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Technical Notes

Efficient Preparation of (*R*)- and (*S*)-2-Amino-1-phenylethanol

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Abstract:

The preparation of optically pure 2-amino-1-phenylethanol was investigated using three methods. The opening of styrene oxide with ammonia, the reduction of mandelamide, and the resolution of (±)-2-amino-1-phenylethanol were compared from a process R&D viewpoint. The resolution using di-*O*-*p*-toluoyltartaric acid was found to be the method of choice and was optimised to yield 62% of optically pure substance.

β-Amino alcohols are widely found as building blocks in organic synthesis[1] and in medicinal chemistry.[2] They have recently been used for the synthesis of 1-phenyl-2-[(2-phenyl-1-alkylethyl)amino]ethanol derivatives, a new important class of antidiabetic agents.[3] As we became interested in the preparation of (*R*)- and (*S*)-2-amino-1-phenylethanol, we found in the literature three methods that would be amenable to scale-up:[4] the opening of styrene oxide with ammonia,[3] the reduction of mandelamide,[5] and the resolution of (±)-2-amino-1-phenylethanol.[6]

Treatment of (*R*)-styrene oxide (**1**) with aqueous ammonia in methanol produced (*R*)-2-amino-1-phenylethanol (**2**) (~70%) with some 2-amino-2-phenylethanol and other by-products.[3] The desired product **2** could be purified via the crystallisation of its HCl salt in ethyl acetate and liberation of the free base in toluene (Scheme 1). **2** was obtained with a global yield of 43% (ee 99%) and contained 3.5% of its regioisomer.[7]

Treatment of (*S*)-mandelic acid (**3**) with acetone under acid catalysis generated the dioxolanone derivative **4**, which, with ammonia in ethanol, gave (*S*)-mandelamide (**5**).[8] Reduction of **5** with $LiAlH_4$ in THF[5] afforded the amine **6** in 60% yield and unreacted **5** (30%) (Scheme 2). All attempts to obtain a complete conversion of **5** failed, and **6** was obtained with only 93% ee due to a partial racemisation of mandelamide. Eventually, we found that a large excess of BH_3 in THF could reduce **5** with 90% yield and without racemisation. However, these conditions were not practical for scaling up.

The resolution of (±)-2-amino-1-phenylethanol (**7**) using tartaric acid had already been described in the literature.[6a,b,d] The authors obtained a moderate yield of the resolved material, which was only 63% enantiomerically pure.[6c] We decided to improve the resolution[6e] and screened 10 different

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(1) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett* **1994**, 509.

(2) Goodman, L. S.; Gilman, A. *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill: New York, 1996.

(3) Daicel Chemical Industries Ltd. European Patent Application No. 0 654 534 A2, Nov 18, 1994.

(4) Other routes to optically active 2-amino-1-phenylethanol exist but were not considered as being easily amenable to scale-up. (a) By chiral hydrogenation of 2-aminoacetophenone: Roucoux, A.; Devocelle, M.; Carpentier, J. F.; Agbossou, F.; Mortreux, A. *Synlett* **1995**, *4*, 358 and references cited therein. The best chiral ligands for this hydrogenation are not commercially available, the turnovers are slow, the ee are not higher than 93%, and pressures higher than 50 atm are needed. (b) By enzymatic resolution: Lundell, K.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 2281; Takayama, S.; Moree, W. J.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6287. The enzymatic monoacylation of (±)-2-amino-1-phenylethanol or deacylation of the corresponding N,O-diacylated compound always leads to the formation of an amide product due to a favourable O → N migration and to the higher stability of an amide product compared to the corresponding ester.[15] In the case of deacylation, a lipase works only at the ester bond, leaving the amide bond unreacted. Therefore, an enzymatic route to optically pure 2-amino-1-phenylethanol needs an additional step for the amide cleavage compared to a classical resolution. (c) *By bakers' yeast reduction of 2-aminoacetophenone:* Sorrilha, A. E. P. M.; Marques, M.; Joekes, I.; Moran, P. J. S.; Rodrigues, J. A. R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 191. All microbial reductions of (±)-2-amino-1-phenylethanol that we encountered in the literature operate under high dilution and with a slow turnover. Therefore, the throughput of this approach is very low. (d) *By resolution of a conglomerate:* Shiraiwa, T.; Nakamura, M.; Taniguchi, S.; Kurokawa, H. *Nippon Kagaku Kaishi* **1985**, *5*, 910. This reference describes the resolution of 2-amino-1-phenylethanol as a salt with 3-aminobenzoic acid. The yields and optical purity are moderate, and the process works only in tetrahydrofuran, which is an expensive solvent. (e) Other exotic routes exist but were not considered since they required several steps.

