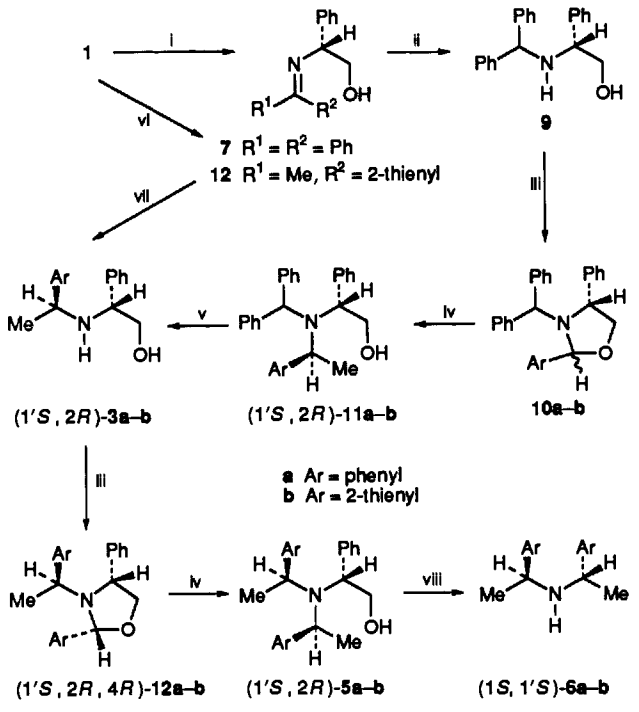


Scheme 1 *Reagents and conditions:* i, carbaldehyde, C_6H_6; ii, MeLi, THF, −55 °C; iii, acetaldehyde, $MgSO_4$, CH_2Cl_2; iv, Grignard reagent, THF, −58 °C; v, $Pb(OAc)_4$, C_6H_6

Results and Discussion

The starting chiral imines **2a–b** for the synthesis of the (1*R*,1'*R*)-bis(α-methylbenzyl)amines **6a–b** were prepared from the (*R*)-phenylglycinol **1** and either benzaldehyde or thiophene-2-carbaldehyde under azeotropic conditions. The reaction of these chiral imines **2a–b** with excess methyllithium in tetrahydrofuran at −55 °C, afforded pairs of the diastereoisomeric amino alcohol **3a–b** in 82 and 68% yields and in a ratio of 97:3 and 94:6, respectively.[2] After separation of the major isomers by silica gel column chromatography, compounds (1*R*,1'*R*)-**3a–b** were condensed with acetaldehyde in dichloromethane, in the presence of anhydrous magnesium sulfate, to give the desired oxazolidines **4a–b** in good yields. Treatment of the oxazolidine **4a** with phenylmagnesium bromide in tetrahydrofuran at −58 °C furnished the tertiary amino alcohol **5a** as a separable diastereoisomeric mixture, formed in a ratio of 76:24. Oxidative cleavage of the major isomer with lead tetraacetate provided the bis(α-methylbenzyl)amine (1*R*,1'*R*)-bis(1-phenylethyl)amine **6a** in 84% yield. The spectroscopic data for compound (1*R*,1'*R*)-**6a**, including the specific optical rotation, were identical with those already reported.[6] In a similar manner, the oxazolidine **6b** was treated with 2-thienylmagnesium bromide to give a diastereoisomeric mixture of compound **5b** in a ratio of 84:16. Although it was not possible to isolate the major product, the diastereoisomeric mixture of compound **5b** was readily converted into the secondary amine **6b** by oxidative cleavage. Further, the major isomer (1*R*,1'*R*)-**6b** could be isolated from the diastereoisomeric mixture by the preferential crystallization of its HCl salt.

Alternatively, the enantiomers (1*S*,1'*S*)-bis(1-arylethyl)-amines **6a–b** were synthesized as follows. Condensation of (*R*)-phenylglycinol **1** with benzophenone by heating in toluene with azeotropic removal of the water and the subsequent reduction of resulting imine **7** with lithium aluminium hydride afforded the (2*R*)-amino alcohol **9** in 60% yield over the two steps. This was then condensed with benzaldehyde dimethyl acetal or thiophene-2-carbaldehyde dimethyl acetal in the presence of 4-methylbenzenesulfonic acid in refluxing toluene to give the chiral oxazolidines **10a–b** as a crystalline solid. These products consisted mainly of the thermodynamic product;[7] the minor component amounted to less than 10% as judged from the ^1H NMR spectra. The reaction of compound **10a–b** with methylmagnesium bromide in tetrahydrofuran at room temperature furnished the tertiary amino alcohols **11a–b** as separable diastereoisomeric mixtures in 82 and 69% yields and in a ratio of 94:6 and 98:2, respectively. After separation of the major isomers, the removal of the *N*-diphenylmethyl group in the compounds (1*S*,1'*R*)-**11a–b** was performed by treatment with 15% hydrochloric acid in ethanol to afford the secondary amine (1'*S*,2*R*)-**3a** in 82% yield from **11a** but gave none of the desired product from compound **11b**. Although the above deprotection of compound **11** failed, the compound (1'*S*,2*R*)-**3b** was readily prepared by an alternate route. The imine **8**, prepared from (*R*)-phenylglycinol **1** and 2-acetylthiophene, was reduced with sodium bis(2-methoxyethyl)aluminium hydride (Red-Al) in toluene to give the secondary amino alcohol **11b** as a separable diastereoisomeric mixture in good yield and in a ratio of 97:3. The condensation of the major isomers (1'*S*,2*R*)-**3a–b** with the corresponding aldehyde dimethylacetal in toluene gave an inseparable diastereoisomeric mixture of the oxazolidines **12a–b**. Subsequent reaction with methylmagnesium bromide in refluxing tetrahydrofuran afforded the tertiary amines **5a–b** as a separable diastereoisomeric mixture in good yield and in a ratio of 95:5 and 98:2, respectively. Finally, oxidative cleavage of the major isomers (1'*S*,2*R*)-**15a–b** provided the (1*S*,1'*S*)-bis(1-arylethyl)amines **6a–b** in 84 and 72% yields.



