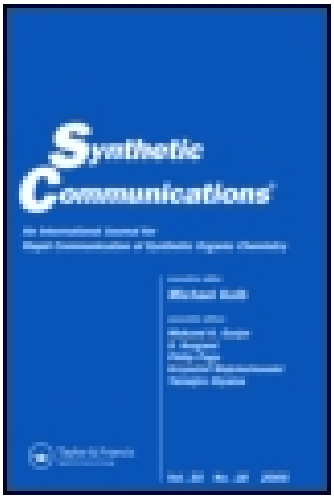

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Preparation of Enantiopure trans-1,2-Cyclohexanediol and trans-2-Aminocyclohexanol

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Preparation of Enantiopure *trans*-1,2-Cyclohexanediol and *trans*-2-Aminocyclohexanol

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Abstract: Trans-1,2-cyclohexanediol and trans-2-aminocycloxexanol are useful chiral auxiliaries. Simple chemical resolution procedures for these molecules are presented.

Keywords: chemical resolution, chiral auxiliaries, epoxide-cleavage

INTRODUCTION

Chiral 1,2-diols[1] and β-amino alcohols[2] are versatile tools because of their use as chiral ligands, auxiliaries, structural motifs, and so on. A variety of procedures have been developed for the preparation of these compounds in optically pure form.[3] However, chemical resolution, an age-old procedure, has remained an attractive methodology, particularly in the large-scale preparation of these compounds.[4]

RESULTS AND DISCUSSION

One such important diol is *trans*-1,2-cyclohexanediol (**1**). This diol has been used successfully in a variety of reactions.[5] Although, a voluminous literature is available for the preparation of this compound, most of them deal with chemoenzymatic methods.[6] Considering the exorbitant cost of these enzymes and limitations for large-scale preparations, we planned to develop

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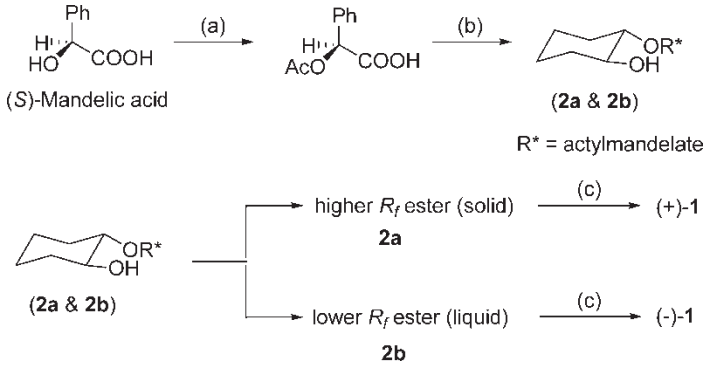


Scheme 1. Resolution of cyclohexane-1,2-diol. Reagents and conditions: (a) AcCl, reflux, 2 h; (b) (±)-**1**, DCC, DMAP, DCM, −10°C, 6 h; (c) NaOH, MeOH.

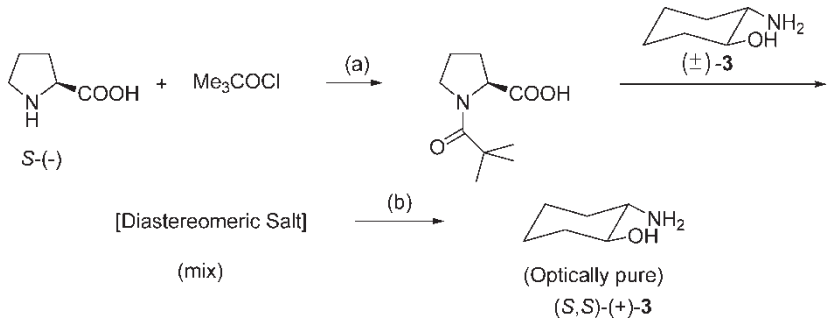
a chemical resolution procedure for this diol. After screening a variety of optically active acids such as hydratropic acid, ω-camphanic acid, *N*-carbethoxy proline, and *N*-tosyl proline, we found *O*-acetyl mandelic acid to be an appropriate resolving agent. Although the separation of the diastereomeric mixture of the monoester (**2a**/**2b**) was achieved through column chromatography, crystallization from a mixed solvent of petroleum ether/diethyl ether was found equally effective when performed on a multigram scale. The only drawback of this resolution was the partial racemization of mandelic acid during workup (Scheme 1).

