DOI: 10.1002/adsc.200505440

A Convenient Preparation of Enantiomerically Pure (+)-(1*R*,2*R*)- and (−)-(1*S*,2*S*)-1,2-Diamino-1,2-diphenylethanes

D. Christopher Braddock,[a,*] Joanna M. Redmond,[a] Stephen A. Hermitage,[b] Andrew J. P. White[a]

[a] Synthesis Section, Department of Chemistry, Imperial College London, South Kensington, London, SW72AZ, U.K. Fax: (+44)-207-594-5805, e-mail: c.braddock@imperial.ac.uk

[b] GlaxoSmithKlineLtd, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

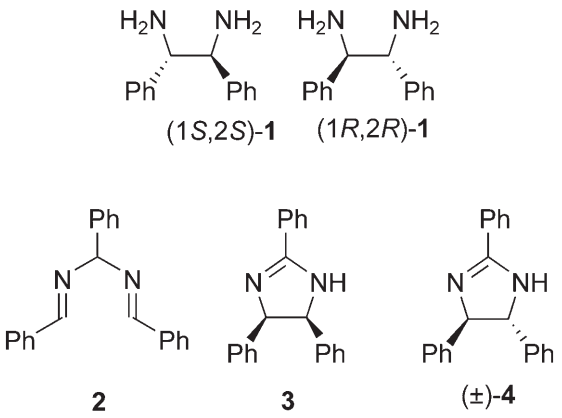
Received: November 12, 2005; Accepted: March 2, 2006

Abstract: A gram-scale preparation of (1*S*,2*S*)- and (1*R*,2*R*)-1,2-diamino-1,2-diphenylethanes, (1*S*,2*S*)-**1** and (1*R*,2*R*)-**1**, is reported *via* (±)-*iso*-amarine **4**. Strategically, the activation of (±)-*iso*-amarine **4** for hydrolysis to the required diamines *and* enantiomeric resolution is achieved simultaneously by formation of two separable diastereoisomeric *N*-acylamidines **5** and **6** derived from direct DCC-mediated coupling of (±)-*iso*-amarine **4** with (*R*)-acetylmandelic acid. *iso*-Amarine **4** is conveniently obtained from amarine **3**, and a one-pot synthesis of the latter is reported from benzaldehyde and hexamethyldisilazane as catalysed by benzoic acid.

Keywords: *iso*-amarine; amines; asymmetric synthesis; enantiomeric resolution; fractional crystallisation

Introduction

Enantiopure C_2-symmetrical 1,2-diphenylethane-1,2-diamines, (1*S*,2*S*)-**1** and (1*R*,2*R*)-**1**, and their *N*-modified derivatives have been widely incorporated into diverse reagents for highly asymmetric dihydroxylation,[1a] allylation,[1b] propargylation[1c] and aldol[1d] reactions. Moreover, they have been used as ligands in important catalytic asymmetric processes such as ruthenium-catalysed hydrogenation of ketones,[1e–g] manganese-catalysed epoxidation of alkenes,[1h,i] aluminium-catalysed Diels–Alder reactions[1j,k] and magnesium-catalysed merged enolisation-aminations.[1l] Racemic diamine (±)-**1** can be resolved into its enantiomers by diastereomeric salt formation with tartaric[2] or mandelic[3] acids. The synthesis of the racemic diamine **1** is less straightforward, however, and has been a long-standing problem. Reductive couplings of *N*-protected aromatic imines generally give mixtures of *meso* and racemic *N*-protected diamines.[4] A dissolving metal reduction of a spiroimidazole successfully gave the desired racemic diamine **1** after hydrolysis.[5] Two direct asymmetric syntheses of enantiopure diamine **1** starting with a Sharpless asymmetric dihydroxylation of stilbene have also been reported.[6] The classical route to the racemic diamine **1** involves the reaction of benzaldehyde and liquid ammonia to give first "hydrobenzamide" and then "amarine".[7] These compounds have a long and venerable history,[8] but the structures were only unequivocally secured by X-ray crystallography in 1997, and are confirmed as **2** and **3**, respectively.[9] Amarine **3** can be readily epimerised to (±)-*iso*-amarine **4** under basic conditions.[7] In principle, direct hydrolysis of (±)-*iso*-amarine **4** should liberate the desired racemic diamine **1**. However, the amidine functional group in *iso*-amarine is resistant to direct acid hydrolysis.[10] Instead, the conjugation in the amidine sub-unit must be broken by conversion to a hydrolysable *N*-acetylamidine, followed by a two-step hydrolysis procedure to racemic diamine **1**.[7,11] The enantiomers can then be resolved by diastereomeric salt formation with tartaric acid or mandelic acid followed by fractional crystallisation and formation of the free bases. Notwithstanding the activation-hydrolysis protocol followed by the resolution of the racemic diamine, the *iso*-amarine route to diamine **1** is inherently attractive because of the inexpensive nature of the starting materials and reagents *viz.*, benzaldehyde and ammonia, the ease of conversion of amarine **3** into *iso*-amarine **4**, and the lack of need for any chromatographic purifications. In this paper, we show that amarine **3** can be produced directly in a single step from benzaldehyde and hexamethyldisilazane (an inexpensive and easily handled liquid as a replacement for ammonia) as *catalysed* by benzoic acid. Further, we couple the activation of (±)-*iso*-amarine **4** for hydrolysis with its enantiomeric resolution by virtue of forming separable diastereomeric *N*-acyl-*iso*-amarines from (*R*)-acetylmandelic acid. Taken together, these strategies dramatically

