Chemo-Enzymatic Synthesis of (*S*)-(+)-Ericlamine and Related Enantiomerically Pure 2,2-Disubstituted-2-aminoethanols

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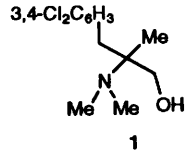
The synthesis of (*S*)-(+)-ericlamine (*S*)-**1** and related disubstituted amino alcohols is described as an example of the stereoselective synthesis of amino alcohols from disubstituted amino acids and their corresponding amides. Thus, the amino alcohols (*S*)-**1**, (*R*)-**6** and (*S*)-**7** are prepared from enantiomerically pure α-methyl-3,4-dichlorophenylalanine (amide), (*R*)-**4** and (*S*)-**5**, respectively, by application of the recently developed sodium–propan-1-ol or $NaBH_4$–H_2SO_4 reduction method followed by reductive alkylation. (*R*)-**4** and (*S*)-**5** were prepared by phase transfer catalysis and subsequent enzymatic hydrolysis of racemic **4** using an amidase from *Ochrobactrum anthropi*.

Enantiomerically pure amino alcohols and diamines are of increasing interest in asymmetric synthesis[1] and as building blocks in the synthesis of pharmaceuticals.[2,3] 2,2-Disubstituted ethanolamines are less frequently employed, mainly because they are not so readily available as the mono-substituted derivatives which can be prepared by reduction of (natural) amino acids. However, the advantage of disubstituted amino acids and ethanolamines in asymmetric synthesis over the mono-substituted compounds has been demonstrated.[4] Increased steric hindrance may increase the chiral discrimination and prevent racemisation. For these reasons, we are interested in the synthesis and use of enantiomerically pure α,α-disubstituted α-amino acids and their derivatives. We have developed an enzymatic resolution of α,α-disubstituted glycine amides using an amino acid amidase from *Mycobacterium neoaurum*.[5] These disubstituted glycine amides can be prepared by Strecker synthesis with the appropriate ketones followed by hydrolysis in conc. H_2SO_4 or HCl–HCO_2H,[6] or more conveniently by phase transfer-catalysed alkylation of the Schiff bases of monosubstituted amino acid amides.[7] Recently, we found a new micro-organism, *Ochrobactrum anthropi*, which is also able to hydrolyse the α,α-disubstituted glycine amides with a much broader substrate specificity.[8] It is also able to hydrolyse α-hydroxy- and α-(hydroxyamino)-substituted carboxamides. Amino alcohols may be prepared by reduction of the corresponding amino acids, or from the corresponding amino acid amides using liquid sodium in refluxing propan-1-ol.[9]

In this article, we present our results in the synthesis of (enantiomerically pure) 2,2-disubstituted ethanolamines, ericlamine **1** being employed as a target molecule, using the



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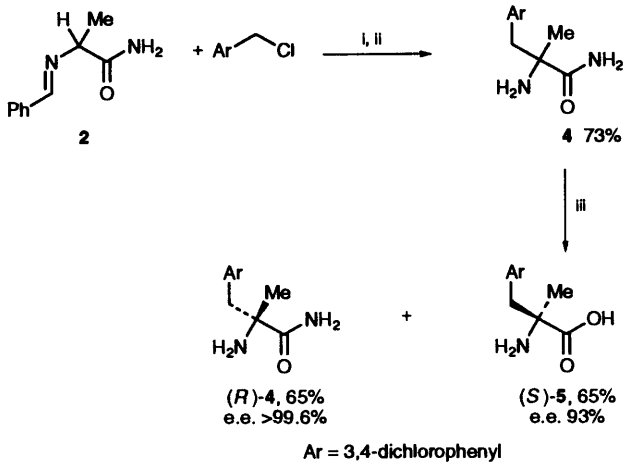
methods mentioned above. Ericlamine hydrochloride is a potent and selective synaptosomal 5-HT uptake inhibitor developed by Jouveinal, currently under investigation in clinical trials as an antidepressant.[3]