trans-2-Aminocyclohexanol (**3**) is another important compound and finds wide application in the literature.[7] The most popular method for the preparation of this compound includes stereoselective ring opening of the epoxide,[8] kinetic resolution,[9] or resolution of its derivatives.[7] All these procedures suffer some drawback or the other.

Herein we report a novel resolution procedure for this compound using a cheap proline derivative. Initially, a variety of optically active acids were examined to separate the diastereomeric salt through fractional recrystallization. Unfortunately, none of them proved to be successful. Finally, we succeeded in obtaining a diastereomerically pure salt using *N*-pivaloyl proline. Three successive crystallizations from EtOH/EtOAc were required to realize the purity. Subsequent hydrolysis of the salt provided the amino alcohol (**3**) in moderate yield and high optical purity (Scheme 2).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, and the chemical shift values were reported in parts per million (ppm) downfield to TMS ($\delta = 0$) for ^{1}H and relative to the central $CDCl_3$ resonance ($\delta = 77$) for ^{13}C NMR



Scheme 2. Resolution of 2-aminocyclohexanol. Reagents and conditions: (a) NaOH, TBABr (cat.), H_2O–DCM, rt, 4 h; (b) (i) three crystallization from EtOAc/EtOH; (ii) aqueous NaOH.

on AC 200-MHz or DRX 500-MHz spectrometer. The abbreviations s, bs, d, t, and m refer to singlet, broad singlet, doublet, triplet, quartet, and multiplet respectively. Melting points were determined on a Yamaco micromelting-point apparatus and are uncorrected. Optical rotations were measured with a Bellingham-Stanley ADP220 digital polarimeter using a sodium lamp ($\lambda = 589$ nm) at 24°C. IR spectra were recorded on a Shimadzu FTIR-8400 spectrophotometer with NaCl as optics. Thin-layer chromatography (TLC) was carried out on 0.25-mm E-Merck silica-gel plates ($60F_{254}$) with UV light / I_2 / anisaldehyde as viewing methods. All solvents and reagents were purified and dried according to procedures given in D. D. Perin's *Purification of Laboratory Reagents*. All reactions were carried out under argon atmosphere using freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to isolated product, purified by chromatography or distillation. (±)-Cyclohexane-1,2-diol (**1**) was prepared as described in the literature.[10]

Resolution of (±)-*trans*-Cyclohexane-1,2-diol (1)

Preparation of (*S*)-*O*-Acetylmandelic Acid

The reported procedure was modified as follows.[11] A flame-dried, 100-mL, two-necked, round-bottomed flask was equipped with a stirring bar and a dropping funnel. *S*-(+)-Mandelic acid (15.2 g, 100 mmol) was placed inside the flask, and acetylchloride (35.5 mL, 500 mmol) was added slowly with vigorous stirring. The stirring was continued initially at room temperature and then under reflux for 2 h. Excess acetylchloride was removed on a rotary evaporator, and the semisolid mass was suspended in a minimum volume of water. The acid was extracted with dichloromethane (DCM) (3×40 mL), and the combined organic layer was washed with brine

(2 × 20 mL). It was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The sticky mass obtained after keeping it in a high vacuum for 2 h at 50°C solidified slowly in the refrigerator (2 days). The solid was crystallized from a combination of petroleum ether and diethyl ether to give white crystals of (*S*)-(+)-*O*-acetylmandelic acid. White solid (12.3 g, 63%); mp 103–105°C [lit.[11] 95–97.5°C]; $[\alpha]_D = +152$ (*c* 1, acetone) [lit.[11] +148 (*c* 1.87, acetone)].

