

An asymmetric dihydroxylation route towards the synthesis of (*R*)-clorprenaline hydrochloride

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Abstract

An efficient asymmetric synthesis of enantiomerically pure (*R*)-clorprenaline hydrochloride is described using Sharpless asymmetric dihydroxylation as the key step.

Keywords: (*R*)-Clorprenaline hydrochloride, asymmetric dihydroxylation, enantioselective synthesis

Introduction

Due to the high demand and preference for the use of enantiomerically pure drugs, there has been an upsurge of interest in the development of potentially useful processes for the asymmetric synthesis of pharmaceutical products. (*R*)-Clorprenaline hydrochloride **1** (Fig. 1) is a β_2 -agonist that is effective for the treatment of diverse disease states such as bronchitis and asthma¹ with only few reports of its synthesis in the literature.² As a part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones and amino alcohols,³ the Sharpless asymmetric dihydroxylation⁴ was envisaged as a powerful tool to obtain chiral dihydroxy compounds offering considerable opportunities for synthetic manipulation. Herein we report a new and highly enantioselective synthesis of (*R*)-clorprenaline hydrochloride by employing Sharpless asymmetric dihydroxylation of *o*-chlorostyrene **2** as the key step.

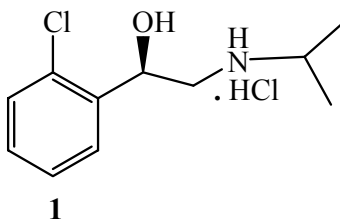
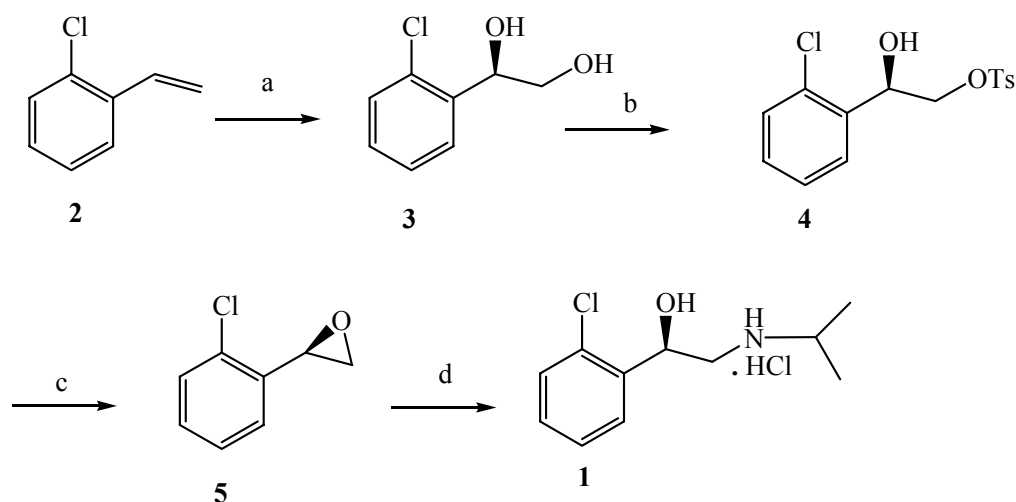


Figure 1

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Results and Discussion

The synthesis of (*R*)-clorprenaline hydrochloride **1** started from *o*-chlorostyrene **2**, a commercially available starting material is shown in Scheme 1. The dihydroxylation of *o*-chlorostyrene **2** with osmium tetroxide and potassium ferricyanide as co-oxidant under Sharpless asymmetric dihydroxylation⁴ gave the diol **3** in 94% yield with 95 % ee,⁵ $[\alpha]_D^{25} = -72.22$ (*c* 2, EtOH). Selective conversion of the primary hydroxyl group of **3** into a tosylate with tosyl chloride in the presence of catalytic amount of dibutyltin oxide^{6, 3e} afforded **4** in excellent yield. We failed in our attempt to synthesise **1** from **4** by nucleophilic displacement with isopropylamine. Accordingly the diol **3** was converted into cyclic sulfite which on reaction with isopropylamine gave only the starting material back. In an alternative approach, the tosylate **4** was converted into the epoxide **5**,^{2a} which on regioselective opening with isopropyl amine followed by treatment with 0.5 M HCl in methanol gave the target compound **1** as hydrochloride in excellent yield. The physical and spectroscopic data of **1** were in full agreement with the literature values.²



Scheme 1. *Reagents and conditions:* (a) (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, t-BuOH:H₂O, OsO₄, 0°C, 24 h, 94%. (b) dibutyltin oxide (0.2 mol%), TsCl, NEt₃, CH₂Cl₂, rt, 45 min, 95%. (c) NaOH/MeOH, 6 h, 95%; (d) isopropylamine, HCl/MeOH, 98%.

