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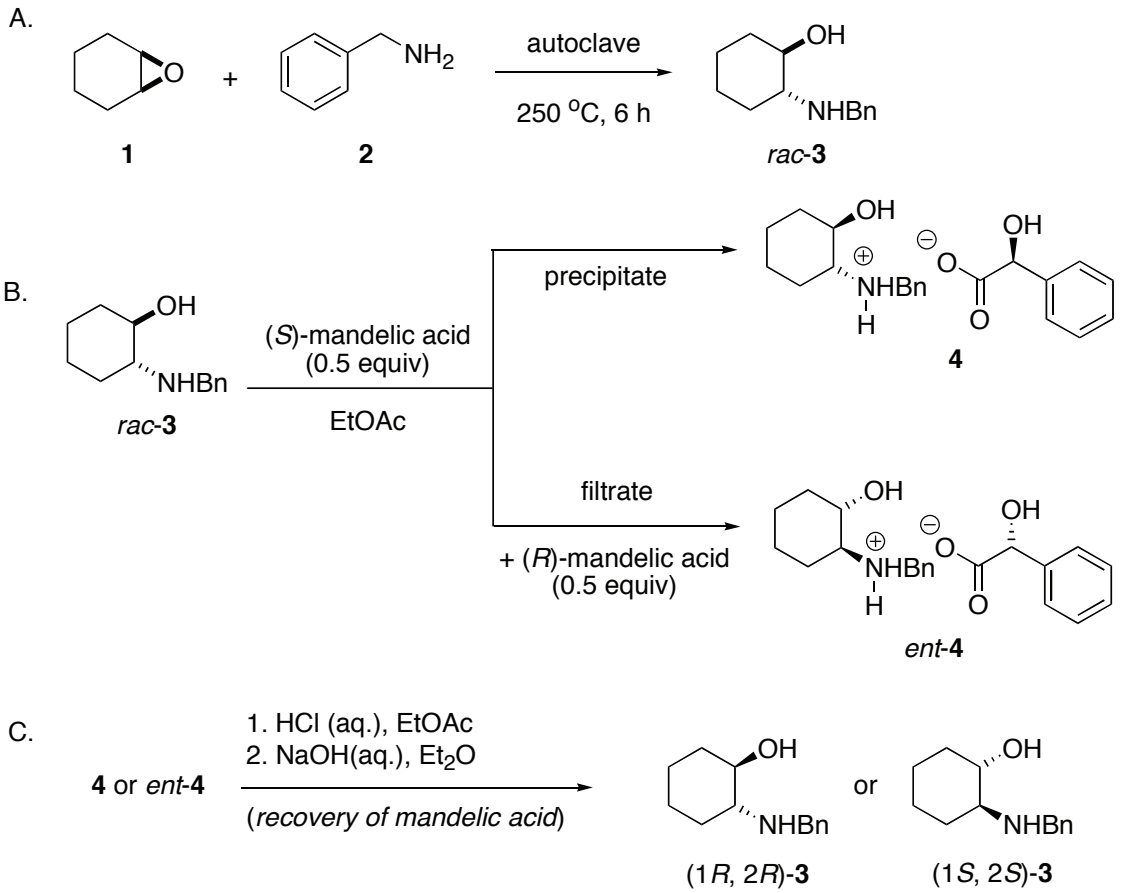
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.085.0106

SYNTHESIS AND RESOLUTION OF RACEMIC *TRANS*-2-(*N*-BENZYL)AMINO-1-CYCLOHEXANOL: ENANTIOMER SEPARATION BY SEQUENTIAL USE OF (*R*)- AND (*S*)-MANDELIC ACID

[Cyclohexanol, 2-(*N*-benzyl)amino, (1*S*,2*S*)- and (1*R*,2*R*)-]



Submitted by Ingo Schiffers and Carsten Bolm.[1]
Checked by Scott E. Denmark, Eric Woerly, Aurélie Toussaint, and Andreas Pfaltz.