Scheme 2 *Reagents and conditions:* i, benzophenone, 4-methylbenzenesulfonic acid, toluene; ii, $LiAlH_4$, THF; iii, aldehyde dimethyl acetal, 4-methylbenzenesulfonic acid, toluene; iv, MeMgBr, THF, room temp.; v, HCl–EtOH; vi, 2-acetylthiophene, 4-methylbenzenesulfonic acid, C_6H_6; vii, Red-Al, toluene, −58 °C; viii, $Pb(OAc)_4$, C_6H_6

Thus, we achieved the asymmetric synthesis of the bis(α-methylbenzyl)amines, (1*R*,1'*R*)- and (1*S*,1'*S*)-bis(1-arylethyl)-amines **6a–b**, by employing the diastereoselective reaction of chiral imines and oxazolidines derived from a single enantiomeric source.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto-Micro Melting Point apparatus and are uncorrected. IR spectra were recorded on a 215 Hitachi Grating I.R. spectrophotometer. ^1H NMR spectra were obtained on a JEOL PMX 270 instrument, and chemical shifts are reported in ppm on the δ scale using tetramethylsilane as the internal reference. Mass spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization (CI) (isobutane) method. Optical rotations were taken with a JASCO-DIP-370 polarimeter.

Condensation of (R)-*Phenylglycinol* **1** *with an Aldehyde.*—A mixture of phenylglycinol (*R*)-**1** (10.0 g, 72.9 mmol) and an aldehyde [benzaldehyde and thiophene-2-carbaldehyde (73.0 mmol)] in benzene (50 cm^3) was refluxed for 3 h using a Dean–Stark apparatus. After cooling, the reaction mixture was concentrated under reduced pressure to leave a crystalline residue, which was purified by recrystallization from hexane to give the imines **2a–b** as crystals.

(2R)-(E)-2-(*Benzylideneamino*)-2-*phenylethanol* **2a**.—Colourless prisms; yield 94%; m.p. 78 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +48.8 (*c* 1.07, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400 (OH) and 1640 (C=N); δ_H(270 MHz; $CDCl_3$) 2.03 (1 H, br s, OH), 3.90 (1 H, dd, *J* 7.9 and 11.0, C*H*$_2$OH), 3.97 (1 H, dd, *J* 4.3 and 11.0, C*H*$_2$OH), 4.50 (1 H, dd, *J* 4.3 and 7.9, PhCHN), 7.24–7.82 (10 H, m, aromatic H) and 8.40 (1 H, s, N=CH); whose spectral data were identical with those of an authentic specimen.[2]

(2R)-(E)-2-*Phenyl*-2-(2-*thienylmethylideneamino*)*ethanol* **2b**.—Yellowish prisms; yield 98%; m.p. 101 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +150.5 (*c* 1.00, $CHCl_3$) (Found: C, 67.4; H, 5.7; N, 6.2. Calc. for $C_{13}H_{13}NOS$: C, 67.52; H, 5.67; N, 6.06%); ν_{max}(film)/cm^{-1} 3400 (OH) and 1620 (C=N); δ_H(270 MHz; $CDCl_3$) 2.39 (1 H, br s, OH), 3.83–3.99 (2 H, m, C*H*$_2$OH), 4.47 (1 H, dd, *J* 4.3 and 8.8, PhCHN), 7.05 (1 H, dd, *J* 3.7 and 4.9, aromatic H), 7.25–7.42 (7 H, m, aromatic H) and 8.44 (1 H, s, N=CH); *m*/*z* (EI) 200 (M^+ − CH_2OH).

Reaction of the Imines (R)-**2a–b** *with Methyllithium.*—Methyllithium (133.2 mmol; 0.8 mol dm^{-3} solution in diethyl ether) was added dropwise at −55 °C to a stirred solution of one of the imines (**2a–b**) (10.0 g, 44.4 mmol) in dry THF (500 cm^3) under nitrogen, over a 50 min period. After the reaction mixture had been stirred at room temperature for 15 h, it was quenched with saturated NH_4Cl (200 cm^3) and then extracted with ethyl acetate (3 × 100 cm^3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave a pale yellow oil, which was subjected to column chromatography on silica gel with MeOH–CH_2Cl_2 (1 : 20) to give a diastereoisomeric mixture of the amine (**2a** or **2b**).

(1'R,2R)-2-*Phenyl*-2-[N-(1'-*phenylethyl*)*amino*]*ethanol* **3a**. Colourless oil; yield 82%; ^1H NMR analysis of the crude product indicated a 97 : 3 ratio of diastereoisomers, which were separated by column chromatography. For the (1'*R*,2*R*)-isomer (major product); colourless needles; yield 52%; m.p. 48 °C (from diethyl ether); $[\alpha]_D^{25}$ −27.8 (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400 (OH); δ_H(270 MHz; $CDCl_3$) 1.37 (3 H, d, *J* 6.7, CH*Me*), 2.58 (2 H, br s, OH and NH), 3.51 (1 H, dd, *J* 4.9 and 10.4, C*H*$_2$OH), 3.74 (1 H, dd, *J* 7.9 and 10.4, C*H*$_2$OH), 3.88 (1 H, q, *J* 6.7, C*H*Me), 3.97 (1 H, dd, *J* 4.9 and 7.9, PhCHN) and 7.13–7.38 (10 H, m, aromatic H); *m*/*z* (CI, isobutane) 242 (M^+ + 1); whose spectral data were identical with those of an authentic specimen.[16]