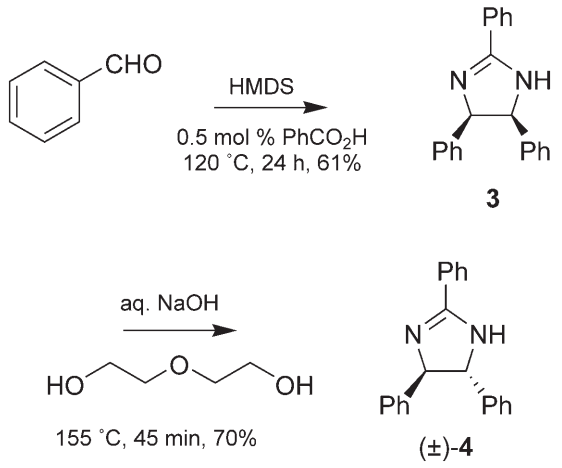


shorten the synthetic route to enantiopure diamines (1*S*,2*S*)-**1** and (1*R*,2*R*)-**1**, and delivers both enantiomers in gram quantities.

Results and Discussion

The direct conversion of benzaldehyde into amarine **3** *via* **2** by heating at 120 °C with hexamethydisilazane in a sealed tube without a solvent has been previously reported.[12] In our hands, attempts to perform this reaction using distilled benzaldehyde under an atmosphere of nitrogen led to minimal conversion. Addition of catalytic quantities of benzoic acid (0.5 mol %), however, led to rapid conversion of benzaldehyde into hydrobenzamide (Scheme 1). Further heating gave amarine **3** in good isolated yield (61%).

It has been previously noted that Lewis acids are good reagents for the conversion of aromatic aldehydes into methanediamines of the type **2**.[13] Further, basic reagents are known to promote the 6π-electrocyclic disrotatory ring-closure of **2** into **3**.[14] In this context, we note that the *in situ* formation of **3** from **2** under our conditions is apparently autocatalytic: once some amarine is formed, the amidine functional group is sufficiently basic to catalyse the reaction (for instance, in a given run the ratio of amarine **3**:hydrobenzamide **2** was determined to be 70:30 by ^{1}H NMR after 15 h – after 18 h the ratio was 100:0). Evidently, benzoic acid catalyses the initial hydrobenzamide formation, and the electrocyclic reaction is probably initiated by excess HMDS. Once isolated, isomerisation of amarine **3** into (±)-*iso*-amarine **4** is readily effected by sodium hydroxide in ethylene glycol (70%).[7]



Scheme 1. Preparation of (±)-*iso*-amarine.

Dicyclohexylcarbodiimide-mediated coupling[15] of (±)-*iso*-amarine **4** with (*R*)-acetylmandelic acid gave a quantitative yield of the two *N*-acyl diastereoisomers (*S*,*S*,*R*)-**5** and (*R*,*R*,*R*)-**6** (Scheme 2). *N*-Acyl-*iso*-amarine **5** was obtained as a single diastereoisomer after fractional crystallisation of the mixture from diisopropyl ether. Evaporation of the mother liquor gave a 1:4 mixture of **5**:**6**. Subsequent hydrolysis of **5** in THF/H_2O/HCl gave the diamide **7** as a single diastereoisomer. The relative configurations and hence the absolute configurations were assigned by X-ray crystallography (Figure 1). The mixture of **5** and **6** from the mother liquor was also hydrolysed in this manner to give a 1:4 mixture of diamides **7** and **8**, respectively. Diamide **8** was obtained as a single diastereoisomer after recystallisation of this mixture from chloroform.[16] Further hydrolysis of **7** and **8** with HBr in glacial acetic acid gave (1*S*,2*S*)-**1** and (1*R*,2*R*)-**1**, respectively, as single enantiomers. Enantiomeric purity (>98%) of the two enantiomers was established by the NMR method of Synder.[17]