1. Procedure

A. Racemic trans-2-(N-benzyl)amino-1-cyclohexanol (*rac-**3***). An autoclave (Note 1) with a properly fitted 400-mL glass insert (Note 2) is charged with cyclohexene oxide (**1**) (61.5 mL, 59.7 g, 0.596 mol, 1.1 equiv) and benzylamine (**2**) (60.0 mL, 58.8 g, 0.543 mol, 1 equiv) (Note 3), equipped with a magnetic stirring bar (Note 4), sealed and flushed with

Org. Synth. **2008**, *85*, 106-117
Published on the Web 10/16/2007

nitrogen. The reaction mixture is placed in a 250 °C preheated oven for 6 h (Note 5), then cooled to ambient temperature, diluted with dichloromethane (60 mL) (Note 6) and transferred into a 1000-mL single-necked, round-bottomed flask. The glass inlay is rinsed with dichloromethane (3 × 50 mL) and the combined organic phases are concentrated using a rotary evaporator (30 mmHg, ambient temperature). The residual cyclohexene oxide is removed under reduced pressure (1 mmHg) at room temperature over 11 h to yield 110.68 g (99%) amino alcohol *rac*-**3** as a light yellow solid, which is suitable for use in the next step without further purification (Note 7).

*B. (S)-Mandelic acid salt of (1R,2R)-trans-2-(N-benzyl)amino-1-cyclohexanol (**4**) and (R)-mandelic acid salt of (1S,2S)-trans-2-(N-benzyl)amino-1-cyclohexanol (ent-**4**).* A 1-L single-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a pressure-equalizing addition funnel fitted with an argon inlet (Note 8). The flask is charged with amino alcohol *rac*-**3** (82.12 g, 0.40 mol, 1.0 equiv) dissolved in ethyl acetate (600 mL) and a solution of (*S*)-mandelic acid (30.43 g, 0.20 mol, 0.5 equiv) (Note 9) in ethyl acetate (200 mL) and diethyl ether (100 mL) (Note 10) is added via the addition funnel over a period of 5 h at room temperature (Note 11). After the addition is complete the dropping funnel is rinsed with diethyl ether (2 × 5 mL) and the reaction mixture is stirred overnight at ambient temperature, followed by 5 h at 0 °C. The precipitated ammonium salt is collected by suction filtration, then is washed with ethyl acetate (100 mL), followed by diethyl ether (2 × 100 mL), and dried *in vacuo* at 0.05 mmHg at room temperature over 1 h (Note 12) to afford 52.86 g (0.15 mol, 74% based on the amount of mandelic acid) of the (*S*)-mandelic acid salt of (1*R*,2*R*)-*trans*-2-(*N*-benzyl)amino-1-cyclohexanol (**4**) as a colorless solid (Note 13). The filtrate from the above procedure is transferred to a 2-L separatory funnel, then is washed with 1 N aq. NaOH solution (3 × 50 mL) and the aqueous layer is back-extracted with diethyl ether (3 × 50 mL). The combined organic layers are dried ($MgSO_4$, approx. 50 g), filtered and concentrated under reduced pressure (40 ˚C, 100 mbar) to give 49.20 g of the crude amino alcohol (1*S*,2*S*)-**3** as a pale yellow oil. The oily residue is dissolved in ethyl acetate (400 mL), transferred into a 1-L flask, and treated with a solution of (*R*)-mandelic acid (30.43 g, 0.20 mol, 0.5 equiv) in ethyl acetate (200 mL) and diethyl ether (100 mL) analogously to the above described procedure, to deliver 55.50 g (0.15 mol, 78% based on the amount of mandelic acid) of the (*R*)-mandelic acid salt of (1*S*,2*S*)-

trans-2-(*N*-benzyl)amino-1-cyclohexanol (*ent*-**4**) as a colorless solid (Note 14).