(1'R,2R)-2-{N-[1'-(2-*Thienyl*)*ethyl*]*amino*}-2-*phenylethanol* **3b**. Pale yellow oil; yield 68%; ^1H NMR analysis of the crude product indicated a 96 : 4 ratio of diastereoisomers, which were separated by column chromatography. For the (2R,1'R)-isomer (major product); pale yellow oil; yield 51%; $[\alpha]_D^{25}$ −20.0 (*c* 1.13, $CHCl_3$) (Found: C, 68.2; H, 6.9; N, 5.9. Calc. for $C_{14}H_{17}NOS$: C, 67.99; H, 6.93; N, 5.66%); ν_{max}(film)/cm^{-1} 3400 (OH); δ_H(270 MHz; $CDCl_3$) 1.45 (3 H, d, *J* 6.7, CH*Me*), 2.27 (2 H, br s, OH and NH), 3.55 (1 H, dd, *J* 4.9 and 10.4, C*H*$_2$OH), 3.69 (1 H, dd, *J* 7.9 and 10.4, C*H*$_2$OH), 3.74 (1 H, dd, *J* 4.9 and 7.9, PhC*H*N), 4.05 (1 H, q, *J* 6.7, C*H*Me), 6.84 (1 H, d, *J* 3.7, aromatic H), 6.87 (1 H, dd, *J* 3.7 and 4.9, aromatic H), 7.17 (1 H, m, aromatic H) and 7.25–7.37 (5 H, m, aromatic H); *m*/*z* (CI, isobutane) 248 (M^+ + 1).

Condensation of the (2R,1'R)-*Amino Alcohols* **3a–b** *with Acetaldehyde.*—To a solution of amine **3a–b** (3.23 mmol) in dry CH_2Cl_2 (30 cm^3) in the presence of anhydrous $MgSO_4$ (2.0 g) was added dropwise a solution of acetaldehyde (0.45 g, 9.76 mmol) in dry CH_2Cl_2 (5 cm^3) over a 10 min period at 0 °C. After the reaction mixture had been stirred for 20 h at room temperature, it was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude oxazolidine **4a–b** was obtained and purified by column chromatography on silica gel with hexane–ethyl acetate (6 : 1).

(1'R,2R,4R)-2-*Methyl*-4-*phenyl*-N-(1'-*phenylethyl*)*oxazolidine* **4a**. Pale yellow oil; yield 78%. An analytical sample was purified by Kugelrohr distillation; oven temperature 170 °C (2.0 mmHg); $[\alpha]_D^{25}$ −100 (*c* 1.10, EtOH) (Found: C, 80.6; H, 8.0; N, 5.2. Calc. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%); δ_H(270 MHz; $CDCl_3$) 1.30 (3 H, d, *J* 5.5, CH*Me*), 1.34 (3 H, d, *J* 7.3, PhCH*Me*), 3.72 (1 H, dd, *J* 5.5, 7.9, CH_2O), 3.97 (1 H, q, *J*

7.3, PhC*H*Me), 4.03 (2 H, m, PhC*H*C*H*$_2$O), 4.73 (1 H, q, *J* 5.5, C*H*Me) and 7.23–7.37 (10 H, m, aromatic H); *m*/*z* (CI, isobutane) 268 ($M^+ + 1$).

(1′R,2R,4R)-2-*Methyl*-4-*phenyl*-N-[1′-(2-*thienyl*)*ethyl*]*oxazolidine* **4b**. Yellow oil; yield 74%. An analytical sample was purified by Kugelrohr distillation; oven temperature 200 °C (7.0 mmHg); $[\alpha]_D^{25}$ −90.7 (*c* 1.40, EtOH) (Found: C, 70.4; H, 7.1; N, 5.1. Calc. for $C_{16}H_{19}NOS$: C, 70.31; H, 7.01; N, 5.13%); δ_H(270 MHz; $CDCl_3$) 1.32 (3 H, d, *J* 5.5, CH*Me*), 1.37 (3 H, d, *J* 7.3, NCH*Me*), 3.71 (1 H, dd, *J* 5.5 and 7.9, CH_2O), 4.00 (1 H, t, *J* 7.9, PhC*H*CH_2O), 4.21 (1 H, dd, *J* 7.9 and 5.5, PhC*H*CH_2O), 4.22 (1 H, q, *J* 7.3, NC*H*Me), 4.72 (1 H, q, *J* 5.5, C*H*Me), 6.87 (1 H, d, *J* 3.7, aromatic H), 6.93 (1 H, dd, *J* 3.7 and 4.9, aromatic H) and 7.20–7.4 (6 H, m, aromatic H); *m*/*z* (CI, isobutane) 274 ($M^+ + 1$).

Reaction of the Oxazolidines **4a–b** *with Grignard Reagents*.—The Grignard reagent [C_6H_5MgBr or C_4H_3SMgBr (12.3 mmol)] was added dropwise at −58 °C to a solution of the oxazolidine **5a–b** (4.4 mmol) in dry THF (40 cm^3), under nitrogen, over a 10 min period. The resulting mixture was warmed up to room temperature, stirred for 20 h, then quenched with saturated NH_4Cl (20 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave the residue, which was subjected to column chromatography on silica gel with hexane–ethyl acetate (6 : 1) to give a diastereoisomeric mixture of the amino alcohol **5a–b** as an oil.

