An improved and efficient process for the scalable preparation of optically pure *trans*-2-aminocyclohexanols

Feng Xue*, Chang-Gong Li, Yong Zhu and Tian-Jun Lou

Key Laboratory of Functional Organic Molecules of Xinxiang City Henan Province, College of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang Henan, 453002, P.R. China

An improved and efficient process has been developed for a green and scalable preparation of optically pure (*1R*,*2R*)- and (*1S*,*2S*)-*trans*-2-aminocyclohexanols. The process utilised hot water to promote the aminolysis of cyclohexene oxide by benzylamine to afford racemic *trans*-2-(benzylamino)cyclohexanols, which were resolved by sequential and repeated use of (*R*)- and (*S*)-mandelic acid. Finally, after treatment of the two salts sequentially with HCl and NaOH and recovery of mandelic acid, liberation was achieved of the optically pure *trans*-2-benzylaminoaminocyclohexanols which were smoothly debenzylated using a low loading of a Pd/C catalyst to the *trans*-2-aminocyclohexanols. The synthetic route has been successfully applied to large-scale (1 mol) preparations in good yield.

Keywords: *trans*-2-(benzylamino)cyclohexanol, chiral resolution, enantiopure (*1R*,*2R*)-*trans*-2-aminocyclohexanol, enantiopure (1S,2S)-*trans*-2-aminocyclohexanol

Enantiopure *trans*-1,2-amino alcohols are versatile synthetic intermediates for the preparation of a wide variety of natural products and biologically active compounds,[1] as well as chiral auxiliaries and ligands in asymmetric synthesis.[2] Despite the impressive success in the preparation of optically pure vicinal amino alcohols, there are only a few efficient procedures for the preparation of highly enantiomerically enriched aminocyclohexanols which are suitable for a broad variety of further derivatisations.[3] Typical examples include Overman's aminolysis of cyclohexene oxide with an aluminium amide stemming from enantiomerically enriched methylbenzylamine and trimethylaluminum,[4] Jacobsen's Cr(III)/salen-catalysed enantioselective ring-opening reaction of cyclohexene oxide by azidosilanes,[5,6] as well as the resolution of racemic 2-azidocyclohexanol[7,8] and 2-aminocyclohexanol derivatives.[9,10] Although these procedures have shown some practical applications in synthesis, their application on a preparative scale has been limited and deficient in view of laborious synthetic processes and harsh reaction conditions. To overcome these problems, we now describe an improved and efficient process for the scalable preparation of optically pure (*1R,2R*)-*trans*-2-aminocyclohexanol, enantiopure (*1S,2S*)-*trans*-2-aminocyclohexanol.

Results and discussion

Following literature precedents,[11] Qu and co-workers proposed that hot water acted as a weak acid catalyst and solvent in the aminolysis of epoxides.[12] Indeed, these authors reported that racemic *trans*-2-(benzylamino)cyclohexanol (*rac*-**2**) was easily available by aminolysis of cyclohexene oxide by benzylamine in hot water in 3.5 h.[12] We adopted these gentle conditions, in contrast to the previously reported protocol[9] in which harsh reaction conditions of high temperature (250 °C) and high pressure were used. This made the reactions safe and practical for large-scale synthesis. When the aminolysis reaction was completed, simple extraction of the aqueous reaction mixture with ethyl acetate (EtOAc) yielded a solution of relatively pure *rac*-**2**, which was directly used in the resolution step. The resolution was achieved by sequential treatment of *rac*-**2** with 0.5 equiv. (*S*)- and (*R*)-mandelic acid (Scheme 1) as reported previously.[9] Subsequently, a simple work-up sequence involving formation of the amine hydrochlorides with aqueous HCl and subsequent liberation of the free bases with NaOH permitted on the one hand the almost quantitative recovery of the (*R*)- and (*S*)-mandelic acids and on the other hand the isolation of enantiopure (*1R,2R*)-**2** and (*1S,2S*)-**2** in 78–80% yields and in analytically pure form. Finally, the enantiopure *trans*-2-aminocyclohexanols **4** were smoothly obtained by debenzylation through hydrogenolysis at room temperature with a Pd/C catalyst. We found that a low loading of 20.5 mg $mmol^{-1}$ Pd/C catalyst was economical and satisfactory, which was a decrease from 80 mg $mmol^{-1}$ used previously.[9]