C. Liberation of the amino alcohols and recovery of mandelic acid. In a 1-L separatory funnel, the mandelic acid ammonium salt **4** or *ent*-**4** (50.04 g, 0.14 mol) is partitioned between ethyl acetate (500 mL) (Note 10) and 2 N aq. HCl solution (200 mL). Then, the mixture is manually and vigorously shaken until the salt is completely dissolved. The organic layer is additionally washed with 2 N aq. HCl solution (2 × 25 mL) and the combined aqueous phases are back-extracted with ethyl acetate (3 × 100 mL). The combined organic phases are dried ($MgSO_4$, approx. 50 g), filtered and concentrated under reduced pressure to provide 19.80–20.02 g (93–94%) of the corresponding mandelic acid enantiomer (Note 17). To a mixture of the acidic aqueous phase and diethyl ether (200 mL) in the same separatory funnel, 5 N NaOH (280 mL) is added carefully in small portions over a period of 45–60 minutes. After separation, the aqueous layer is extracted with diethyl ether (4 × 100 mL) and the combined organic phases are dried ($MgSO_4$, approx. 30 g), filtered, and concentrated under reduced pressure (40 ˚C, 100 mbar) to yield 25.80–26.74 g (90–93%) (Note 18) of the corresponding *trans*-2-(*N*-benzyl)amino-1-cyclohexanol enantiomer (1*R*,2*R*)-**3** or (1*S*,2*S*)-**3** as a white solid (Note 19).

2. Notes

1. A custom made high-pressure autoclave was used. See Figures 1 and 2 for autoclave dimensions. The dimensions for the Teflon and rubber O-rings are: Teflon ring 4 ¼" (ID) x 4 7/16" (OD) x 3/32" thick; rubber O-ring 3" (ID) x 3 3/16" (OD) x 3/32" thick.

2. Glass inlay dimensions: outer diameter = 7 cm; inner diameter = 6.5 cm; height = 13 cm.

3. Benzylamine (99%) and cyclohexene oxide (98%) were purchased from Acros Organics and used as received.

4. Magnetic stirring was used when purging the system with nitrogen. In the original procedure, magnetic stirring was used during the reaction. Magnetic stirring was not used in the Checker's procedure.

5. A Stabil-Therm Oven (model #OV-12A) at a high power setting of 5 was used as a heat source.

6. Dichloromethane (>99.5%) was purchased from Sigma-Aldrich and used as supplied. The Submitters used dichloromethane (>99%) purchased from Merck as received.

7. The NMR spectra indicated a purity of 91–94% for *rac*-**3**. It is also available from Acros Organics (>99%). mp 57.6 – 58.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (q, *J* = 10 Hz, 1 H), 1.06–1.56 (m, 5 H), 1.60–1.94 (m, 3 H), 1.94–2.12 (m, 1 H), 2.19 (d, *J* = 10 Hz, 1 H), 2.26–2.50 (m, 1 H), 3.21–3.30 (m, 1 H), 3.69 (d, *J* = 15 Hz, 1 H), 3.96 (d, *J* = 15 Hz, 1 H), 7.10–7.58 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3, 25.1, 30.5, 33.2, 50.7, 63.1, 73.8, 127.0, 128.1, 128.4, 140.5; IR (thin film): 3305 (m), 3062 (m), 3028 (m), 2930 (s), 2857 (s), 1604 (w), 1496 (w), 1452 (s), 1354 (w), 1199 (w), 1074 (m), 1029 (m), 977 (w), 845 (w), 747 (m), 699 (s) cm^{-1}. MS (EI, 70eV) *m/z* : 205 (M^+ (11%)), 146 (27%), 121 (20%), 115 (16%), 106 (27%), 92 (17%), 91 (100%), 56 (58%).

8. In the original procedure, a gas inlet adapter with stopcock connected to a nitrogen-filled balloon was used.

9. (*S*)-Mandelic acid (>99%) and (*R*)-mandelic acid (99%) were purchased from Acros Organics and used as received.