(1′R,2R)-2-*Phenyl*-2-[N-*bis*(1′-*phenylethyl*)*amino*]*ethanol* **5a**. Pale yellow oil; yield 72%. ^1H NMR analysis of the crude product indicated a 76 : 24 ratio of diastereoisomers, which were separated by column chromatography. For the (1′*R*,2*R*)-isomer (major product); pale yellow oil; yield 52%; $[\alpha]_D^{25}$ +7.2 (*c* 1.13, EtOH) (Found: C, 83.5; H, 7.9; N, 3.9. Calc. for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05%); δ_H(270 MHz; $CDCl_3$) 1.36 (6 H, d, *J* 7.3, CH*Me*), 1.54 (1 H, br s, OH), 3.40 (1 H, dd, *J* 5.5 and 11.0, CH_2OH), 3.87 (1 H, dd, *J* 7.2 and 11.0, CH_2OH), 4.04 (1 H, dd, *J* 5.5 and 9.2, PhC*H*N), 4.36 (2 H, q, *J* 7.3, C*H*Me) and 7.10–7.53 (15 H, m, aromatic H); *m*/*z* (CI, isobutane) 346 ($M^+ + 1$).

(1′R,2R)-2-*Phenyl*-2-{N-*bis*[1′-(2-*thienyl*)*ethyl*]*amino*}*ethanol* **5b**. Yellowish oil; yield 53%. ^1H NMR analysis of the crude product indicated a 84 : 16 ratio of diastereoisomers, which were inseparable by column chromatography (Found: C, 67.1; H, 6.7; N, 3.7. Calc. for $C_{20}H_{23}NOS_2$: C, 67.21; H, 6.49; N, 3.92%). For the (1′*R*,2*R*)-isomer (major product); δ_H(270 MHz; $CDCl_3$) 1.46 (6 H, d, *J* 6.7, CH*Me*), 1.71 (1 H, br s, OH), 3.53 (1 H, dd, *J* 7.9 and 11.0, CH_2OH), 3.91 (1 H, dd, *J* 6.1 and 11.0, CH_2OH), 4.14 (1 H, dd, *J* 6.1 and 7.9, PhC*H*H), 4.55 (2 H, q, *J* 6.7, C*H*Me), 6.87–6.93 (4 H, m, aromatic H) and 7.20–7.53 (7 H, m, aromatic H); *m*/*z* (CI, isobutane) 358 ($M^+ + 1$).

Oxidation of the Amino Alcohols **5a–b** *with Lead Tetraacetate*.—To a stirred solution of the amino alcohol **5a–b** (0.87 mmol) in benzene (20 cm^3) was added lead tetraacetate (0.77 g, 1.74 mmol) in one portion and the mixture was stirred for 4 h at room temperature. After treatment with diluted hydrochloric acid (3 cm^3), the reaction mixture was basified with saturated K_2CO_3 solution and extracted with benzene (3 × 10 cm^3). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel with hexane–diethyl ether (3 : 1–6 : 1) to give the amine **6a–b**.

(1R,1′R)-*Bis*(1-*phenylethyl*)*amine* **6a**. Colourless oil; yield 84%. An analytical sample was purified by Kugelrohr distillation; oven temperature 160 °C (7.0 mmHg); $[\alpha]_D^{25}$ +158 (*c* 3.30, EtOH) {lit.,[6] (1*S*,1′*S*)-**6a**; $[\alpha]_D^{25}$ −157 (*c* 2.40, EtOH)}. δ_H(270 MHz; $CDCl_3$) 1.26 (6 H, d, *J* 6.7, CH*Me*), 1.60 (1 H, br s, NH), 3.50 (2 H, q, *J* 6.7, C*H*Me) and 7.20–7.35 (10 H, m, aromatic H); *m*/*z* (CI, isobutane) 226 ($M^+ + 1$); whose spectral data were identical with those reported.[6]

(1R,1′R)-*Bis*[1-(2-*thienyl*)*ethyl*]*amine* **6b**. Colourless oil; yield 75%. ^1H NMR analysis of the crude product indicated a 84 : 16 ratio of diastereoisomers, which were inseparable by column chromatography. An analytical sample was purified by Kugelrohr distillation; oven temperature 130 °C (7.0 mmHg) (Found: C, 60.7; H, 6.4; N, 5.9. Calc. for $C_{12}H_{15}NS_2$: C, 60.75; H, 6.37; N, 5.90%). For the (1*R*,1′*R*)-isomer (major product); δ_H(270 MHz; $CDCl_3$) 1.39 (6 H, d, *J* 6.7, CH*Me*), 2.04 (1 H, br s, NH), 4.00 (2 H, q, *J* 6.7, C*H*Me), 6.84 (2 H, d, *J* 3.1, aromatic H), 6.95 (1 H, dd, *J* 3.1 and 4.9, aromatic H) and 7.21 (2 H, d, *J* 4.9, aromatic H); *m*/*z* (CI, isobutane) 238 ($M^+ + 1$). For the (1*R*,1′*S*)-isomer (minor product); δ_H(270 MHz; $CDCl_3$) 1.46 (6 H, d, *J* 6.7, CH*Me*), 2.04 (1 H, br s, NH) and 4.14 (2 H, q, *J* 6.7, C*H*Me); the (1*R*,1′*R*)-isomer could be obtained in a pure form by recrystallization of its HCl salt: colourless needles; m.p. 192 °C (from ethyl acetate–hexane); $[\alpha]_D^{25}$ +46.5 (*c* 1.00, EtOH).