Results and Discussion

The racemic amide **4** was prepared by phase transfer-catalysed benzylation of *N*-benzylidenealanine amide (see Scheme 1). As observed previously,[7] alkylation occurred only at the α-position and not at the amide nitrogen atom. After acidic work-up of



Scheme 1 *Reagents and conditions:* i, NaOH (10 mol dm^{-3}), CH_2Cl_2, phase-transfer catalysis; ii, HCl; iii, amidase from *O. anthropi*, pH 5.3, 40 °C

the intermediate Schiff base, **4** was obtained in 73% yield. The amide **4** is only sparingly soluble in water; the solubility at pH 8 is less than 0.2%, but increases to 2.5% at pH 5.3 (both at 40 °C).

α,α-Disubstituted amino acid amides can be resolved into the (*S*)-acid and the (*R*)-amide, using the amino acid amidase from *Mycobacterium neoaurum*.[5] However, since the pH optimum of this enzymatic hydrolysis is approximately 8–9, poorly soluble substrates like **4** are difficult to hydrolyse. A good alternative was found in employment of a stereospecific amidase from *Ochrobactrum anthropi*,[8] the pH optimum of which is broader; thus, although it has a pH optimum at pH 8–9, approximately 50% of the maximum activity is still preserved at pH 5–6 (observed for the hydrolysis of mandel amide).

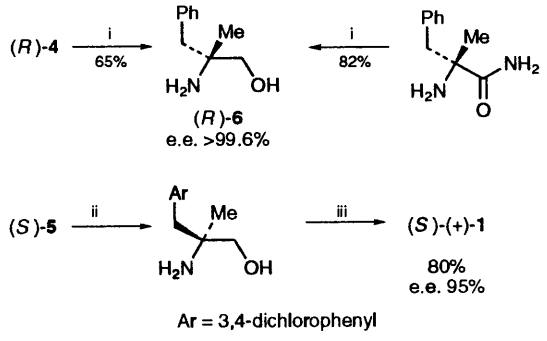
Under these conditions (pH 5.3, 40 °C), compound **4** was smoothly hydrolysed in 15 h to the (*S*)-acid **5** while the (*R*)-amide **4** remained unaffected. (*R*)-**4** and (*S*)-**5** were both isolated in 65% yield (based on the single enantiomers) with enantiomeric excesses of ≥99.6 and 93%, respectively. Hydrolysis under these conditions occurred for more than 50% (the conversion was 51.7%). The enantiomeric ratio *E* of this enzymatic reaction was calculated using the method of Sih and co-workers[10] and found to be 170. Because of the low solubility of the amide **4** and of the acid **5** in both aqueous solutions and organic solvents, separation of the enzymatic reaction mixture could only be accomplished using large amounts of solvents.

The enantiomeric excesses of (*S*)-**5** and (*R*)-**4** were

determined by means of reverse-phase HPLC with pre-column derivatisation using *o*-phthalaldehyde in combination with (*R*)-2-methyl-3-sulfanylpropionic acid.[11] The absolute stereochemistry was elucidated by chemical correlation of remaining (*R*)-amide **4** with (*R*)-(α-methyl)phenylalanine amide[5] (*vide infra*). This confirms our earlier observation that the amidase from *Ochrobactrum anthropi* is always *S*-stereospecific.[8]

Worthy of note is the remarkable difference in m.p. between racemic and enantiomerically pure **4** (137.5–138.0 and 100–101 °C, respectively). The higher m.p. of the racemate indicates a high eutectic composition of the (*R*) and (*S*) enantiomers in **4**. As a consequence, enrichment of partially resolved **4** by crystallisation would be difficult, illustrating the great advantage of the high stereospecificity of the enzymatic resolution.

