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Tetrahedron: *Asymmetry* 17 (2006) 2935–2937
Tetrahedron: Asymmetry

Fractional crystallisation of (±)-*iso*-amarine with mandelic acid: convenient access to (*R*,*R*)- and (*S*,*S*)-1,2-diamino-1,2-diphenylethanes

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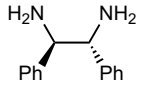
Received 5 October 2006; accepted 30 October 2006

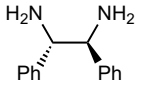
Abstract—(±)-*iso*-Amarine can be conveniently resolved via 1:1 salt formation with either hand of mandelic acid. Enantiopure *iso*-amarine can be acetylated and hydrolysed to give enantiopure 1,2-diamino-1,2-diphenylethanes.

1. Introduction

We have recently described a convenient gram-scale preparation of enatiomerically pure (*R*,*R*)- and (*S*,*S*)-1,2-diamino-1,2-diphenylethanes **1** and **2** from (±)-*iso*-amarine **3**.[1] The activation of *iso*-amarine for hydrolysis to the required diamines and enantiomeric resolution was achieved simultaneously by the formation of two separable *N*-acylamidines derived from DCC-mediated coupling with (*R*)-acetylmandelic acid. Herein, we report an alternative method for accessing the enantiopure diamines in which (±)-*iso*-amarine **3** is resolved by fractional crystallisation with mandelic acid. Subsequent N-acetylation of the resolved amarine and hydrolysis provides the enantiomerically pure diamine.



1



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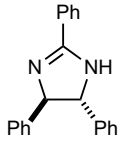

(±)-3

2. Results and discussion

(±)-*iso*-Amarine **3** was prepared in multi-gram quantities as previously described in a simple two-step procedure starting with benzaldehyde and hexamethyldisilazane.[1] A 1:1 salt **5** was found to precipitate from *iso*-propanol in an excellent yield on treatment of (±)-*iso*-amarine with one equivalent of (*S*)-mandelic acid **4** (Scheme 1). The 1:1 composition of the salt, and the selection of the (*R*,*R*)-hand of *iso*-amarine with (*S*)-mandelic acid was confirmed by X-ray crystallography (Fig. 1) after recrystallisation. Treatment of salt **5** with base gave enantiopure (*R*,*R*)-*iso*-amarine **3** in a quantitative yield. The enantiomeric purity of resolved **3** was confirmed by DCC coupling with (*R*)-acetyl mandelic acid **6** to give amide **7** as a single diastereoisomer (Scheme 2).[1,†]

Resolving (±)-*iso*-amarine **3** with (*R*)-mandelic acid instead, gave access to the (*S*,*S*)-amidine in essentially identical yields, as expected. One-pot acetylation and hydrolysis under Lifschitz and Bos' conditions[2] gave enantiomerically pure (*S*,*S*)-diamide **8** (Scheme 3). Further hydrolysis using Williams and Bailar's protocol[3] gave enantiomerically pure diamine **2**.

Since mandelic acid is readily available in both enantiomeric forms, the resolution procedure above therefore gives access to both enantiopure diamines **1** and **2**. Tartaric acid

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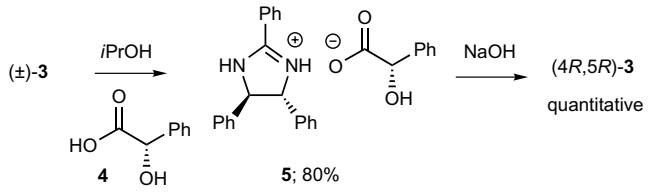
doi:10.1016/j.tetasy.2006.10.044

† The diastereomeric purity of (*R*,*R*,*R*)-**7** can be readily assessed by ^{1}H NMR spectroscopy, the C*H*OAc resonance (singlet) is at δ_H 5.06 ppm. The (*S*,*S*,*R*) diastereoisomer that would derive from (*S*,*S*)-**3** has its corresponding resonance at 5.55 ppm.



Scheme 1.