(5) (a) Schöpf, C.; Wüst, W. *Justus Liebigs Ann. Chem.* **1959**, *626*, 150. (b) Pratesi, P; Grassi, M. *Farmaco, Ed. Sci.* **1953**, *8*, 86. (c) Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.

(6) (a) Rupe, H.; Engel, K. *Helv. Chim. Acta* **1935**, *18*, 1190. (b) Read, J.; Campbell, G. M. *J. Chem. Soc.* **1930**, 2682. (c) When we tried to reproduce[6e] the results of Rupe and Engel,[6a] we obtained only a 3.7% yield (three recrystallisations) of a compound having 63% ee according to chiral HPLC. We tried briefly to optimise the resolution using tartaric acid, but we always obtained erratic results (the crystallisation was occurring very rapidly or not at all in a temperature range of 5 °C). Since the p and n salts (made from commercially available (*R*)- and (*S*)-2-amino-1-phenylethanol)[13] were found to have similar solubilities, our understanding is that this resolution is kinetically controlled and therefore difficult to control. More details can be found in Jacques et al.: Jacques, J.; Collet, A.; Wilen, S. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981. (d) Green, A. L.; Fielden, R.; Bartlett, D. C.; Cozens, M. J.; Eden, R. J.; Hills, D. W. *J. Med. Chem.* **1967**, *10*, 1006. We were not able to reproduce Hills's results when using technical grade 2-amino-1-phenylethanol. The problem of a spontaneous crystallisation of a racemic mixture is also described as a footnote in ref 6d, which is in good agreement with our previous remark.[6c] (e) All experiments were conducted using technical grade (±)-2-amino-1-phenylethanol.

(7) Methods for improving the regioselectivity of the epoxide opening exist. However, we judged that the process would become too complicated and too expensive. For examples, see: (a) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195. (b) Atkins, R. K.; Frazier, J.; Moore, L. L.; Weigel, L. O. *Tetrahedron Lett.* **1986**, *27*, 2451. (c) Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831. (d) Carre, M. C.; Houmounou, J. P.; Caubere, P. *Tetrahedron Lett.* **1985**, *26*, 3107.

(8) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2223.

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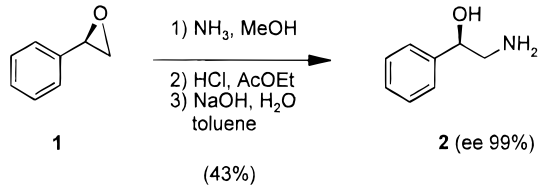
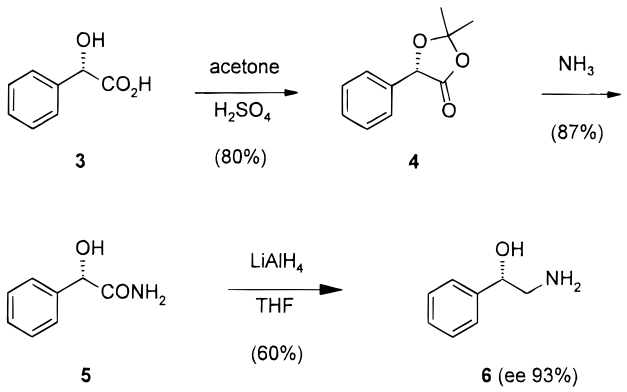
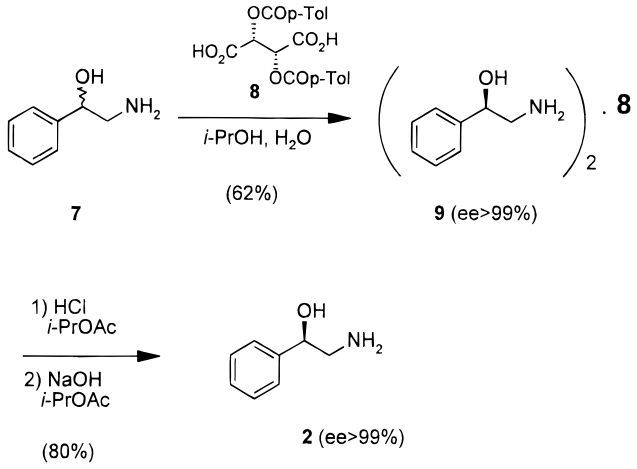
Scheme 1. **Synthesis of (*R*)-2-amino-1-phenylethanol from (*R*)-styrene oxide**



Scheme 2. **Conversion of (*S*)-mandelic acid into (*S*)-2-amino-1-phenylethanol**