Recently, we developed a new method for the transformation of amino acid amides into amino alcohols by a dissolving metal reduction (sodium in refluxing propan-1-ol).[9] Although considerable racemisation was observed for α-monosubstituted-α-amino acid amides, α,α-disubstituted α-amino acid amides were reduced without any racemisation. Initial attempts at reducing (*R*)-**4** by this method, using 8 equiv. of sodium, resulted in poor yields of the desired product (*R*)-**7**. Dehalogenation accompanied the amide reduction to such an extent that **6** and dehalogenated **4** were isolated as the main products. By using a large excess of sodium (17 equiv.), (*R*)-**6** could be isolated in moderate yield without racemisation (see Scheme 2). The same



Scheme 2 *Reagents and conditions:* i, Na, propan-1-ol, reflux; ii, $NaBH_4$, H_2SO_4; iii, CH_2O, HCO_2H

amino alcohol was prepared in 82% yield by reduction of (*R*)-(α-methyl)phenylalanine amide.

The (*S*)-enantiomer of **7** was prepared by reduction of (*S*)-**5** using the $NaBH_4$–H_2SO_4 method described by Abiko and Masamune[12] for the reduction of α-hydrogen amino acids. After basic work-up of the reaction, a mixture of (*S*)-**7** and its oxaborazoline remained. The latter could be hydrolysed to (*S*)-**7** by acidic work-up. This method is a good alternative for the BH_3- or $LiAlH_4$-mediated reductions which are frequently used. Finally, Eschweiler–Clarke methylation of the amino alcohol (*R*)-**7** as reported by Gouret *et al.*[3] resulted in (*S*)-(+)-cericlamine **1** in 80% yield. The same procedure was repeated for the synthesis of racemic cericlamine after hydrolysis of **4** in refluxing hydrochloric acid. The enantiomeric excess of (*S*)-(+)-**1** was determined by HPLC using a (chiral) Sumichiral OA-4400 column. The (*R*)-enantiomer of cericlamine can be prepared in a similar manner after hydrolysis of enantiomerically pure (*R*)-**4**.

In conclusion, phase transfer-catalysed alkylation of Schiff bases of amino acid amides, followed by enzymatic resolution by *Ochrobactrum anthropi* under acidic conditions offer a good method for the synthesis of hydrophobic enantiomerically pure α,α-disubstituted amino acid derivatives. From these derivatives, the amino alcohols can be readily prepared by reduction of the amino acid amide (Na–C_3H_7OH) or by reduction of the amino acid itself ($NaBH_4$–H_2SO_4).

Experimental

General Remarks.—Solvents of p.a. grade were purchased from Baker, Merck and Riedel-de Haën, and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 and 50.31 MHz, respectively. *J* Values are given in Hz. Exact mass determinations were performed on an MS80 spectrometer by chemical ionisation (CI/NH_3). Enantiomeric excesses of compounds (*R*)-**4**, (*S*)-**5**, (*R*)-**6** and (*S*)-**7** were determined by HPLC using the *o*-phthalaldehyde/(*R*)-2-methyl-3-sulfanylpropionic acid reagent.[11] The percentage of methanol in the mobile phase was 45 (compounds **4** and **5**), 60 (compound **6**) and 50 (compound **7**). The e.e. of (*S*)-**1** was determined by HPLC [column: Sumichiral OA-4400; mobile phase: hexane–1,2-dichloroethane–methanol–trifluoroacetic acid (240:140:20:1)]. Elemental analyses were performed by combustion analysis. *N*-Benzylidenealanine amide was prepared from alanine amide according to ref. 13 and (*R*)-(α-methyl)phenylalanine amide according to ref. 5.