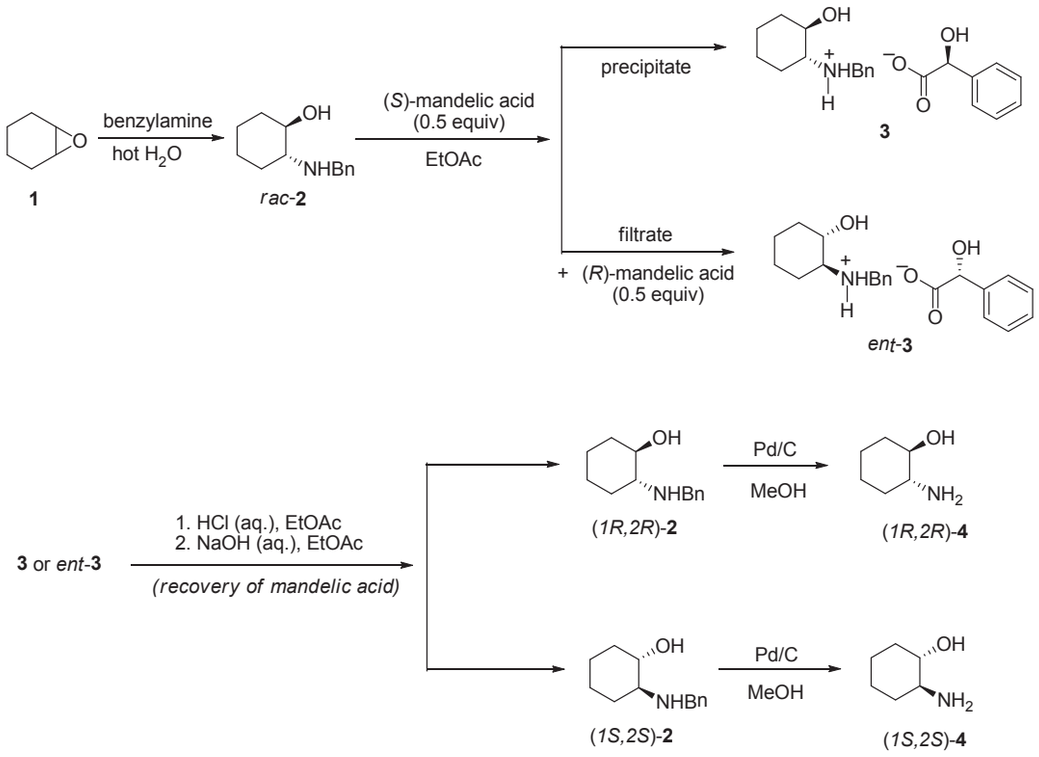
In conclusion, we report an improved and efficient process for the scalable preparation of optically pure (*1R,2R*)- and (*1S,2S*)-*trans*-2-aminocyclohexanols with smooth and simplified reaction procedures. The advantages of this improved method are its preparative ease and its efficiency in large scale resolutions delivering both amino alcohol enantiomers with 99% ee. Compared with the reported procedures, the overall process is more environmentally friendly as well as cost-effective, which will satisfy both laboratory and industrial operations.

Experimental

Solvents and reagents were purchased from the Sigma-Aldrich company and used without further purification. Melting points were determined on a Mettler FP5 melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer in DMSO-d_6 or$CDCl_3$ with tetramethylsilane (TMS) as internal standard. Optical rotations were measured with a JASCO P-1020 automatic polarimeter. High resolution mass spectra were recorded on an Applied Biosystems Mariner System 5303. Enantiomeric excess (ee) determination was carried out using HPLC with a Chiralcel AS-H and AD-H column on an Agilent 1100 Series HPLC instrument.

*A. Racemic trans-2-(benzylamino)cyclohexanol(**rac**-**2**):* A 1-L autoclave equipped with mechanical stirring, a thermometer and a refluxing condenser was charged with cyclohexene oxide (**1**) (100.0 g, 1.02 mol 1.1 equiv.) and benzylamine (99.2 g, 0.927 mol, 1 equiv.) in water (158 g, 9.5 equiv.). The reaction mixture was heated at 95 °C for 3.5 h, then cooled to ambient temperature, diluted with EtOAc (150 mL), and transferred into a 1000-mL separatory funnel, then rinsed with EtOAc (3 × 50 mL). Amino alcohol *rac*-**2** (97% purity) in EtOAc solution was obtained, which was suitable for use in the next step without further purification.