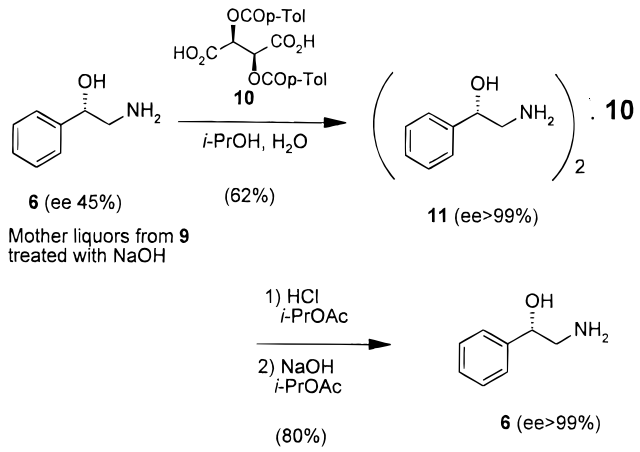


Scheme 3. **Resolution of (±)-2-amino-1-phenylethanol with di-*O*-*p*-toluoyl-L-tartaric acid**



chiral acids[9] in various solvents.[10] We finally found that di-*O*-*p*-toluoyl-L-tartaric acid (**8**) in 2-propanol−water gave the best results (Scheme 3). The resolution was conducted using "the method of half quantities", first described by Marckwald.[11] By using only 0.25 equiv of the chiral diacid **8** and two recrystallisations, the chiral salt **9** was obtained with 62% yield and an optical purity higher than 99%.[12] Using technical grade (±)-2-amino-1-phenylethanol (**7**) (purity 88%), the chemical purity of the salt **9** was greater than 99%. The free base **2** was released from **9** by a classical acid−base extraction with 80% yield (purity and ee >99%, 90% recovery of **8**).

Scheme 4. **Purification of (*S*)-2-amino-1-phenylethanol via diastereomeric crystallisation**



From the mother liquors of the crystallisation, the salt **11** was obtained with 62% yield and the same purity as **9** (Scheme 4). The free amino alcohol **6** was released using the same conditions as for **2**.

From the three different approaches[4] to optically pure 2-amino-1-phenylethanol, we found that the resolution was the least expensive and the easiest to perform on a large scale.[13] It had the additional advantage that it did not lead to any regioisomer problem as experienced in the styrene oxide opening. The resolution was successfully scaled up to 9 kg.[14]

Experimental Section

General Remarks. Technical grade solvents were used. (±)-2-Amino-1-phenylethanol was purchased from Fluka. It contained 6.9% regioisomer and 5.1% unknown by-products. Di-*O*-*p*-toluoyl-L-tartaric acid was purchased from Chemie Uetikon (Switzerland) and di-*O*-*p*-toluoyl-D-tartaric acid from Fluka.

Analytical Procedures. HPLC were recorded on a Hewlett-Packard 1050.

Chemical Purity of the Salt and Free Base. Column: Speri-5 cyano 5 μm, 100 × 4.6 mm (Brownlee Appl. Syst.). Gradient: from 95% buffer −5% acetonitrile to 20% buffer in 20 min. Buffer: 1.32 g of diammonium hydrogen phosphate in 1 L of bidistilled water. Flow: 1 mL/min at 60 °C. Detection: 210 nm. Method: dissolve 10 mg of sample in 20 mL acetonitrile and inject 10 μL. Retention time: 2-amino-1-phenylethanol, 6.25 min; 2-amino-2-phenylethanol, 4.59 min; di-*O*-toluoyltartaric acid, 0.82 min.

Enantiomeric Purity of the Salt and Free Base. Column: Chiracel OJ 10 μm, 250 × 4.6 mm. Solvent: 8.0% v/v 2-propanol in *n*-hexane. Flow: 0.5 mL/min at 10 °C. Detection: 210 nm. Method: Dissolve 5 mg of sample in

(9) The number in parentheses represents the best ee obtained after one crystallisation: (+)-camphoric acid (38%), (*R*)-10-camphorsulfonic acid (1.5%), di-*O*-*p*-toluoyl-L-tartaric acid (91%), BOC-L-alanine (69%), mandelic acid (9.5%), L-pyroglutamic acid (67%), di-*O*-benzoyl-L-tartaric acid (no crystallisation), di-*O*-naphthoyl-L-tartaric acid (65%), L-tartaric acid (25%), and di-*O*-benzoyl-L-tartaric acid monoamide (no crystallisation).

(10) Among the solvents tested: MeOH, EtOH, *i*-PrOH, *n*-BuOH, *i*-BuOH, AcOEt, *t*-BuOMe, and alcohol−water mixtures.