(2R)-2-[N-(*Diphenylmethylidene*)*amino*]-2-*phenylethanol* **7**.—A mixture of phenylglycinol (*R*)-1 (20.0 g, 145.8 mmol), benzophenone (26.6 g, 146.0 mmol) and 4-methylbenzenesulfonic acid (1.0 g, 5.8 mmol) in toluene (300 cm^3) was refluxed for 40 h using a Dean–Stark apparatus. After cooling, the mixture was poured into 200 cm^3 of saturated aqueous $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with C_6H_6 (2 × 50 cm^3). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was crystallized to afford the imine **7** (26.36 g, 60%) as colourless needles, m.p. 125–126 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{25}$ −27.61 (*c* 1.03, $CHCl_3$) (Found: C, 83.7; H, 6.3; N, 4.6. Calc. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65%); ν_{max}(film)/cm^{-1} 3460 (OH) and 1660 (C=N); imine component; δ_H(270 MHz; $CDCl_3$) 2.00 (1 H, br s, OH), 3.81 (1 H, dd, *J* 4.3 and 10.4, CH_2OH), 3.98 (1 H, dd, *J* 7.6 and 10.4, CH_2OH), 4.56 (1 H, dd, *J* 4.3 and 7.6, PhC*H*N) and 7.02–7.75 (15 H, m, aromatic H); oxazolidine component; δ_H(270 MHz; $CDCl_3$) 2.00 (1 H, br s, NH), 3.87 (1 H, t, *J* 7.3, PhC*H*N), 4.24 (1 H, t, *J* 7.3, CH_2OH), 4.38 (1 H, t, *J* 7.3, CH_2OH) and 7.02–7.75 (15 H, m, aromatic H); *m*/*z* (CI, isobutane) 302 ($M^+ + 1$).

(2R)-2-(*Diphenylmethyl*)*amino*-2-*phenylethanol* **9**.—To a suspension of lithium aluminium hydride (4.5 g, 118.58 mmol) in dry THF (200 cm^3) at room temperature was added dropwise a solution of the imine **7** (25.0 g, 82.41 mmol) in THF (100 cm^3) over a 20 min period. The reaction mixture was refluxed for 2.5 h after which the excess hydride was decomposed by the slow addition of water (10 cm^3) and the mixture was filtered through a little Celite. Evaporation of the filtrate gave a colourless oil, which was distilled to give the amino alcohol **9** (24.9 g, 99%) as a colourless, viscous oil, b.p. 274 °C (1.1 mmHg); ν_{max}(film)/cm^{-1} 3500 (OH); $[\alpha]_D^{25}$ −74.58 (*c* 3.90, $CHCl_3$) (Found: C, 83.3; H, 6.9; N, 4.6. Calc. for $C_{21}H_{21}NO$: C, 83.15; H, 6.98; N, 4.62%); δ_H(270 MHz; $CDCl_3$) 2.38 (2 H, br s, OH and NH), 3.58 (1 H, dd, *J* 8.5 and 10.4, CH_2OH), 3.66 (1 H, dd, *J* 4.3 and 10.4, CH_2OH), 3.72 (1 H, dd, *J* 4.3 and 8.5, PhC*H*N), 4.71 (1 H, s, Ph_2CH) and 7.15–7.39 (15 H, m, aromatic H); *m*/*z* (CI, isobutane) 304 ($M^+ + 1$).

Condensation of (2R)-N-(*Diphenylmethyl*)-2-*phenylglycinol* **9** *with Carbaldehyde Dimethyl Acetals*.—A mixture of an aromatic aldehyde dimethyl acetal [benzaldehyde dimethyl acetal or thiophene-2-carbaldehyde dimethyl acetal (66.0

mmol)], the amino alcohol (*R*)-**8** (16.7 g, 55.0 mmol) and a catalytic amount of 4-methylbenzenesulfonic acid in toluene (150 cm^3) was refluxed for 48 h. After being cooled, the reaction mixture was poured into saturated aqueous $NaHCO_3$, the phases were separated, and the aqueous phase was extracted with C_6H_5 (2 × 30 cm^3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave a crystalline residue, which was purified by recrystallization to give a diastereoisomeric mixture of the oxazolidine **10a–b**.

(2R,4R)-2,4-*Diphenyl*-N-(*diphenylmethyl*)*oxazolidine* **10a**. Colourless needles; yield 72%; m.p. 130 °C (from CH_2Cl_2–hexane). ^1H NMR analysis of the crude product indicated a 89:11 ratio of diastereoisomers, which were inseparable by column chromatography; $[\alpha]_D^{25}$ −13.54 (*c* 1.00, $CHCl_3$) (Found: C, 86.0; H, 6.4; N, 3.5. Calc. for $C_{28}H_{25}NO$: C, 85.90; H, 6.44; N, 3.85%). For the (2*R*,4*R*)-isomer (major product); δ_H(270 MHz; $CDCl_3$) 3.90 (1 H, dd, *J* 6.1 and 8.5, CH_2O), 4.22 (1 H, dd, *J* 6.1 and 7.3, PhC*H*CH_2O), 4.32 (1 H, dd, *J* 7.3 and 8.5, CH_2O), 5.11 (1 H, s, Ph_2CH), 5.61 (1 H, s, NCHO) and 7.01–7.45 (20 H, m, aromatic H); *m*/*z* (CI, isobutane) 392 (M^+ + 1).

(2R,4R)-4-*Phenyl*-N-(*diphenylmethyl*)-2-(2-*thienyl*)*oxazolidine* **10b**. Colourless prisms; yield 73%; m.p. 129 °C (from EtOH). ^1H NMR analysis of the crude product indicated a 90:10 ratio of diastereoisomers, which were inseparable by column chromatography. $[\alpha]_D^{25}$ −8.83 (*c* 1.20, $CHCl_3$) (Found: C, 78.5; H, 5.8; N, 3.6. Calc. for $C_{26}H_{23}NOS$: C, 78.57; H, 5.83; N, 3.58%). For the (2*R*,4*R*)-isomer (major product); δ_H(270 MHz; $CDCl_3$) 3.96 (1 H, dd, *J* 7.3 and 8.5, CH_2O), 4.22 (1 H, t, *J* 7.3, PhC*H*CH_2O), 4.34 (1 H, dd, *J* 7.3 and 8.5, CH_2O), 5.12 (1 H, s, Ph_2CH), 5.91 (1 H, s, NCHO) and 7.02–7.47 (16 H, m, aromatic H); *m*/*z* (CI, isobutane) 398 (M^+ + 1).