In summary, a practical and highly enantioselective synthesis of (*R*)-clorprenaline **1**, has been achieved using the Sharpless asymmetric dihydroxylation as the key step and source of chirality. The synthetic strategy described can be further extended to other enantiomers and related analogs.

Experimental Section

General Procedures. The solvents were purified and dried by standard procedure prior to use; petroleum ether of boiling range 60-80°C was used. Optical rotation was measured using sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer. The Mass spectra were recorded either with GC MS or with a Finnigan LCMS mass spectrometer. Enantiomeric excess was measured using either the chiral HPLC or by comparison with optical rotation.

(R)-(-)-*o*-Chlorophenylethanediol (3). To a mixture of $K_3Fe(CN)_6$ (10.67 g, 32.49 mmol), K_2CO_3 (4.49 g, 32.49 mmol) and $(DHQD)_2PHAL$ (0.085g, 0.011 mmol) in *t*-BuOH-H₂O (1:1, 55 mL) cooled to 0°C was added osmium tetroxide (0.44 ml, 0.1M solution in toluene). After stirring for 5 min at 0°C, the olefin **2** (1.5 g, 10.83 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfate (2g), the stirring was continued for an additional 45 min and then solution was extracted with EtOAc (3 x 50 mL). The combined organic phase were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (1:1) as eluent gave diol **3** (1.76g, 94%) as a white solid. mp 98-99°C; $[\alpha]_D^{25} = -72.22$ (*c* 2, EtOH) [Lit.^{2a} $[\alpha]_D^{22} -57^\circ$ (*c* 1.8, EtOH) for 85% ee]. ¹H NMR (200 MHz, CDCl₃): δ 3.21 (bs, 2 H), 3.30 (d, *J* = 2 Hz, 1H), 3.63 (dd, *J* = 4.3, 2 Hz, 1H), 4.98 (dd, *J* = 4.5, 2.3 Hz, 1H), 7.12-7.4 (m, 4H). IR (CHCl₃): 3401, 2328, 2818, 1604, 1590, cm⁻¹; Mass (ESI): 172 (M^+). Anal. Calcd for C₈H₉ClO₂: C, 55.67; H, 5.26; Cl, 20.54. Found: C, 55.63; H, 5.30; Cl, 20.50.

(R)-(-)-Toluene-4-sulfonic acid 2-hydroxy-2-*o*-chlorophenylethyl ester (4). To a mixture of diol **3** (1.0 g, 5.76 mmol) in dry dichloromethane (12 ml) was added dibutyltin oxide (0.003 g, 0.2 mol % of diol) followed by the addition of *p*-toluenesulfonyl chloride (1.10 g, 5.76 mmol) and triethylamine (0.586 g, 5.76 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC. After completion of reaction (45 min), the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 15 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (7:3) as eluent afforded the monotosyl compound **4** (1.80 g, 95%) as a viscous liquid. $[\alpha]_D^{25} = -52.53$ (*c* 1.02, CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ 1.70 (s, 1H, OH), 2.10 (s, 3H), 3.68 (m, 1H), 3.96 (m, 1H), 5.05 (dd, 1H, *J* = 8.8, 2.9 Hz), 6.96 (m, 4H), 7.29-7.50 (m, 4H). IR (Neat): 3525, 3021, 2951, 1598, 1215 cm⁻¹. Mass (ESI): 326 (M^+). Anal. Calcd for C₁₅H₁₅ClO₄S: C, 55.13; H, 4.63; Cl, 10.85; S, 9.81 Found: C, 55.18; H, 4.50; Cl, 10.70; S, 9.90.