Preparation of Monoesters **2a** and **2b**

A flame-dried, two-necked, round-bottomed flask was charged with dicyclohexylcarbofiimide (DCC) (9.06 g, 44 mmol), (±)-1,2-cyclohexanediol (**1**) (4.65 g, 40 mmol), and NN-dimethylaminopyridine (DMAP) (0.48 g, 4 mmol) under an argon atmosphere. Freshly distilled DCM (80 mL) was introduced into the flask, and the solution was cooled to −10°C. (*S*)-(+)-*O*-Acetylmandelic acid (7.76 g, 40 mmol) was added slowly as a solution in DCM (20 mL). Stirring was continued for 6 h until the completion of the reaction (TLC). The reaction mixture was filtered to remove the urea derivative, and the filtrate was evaporated to obtained a pasty mass, which was chromatographed using 230 to 400-mesh silica gel and 10% EtOAc/petroleum ether as eluent. The solid monoester (**2a**) was crystallized from a combination of petroleum ether and ethylacetate. Monoester **2a:** White solid (4.1 g, 35% overall); $R_f = 0.25$ (EtOAc/ petroleum ether 1:4); mp 101–103°C; $[\alpha]_D = +78.3$ (*c* 1.2, acetone); IR ($CHCl_3$) cm^{-1}: 3544, 2943, 1741; ^1H NMR ($CDCl_3$) δ 1.17–1.39 (m, 4H, CH_2), 1.66–1.74 (m, 3H, CH_2, O*H*), 1.90–2.08 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 3.39–3.50 (m, 1H, C*H*), 4.58–4.64 (m, 1H, C*H*), 5.91 (s, 1H, C*H*Ph), 7.37–7.50 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 20.3, 23.1, 23.3, 29.2, 32.0, 71.6, 74.6, 79.0, 127.3, 128.5, 128.9, 133.8, 168.2, 170.3. Monoester **2b:** Liquid (4.65 g, 40%); $R_f = 0.22$ (EtOAc/ petroleum ether 1:4); $[\alpha]_D = +40.8$ (*c* 1.2, acetone); IR ($CHCl_3$) (cm^{-1}): 3523, 2943, 1741; ^1H NMR ($CDCl_3$) δ 1.14–1.39 (m, 4H, CH_2), 1.60–1.73 (m, 2H, CH_2), 1.77–1.85 (m, 2H, CH_2, O*H)*, 2.0–2.10 (m, 1H, CH_2), 2.20 (s, 3H, CH_3), 3.57–3.64 (m, 1H, C*H*), 4.66–4.74 (m, 1H, C*H*), 5.85 (s, 1H, C*H*Ph), 7.36–7.52 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 20.3, 23.2, 23.3, 28.9, 32.1, 71.6, 74.6, 78.9, 127.3, 128.4, 128.9, 133.5, 168.5, 170.4.

Preparation of (*S*,*S*)-(+)-1,2-Cyclohexanediol (**1**)

The solid monoester (**2a**) (4.1 g) was stirred in 1 N methanolic NaOH solution (36 mL) at room temperature for 4 h. When the TLC showed the disappearance of the ester, MeOH was evaporated, and the diol was extracted with DCM (4 × 20 mL). The crude product was purified through Kugelrohr distillation (120°C at 4 mm Hg) to obtain (*S*,*S*)-(+)-**1** in 97% optical purity. White solid (1.5 g, 92%); mp 115–116°C [lit.[6e] 107.5–108.5]; $[\alpha]_D = +40$ (*c* 1.6, H_2O) [lit.[6b] −36.9 (*c* 1.4, H_2O) for 89% ee].

Preparation of (*R*,*R*)-(-)-1,2-Cyclohexanediol (**1**)

Compound (*R*,*R*)-(-)-**1** was obtained in a similar way from liquid monoester (**2b**). The diol was recrystallized from ethylacetate. White solid (1.5 g, 81%); mp 110–112°C [lit.[6e] 107.5–108.5]; $[\alpha]_D = -39.4$ (*c* 1.6, H_2O) (96% ee) [lit.[6b] −36.9 (*c* 1.4, H_2O) for 89% ee].