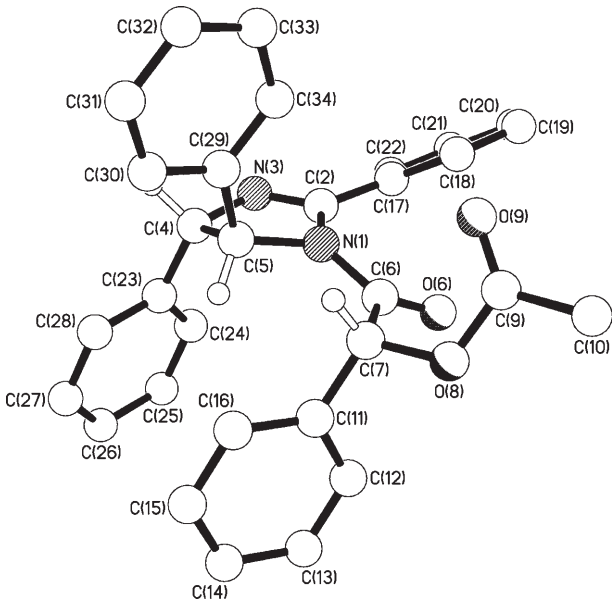
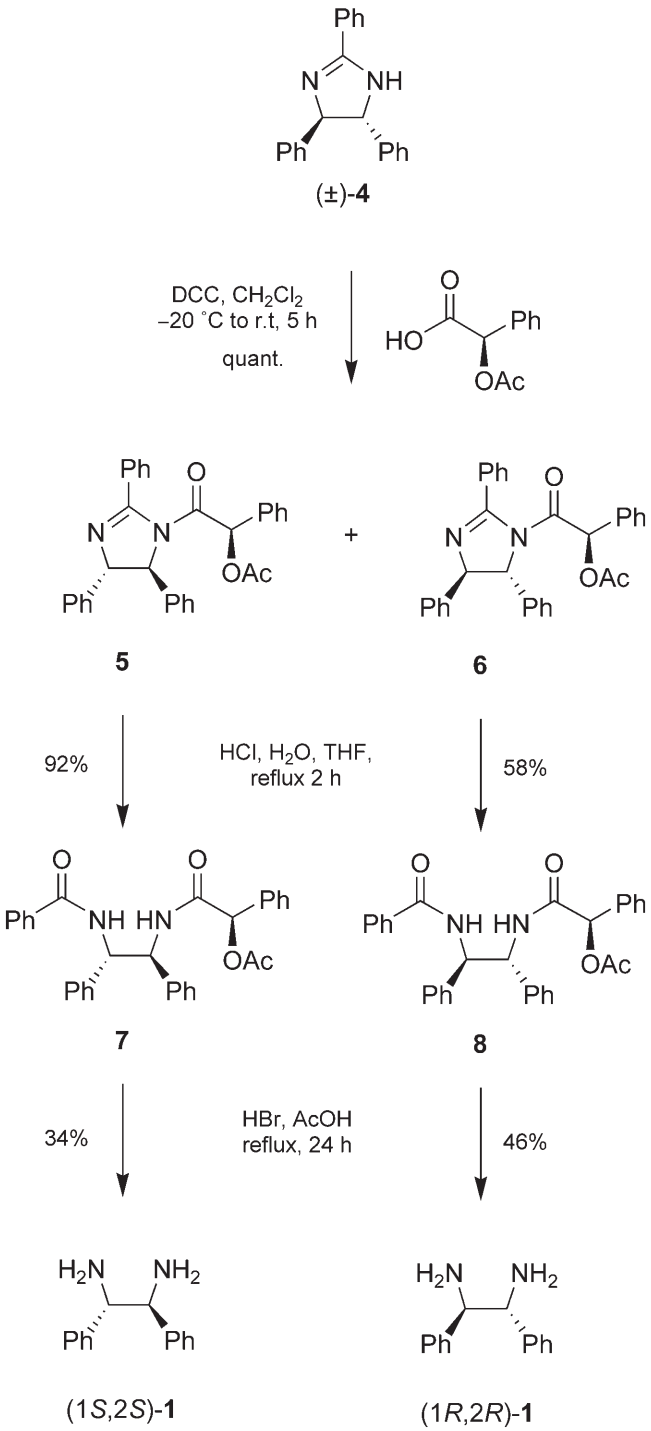


Figure 1. The molecular structure of **5** (30% probability ellipsoids).



Scheme 2. Preparation of (*R*,*R*)-**1** and (*S*,*S*)-**1**.