2-Amino-3-(3,4-dichlorophenyl)-2-methylpropionamide **4**.—α,3,4-Trichlorotoluene **3** (20 g, 0.102 mol) was added to a mixture of *N*-benzylidenealanine amide **2** (17.6 g, 0.10 mol), CH_2Cl_2 (150 cm^3), aqueous NaOH (10 mol dm^{-3}) and Bu_4N^+-HSO_4^- (700 mg, 2.0 mmol). The mixture was vigorously stirred for 18 h at room temperature and then diluted with water. The aqueous layer was separated and the organic layer was washed with water. The aqueous layers were again extracted with CH_2Cl_2 (100 cm^3). To the combined organic layers were added HCl solution (500 cm^3; 1 mol dm^{-3}) and additional CH_2Cl_2 (300 cm^3). After being stirred for 1 h the mixture was heated to 40 °C to facilitate separation. The aqueous layer was washed with $CHCl_3$, and basified with aqueous NaOH (4 mol dm^{-3}). The resulting aqueous suspension was extracted with $CHCl_3$ (3 × 500 cm^3). The combined extracts were dried (Na_2SO_4), concentrated to 50 cm^3, and left to crystallise. The resulting colourless crystals were filtered off and washed with toluene and hexane to give the title compound **4** (18.0 g, 73 mmol, 73%), m.p. 137.5–138.0 °C (Found: C, 48.1; H, 4.7; N, 11.3%; M^+, 247.0398. Calc. for $C_{10}H_{12}Cl_2N_2O$: C, 48.6; H, 4.9; N, 11.3%; *M*, 247.0405); δ_H([$^2H_6$]DMSO) 1.16 (s, 3 H), 1.64 (br, 2 H), 2.65 (d, 1 H, *J* 12.8), 2.97 (d, 1 H, *J* 12.8), 7.02 (br, 1 H), 7.17 (dd, 1 H, *J* 8.2, 2.0), 7.23 (br, 1 H), 7.44 (d, 1 H, *J* 2.0) and 7.52 (d, 1 H, *J* 8.2). δ_C([$^2H_6$]DMSO); 26.97 (q), 44.77 (t), 57.87 (s), 128.75 (s), 129.66 (d), 130.12 (s), 130.61 (d), 131.99 (d), 139.04 (s) and 178.34 (s).

Enzymatic Resolution of 2-Amino-3-(3,4-dichlorophenyl)-2-methylpropionamide **4**.—A suspension of racemic **4** (5.0 g, 20 mmol) in water (250 cm^3) was acidified to pH 5.3 with aqueous HCl (approx. 16 mmol). Crude cell mass (7 cm^3) of *Ochrobactrum anthropi* NCIMB 403218 was added to the mixture which was then stirred for 15 h at 40 °C. At 55% conversion (NH_3 determination), the reaction mixture was acidified to pH 1.5. After removal of the cell mass by centrifugation (8000 rpm, 20 min), the supernatant was made basic with aqueous NaOH and extracted with CH_2Cl_2 (2 × 200 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated to dryness. The residual white solid was washed with toluene to yield (*R*)-**4** [1.6 g, 6.5 mmol, 65% based on (*R*)-enantiomer], m.p. 100–101 °C; R_F 0.83 ($CHCl_3$–MeOH–conc. NH_4OH 60:45:20); $[\alpha]_D^{25}$ +27.3 (*c* 1 in MeOH); e.e. ≥99.6% (*R*)-isomer; for spectroscopic data, see (*RS*)-**4**.