* Correspondent. E-mail: fxuehist@sina.com



Scheme 1 Preparation of optically pure (*1R,2R*)- and (*1S,2S*)-*trans*-2-aminocyclohexanols **4**.

B. (S)-Mandelic acid salt of (1R,2R)-2-trans-2-(benzylamino) cyclohexanol (**3**) *and (R)-Mandelic acid salt of (1S,2S)-2-trans-2-(benzylamino)cyclohexanol (**ent-3**):* A 1-L single-necked, round-bottomed flask containing equipped with a mechanical stirrer and a pressure-equalising addition funnel was charged with the prepared ethyl acetate solution (300 mL) containing amino alcohol *rac*-**2**, and a solution of (*S*)-mandelic acid (70.4 g, 0.46 mol, 0.5 equiv.) in EtOAc (150 mL) was added *via* the addition funnel over a period of 2 h at room temperature. After the addition was complete the dropping funnel was rinsed with EtOAc (2 × 5 mL) and the reaction mixture was stirred overnight at ambient temperature, followed by 5 h at 0 °C. The precipitated ammonium salt was collected by suction filtration, washed with ethyl acetate (2 × 50 mL), and dried under reduced pressure at room temperature over 1 h to afford the (*S*)-mandelic acid salt of (*1R,2R*)-2-*trans*-2-(benzylamino)cyclohexanol (**3**) as a colourless solid (131.8 g, 0.37 mol), yield 80% based on mandelic acid, m.p. 147–149 °C (lit.[10] 146 °C); $[\alpha]_D^{25}$ = +14.7 (*c* = 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96–1.29 (m, 4 H), 1.58–1.73 (m, 3 H), 1.90 (d, *J* = 12.6 Hz, 1 H), 2.53 (dt, *J* = 4.0, *J* = 12.0 Hz, 1 H), 3.03 (dt, *J* = 4.3, 10.6 Hz, 1 H), 3.46 (d, *J* = 12.9 Hz, 1 H), 3.89 (d, *J* = 12.6 Hz, 1 H), 4.90 (s, 1 H), 7.19–7.35 (m, 8 H), 7.49–7.52 (m, 2H). The filtrate from the above procedure was concentrated under reduced pressure to give a pale yellow oily residue (518.2 g) which was dissolved in EtOAc (200 mL), transferred into a 1-L flask, and treated with a solution of (*R*)-mandelic acid ((70.4 g, 0.46 mol, 0.5 equiv.) in ethyl acetate (100 mL) similar to the above described procedure, to deliver the (*R*)-mandelic acid salt of (*1S,2S*)-2-*trans*-2-(benzylamino) cyclohexanol (*ent*-**3**) as a colourless solid (132.8 g, 0.36 mol), yield 78% based on mandelic acid), $[\alpha]_D^{25}$ = –15.3 (*c* = 2.0, $CHCl_3$). The analytical data were in accordance with those observed for the corresponding enantiomer of opposite configuration.

C. Liberation of the amino alcohols and recovery of mandelic acid: In a 1-L separatory funnel, the mandelic acid ammonium salt **3** or *ent*-**3** (60.0 g, 0.17 mol) was partitioned between ethyl acetate (500 mL) and 2N aq. HCl solution (220 mL). Then, the mixture was manually and vigorously shaken until the salt was completely dissolved. The organic layer was additionally washed with 2 N aq. HCl solution (2 × 30 mL) and the combined aqueous phases were back-extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure to give the corresponding mandelic acid enantiomer (23.7–24.3 g, 93–94%), which showed an identical value for the optical rotation in comparison with the starting material to fully satisfy the next use. To a mixture of the acidic aqueous phase and ethyl acetate (200 mL) in the same separatory funnel, 5 N NaOH (300 mL) was added carefully in small portions over a period of 45–60 minutes. After separation, the aqueous layer was extracted with ethyl acetate (4 × 100 mL) and the combined organic phases were dried, filtered, and concentrated under reduced pressure to yield the corresponding *trans*-2-(benzylamino)cyclohexanol enantiomers (*1R,2R*)-**2** and (*1S,2S*)-**2** as white solids (31.3–32.5 g, 90–93%). The products had the following physicochemical characteristics: $[\alpha]_D^{25}$ = –78.4 (*c* = 1.12, MeOH) for (1*R*,2*R*)-**2**, $[\alpha]_D^{25}$ = +80.2 (*c* = 1.05, MeOH) for (1*S*,2*S*)-**2**; m.p. 89–90 °C (lit.[10] 91 °C); ee > 99% [HPLC analysis: Chiralcel AD-H at room temperature, *n*-heptane/ethanol = 80 : 20, 0.8 mL min^{-1}, 220 nm, t_R(1*R*,2*R*)-**2** = 7.75 min, t_R (1*S*,2*S*)-**2** = 14.52 min]; ^{1}H NMR ($CDCl_3$) δ 0.92–1.04 (m, 1 H), 1.14–1.30 (m, 3 H), 1.63–1.78 (m, 2 H), 1.99–2.07 (m, 1 H), 2.11–2.24 (m, 1 H), 2.30–2.36 (m, 1H), 3.17–3.22(m, 1 H), 3.70 (d, *J* = 12.9 Hz, 1 H), 3.96 (d, *J* = 12.9 Hz, 1 H), 7.29–7.52 (m, 5 H).