Resolution of (±)-*trans*-2-Aminocyclohexanol (3)

Preparation of (±)-*trans*-2-Azidocyclohexanol

To a solution of cyclohexene oxide (22 mL, 200 mmol) in EtOH (300 mL), NaN_3 (26 g, 400 mmol) and NH_4Cl (21.2 g, 400 mmol) were added. The heterogeneous mixture was refluxed for 24 h. Most EtOH was evaporated on a rotavapor, and the solid was triturated with THF and finally filtered. After evaporating the solvent, the crude azidoalcohol was obtained, which was purified through Kugelrohr distillation. Colorless liquid at room temperature (26.33 g, 93%); bp 90°C at 4 mm of Hg (lit.[12] 70–71°C at 1.5 mm of Hg).

Preparation of (±)-*trans*-2-Aminocyclohexanol

(±)-*trans*-2-Azidocyclohexanol (14 g, 100 mmol) was reduced using 5% Pd/C (1 g) in MeOH (100 mL). The solution was shaken at 50 psi of hydrogen for 8 h in a Parr apparatus. The reaction mixture was filtered through a short bed of Celite®, and MeOH was evaporated on a rotary evaporator. The crude compound was distilled in a Kugelrohr to obtain the (±)-*trans*-2-aminocyclohexanol as a white hygroscopic solid (10.35 g, 90%); mp 60°C (lit.[13] 65°C); bp 120°C at 10 mm of Hg (lit.[12] 70°C at 2 mm of Hg); IR ($CHCl_3$) (cm^{-1}): 3359, 2860, 2931.

Resolution of (±)-*trans*-2-Aminocyclohexanol

Preparation of N-pivaloyl Proline

To a solution of L-proline (25.3 g, 220 mmol) in water (100 mL), NaOH solution (17.6 g dissolved in 50 mL of H_2O) was added slowly at 0°C. TBABr (3.5 g, 11 mmol) was added to the solution, and the stirring was continued for an hour. Pivaloylchloride (24.6 mL, 200 mmol) dissolved in 70 mL of DCM was added slowly to the vigorously stirred reaction mixture at such a rate so that the addition completed in 1 h. After the addition, stirring continued at 0°C for 1 h. It was further stirred for 4 h at room temperature. The aqueous layer was separated and washed with DCM (1 × 30 mL) to remove neutral impurities. It was then acidified to pH∼3 with concentrated HCl and extracted with DCM (3 × 50 mL). The combined organic layer was washed with brine (1 × 30 mL) and kept over anhydrous Na_2SO_4. The pasty mass

obtained after evaporating the solvent partly solidified when kept under vacuum for a long time. However, the material was kept in a refrigerator for 24 h after adding 10 mL of petroleum ether, where it solidified completely. It was crystallized twice from EtOAc to obtain *N*-pivaloyl proline. White solid. (28.6 g, 72%); mp 130–135°C [lit.[14] 138–140°C]; $[\alpha]_D = -73$ (*c* 1, EtOH) [lit[14] −15 (*c* 0.36)]; IR ($CHCl_3$) (cm^{-1}): 3294, 2981, 1749; ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H, C*H*$_3$), 1.90–2.22 (m, 4H, C*H*$_2$), 3.66–3.83 (m, 2H, C*H*$_2$), 4.51–4.63 (m, 1H, C*H*), 10.01 (bs, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.7, 27.0, 38.4, 47.9, 60.8, 175.8, 177.4. Anal. calcd. for $C_{10}H_{17}NO_3$: C, 60.26; H, 8.62; N, 7.03. Found: C, 60.01; H, 8.69; N, 7.09.