Conclusion

In conclusion, we have demonstrated a convenient gram-scale synthesis of both enantiopure diamines (*R*,*R*)-**1** and (*S*,*S*)-**1** by a strategy of activation of (±)-*iso*-amarine **4** for hydrolysis to the required diamines *and* simultaneous enantiomeric resolution *via* formation of two separable diastereoisomeric *N*-acyl amidines **5** and **6**. This strategy considerably shortens the synthetic route to (*R*,*R*)-**1** and (*S*,*S*)-**1** from (±)-*iso*-amarine. In addition, we have improved the synthetic access to (±)-*iso*-amarine **4** by developing an acid-catalysed condensation of readily available benzaldehyde and hexamethyldisilazane to give amarine **3**, which is readily converted into (±)-*iso*-amarine **4**. All of the reagents used in this synthesis – starting with the neat condensation of benzaldehyde and hexamethyldisilazane as catalysed by benzoic acid, followed by sodium hydroxide, acetylmandelic acid, DCC, aqueous HCl and aqueous HBr – are readily available, inexpensive, and convenient to handle.

Experimental Section

Methods

Melting points were recorded on a Reichart Thermovar melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm using the 589.3 D-line of sodium. Solutions were prepared using spectroscopic grade solvents and concentrations (*c*) are quoted in g/100 mL. Fourier transform infrared (IR) spectra were recorded as thin films on NaCl plates using a Mattson 500 FT IR spectrometer. ^{1}H NMR were recorded at 270 MHz on a Jeol GSX-270 spectrometer and 300 MHz on a 300 MHz Bruker RX spectrometer. ^{13}C NMR were recorded at 68 MHz or 75 MHz on a Jeol GSX-270 spectrometer or a 300 MHz Bruker DRX spectrometer respectively. NMR samples were run in the indicated solvents and were referenced internally. All chemical shift values are quoted in ppm and coupling constants are quoted in Hz. The following abbreviations are used for the multiplicity of NMR signals: br = broad, s = singlet, d = doublet, dd = doublet of doublets, t = triplet. Low resolution mass spectra (MS) [EI, CI and FAB] and high resolution mass spectra (HR-MS) [CI] were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service. Microanalyses were performed by Mr. S. Boyer at London Metropolitan University, UK.

Materials

CH_2Cl_2 was distilled from CaH_2. Petrol refers to BDH Anal® petroleum spirit 40–60 °C. Water refers to distilled water. Benzaldehyde was distilled under N_2 immediately before use. (*S*)-Mandelic acid was recrystallised from $CHCl_3$. (*R*)-(−)-(α)-Acetoxyphenyl acetic acid was prepared from (*R*)-(−)-mandelic acid and acetyl chloride by the published method.[18] All other reagents and solvents were used as received.

(4R,5S*)*-4,5-Dihydro-2,4,5-triphenyl-1*H*-imidazole (Amarine) (3)

Benzaldehyde (96 mL, 950 mmol), hexamethyldisilazane (240 mL, 1.15 mol) and a catalytic amount of benzoic acid (575 mg, 4.7 mmol) were stirred at 120 °C under nitrogen for

24 h. The mixture was allowed to cool to room temperature, an amorphous yellow solid formed and the entire mixture was taken up in toluene (500 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (2 × 250 mL), water (250 mL), brine (250 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting yellow residue was purified by mixed solvent recystallisation (toluene, diethyl ether) to afford amarine **3** as a white crystalline solid; yield: 57.2 g (191 mmol, 61%); mp 124–127 °C (lit.[7] 128–131 °C); FT-IR (NaCl): ν_{max} = 3377, 1615, 1599 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.97 (d, $^3J_{H,H}$ = 6.9 Hz, 2H, Ar-*H*), 7.49–7.47 (m, 3H, Ar-*H*), 7.00–6.95 (m, 10H, Ar-*H*), 5.45 (s, 2H, NC*H*), 4.75 (br s, 1H, N*H*); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 164.6, 138.9, 131.2, 129.9, 128.8, 127.7, 127.6, 127.4, 126.9, 70.8 (br s); MS (CI^+): *m*/*z* = 299 ($M+H^+$); HR-MS: calcd. for $C_{21}H_{19}N_2$: 299.1548 ($M+H^+$), found: 299.1543.

(4*S**,5*S**)-4,5-Dihydro-2,4,5-triphenyl-1*H*-imidazole [(±)-*iso*-Amarine] (4)