Reaction of the Oxazolidines (2R,4R)-**10a–b** *with Methylmagnesium Bromide*.—Methylmagnesium bromide (15.3 mmol; 3 mol dm^{-3} solution in diethyl ether) was added dropwise to a stirred solution of the oxazolidine **10a–b** (7.6 mmol) in dry THF (50 cm^3) at room temperature and under nitrogen, over a 10 min period. After the reaction mixture had been stirred at 40 °C for 6 days, it was quenched with water (3 cm^3) and diluted with diethyl ether (20 cm^3). The resulting white precipitate was filtered off, and the filtrate was washed with saturated aqueous NH_4Cl (20 cm^3). The phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 30 cm^3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave an oily residue, which was subjected to column chromatography on silica gel with diethyl ether–hexane (2:1) to give a diastereoisomeric mixture of the amino alcohol **11a–b** as an oil.

(1′R,2S)- *And* (1′S,2R)-2-[N-(1′-*phenylethyl*)-N-(*diphenylmethyl*)*amino*]-2-*phenylethanol* **11a**. ^1H NMR analysis of the crude product indicated a 6:94 ratio of diastereoisomers, which were separated by column chromatography. For the isomer (1′*S*,2*R*)-**11a** (major product); colourless oil; yield 82%; $[\alpha]_D^{25}$ −35.80 (*c* 1.17, $CHCl_3$) (Found: M^+, 407.2241. Calc. for $C_{29}H_{29}NO$: *M*, 407.2247); δ_H(270 MHz; $CDCl_3$) 1.46 (3 H, d, *J* 6.7, CH*Me*), 1.78 (1 H, br s, OH), 3.94 (2 H, m, CH_2OH), 4.41 (1 H, t, *J* 7.9, PhC*H*CH_2OH), 4.46 (1 H, q, *J* 6.7, C*H*Me), 5.28 (1 H, s, Ph_2CH) and 6.82–7.36 (20 H, m, aromatic H); *m*/*z* (CI, isobutane) 408 (M^+ + 1). For the isomer (1′*R*,2*R*)-**11a** (minor product); colourless needles; yield 3%; m.p. 132 °C (from hexane–ethyl acetate); $[\alpha]_D^{25}$ +63.44 (*c* 1.04, $CHCl_3$) (Found: C, 85.3; H, 7.1; N, 3.4. Calc. for $C_{29}H_{29}NO$: C, 85.46; H, 7.17; N, 3.44%); δ_H(270 MHz; $CDCl_3$) 1.01 (3 H, d, *J* 6.7, CH*Me*), 2.09–2.13 (1 H, m, OH), 3.68–3.77 (1 H, m, CH_2OH), 3.93–4.02 (1 H, m, CH_2OH), 4.35–4.46 (2 H, m, PhC*H*CH_2OH and C*H*Me), 5.18 (1 H, s, Ph_2CH) and 7.00–7.39 (20 H, m, aromatic H); *m*/*z* (CI, isobutane) 408 (M^+ + 1).

(1′R,2R)- *And* (1′S,2R)-2-{N-(*diphenylmethyl*)-N-[1′-(2-*thienyl*)*ethyl*]*amino*}-2-*phenylethanol* **11b**. ^1H NMR analysis of the crude product indicated a 2:98 ratio of diastereoisomers, which were separated by column chromatography. For the isomer (1′*S*,2*R*)-**10b** (major product); colourless oil; yield 69%; $[\alpha]_D^{25}$ −16.62 (*c* 1.42, $CHCl_3$) (Found: C, 78.7; H, 6.6; N, 3.7. Calc. for $C_{27}H_{27}NOS$: C, 78.42; H, 6.58; N, 3.39%); δ_H(270 MHz; $CDCl_3$) 1.56 (3 H, d, *J* 7.3, CH*Me*), 1.79 (1 H, br s, OH), 3.99 (2 H, m, CH_2OH), 4.41 (1 H, t, *J* 7.9, PhC*H*CH_2OH), 4.71 (1 H, q, *J* 7.3, C*H*Me), 5.20 (1 H, s, Ph_2CH), 6.40 (1 H, d, *J* 3.7, aromatic H), 6.79–6.84 (3 H, m, aromatic H) and 7.16–7.39 (14 H, m, aromatic H); *m*/*z* (CI, isobutane) 414 (M^+ + 1). For the isomer (1′*R*,2*R*)-**10b** (minor product); colourless needles; yield 1.4%; m.p. 115 °C (from hexane–ethyl acetate); δ_H(270 MHz; $CDCl_3$) 1.02 (3 H, d, *J* 6.7, CH*Me*), 2.09 (1 H, br s, OH), 3.65–3.78 (1 H, m, CH_2OH), 3.98–4.07 (1 H, m, CH_2OH), 4.36 (1 H, t, *J* 7.3, PhC*H*CH_2OH), 4.62 (1 H, q, *J* 6.7, C*H*Me), 5.21 (1 H, s, Ph_2CH), 6.47 (1 H, d, *J* 3.7, aromatic H), 6.76 (1 H, dd, *J* 3.7 and 4.9, aromatic H) and 7.02–7.40 (16 H, m, aromatic H); *m*/*z* (CI, isobutane) 414 (M^+ + 1).