(R)-1-(2-Chlorophenyl)-1,2-epoxypropane (5).^{2a} The tosyl compound **4** (1.6 g, 4.89 mmol) was dissolved in methanol (14 mL). The mixture was cooled in ice-salt bath before the methanolic solution (14 mL) of NaOH (0.22 g, 5.6 mmol) was added. The reaction mixture was stirred at -10°C for 6 h. After that it was diluted with 100 ml ether and water (25 mL) was added. The organic layer was separated and washed with water, dried. Removal of the solvent and purification of residue by silica gel column chromatography using pet ether: ethyl acetate (50:1)

as eluent furnished the epoxide **5** (722 mg, 95%) as colorless oil. $[\alpha]_D^{25} = -56.93$ (*c* 1, CHCl₃) [Lit.^{2a} $[\alpha]_D^{22} -43.4^\circ$ (*c* 1.5, CHCl₃ for 65% ee). ¹H NMR (200 MHz, CDCl₃): 2.69 (dd, *J*= 5.8, 2.4 Hz, 1H), 3.22 (dd, *J*= 5.8, 4.1 Hz, 1H), 4.23 (dd, *J*=4.3, 2.4 Hz, 1H), 7.26-7.39 (m, 4H); MS *m/z*: 154 (M⁺).

(R)-Clorprenaline hydrochloride (1). A solution of epoxide **5** (0.2 g, 1.29 mmol), excess of isopropyl amine (4 mL) and 4 drops of water was stirred at room temperature for 30 min. After that mixture was heated at 60°C for 6 h, after removal of the excess isopropyl amine, the residue was dissolved in 50 mL ether, filtered, dried and concentrated. The solid was recrystallized from hexane to afford (*R*)-clorprenaline (270 mg, 98%) as a white solid, mp 79-80°C; $[\alpha]_D^{25} = -69.21$ (*c* 1.4, EtOH) [Lit.^{2a} $[\alpha]_D^{23} -61.8^\circ$ (*c* 1.3, EtOH)]. ¹H NMR (300 MHz, CDCl₃) δ 1.11 (dd, *J*=6.2, 4.2 Hz, 6H), 2.47 (dd, *J*=12.2, 9 Hz, 1H), 2.70-2.90 (m, 3H), 3.00 (dd, *J*=12.2, 3.3 Hz, 1H), 5.02 (dd, *J*=8.9, 3.3Hz, 1H), 7.18-7.50 (m, 4H): IR (CHCl₃): 3320, 3018, 2982, 2788, 2704, 1593, 763 cm⁻¹.

The hydrochloride was obtained as follow: The clorprenaline was dissolved in methanol (1 ml), and 2 ml of 0.5 M HCl methanol was added. Removal of the solvent afforded (*R*)-clorprenaline hydrochloride as a white solid. The physical and spectroscopic data were in full agreement with the literature.²

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Reference and Footnotes

1. Tatsumi, K.; Arima, N.; Yamato, C.; Yoshimura, H.; Tsukamoto, H. *Chem. Pharm. Bull.* **1970**, *18*, 1254.
2. (a) Wei, Z-L; Li, Z-Y; Lin, G-Q, *Tetrahedron* **1998**, *54*, 13059. (b) Noe, C. R.; Knollmueller, M.; Gaertner, P.; Fleischhacker, W.; Katikarides, E. *Monatshefte fuer Chemie* **1995**, *126*, 557. (c) Ou, Z-M; Jin, Z-H; Wu, J-P; Yang, L-R; Cen, P-L, *Gaoxiao Huaxue Gongcheng Xuebao* **2005**, *19*, 511. (d) Furuhashi, K.; Takagi, K. *Jpn. Kokai Tokkyo Koho* **1986**, 6.
3. (a) Pandey R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425. (b) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035. (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957. (d) Pandey, R. K.; Upadhyay, P. K.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6245. (e) Kumar, P.; Upadhyay, R. K.; Pandey, R. K. *Tetrahedron Asymmetry* **2004**, *15*, 3955. (f) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877. (g) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*,

4091. (h) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360. (i) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207. (j) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843–2846. (k) Sadyandy, R.; Fernandes, R. A.; Kumar, P. *Arkivoc* **2005**, 3, 36.
4. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448.
5. The enantiomeric excess was determined by HPLC. HPLC model: Merck-Hitachi Lachrom Photo Diode Array detector (PDA); Column: Astec Cyclobond I (4.6 mm ID x 250 mmL); Mobile phase: methanol: water: (40: 60); Flow: 1 ml / min.
6. Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578.