Preparation of the Diastereomeric Salt

To a solution of (±)-*trans*-2-aminocyclohexanol (8.06 g, 70 mmol) in MeOH (25 mL), a solution of (*S*)-(-)-*N*-pivaloyl proline (13.9 g, 70 mmol) in MeOH (25 mL) was added slowly. After few minutes of stirring, the solvent was evaporated on a rotavapor, and the white salt was recrystallized from a mixture of EtOAc/EtOH (three times) to obtain diastereomeric pure salt (7.15 g, 32.5% overall); mp 188–194°C; $[\alpha]_D = -30.4$ (*c* 1, H_2O).

Hydrolysis of the Salt

To an aqueous solution of the aforementioned salt (7.15 g in 5 mL of H_2O), a NaOH solution (1.6 g in 10 mL of H_2O) was added slowly at 0°C. The resulting amino alcohol was extracted with a solvent mixture of THF/diethyl ether (1:4, 4 × 20 mL). The combined organic layer was washed with brine (1 × 10 mL) and then kept over anhydrous K_2CO_3. On evaporating the solvent, a viscous liquid was obtained, which was distilled in a Kugelrohr at 140°C at 4 mm of Hg. After cooling, the (*S*,*S*)-(+)-2-aminocyclohexanol (**3**) solidified as hygroscopic mass (2.1 g, 80%); mp 92–94°C (lit.[8d] 88–89°C); $[\alpha]_D = +49.01$ (*c* 1, MeOH) [lit.[8d] +48.2 (*c* 1, MeOH) for 96% ee].

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REFERENCES

1. (a) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957–1960; (b) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24–25; (c) Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442–2469; (d) Whitesell, J. K. *Chem Rev.* **1989**, *89*, 1581;

(e) Andres, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035.

2. (a) Shaw, G. *Comprehensive Heterocyclic Chemistry II*, 5th ed.; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., (eds.); Pergamon: New York, 1996; Vol. 7, p. 397; (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules using Amino Acids*; Wiley: New York, 1987; (c) Ager, D.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
3. (a) Chatterjee, A.; Bennur, T. H.; Joshi, N. N. *J. Org. Chem.* **2003**, *68*, 5668–5671; (b) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888–3889; (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (d) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576; (e) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733–2746.
4. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*; John Wiley and Sons: New York, 1981.
5. (a) Fang, C.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1990**, *31*, 4751–4754; (b) Hayward, R. C.; Overton, C. H.; Whitham, G. H. *J. Chem. Soc.; Perkin Trans. 1* **1976**, 2413–2415.
6. (a) Itano, K.; Yamasaki, K.; Kihara, C.; Tanaka, O. *Carbohyd. Res.* **1980**, *87*, 27–34; (b) Kasai, M.; Kawai, K.; Imuta, M.; Ziffer, H. *J. Org. Chem.* **1984**, *49*, 675–679; (c) Crout, D. H. G.; Gandet, V. S. B.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 808–810; (d) Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966–967; (e) Caron, G.; Kazlauskas, R. J. *J. Org. Chem.* **1991**, *56*, 7251–7256; (f) Chang, D.; Wang, Z.; Heringa, M. F.; Wirthner, R.; Witholt, B.; Li, Z. *Chem. Commun.* **2003**, 960–961; (g) Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D. S.; Zhu, Z.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157, and references therein.
7. Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320–2331, and references therein.
8. (a) Carreé, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, *7*, 1023–1026; (b) Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694; (c) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898; (d) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154–4155.
9. (a) Guangyou, Z.; Yuquing, L.; Zhaohui, W.; Nohira, H.; Hirose, T. *Tetrahedron: Asymmetry* **2003**, *14*, 3297–3300; (b) Takada, H.; Takagi, S.; Kawakubo, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1196–1197; (c) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350–4360.
10. Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman: London, 1978; p. 380.
11. Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1974**, *39*, 1311–1312.
12. VanderWerf, C. A.; Heisler, R. V.; McEwen, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 1231–1235.
13. Osterberg, A. E.; Kendall, E. C. *J. Am. Chem. Soc.* **1920**, *42*, 2616–2626.
14. Boto, A.; Hernández, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930–4937.