(1′S,2R)-2-*Phenyl*-2-[*N*-(1′-*phenylethyl*)*amino*]*ethanol* **3a**.—A solution of the isomer (1′*S*,2*R*)-**11a** (1.9 g, 4.7 mmol) in concentrated hydrochloric acid–ethanol (1:2; 60 cm^3) was heated under reflux for 3 h. After being cooled to room temperature, the reaction mixture was diluted with water (50 cm^3) and washed with diethyl ether (20 cm^3). The resulting aqueous phase was basified with 20% NaOH solution and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave an oily residue, which was subjected to column chromatography on silica gel with CH_2Cl_2–MeOH (99:1) to give the (1′S,2R)-isomer **3a** (0.91 g, 82%) as colourless prisms; m.p. 75 °C (from ethyl acetate–hexane); $[\alpha]_D^{25}$ −182.0 (*c* 1.02, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.32 (3 H, d, *J* 6.7, CH*Me*), 2.21 (1 H, br s, OH), 3.45–3.60 (3 H, m, PhC*H*CH_2OH), 3.63 (1 H, q, *J* 6.7, C*H*Me) and 7.17–7.39 (10 H, m, aromatic H); *m*/*z* (CI, isobutane) 242 (M^+ + 1); whose spectral data were identical with those reported.[6]

(1′S,2R)-2-*Phenyl*-2-{N-[1′-(2-*thienyl*)*ethyl*]*amino*}*ethanol* **3b**.—A mixture of phenylglycinol (*R*)-**1** (6.86 g, 50 mmol), 2-acetylthiophene (6.93 g, 55 mmol) and a catalytic amount of 4-methylbenzenesulfonic acid in benzene (50 cm^3) was refluxed for 20 h using a Dean–Stark apparatus. After being cooled, the mixture was poured into saturated aqueous Na_2CO_3 (20 cm^3), the organic layer was separated and the aqueous layer was extracted with C_6H_6 (2 × 10 cm^3). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave an oily residue, which was purified by Kugelrohr distillation to give the imine **8** (11.77 g, 96%) as a yellowish oil, oven temperature 130 °C (4.0 mmHg); $[\alpha]_D^{25}$ +145.78 (*c* 5.60, $CHCl_3$) (Found: C, 68.4; H, 6.3; N, 5.8. Calc. for $C_{14}H_{15}NOS$: C, 68.55; H, 6.16; N, 5.71%); δ_H(270 MHz; $CDCl_3$) 2.13 (3 H, s, Me), 2.36 (1 H, br s, OH), 3.76–4.16 (3 H, m, PhC*H*CH_2OH), 6.91 (1 H, m, aromatic H), 6.98 (1 H, m, aromatic H) and 7.15–7.32 (6 H, m, aromatic H); *m*/*z* (CI, isobutane) 246 (M^+ + 1). Red-Al (26.2 mmol; 3.4 mol dm^{-3} solution in toluene) was then added dropwise to a stirred solution of the imine **8** (4.0 g, 16.3 mmol) in toluene (50 cm^3) at −58 °C under a nitrogen atmosphere. After being stirred for 20 h at room temperature, the reaction mixture was treated with water (5 cm^3). The resulting white precipitate was filtered off, and the filtrate was concentrated under reduced pressure to leave the amino alcohol **3b** as a yellowish oil. ^1H NMR analysis of the crude product indicated a 97:3 ratio of diastereoisomers, which were separated by column chromatography on silica gel with diethyl ether–hexane (2:1). For the isomer (1′*S*,2*R*)-**3b**

(major product); colourless plates; yield 77%; m.p. 62 °C (from hexane); $[\alpha]_D^{25}$ −166.92 (*c* 1.03, $CHCl_3$) (Found: C, 68.0; H, 7.0; N, 5.7. Calc. for $C_{14}H_{17}NOS$: C, 67.99; H, 6.93; N, 5.66%); δ_H(270 MHz; $CDCl_3$) 1.45 (3 H, d, *J* 6.1, CH*Me*), 1.63 (1 H, br s, OH), 3.51 (1 H, dd, *J* 4.3 and 10.4, CH_2OH), 3.62 (1 H, dd, *J* 9.2 and 10.4, CH_2OH), 3.70 (1 H, dd, *J* 4.3 and 9.2, PhC*H*CH$_2$OH), 3.98 (1 H, q, *J* 6.1, C*H*Me), 6.80 (1 H, m, aromatic H), 6.93 (1 H, m, aromatic H) and 7.25–7.34 (6 H, m, aromatic H); *m*/*z* (CI, isobutane) 248 (M^+ + 1).

Condensation of the Amino Alcohol **3a–b** *with Aldehyde Dimethyl Acetals*.—The reaction was carried out by using the amino alcohol (1′*S*,2*R*)-**3a–b** (3.81 mmol), an aromatic aldehyde dimethyl acetal [benzaldehyde dimethyl acetal, thiophene-2-carbaldehyde dimethyl acetal (11.43 mmol)] and catalytic amount of 4-methylbenzenesulfonic acid in toluene (30 cm^3). Work up as previously described for compounds **10a–b**, gave an oily product **12a–b** which was purified by column chromatography on silica gel with hexane–ethyl acetate (4:1).

(1′S,2R,4R)-2,4-*Diphenyl*-N-(1′-*phenylethyl*)*oxazolidine* **12a**. Colourless oil; yield 72%. ^{1}H NMR analysis of the crude product indicated a 92:8 ratio of diastereoisomers, which were inseparable by column chromatography. An analytical sample was purified by Kugelrohr distillation; oven temperature 220 °C (7.0 mmHg); $[\alpha]_D^{25}$ +18.32 (*c* 1.10, EtOH) (Found: C, 83.8; H, 7.0; N, 4.3. Calc. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25%); δ_H(270 MHz; $CDCl_3$); for the (1′*S*,2*R*,4*R*)-isomer (major product); 1.18 (3 H, d, *J* 6.7, CHMe), 3.78 (1 H, t, *J* 7.9, CH_2O), 4.01 (1 H, q, *J* 6.7, C*H*Me), 4.01–4.20 (2 H, m, PhC*H*C*H*$_2$O), 5.34 (1 H, s, NCHO), 7.11–7.40 (12 H, m, aromatic H) and 7.53–7.62 (3 H, m, aromatic H); *m*/*z* (CI, isobutane) 330 (M^+ + 1).