Following the procedure of Williams and Bailar,[7] a stirred mixture of amidine **3** (42 g, 141 mmol), water (6 mL), diethylene glycol (35 mL) and sodium hydroxide (9.0 g, 225 mmol) was boiled in an open beaker until the temperature reached 155 °C. The temperature was maintained for 45 min, during which time the sodium salt of the *iso*-amarine had precipitated and the solution became a thick slurry. The mixture was allowed to cool to room temperature and treated with glacial acetic acid (25 mL), diluted with ethanol (125 mL) and heated to boiling (105 °C) until all remaining solid had dissolved. After cooling, the solution was basified to pH = 9 with concentrated aqueous ammonia solution (*ca.* 22 mL). The resulting tan precipitate was filtered, washed with cold ethanol, and dried under vacuum (yield: 32.4 g). The crude product was recrystallised from toluene to afford racemic *iso*-amarine **4** as a pale yellow crystalline solid; yield: 29.3 g (70%); mp 199–204 °C [lit.[7] 198–201 °C]; FT IR (NaCl): ν_{max} = 3400–2800, 1594 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.94 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, Ar-*H*), 7.51–7.25 (m, 13H, Ar-*H*), 5.42 (br s, 1H, N*H*) 4.90 (s, 2H, NC*H*); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 163.1, 143.6, 131.1, 130.2, 128.8, 128.7, 127.6, 127.5, 126.9, 71.8 (br); MS (CI^+): *m*/*z* = 299 ($M+H^+$); HR-MS: calcd. for $C_{21}H_{19}N_2$: 299.1548 ($M+H^+$), found: 299.1554.

(−)-(4*S*,5*S*)-1-[(*R*)-α-Acetoxyphenylacetyl]-4,5-dihydro-2,4,5-triphenylimidazole (5) and (−)-(4*R*,5*R*)-1-[(*R*)-α-Acetoxyphenylacetyl]-4,5-dihydro-2,4,5-triphenylimidazole (6)

Dicyclohexylcarbodiimide (27.0 g, 129 mmol) was added to a stirred solution of *iso*-amarine **4** (32.0 g, 107 mmmol) and (*R*)-α-acetoxyphenylacetic acid (25.0 g, 129 mmol) in CH_2Cl_2 (350 mL) at −20 °C under nitrogen, and the reaction mixture was allowed to warm to room temperature. After 5 h a voluminous white precipitate had formed. The mixture was filtered and the filtrate was concentrated under vacuum to afford a crude mixture of diastereoisomers **5** and **6** (yield: 58.8 g, quantitative) as a pale yellow solid mass. The crude mixture was taken up in refluxing diisopropyl ether (1050 mL). The solution was allowed to cool gradually to room temperature and, after 15 h, was cooled to 0 °C for further 5 h. The resulting crystals were separated by filtration, washed with a small amount of cold diisoproyl ether (50 mL) and dried under reduced pressure to afford the pure *N*-acyl-*iso*-amarine **5** as a white crystalline solid; yield: 17.2 g (68%); mp 170–171 °C; $[\alpha]_D^{25}$: −107.5 (*c* 9.1, $CHCl_3$); FT IR (NaCl): ν_{max} = 1737, 1707, 1626 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.83 (d, $^3J_{H,H}$ = 6.5 Hz, 2H, Ar-*H*), 7.51–7.12 (m, 16H, Ar-*H*), 6.97–6.92 (m, 2H, Ar-*H*), 5.55 (s, 1H, C*H*), 5.04 (br s 1H, NC*H'*), 4.99 (br s, 1H, NC*H*), 2.03 (s, 3H, $COOCH_3$); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.4, 166.2, 159.8, 140.3, 140.2, 131.8, 131.1, 130.9, 129.9, 129.5, 129.2, 128.9, 128.9, 128.6, 128.2, 127.9, 126.0, 125.3, 78.6, 75.1, 68.1, 20.7; MS (CI^+): *m*/*z* = 475 ($M+H^+$); HR-MS: calcd. for $C_{31}H_{27}N_2O_3$: 475.2022 ($M+H^+$), found: 475.2030; anal. calcd. for $C_{31}H_{26}N_2O_3$: C 78.46, H 5.52, N 5.90; found: C 78.53, H 5.47, N 5.94.

The combined filtrates were concentrated under vacuum to give an amorphous solid (yield: 37.5 g, 79.1 mmol) containing (*R*,*R*,*R*) diastereomer **6** in a 4:1 excess over (*R*,*S*,*S*) diastereomer **5**. A portion of this mixture could be purified by column chromatography (petrol:ethyl acetate, gradient elution: 4:1 to 3:1) to produce pure (*R*,*R*,*R*) diastereomer **6**: mp 67–73 °C; R_f = 0.39 (2:1, petrol:ethyl acetate); $[\alpha]_D^{25}$: −38.8 (*c* 2.3, $CHCl_3$); FT-IR (NaCl): ν_{max} = 1737, 1704, 1693 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.70–6.86 (m, 20H, Ar-*H*), 5.83 (br s, 1H, NC*H'*), 5.45 (br s, 1H, NC*H*), 5.06 (s, 1H, C*H*), 1.98 (s, 3H, $COOCH_3$); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 170.7, 142.3, 140.4, 132.2, 131.3, 131.1, 129.6, 129.5, 129.0, 128.8, 128.5, 128.3, 128.0, 126.4, 125.6, 78.5 (br), 75.6, 70.7, 20.5; MS (CI^+): *m*/*z* = 475 ($M+H^+$); HR-MS: calcd. for $C_{31}H_{27}N_2O_3$: 475.2022 ($M+H^+$), found: 475.2018.