10. Ethyl acetate (>99%) and diethyl ether (>99%) were purchased from Fluka and used as received.

11. After addition of one-third of the mandelic acid solution, the ammonium salt began to precipitate.

12. A sintered glass funnel (100 mm diameter) was used. After washing the filter cake, suction filtration was continued for 5 min to dry the ammonium salt by a stream of air. Then, the damp solid was transferred into a 250-mL single-necked, round-bottomed flask to remove residual solvents under vacuum.

13. In a run carried out on half-scale, 25.70 g of product was obtained (72% yield). The product has the following characteristics: mp 146 °C; $[\alpha]_D^{25}$ +16.0 (*c* 2.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96–1.35 (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 Hz, *J* = 12.0 Hz, 1 H), 3.03 (dt, *J* = 4.3 Hz, *J* = 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), 7.15–7.32 (m, 8 H), 7.49 (s, 1 H), 7.52 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 24.2, 26.6, 34.0, 48.4, 62.5, 70.4, 74.4, 76.8, 126.7, 127.3, 128.1, 128.9, 129.1, 130.0, 131.4, 142.3, 178.6. IR (KBr) 3362, 3036, 2937, 2859, 1606, 1554, 1490, 1447, 1370, 1086, 1061, 1041 cm^{-1}; MS (EI, 70 eV) *m/z* : 205 (34), 146 (88),

114 (12), 107 (51), 91 (100), 79 (29), 77 (22); Anal. Calcd for $C_{21}H_{27}NO_4$ (357.44): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.54; H, 7.50; N, 3.75.

14. In a run carried out on half-scale, 27.92 g of product *ent*-**4** was obtained (78% yield); $[\alpha]_D^{25}$ –14.3 (*c* 2.15, $CHCl_3$). Both ammonium salts, **4** and *ent*-**4**, were diastereomerically pure according to NMR analysis. To determine the enantiomeric excess (ee) of the free amino alcohol, a 50 mg sample of the mandelic acid salt was partitioned between 1 N aq. NaOH solution (4 mL) and diethyl ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$, 50 mg), filtered, concentrated under reduced pressure (40 ˚C, 300 mbar), and analyzed by HPLC analysis using a chiral stationary phase (for conditions, see Note 19). The described procedure yields (1*R*,2*R*)-**3** with 99% ee and (1*S*,2*S*)-**3** with >99% ee (no signal detected for the minor enantiomer in HPLC analysis). One recrystallization (Note 15) of (1*R*,2*R*)-**3** followed by liberation of the amino alcohol as described in Step C, provides product that showed no signal for the minor enantiomer in the CSP-HPLC analysis.

15. General procedure for the recrystallization: A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two rubber septa, and a reflux condenser fitted with an argon inlet (Note 8) is charged with mandelic acid salt **4** (20 g, 56 mmol) and ethyl acetate (600 mL). The suspension is heated to reflux before ethanol (Note 16) is added in portions via syringe until complete dissolution occurs (25 mL in total). Then the stirring is stopped, the oil bath is removed, and the clear solution is allowed to cool to room temperature overnight. The crystallized ammonium salt is collected by suction filtration (Note 12), washed with ethyl acetate (15 mL), followed by diethyl ether (2 × 30 mL), and dried *in vacuo* affording 18.30 g (91%) of enantiomerically pure **4**.

16. Ethanol (≥ 99.9%) was purchased from Fluka and used as received.

17. The recovered mandelic acid showed an identical value for optical rotation in comparison to the starting material; (*R*)-mandelic acid $[\alpha]_D^{25}$ –152.4 (*c* 2.5, H_2O), (*S*)-mandelic acid $[\alpha]_D^{25}$ +153.5 (c 2.8, H_2O). These values are in accord with the literature (–150 to –155 for (*R*)-mandelic acid and +153 to +155 for (*S*)-mandelic acid).