(1′S,2R,4R)-4-*Phenyl*-2-(2-*thienyl*)-N-[1′-(2-*thienyl*)*ethyl*]-*oxazolidine* **12b**. Colourless oil; yield 72%. ^{1}H NMR analysis of the crude product indicated a 97:3 ratio of diastereoisomers, which were inseparable by column chromatography. An analytical sample was purified by Kugelrohr distillation; oven temperature 260 °C (7.0 mmHg); $[\alpha]_D^{25}$ +11.20 (*c* 2.09, EtOH) (Found: C, 67.0; H, 5.8; N, 4.0. Calc. for $C_{19}H_{19}NOS_2$: C, 66.85; H, 5.61; N, 4.10%); δ_H(270 MHz; $CDCl_3$); for the (1′*S*,2*R*,4*R*)-isomer (major product); 1.35 (3 H, d, *J* 6.7, CH*Me*), 3.80 (1 H, dd, *J* 8.5 and 9.2, CH_2O), 4.09 (1 H, dd, *J* 6.7 and 8.5, PhC*H*CH$_2$O), 4.23 (1 H, dd, *J* 6.7 and 9.2, CH_2O), 4.30 (1 H, q, *J* 6.7, C*H*Me), 5.90 (1 H, s, NCHO) and 6.86–7.42 (11 H, m, aromatic H); *m*/*z* (CI, isobutane) 342 (M^+ + 1).

Reaction of the Oxazolidines (1′S,2R,4R)-**12a–b** *with Methylmagnesium Bromide*.—Methylmagnesium bromide (23.3 mmol, 3 mol dm^{-3} solution in diethyl ether) was added dropwise to a stirred solution of the oxazolidine **12a–b** (21.3 mmol) in dry THF (30 cm^3) at room temperature, under nitrogen, over a 10 min period. After the reaction mixture had been refluxed for 48 h, it was poured into saturated aqueous $NaHCO_3$, the phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 10 cm^3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave the amino alcohols **5a–b** as an oily residue, which was purified by column chromatography on silica gel with ethyl acetate–hexane (3:1).

(1′S,2R)-2-[N-*Bis*(1′-*phenylethyl*)*amino*]-2-*phenylethanol* **5a**. ^{1}H NMR analysis of the crude product indicated a 95:5 ratio of diastereoisomers, which were separated by column chromatography. For the (1′*S*,2*R*)-isomer (major product); colourless prisms; yield 71%; m.p. 168 °C (from ethyl acetate–hexane); $[\alpha]_D^{25}$ −117.79 (*c* 1.37, EtOH) (Found: C, 83.3; H, 7.9; N, 3.9. Calc. for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05%); δ_H(270 MHz; $CDCl_3$) 1.56 (6 H, d, *J* 7.3, CH*Me*), 1.57 (1 H, br s, OH), 4.06 (1 H, dd, *J* 5.5 and 9.8, CH_2OH), 4.16 (2 H, m, PhC*H*C*H*$_2$OH), 4.27 (2 H, q, *J* 7.3, C*H*Me), 6.70 (5 H, m, aromatic H) and 7.13–7.19 (10 H, m, aromatic H); *m*/*z* (CI, isobutane) 346 (M^+ + 1).

(1′S,2R)-2-*Phenyl*-2-{N-*bis*[1′-(2-*thienyl*)*ethyl*]*amino*}*ethanol* **5b**. ^{1}H NMR analysis of the crude product indicated a 96:4 ratio of diastereoisomers, which were separated by column chromatography. For the (1′*S*,2*R*)-isomer (major product); colourless prisms; yield 68%; m.p. 107 °C (from ethyl acetate–hexane); $[\alpha]_D^{25}$ −25.00 (*c* 1.01, EtOH) (Found: C, 67.4; H, 6.5; N, 3.9. Calc. for $C_{20}H_{23}NOS_2$: C, 67.21; H, 6.49; N, 3.92%); δ_H(270 MHz; $CDCl_3$) 1.64 (6 H, d, *J* 6.7, CH*Me*), 1.65 (1 H, br s, OH), 4.03–4.15 (2 H, m, CH_2OH), 4.23 (1 H, t, *J* 6.7, PhC*H*CH$_2$OH), 4.56 (2 H, q, *J* 6.7, C*H*Me), 6.59 (2 H, d, *J* 3.7, aromatic H), 6.84–6.92 (4 H, m, aromatic H) and 7.11–7.24 (5 H, m, aromatic H); *m*/*z* (CI, isobutane) 358 (M^+ + 1).

Oxidation of the Amino Alcohols **15a–b** *with Lead Tetraacetate*.—The reaction was performed as previously described for the amino alcohols (1′*R*,2*R*)-**5a–b**, using compounds (1′*S*,2*R*)-**5a–b** (1.0 mmol) and lead tetraacetate (0.89 g, 2.0 mmol) in benzene (25 cm^3) to yield the amine (1*S*,1′*S*)-**6a–b**.

(1S,1′S)-*Bis*(1-*phenylethyl*)*amine* **6a**. Colourless oil; yield 84%. An analytical sample was purified by Kugelrohr distillation; oven temperature 160 °C (7.0 mmHg); $[\alpha]_D^{25}$ −151 (*c* 2.2, EtOH), whose spectral data were identical with those reported.[6]

(1S,1′S)-*Bis*[1-(2-*thienyl*)*ethyl*]*amine* **6b**. Yellowish solid; yield 72%; $[\alpha]_D^{25}$ −99.0 (*c* 0.48, EtOH), which was further purified by recrystallization of its HCl salt. Colourless needles; m.p. 192 °C (from ethyl acetate–hexane); $[\alpha]_D$ −49.1 (*c* 1.02, EtOH). The spectral data of this product was identical with the major product obtained by the reaction of the amino alcohol (1′*R*,2*R*)-**5b** on the basis of ^{1}H NMR spectral comparison.

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