Crystal data for 5

$C_{31}H_{26}N_2O_3$, *M* = 474.54, orthorhombic, $P2_12_12_1$, (no. 19), *a* = 10.1710(7), *b* = 14.6196(9) *c* = 17.2572(11) Å, *V* = 2566.1(3) $Å^3$, *Z* = 4, D_c = 1.228 g cm^{-3}, μ(Cu-Kα) = 0.633 mm^{-1}, *T* = 173 K, colourless blocks, Oxford Diffraction Xcalibur PX Ultra diffractometer; 4696 independent measured reflections, F^2 refinement, R_1 = 0.039, wR_2 = 0.101, 4638 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 137°], 329 parameters. The absolute structure of 5 could not be unambiguously determined by either an *R*-factor test [R_1^+ = 0.0390, R_1^- = 0.0392] or by use of the Flack parameter [x^+ = 0.0(2), x^- = 1.1(2)] and so was assigned by internal reference. CCDC 283432.

(+)-(1*S*,2*S*)-*N*-[(*R*)-α-Acetoxyphenylacetyl]-*N'*-benzoyl-1,2-diamino-1,2-diphenylethane (7)

A stirred suspension of *N*-acyl-*iso*-amarine **5** (16.8 g, 35.4 mmol) in a mixture of THF (50 mL), water (100 mL) and concentrated hydrochloric acid (10 mL) was heated to reflux for 2 h. The reaction mixture was allowed to cool to room temperature and concentrated to 2/3 of its original volume under vacuum. After standing at room temperature for 1 h, the white precipitate was collected by filtration, washed with cold water and dried by dry stirring at 60 °C under vacuum to afford diamide **7** as a fine colourless solid; yield: 16.1 g (92%); mp > 230 °C; $[\alpha]_D^{25}$: +7.3 (*c* 4.3, 10:1, $CHCl_3$:MeOH);

FT-IR (NaCl): $\nu_{max}=3308$, 1731, 1668, 1641 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta=9.05$ (d, $^3J_{HH}=7.6$ Hz, 1H, OCN*H*), 8.98 (d, $^3J_{H,H}=7.4$ Hz, 1H, N*H*), 7.78 (d, $^3J_{H,H}=6.9$ Hz, 2H, Ar-*H*), 7.54–7.44 (m, 3H, Ar-*H*), 7.26–7.10 (m, 15H, Ar-*H*), 5.88 (s, 1H, C*H*), 5.47 (m, 2H, NC*H* × 2) 2.11 (s, 3H, COOCH_3); ^{13}C NMR (68 MHz, DMSO-d_6): $\delta=170.0$, 168.1, 166.9, 140.9, 140.6, 136.0, 135.1, 131.8, 128.9, 128.8 (× 2), 128.4, 128.3, 128.1, 128.0, 128.0, 127.8, 127.4, 75.7, 58.2, 57.3, 21.3; MS (CI^+): $m/z=493$ ($M+H^+$); HR-MS: calcd. for $C_{31}H_{29}N_2O_4$: 493.2127 ($M+H^+$), found: 493.2123; anal. calcd. for $C_{31}H_{28}N_2O_4$: C 75.59, H 5.73, N 5.69; found: C 75.52, H 5.80, N, 5.71.

(−)-(1*R*,2*R*)-*N*-[(*R*)-α-Acetoxyphenylacetyl]-*N*′-benzoyl-1,2-diamino-1,2-diphenylethane (8)