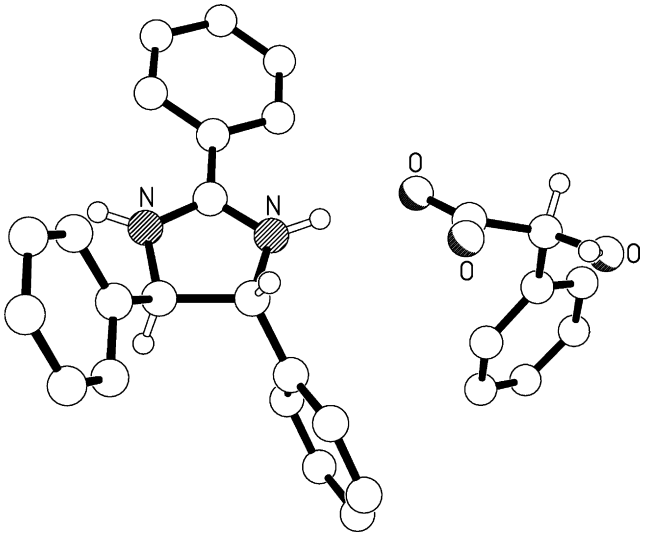
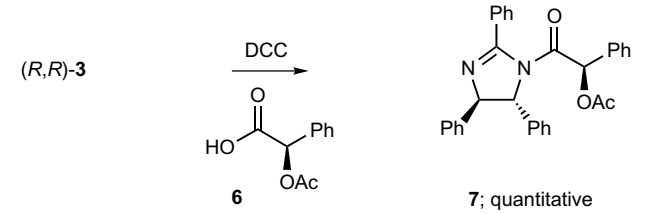
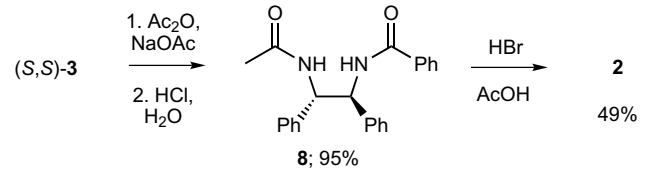


Figure 1. Molecular structure of **5**. The crystal studied was enantiomerically pure; since the absolute structure could not be determined by purely crystallographic methods the known chirality of the (*S*)-mandelic acid moiety was used as an internal reference.



Scheme 2.



Scheme 3.

has previously been used as a resolving agent for (±)-*iso*-amarine, but a yield was not given.[4] This resolution procedure also provides a convenient alternative to the preparation of enantiomerically pure *iso*-amarines from activated benzoic acid derivatives with (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane.[5]

3. Conclusion

We have shown that enantiomerically pure *iso*-amarine can be accessed by the fractional crystallisation of the salts formed from racemic *iso*-amarine and scalemic mandelic acid. Acetylation of the free base and subsequent hydrolysis provided enantiomerically pure 1,2-diamino-1,2-diphenylethanes.

4. Experimental

4.1. Materials and methods

CH_2Cl_2 was distilled from CaH_2. All other reagents were used as received. Concentrated refers to the removal of the solvent under reduced pressure on a rotary evaporator. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm using the 589.3 nm D-line of sodium. Solutions were prepared using spectroscopic grade solvents and concentrations (*c*) are quoted in g/100 mL. Melting points were recorded on a Reichart Thermovar melting point apparatus and are uncorrected. Fourier transform infra-red (IR) spectra were recorded through diffuse reference infra-red Fourier transform spectroscopy (DRIFTS) or as thin films on NaCl plates using a Mattson 500 FTIR spectrometer. ^{1}H NMR were recorded at 270 MHz on a Jeol GSX-270 spectrometer or at 400 MHz on a 400 MHz Bruker DRX spectrometer. ^{13}C NMR were recorded at 68 and 100 MHz on a Jeol GSX-270 spectrometer or a 400 MHz Bruker DRX spectrometer, respectively. NMR samples were run in the indicated solvents and were referenced internally. All chemical shift values are quoted in parts per million and coupling constants quoted in Hertz. The following abbreviations are used for the multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, m = multiplet. Low resolution mass spectra (MS) [FAB, EI & CI] and high resolution mass spectra (HRMS) were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service. Elemental analyses were carried out by the University of North London Analytical Service.

4.2. (+)-(4*R*,5*R*)-4,5-Dihydro-2,4,5-triphenyl-1*H*-imidazole 3

Racemic *iso*-amarine **3** (5.00 g, 16.8 mmol) and (*S*)-(+)-mandelic acid **4** (2.55 g, 16.8 mmol) were dissolved in refluxing *iso*-propanol (28 mL). After refluxing for 1 h heating was stopped, and the flask was left in the oil bath to cool slowly to rt with gentle stirring. After 16 h, the solution was cooled to 0 °C and left to stir for a further 4 h. The resulting white crystals were collected by filtration and dried in vacuo. The material was recrystallised from *iso*-propanol to yield the 1:1 mandelic acid–*iso*-amarine diastereomeric salt **5** (2.99 g, 80%) as a white crystalline solid: $[\alpha]_D^{25} = +128.0$ (*c* 2.3, EtOH); FT IR (NaCl, Nujol®) ν_{max} 3430, 3100–2100 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.05 (d, $^3J_{HH} = 6.7$ Hz, 2H, Ar–*H*), 8.62–8.52 (m, 3H, Ar–*H*), 7.41–7.20 (m, 15H, Ar–*H*), 4.95 (s, 2H, NC*H*), 4.82 (s, 1H, C*H*CO$_2$) ppm; ^{13}C NMR (68 MHz, DMSO-d_6) δ 174.7, 163.3, 143.1, 142.0, 132.5, 129.3, 129.3, 129.1,