18. In the runs carried out on half-scale, 12.86–12.97 g of products were obtained (89–90% yield). CSP-HPLC separation conditions: t_R (1*S*,2*S*)-**3**, 24.2 min; t_R (1*R*,2*R*)-**3**, 30.0 min (Daicel CHIRALCEL OB-H (4.6 × 250 mm); *n*-heptane/2-propanol, 98:2; 0.5 mL/min; 220 nm). For (1*R*,2*R*)-**3,** the

enantiomeric excess measured was 99% and for (1*S*,2*S*)-**3**, the minor enantiomer was not detected (*ee*>99%).

19. The products have the following physicochemical characteristics (data reported for (1*S*,2*S*)-**3**): $[\alpha]_D^{25}$ +82.2 (*c* 1.05, MeOH) for (1*S*,2*S*)-**3**, $[\alpha]_D^{25}$ −79.8 (*c* 1.22, MeOH) for (1*R*,2*R*)-**3**; mp 91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92–1.02 (m, 1 H), 1.18–1.30 (m, 3 H), 1.68–1.78 (m, 2 H), 1.99–2.06 (m, 1 H), 2.10–2.22 (m, 1 H), 2.29 (ddd, *J* = 4.0, 9.4, 11.4 Hz, 1 H), 3.20 (dt, *J* = 4.5,10.1 Hz, 1 H), 3.70 (d, *J* = 12.9 Hz, 1 H), 3.96 (d, *J* = 12.9 Hz, 1 H),7.22–7.28 (m, 1 H), 7.30–7.35 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.5, 25.3,30.8, 33.4, 50.9, 63.3, 74.1, 127.1, 128.2, 128.6, 140.8; IR (KBr) 3295, 3060, 2933, 2854, 1602, 1496, 1449, 1356, 1292, 1219, 1152, 1077 cm^{-1}; MS (EI, 70 eV) *m*/*z* : 205 (36), 146 (90), 114 (10), 91 (100); Anal. Calcd for $C_{13}H_{19}NO$ (205.30): C, 76.06; H, 9.33; N, 6.82. Found: C, 75.87; H, 9.18; N, 6.72.

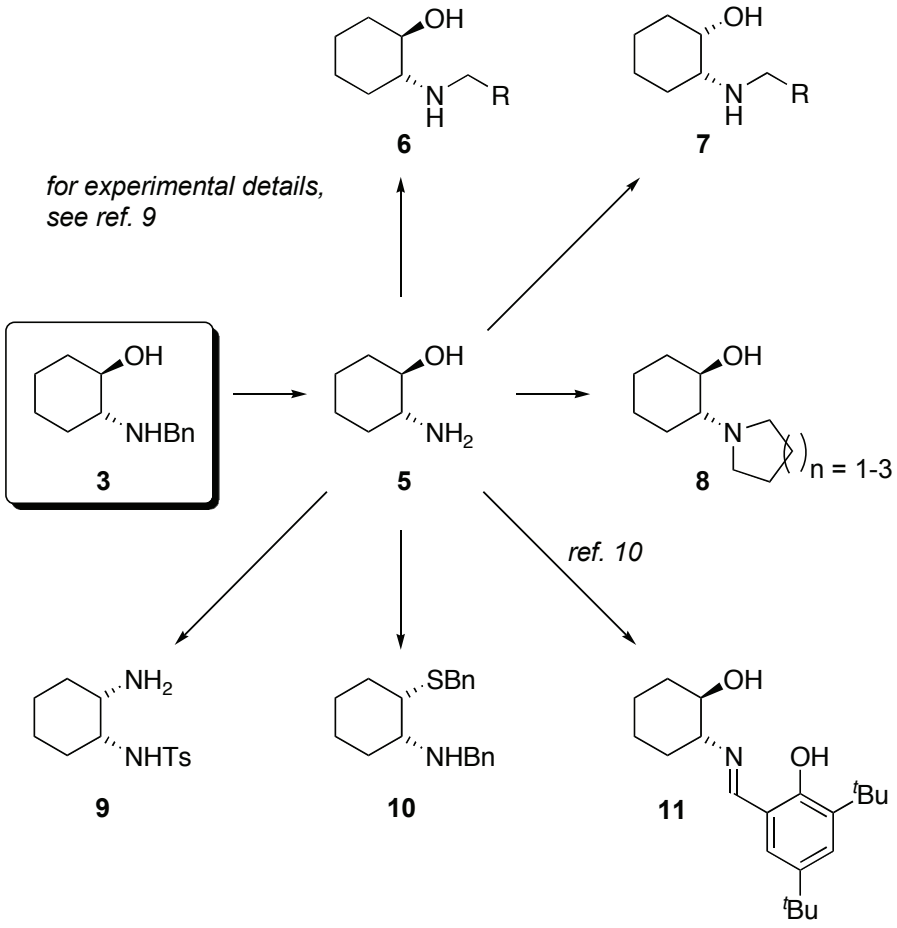
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Enantiopure amino alcohols are versatile synthetic intermediates for the preparation of a wide variety of natural products and biologically active compounds.[2] Also their importance in asymmetric synthesis, where the need for chiral auxiliaries and ligands is continually increasing, has been well recognized in recent years.[3] Despite the great interest in this field and the impressive success that have been made in the development of new procedures for the preparation of optically pure vicinal amino alcohols, there are only few efficient procedures for the preparation of highly enantiomerically enriched aminocyclohexanols which are suitable for a broad variety of further derivatizations.[4] Among those few procedures, only Overman's aminolysis of cyclohexene oxide with an aluminum amide stemming from enantiomerically enriched methylbenzylamine and trimethylaluminum,[5] Jacobsen's Cr(III)/salen-catalyzed enantioselective ring-opening reaction of cyclohexene oxide by azidosilanes,[6] and the enzymatic resolution of racemic 2-azidocyclohexanol[7] have found