(11) (a) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 42. (b) For all the chiral acids tested, we observed that the resolution was more efficient when only 0.5 equiv of the resolving agent was used. For example, the resolution with 0.5 equiv of di-*O*-*p*-toluoyl-L-tartaric acid (diacid ⇒ 1 equiv of acidic function) gave only 25% ee (91% ee with 0.25 equiv).

(12) The stoichiometry of the salt **9** was proven by NMR (DMSO).

(13) (*R*)- and (*S*)-2-amino-1-phenylethanol are commercially available from Oxford Asymmetry.

(14) Remarkably, the procedure used for the first 2 g in the lab and for the 9 kg batch in the plant is exactly the same and gave the same yield and purity on both scales (scale-up factor: 4500).

(15) Kanerva, L. T.; Kosonen, M.; Vänttinen, E.; Huuhtanen, T. T.; Dahlqvist, M. *Acta Chem. Scand.* **1992**, *46*, 1101.

2 mL of saturated aqueous sodium carbonate. Add 50 μL of benzoyl chloride, shake, and let stand at room temperature for 5 min. Adjust the volume to 10 mL with 20% v/v 2-propanol in *n*-hexane. Inject 20 μL. Retention time: *R* isomer, 31.25 min; *S* isomer, 39.95 min.

Salt 9. (±)-2-Amino-1-phenylethanol (**7**) (131.3 g; purity 88%: 115.6 g of 100%, 0.842 mol) was suspended in *i*-PrOH−H_2O (1235 mL, 1:1 mixture), and 86.9 g of di-*O*-p-toluoyl-L-tartaric acid (**8**) (purity 97%; 84.3 g of 100%, 0.218 mol, 0.26 equiv) was added. The mixture was heated to 55 °C, at which point it went into solution. The temperature was cooled down to 30 °C in 2 h, and the solution was seeded. It was stirred at 20 °C for 20 h and at 5 °C for 1.5 h. The suspension was filtered and washed with 100 mL of cold *i*-PrOH−H_2O (1:1). The solid (108 g, ee 86.6%) was recrystallised a first time from 860 mL of *i*-PrOH−H_2O (1:1) (100.5 g, ee 95.6%) and a second time from 700 mL of *i*-PrOH−H_2O (1:1), and yielded 95 g of salt **9** (62%).[12] The salt contained 4.1% water and 5.8% *i*-PrOH. HPLC purity: 99.9%; HPLC ee: 99.1%. **9** was used without drying in the next step.

(*R*)-2-Amino-1-phenylethanol (2). Salt **9** (15 g; 13.51 g of 100%, 98.5 mmol) was suspended in 75 mL of water and 75 mL of *i*-PrOAc, and the mixture was cooled down to 5 °C. Concd HCl (10 mL) was slowly added, and the solution was stirred for 1 h. The water phase was extracted twice with 20 mL of *i*-PrOAc. To the cooled water phase were added 75 mL of *i*-PrOAc, 30 g of NaCl, and 12 mL of aqueous 30% NaOH (until pH = 13). The water phase was extracted twice with 30 mL of *i*-PrOAc, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent and drying at 25 °C under high vacuum for 24 h yielded 4.46 g (80%) of pure **2**: HPLC purity 99.4%; HPLC ee 99.8%; $[\alpha]^{25}_D$ −43.8° (*c* 2, EtOH) (lit.[5b] $[\alpha]^{25}_D$ −42.6°); mp 61−62 °C (lit.[5b] mp 61−62 °C).

Salt 11. The first mother liquors of **9** were evaporated to dryness. Toluene (1 L) was added, followed by 300 mL of water and 600 mL of aqueous 30% NaOH. The mixture was heated to 55 °C, and the phases were separated. The water phase was extracted twice at 55 °C with 400 mL of toluene. The combined organic phases were evaporated and afforded 82.9 g of optically enriched **6**. It was dissolved in 1115 mL of *i*-PrOH−H_2O (1:1) and treated with 78.6 g of di-*O*-*p*-toluoyl-D-tartaric acid (**10**). Recrystallisation of **11** was conducted as described for **9** and yielded 96.3 g of pure salt (containing 3.7% water and 6% *i*-PrOH: 87 g of 100%, 62% yield): HPLC purity 99.9%; HPLC ee 99.9%.

(*S*)-2-Amino-1-phenylethanol (6). A 4.42 g sample was obtained by treating 15 g of **11** as described above: HPLC purity 99.2%; HPLC ee 99.1%; $[\alpha]^{25}_D$ +43.9° (*c* 2, EtOH) (lit.[5b] $[\alpha]^{25}_D$ +44.6°); mp 61−62 °C (lit.[5b] mp 61−62 °C).

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