128.5, 128.4, 127.6, 127.2, 127.1, 101.8, 73.3; MS (FAB^+) 299 (cation) 452 (cation+anion+$2H^+$); MS (FAB^-) 151 (anion); Anal. Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.82; N, 6.22. Found: C, 77.42; H, 5.91; N, 6.15. *Crystal data for* **5**: $C_{29}H_{26}N_2O_3$, $M = 450.52$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 8.6149(5)$, $b = 16.0588(8)$, $c = 17.2764(8)$ Å, $V = 2390.1(2)$ Å^3, $Z = 4$, $d_c = 1.252$ g cm^{-3}, μ(Cu Kα) = 0.650 mm^{-1}, $T = 293$ K, colourless prisms, Oxford Diffraction Xcalibur PX Ultra diffractometer; 4365 independent measured reflections, F^2 refinement, $R_1 = 0.047$, $wR_2 = 0.107$, 3623 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 137°$], 317 parameters. The absolute structure of **5** could not be unambiguously determined by either an *R*-factor test [$R_1^+ = 0.0472$, $R_1^- = 0.0472$] or by use of the Flack parameter [$x^+ = 0.1(3)$, $x^- = 0.9(3)$] and so was assigned by an internal reference. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 283433. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk]. The salt **5** (2.77 g, 6.16 mmol) was suspended in CH_2Cl_2 (150 mL) and 1 M aqueous NaOH (100 mL) was added. The biphasic mixture was stirred rapidly until all the solid had dissolved. The organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$ and concentrated to give (*R*,*R*)-*iso*-amarine **3** (1.83 g, quantitative) as a white crystalline solid: mp 175–178 °C [lit.[6] 177–180 °C]; $[\alpha]_D^{25} = +46.0$ (*c* 2.0, EtOH) {lit.[4] $[\alpha]_D^{20} = +46.0$ (*c* 1, EtOH)}. Other spectral data are identical to that of (±)-**3**.[1]

4.3. (+)-(1*S*,2*S*)-*N*-Acetyl-*N*′-benzoyl-1,2-diamino-1,2-diphenylethane 8

Following the procedure of Lifshitz and Bos,[2] and starting from (*S*,*S*)-**3** (5.0 g, 16.8 mmol), gave diamide **8** (5.7 g, 15.9 mmol, 95%) as a colourless solid: mp >230 °C; $[\alpha]_D^{25} = +64.9$ (*c* 1.0, 9:1, $CHCl_3$–MeOH); FT IR (NaCl, Nujol®) ν_{max} 3314, 1651, 1633 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, $J = 8.8$ Hz, 1H, N*H*), 8.70 (d, $J = 8.8$ Hz, 1H, N*H*), 7.76 (d, $J = 6.8$ Hz, 2H, Ar–*H*), 7.55–7.45 (m, 3H, Ar–*H*), 7.32–7.12 (m, 10H, Ar–*H*), 5.46 (t, $J = 8.4$ Hz, 1H, NC*H*), 5.38 (t, $J = 8.4$ Hz, 1H, NC*H*) 1.80 (s, 3H, COOCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 166.9, 141.0, 141.0, 134.9, 131.8 128.8, 128.4, 127.8, 127.7, 127.4, 58.2, 57.3, 23.1 ppm; MS (CI^+) 359 (M+H^+); HRMS calcd for $C_{23}H_{23}N_2O_2$ (M+H^+) 359.1760, found 359.1771 (M+H^+).

4.4. (−)-(1*S*,2*S*)-1,2-Diamino-1,2-diphenylethane 2

Following the procedure of Williams and Bailar,[3] starting from diamide **8** (5.0 g, 14.0 mmol), gave diamine **2** (1.44 g, 6.8 mmol, 49%) as a colourless solid after recrystallisation (Et_2O–petroleum ether): $[\alpha]_D^{25} = -106.0$ (*c* 1, EtOH); other data identical to that previously reported.[1]

Acknowledgements

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

References

1. Braddock, D. C.; Redmond, J. M.; Hermitage, S. A.; White, A. J. P. *Adv. Synth. Catal.* **2006**, *348*, 911–916, and references cited therein.
2. Lifschitz, I.; Bos, J. G. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 173–183.
3. Williams, O. F.; Bailar, J. C., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4464–4469.
4. Lifschitz, I.; Bos, J. G. *Recl. Trav. Chim. Pays-Bas* **1939**, *58*, 638–642.
5. For example, see: Dauwe, C.; Buddrus, J. *Synthesis* **1995**, 171–172.
6. Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999–1002.