Following the procedure for the conversion of *N*-acyl-*iso*-amarine **5** into diamide **7** above, diastereomerically enriched (*R*,*R*,*R*)-amide **6** (37.5 g, 79.1 mmol) was converted to diamide **8** as a 4:1 (*R*,*R*,*R*):(*R*,*S*,*S*) mixture of diastereomers (yield: 30.8 g, 79%). The crude solid was dissolved in refluxing $CHCl_3$ (1.9 L) and the hot solution was allowed to cool slowly to room temperature. On cooling the pure (*R*,*R*,*R*) diamide **8** precipitated, and was collected by filtration. Removal of a further 600 mL of solvent under vacuum and cooling to 0^0C resulted in the precipitation of a second crop of diastereomerically pure (*R*,*R*,*R*) diamide **8**, which was again collected by filtration. The two crops were combined and dried under vacuum to afford pure (*R*,*R*,*R*)-diamide **8** as a white crystalline solid; yield: 13.6 g (58%): mp > 230 °C; $[\alpha]_D^{25}$: −69.5 (*c* 2.3, 10:1 $CHCl_3$:MeOH); FT-IR (NaCl): $\nu_{max}=3305$, 1739, 1667, 1633 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): $\delta=9.08$ (d, $^3J_{H,H}=8.1$ Hz, 1H, OCN*H*), 8.81 (d, $^3J_{H,H}=8.8$ Hz, 1H, OCN*H*), 7.66 (d, $^3J_{H,H}=7.4$ Hz, 2H, Ar-*H*), 7.56–7.41 (m, 3H, Ar-*H*), 7.31–7.10 (m, 15H, Ar-*H*), 5.88 (s, 1H, C*H*), 5.45 (t, $^3J_{H,H}=8.6$ Hz, 1H, NC*H*′), 5.32 (t, $^3J_{H,H}=8.4$ Hz, 1H, NC*H*), 2.01 (s, 3H, COOCH_3); ^{13}C NMR (68 MHz, DMSO-d_6): $\delta=170.1$, 168.0, 166.6, 140.9, 140.9, 136.0, 135.0, 131.7, 128.7, 128.3, 127.9, 127.8, 127.6, 127.4, 127.3, 75.6, 57.9, 57.6, 21.1; MS (CI^+): $m/z=493$ ($M+H^+$); HR-MS: calcd. for $C_{31}H_{29}N_2O_4$: 493.2127 ($M+H^+$), found: 493.2148; anal. calcd. for $C_{31}H_{28}N_2O_4$: C 75.59, H 5.73, N 5.69; found: C 75.64, H 5.77, N, 5.61.

(−)-(1*S*, 2*S*)-1,2-Diamino-1,2-diphenylethane (1)

Following a modified hydrolysis method of Williams and Bailar,[7] a mixture of diamide **7** (12.8 g, 25.9 mmol), glacial acetic acid (33 mL) and 48% aqueous hydrobromic acid (65 mL) was refluxed for 6 h. Further portions of HBr (15 mL) and acetic acid (8 mL) were added, and the reaction mixture was refluxed for further 20 h. The solution was concentrated to 1/3 its original volume, cooled to 5 ^{0}C and allowed to stand for 15 h. The resulting precipitate was filtered, washed with cold ether and dissolved in 30 mL of water. The aqueous solution was filtered to remove insoluble by-products, and aqueous sodium hydroxide solution (40%, *ca.* 4.5 mL) was added slowly to the filtrate such that the temperature did not exceed 25 °. The mixture was cooled to 5 °C for 15 min and the resulting precipitate from the aqueous phase was extracted with ether (3 × 80 mL). The organic layers were combined, dried over solid NaOH, filtered and concentrated under vacuum. The crude product was recrystallised from diethyl ether:petroleum ether 40–60 °C °C (10 mL:20 mL) to afford diamine **1** as a colourless, crystalline solid; yield: 1.9 g (34%); mp 81–84 °C [lit.[19] 83–85 °C]; $[\alpha]_D^{25}$: −91.0 (*c* 4.6, EtOH) {lit.[20] $[\alpha]_D^{25}$: −87.1 (*c* 2.3, EtOH)}; FT-IR (NaCl): $\nu_{max}=3360$ (br), 3295 (br), 3060, 3028, 2908, 2857 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=7.27-7.25$ (m, 10H, Ar-*H*), 4.09 (s, 2H, NC*H*), 1.62 (br s, 4H, NH_2); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta=143.5$, 128.3, 127.1, 127.0, 62.0; MS (CI^+; NH_3) 213 ($M+H^+$); HR-MS: calcd. for $C_{14}H_{16}N_2$: 213.1392 ($M+H^+$), found: 213.1390. The optical purity (> 98%) was assessed by the method of Synder,[17] using 2 equivalents of (*R*)-mandelic acid and integrating the doublet at 6.83 *versus* 6.78 ppm.

(+)-(1*R*, 2*R*)-1,2-Diamino-1,2-diphenylethane (1)

Following the above procedure starting from diamide **8** (12.5 g, 25.5 mmol) gave diamine **1** as a colourless, crystalline solid; yield: 2.46 g (46%); mp 78–82 °C [lit.[19] 79–83 °C]; $[\alpha]_D^{25}$: +90.7 (*c* 3.4, EtOH) {lit.[20] $[\alpha]_D^{25}$: +90.4 (*c* 1.9, EtOH)}. The optical purity (> 98%) was assessed by the method of Synder,[17] using 2 equivalents of (*S*)-mandelic acid and integrating the doublet at 6.83 versus 6.78 ppm. The other spectral data are identical to those for its enantiomer.

Acknowledgements

We thank GlaxoSmithKline Ltd and the EPSRC for an Industrial CASE award (to. J. M. R.).