*D. Trans-2-aminocyclohexanol enantiomers (1R,2R)-**4** and (1S,2S)-**4**:* A solution of the *trans*-2-(benzylamino)cyclohexanol enantiomers (*1R,2R*)-**2** or (*1S,2S*)-**2** (60.00 g, 292.3 mmol) in dry MeOH (119 mL) was hydrogenated over 10% Pd/C (6.0 g, 20.5 mg $mmol^{-1}$) for 1–2 h at room temperature and at 3 atm. After the reaction was completed, the catalyst was removed by filtration through Celite®, washed with MeOH and the filtrate was evaporated to give the corresponding *trans*-2-aminocyclohexanol enantiomers (*1R,2R*)-**4** (32.6 g, 97%) yield or (*1S,2S*)-**4** (32.9 g, 98% yield) as colourless solids. The products had the following physicochemical characteristics: $[\alpha]_D^{25}$ = +40.3 (*c* = 1.15, MeOH) for (*1S,2S*)-**4**, $[\alpha]_D^{25}$ = –39.8 (*c* = 2.0, MeOH) for (1*R*,2*R*)-**4**; m.p. 69–70 °C (lit.[9] 68 °C); ee > 99% [HPLC analysis: Chiralcel AD-H at room temperature, *n*-heptane/ethanol = 80 : 20, 0.8 mL min^{-1}, 220 nm, t_R(1*R*,2*R*)-**4** = 10.50 min, t_R (1*S*,2*S*)-**4** = 14.50 min]; ^{1}H NMR (DMSO-d_6) δ 0.96–1.17 (4 H, m), 1.55–1.74 (4 H, m), 2.10–2.25 (1 H, m), 2.74–2.89 (1 H, m).

Received 4 March 2014; accepted 26 March 2014
Paper 1402506 doi: 10.3184/174751914X13977299691549
Published online: 6 May 2014

References

1 G. Shaw, *Comprehensive heterocyclic chemistry II*; 5th edn, eds A.R. Katrizky, C.W. Rees and E.F.V. Scriven. Pergamon: New York, 1996. Vol. 7, p. 397.
2 F. Fache, E. Schulz, M.L. Tommasino and M. Lemaire, *Chem. Rev.,* 2000, **100**, 2159.
3 J. González-Sabín, V. Gotor and F. Rebolledo, *Tetrahedron: Asymmetry,* 2004, **15**, 1335.
4 L.E. Overman and S. Sugai, *J. Org. Chem.,* 1985, **50**, 4154.
5 L.E. Martinez, J.L. Leighton, D.H. Carsten and E.N. Jacobsen, *J. Am. Chem. Soc.,* 1995, **117**, 5897.
6 J.A. Birrell and E.N. Jacobsen, *Org. Lett.,* 2013, **15**, 2895.
7 E. Ami and H. Ohrui, *Biosci. Biotechnol. Biochem.,* 1999, **63**, 2150.
8 H. Honig and P. Seufer-Wasserthal, *J. Chem. Soc., Perkin Trans. 1,* 1989, 2341.
9 I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani and C. Bolm, *J. Org. Chem.,* 2006, **71**, 2320.
10 I. Schiffers and C. Bolm, *Org. Synth.,* 2008, **85**, 106.
11 C.J. Li, *Chem. Rev.,* 2005, **105**, 3095.
12 Z. Wang, Y.T. Cui, Z.B. Xu and J. Qu, *J. Org. Chem.,* 2008, **73**, 2270.