The aqueous layer containing the amino acid (*S*)-**5** was

neutralised to pH 7 with aqueous HCl (4 mol dm^{-3}) after which the solid was collected and washed with water and acetone; (*S*)-**5** [1.6 g, 6.5 mmol, 65% based on (*S*)-enantiomer] was obtained as a white solid, m.p. > 290 °C (Found: M^+, 248.0257. Calc. for $C_{10}H_{12}Cl_2NO_2$: *M*, 248.0245); R_F 0.68 ($CHCl_3$–MeOH–conc. NH_4OH 60:45:20). HCl salt: $[\alpha]_D^{25}$ +9.9 (*c* 1.2 in MeOH); e.e. 93% (*S*)-isomer; $\delta_H(D_2O$–DCl) 1.58 (s, 3 H), 3.16 (d, 1 H, *J* 14.3), 3.25 (d, 1 H, *J* 14.3), 7.24 (dd, 1 H, *J* 8, 2), 7.46 (d, 1 H, *J* 2) and 7.60 (d, 1 H, *J* 8). $\delta_C(D_2O$–DCl) 21.68 (s), 40.40 (t), 59.32 (s), 130.30 (s), 130.54 (2 d), 130.95 (s), 132.12 (d), 134.66 (s) and 171.44 (s).

(R)-2-*Amino*-2-*methyl*-3-*phenylpropan*-1-*ol* (R)-**6**.—*From* 2-*amino*-3-(3,4-*dichlorophenyl*)-2-*methylpropionamide*. To a refluxing solution of (*R*)-**4** (800 mg, 3.24 mmol) in propan-1-ol (10 cm^3) under N_2 was added sodium metal (1.3 g, 55 mmol) in small portions over a period of 1 h. After the addition was complete the mixture was refluxed for a further 1 h. After the mixture had cooled it was diluted with water (10 cm^3) and evaporated to dryness. The residual solid was dissolved in water and the solution extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to provide the title compound, (*R*)-**6** (350 mg, 2.12 mmol, 65%) as a slowly crystallising colourless oil, e.e. ≥99.6%.

From (R)-(α-*methyl*)*phenylalanine amide*. To a refluxing solution of (*R*)-(α-methyl)phenylalanine amide (3.3 g, 18.5 mmol) in propan-1-ol (30 cm^3) under N_2 was added sodium metal (3.9 g, 170 mmol) over a period of 1.5 h. After an additional 1 h under reflux, the reaction mixture was worked up as above. The residual oil was distilled (bulb-to-bulb, b.p. 110–115 °C/0.1 Torr)* to yield (*R*)-**6** (2.5 g, 15.2 mmol, 82%), m.p. 64–66 °C (Found: M^+, 166.1228. Calc. for $C_{10}H_{15}NO$: *M*, 166.1232); $[\alpha]_D^{22}$ +5.9 (*c* 1 in MeOH); e.e. ≥99.6%; $\delta_H(CDCl_3)$ 1.03 (s, 3 H), 2.63 (br, 3 H), 2.71 (s, 2 H), 3.37 (AB pattern, 2 H, *J* 10.8) and 7.15–7.35 (m, 5 H); $\delta_C(CDCl_3)$ 23.95 (q), 45.07 (t), 53.11 (s), 68.90 (t), 125.91 (d), 127.65 (d), 130.30 (d) and 136.90 (s).

(RS)-2-*Amino*-3-(3,4-*dichlorophenyl*)-2-*methylpropionic Acid* **6**.—The racemic amide **4** (1.24 g, 5.0 mmol) in conc. HCl solution (25 cm^3) was refluxed for 15 h, after which the reaction mixture was allowed to cool and then concentrated under reduced pressure. The residual solid was dissolved in water (25 cm^3) and the solution neutralised with aqueous NaOH (4 mol dm^{-3}). The white precipitate was filtered off and washed with water and acetone to yield the title compound **6** (800 mg, 3.2 mmol, 64%); for spectroscopic data, see (*S*)-**6**.