occasional applications in synthesis.[8] The procedure described here is an improved version of the previously reported protocol for the resolution of racemic *trans*-2-(*N*-benzyl)amino-1-cyclohexanol (*rac*-**3**), which is easily available in 100 g scale by a solvent-free aminolysis of cyclohexene oxide at high temperature.[9] The advantages of this novel method are its preparative ease and its efficiency in large scale resolutions delivering both amino alcohol enantiomers with 99% ee by sequential use of inexpensive (*S*)- and (*R*)-mandelic acid. A simple aqueous workup procedure permits the isolation of the amino alcohol in analytically pure form and the recovery of mandelic acid in high yield. The synthetic usefulness of the method was demonstrated by debenzylation of enantiopure *trans*-2-(*N*-benzyl)amino-1-cyclohexanol (**3**) by hydrogenolysis, leading to the easily modifiable deprotected amino alcohol **5** (Scheme 1), which gave access to a broad variety of diversely substituted derivatives and their corresponding cis isomers **6**-**8**.[9] These enantiomerically pure aminocyclohexanols have been



Scheme 1

applied as ligands in catalyzed, asymmetric phenyl transfer reactions to benzaldehyde and transfer hydrogenations of aryl ketones, leading to enantioselectivities of up to 96% ee.

In addition, it was demonstrated that enantiopure *trans*-2-aminocyclohexanol **5** is a valuable building block for the preparation of enantiomerically pure *cis*-diaminocyclohexane **9** and chiral *cis*-amino thiol derivative **10**. The latter compound showed an impressive activity in the iridium-catalyzed transfer hydrogenation reaction. Syntheses of new analogues of well-known classes of amino alcohol derived ligands, like oxazolines, oxazaborolidines and Schiff bases **11**, starting from **5** are currently in progress.[10]