References and Notes

[1] a) E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, R. D. Connell, *J. Am. Chem. Soc.* **1989**, *111*, 9243–9244; b) E. J. Corey, C.-M. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496; c) E. J. Corey, C.-M. Yu, D.-H. Lee, *J. Am. Chem. Soc.* **1990**, *112*, 878–879; d) E. J. Corey, S. S. Kim, *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977; e) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022 and references cited therein; f) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; g) M. J. Burk, W. Hems, D. Herzberg, C. Malan, A. Zanotti-Gerosa, *Org. Lett.* **2000**, *2*, 4173–4176; h) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803; i) W. Zhang, E. N. Jacobsen, *J. Org. Chem.* **1991**, *56*, 2296–2298; j) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495; k) E. J. Corey, N. Imai, S. Pikul, *Tetrahedron Lett.* **1991**, *32*, 7517–7520; l) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453.

[2] For example, see: R. R. Fenton, R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1988**, *148*, 37–44 and references cited therein.

[3] K. Saigo, N. Kubota, S. Takebayashi, M. Hasegawa, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 931–932.

[4] An enantioselective oxazaborolidine reduction of 1,2-bis(*p*-methoxyphenylimino)-1,2-diphenylethane to the *N,N′*-protected diamine has been reported. Subsequent imidazolidinone formation allows separation of the *meso*-isomer. Oxidative removal of the *p*-anisyl groups and aqueous hydrolysis gives enantiopure diamine **1**; a) M. Shimizu, M. Kamei, T. Fujisawa, *Tetrahedron Lett.* **1995**, *36*, 8607–8610; a 2005 paper reports the double addition of phenyllithium to chiral bisimines derived from *tert*-butanesulfinamide to give *N,N*-diprotected diamines in up to a 97:3 ratio *dl:meso*; the method requires $AlMe_3$ as an additive; b) X. Sun, S. Wang, S. Sun, J. Zhu, J. Deng, *Synlett* **2005**, 2776–2780.

[5] S. Pikul, E. J. Corey, *Org. Synth.* **1993**, *71*, 22–29.

[6] a) From a diazide: D. Pini, A. Iuliano, C. Rosini, P. Salvadori, *Synthesis* **1990**, 1023–1024; b) from a cyclic sulfate: R. Oi, K. B. Sharpless, *Tetrahedron Lett.* **1991**, *32*, 999–1002.

[7] O. F. Williams, J. C. Bailar, Jr., *J. Am. Chem. Soc.* **1959**, *81*, 4464–4469 and references cited therein.

[8] D. H. Hunter, S. K. Sim, *Can. J. Chem.* **1972**, *50*, 669–677 and references cited therein.

[9] E. J. Corey, F. N. M. Kühnle, *Tetrahedron Lett.* **1997**, *38*, 8631–8634 and references cited therein.

[10] It is also resistant to reduction with hydride-transfer reagents. Reduction to the desired racemic diamine **1** has been achieved by the action of aluminium amalgam in moist THF (ref.[9]).

[11] I. Lifschitz, J. G. Bos, *Recl. Trav. Chim. Pays Bas* **1940**, *59*, 173–183 and references cited therein.

[12] a) H. Uchida, T. Shimizu, P. Y. Reddy, S. Nakamura, T. Toru, *Synthesis* **2003**, 1236–1240; b) for a microwave-accelerated method over solid catalysts see: H. Uchida, H. Tanikoshi, S. Nakamura, P. Y. Reddy, T. Toru, *Synlett* **2003**, 1117–1120; c) for a one-pot synthesis of *iso*-amarine from benzaldehyde and HMDS with LiBr in DMSO see: E. A. Mistryukov, *Mendeleev Commun.* **2001**, 29–30.

[13] K. Nishiyama, M. Saito, M. Oba, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 609–611.

[14] D. H. Hunter, S. K. Sim, *Can. J. Chem.* **1972**, *50*, 678–689.

[15] J. C. Sheenan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068; attempts to utilise the corresponding acid chloride, led instead to the formation of *racemic* diastereomers. Presumably, this occurs *via* amidine-promoted ketene formation.

[16] The diastereomeric purity of **7** and **8** can be readily assessed by ^1H NMR spectroscopy: the acetate methyl resonances (singlets) are at $\delta_H = 2.11$ and 2.01 ppm, respectively. In each case, the diastereomers are produced $>98\%$ pure.

[17] S. C. Benson, P. Cai, M. Colon, M. A. Haiza, M. Tokles, J. K. Snyder, *J. Org. Chem.* **1988**, *53*, 5335–5341.

[18] P. Saravanan, A. Bisai, S. Baktharaman, M. Chandrasekhar, V. K. Singh, *Tetrahedron* **2002**, *58*, 4693–4706.

[19] As stated by the Sigma-Aldrich catalogue for the enantiomerically pure material.

[20] Reading taken from authentic enantiomerically pure sample purchased from Sigma-Aldrich.