(S)-2-*Amino*-3-(3,4-*dichlorophenyl*)-2-*methylpropan*-1-*ol* (S)-**7**.—Upon addition of $NaBH_4$ (380 mg, 10 mmol) to a suspension of (*S*)-**5** (1.0 g, 4.0 mmol) in THF (10 cm^3) gas was evolved. At room temperature, a solution of H_2SO_4 (490 mg, 5.0 mmol) in Et_2O (2 cm^3) was added dropwise over 1 h to the mixture which was then stirred for 3 d at room temperature. After this MeOH (1 cm^3), followed by aqueous NaOH (4 mol dm^{-3}; 5 cm^3) and aqueous HCl (4 mol dm^{-3}; 10 cm^3) were added to the mixture which was then heated at 60 °C for 30 min. After this the mixture was washed with $CHCl_3$ and neutralised with aqueous NaOH (4 mol dm^{-3}). The aqueous suspension was then extracted with $CHCl_3$ (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to afford the title compound (*S*)-**7** (788 mg, 3.37 mmol, 84%) as a slowly crystallising colourless oil, m.p. 83–84 °C (Found: M^+, 234.0436. Calc. for $C_{10}H_{13}Cl_2NO$: *M*, 234.0452); $[\alpha]_D^{20}$ −2.7 (*c* 1.2 in MeOH); e.e. 95% (*S*)-isomer; $\delta_H(CDCl_3)$ 1.03 (s, 3 H), 1.9 (br, 3 H), 2.67 (AB pattern, 2 H, *J* 13), 3.32 (AB pattern, 2 H, *J* 10), 7.05 (dd, 1 H, *J* 7, 2), 7.81 (d, 1 H, *J* 2) and 7.88 (d, 1 H, *J* 7); $\delta_C(CDCl_3)$ 25.89 (q), 45.91 (t), 54.73 (s), 70.60 (t), 131.16 (d), 131.84 (s), 133.4 (s), 133.45 (d) and 139.17 (s).

The racemic compound **7** was prepared identically to **6** (700 mg) in 88% yield (m.p. 94–96 °C); for spectroscopic data, see (*S*)-**7**.

(S)-3-(3,4-*Dichlorophenyl*)-2-(*dimethylamino*)-2-*methylpropan*-1-*ol* (S)-**1**.—A solution of (*S*)-**7** (470 mg, 2.0 mmol), formic acid (3.0 g) and formaldehyde (1.5 g, 37% solution) was refluxed for 1.5 h and then allowed to cool. Aqueous HCl (4 mol dm^{-3}; 2 cm^3) was added to the solution which was then concentrated. The residue was dissolved in water and the solution washed with $CHCl_3$. The aqueous layer was made alkaline by addition of aqueous NaOH (4 mol dm^{-3}) after which it was extracted with $CHCl_3$ (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) to afford a slowly crystallising oil which was purified by chromatography on silica gel [Merck Kieselgel 60 (230–400 mesh); eluent toluene–MeOH 6:1]. This yielded (*S*)-**1** (420 mg, 1.6 mmol, 80%) as a slowly crystallising, colourless oil, m.p. 76–78 °C (Found: M^+, 262.0754. Calc. for $C_{12}H_{17}Cl_2NO$: *M*, 262.0765); R_F 0.08 (toluene–MeOH 8:1); $[\alpha]_D^{22}$ +6.3 (*c* 1 in EtOH); e.e. 95%; $\delta_H(CDCl_3)$ 0.91 (s, 3 H), 2.37 (s, 6 H), 2.65 (d, 1 H, *J* 12.8), 2.81 (d, 1 H, *J* 12.8), 3.28 (AB pattern, 2 H, *J* 11.0), 3.61 (br, 1 H), 67.07 (dd, 1 H, *J* 2.0, 8.3), 7.31 (d, 1 H, *J* 2.0) and 7.34 (d, 1 H, *J* 8.3). $\delta_C(CDCl_3)$ 16.70 (q), 38.99 (q), 39.33 (t), 61.28 (s), 64.88 (t), 130.87 (d), 131.07 (d), 131.30 (s), 132.87 (s), 133.28 (d) and 137.55 (s). Racemic **1** was prepared in an identical manner in 86% yield from **7** (570 mg). The product was purified by crystallisation from hexane, m.p. 86–87 °C; for spectroscopic data, see (*S*)-**1**.

* 1 Torr = 133.322 Pa.

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