Figure 1

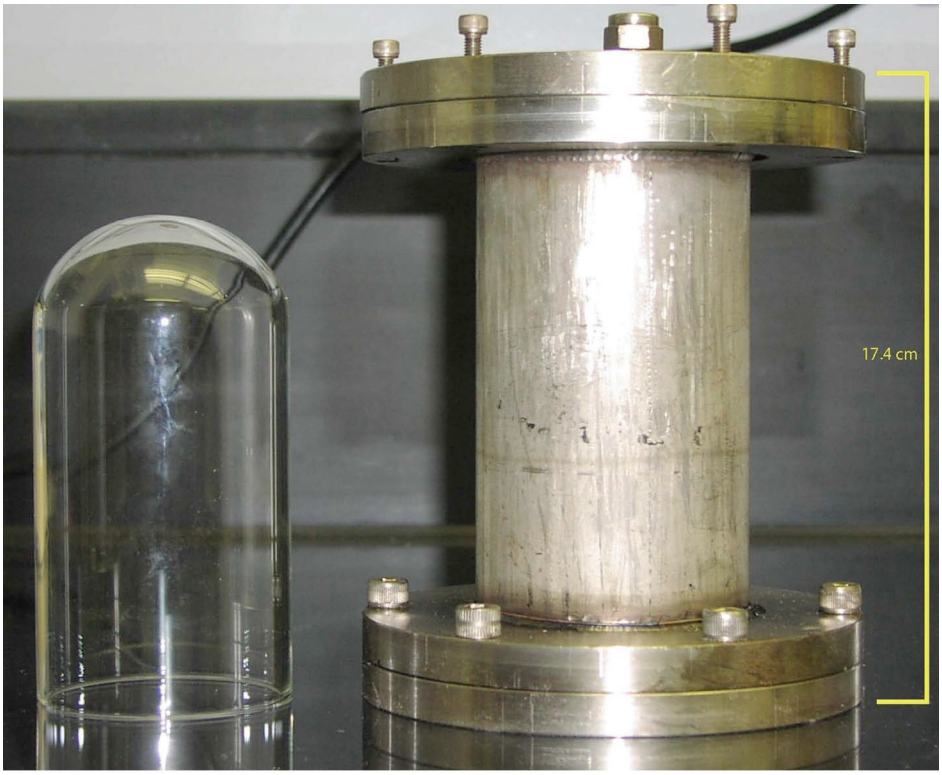
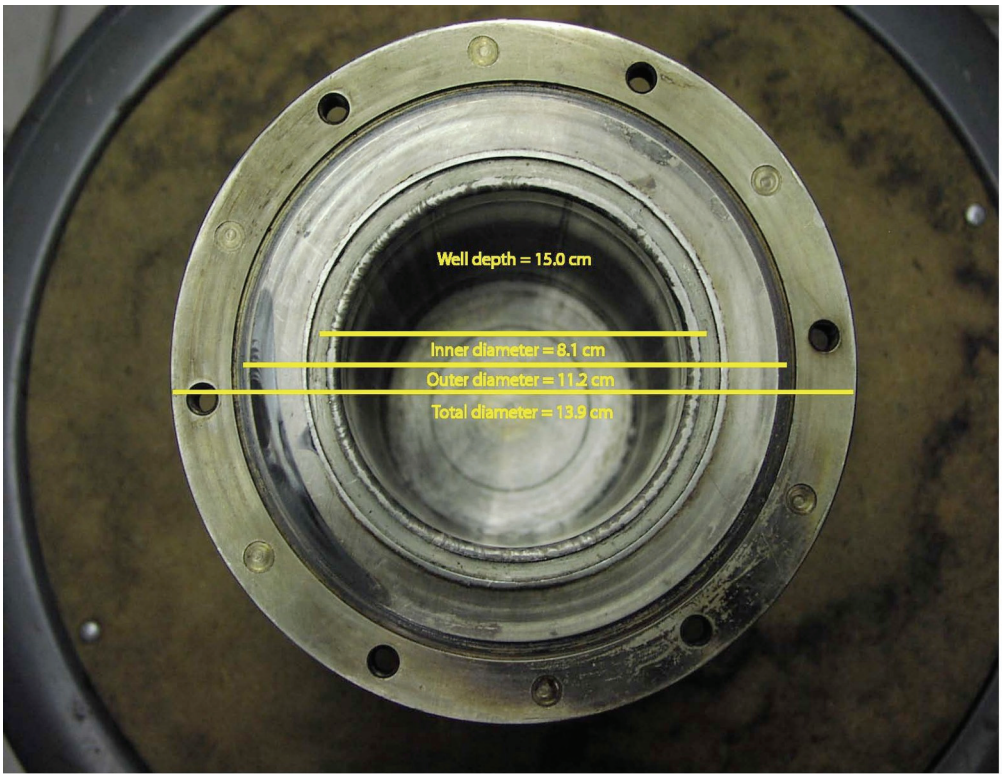


Figure 2



1. Institut für Organische Chemie der RWTH Aachen, Landoltweg 1, D-52056 Aachen, Germany.

2. For reviews, see: (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576; (b) *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; (c) *The Merck Index*, 12th Edition.; Chapman & Hall: New York, 1996; (d) Shaw, G. In *Comprehensive Heterocyclic Chemistry II*; 5th Edition.; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 7, p 397; (e) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Cyclohexene oxide; (286-20-4)
Benzylamine; (100-46-9)
(*S*)-(+)-Mandelic acid; (17199-29-0)
(*R*)-(-)-Mandelic acid; (611-71-2)

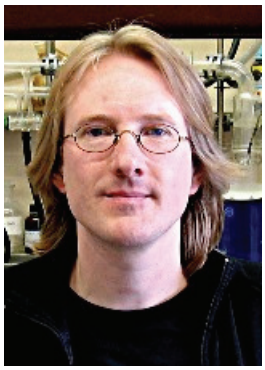
(*S*)-Mandelic acid salt of (1*R*,2*R*)-*trans*-2-(*N*-benzyl)amino-1-cyclohexanol; (882409-01-0)

(*R*)-Mandelic acid salt of (1*S*,2*S*)-*trans*-2-(*N*-benzyl)amino-1-cyclohexanol; (882409-00-9)

(1*R*,2*R*)-*trans*-2-(*N*-Benzyl)amino-1-cyclohexanol; (141553-09-5)

(1*S*,2*S*)-*trans*-2-(*N*-Benzyl)amino-1-cyclohexanol; (322407-34-1)

Carsten Bolm was born in Braunschweig in 1960. He studied chemistry at the TU Braunschweig (Germany) and at the University of Wisconsin, Madison (USA). In 1987 he obtained his doctorate with Professor Reetz in Marburg (Germany). After postdoctoral training with Professor Sharpless at MIT, Cambridge (USA), Carsten Bolm worked in Basel (Switzerland) with Professor Giese to obtain his habilitation. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he has a chair of Organic Chemistry at the RWTH Aachen (Germany).



Ingo Schiffers was born in Mönchengladbach (Germany) and studied chemistry at the RWTH Aachen University (Germany). In 2002 he completed his doctoral studies under the supervision of Professor Bolm in which he investigated the asymmetric methanolysis of meso-anhydrides. Since 2003 he is holding a position as a permanent researcher in the group of Professor Bolm.

Eric Woerly was born in Illinois and raised in Indiana. He received his B.S. degree in Chemistry from Indiana University Purdue University Indianapolis (IUPUI), where he performed undergraduate research with Professors Martin J. O'Donnell and William L. Scott. His research focused on the solid-phase synthesis of oligopeptides. In 2007, he began his graduate studies at the University of Illinois at Urbana Champaign. His work on this Organic Syntheses check was completed under the guidance of Professor Scott Denmark.

Aurélie Toussaint was born in Besançon (France). In 2004, she received her diploma in engineering at the Ecole Supérieure de Physique et de Chimie Industrielles (Paris, France) and her master diploma in organic chemistry (Université Pierre et Marie Curie, Paris, France). Since October 2004, she is a PhD student in the research group of Prof. Andreas Pfaltz at the University of Basel.