An efficient synthesis of enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine

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A new pathway is described to produce a highly optically pure isomer of *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine through four simple steps. Reaction of cyclohexene oxide with aqueous methylamine, followed by cyclisation with Mitsunobu reagent and ring-opening reactions gave *rac-trans*- N^1,N^2-dimethylcyclohexane-1,2-diamine, and the enantiomers were obtained via a kinetic resolution using tartaric acid.

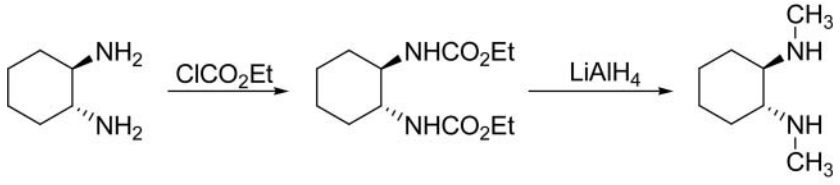
Keywords: kinetic resolution, chirality, cyclohexene oxide, N^1,N^2-dimethylcyclohexane-1,2-diamine, ring-opening reactions

Chiral diamines possessing C2 symmetry are particularly attractive in asymmetric synthesis. Among these, enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine are excellent ligands for many metal ions (Cu^{2+}, Ru^{2+}, Ni)[1–4] as well as for a multitude of pharmacological applications[5–7]. For example, they can form catalytically active complexes for use in asymmetric hydrogenation of aryl ketones[2] and N-arylation of amides[4]. In addition, enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine is an important pharmaceutical intermediate. For example, their Pt(II) complexes are effective in cancer therapy[7]. So, the synthesis of enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine is particularly attractive and well documented[8–11]. A typical chemical protocol is as follows[10,11]: condensation of enantiopure *(R,R)*-1,2-diaminocyclohexane with ethyl carbonochloridate in the presence of sodium hydroxide, followed by reduction using $LiAlH_4$ in THF gives enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine (Scheme 1). However, large-scale processing is severely limited by the high cost of this starting material and the danger of working with a great deal of $LiAlH_4$.

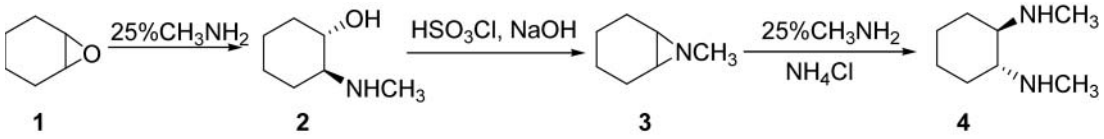
Horwell *et al.*[12] have reported a three-step manufacturing process for *rac-trans*-N^1,N^2-dimethylcyclohexane-1,2-diamine. Cyclohexene oxide **1** was converted into *trans*-2-(methylamino) cyclohexanol **2** by reflux with aqueous methylamine, followed by cyclisation with chlorosulfonic acid and ring-opening reactions with methylamine (Scheme 2).

We now report a convenient and efficient process for the synthesis of enantiomerically pure *trans*-N^1,N^2-dimethylcyclohexane-1,2-diamines based on the Horwell approach, see Scheme 3.

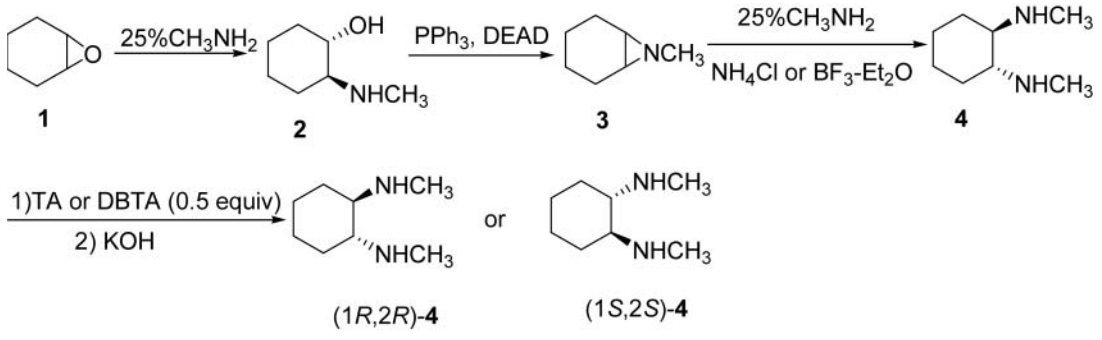
Cyclohexene oxide (**1**) was reacted with 25–30% aqueous methylamine (1.5 equiv.) in a sealed reactor to form *trans*-2-(methylamino)cyclohexanol **2** at 80 °C within 5h. Compound **2** was subjected to Mitsunobu reaction at room temperature



Scheme 1



Scheme 2



Scheme 3

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followed by adjusting the pH from 2 to 10 to yield 7-methyl-7-azabicyclo[4.1.0]-heptane **3**, which was directly subjected to the next reaction without purification. Ring-opening reactions of compound **3** with a methylamine aqueous solution was complete in a sealed reactor at 110 °C after 6h to yield *rac-trans-N¹,N²*-dimethylcyclohexane-1,2-diamine **4**. Various catalysts such as NH_4Cl, BF_3–Et_2O were investigated. It was shown that using NH_4Cl as catalyst was the optimum to obtain the desired compound **4**. The ratio of reactants was also investigated and compound **3**:methylamine = 1:2 was the optimum under similar conditions.

Finally, we investigated the resolution of *rac-trans-N¹,N²*-dimethylcyclohexane-1,2-diamine using tartaric acid (TA) and dibenzyl tartaric acid (DBTA) and found that both are efficient resolving agent. Considering the cost for large scale-up, the cheaper TA was chosen as the resolving agent. *Rac-trans-N¹,N²*-dimethylcyclohexane-1,2-diamine was reacted with 0.5 equiv. (L)-TA in ethanol to yield diastereomeric salts of (*1S,2S*)-**4**-(L)-TA following filtration. Then dichloromethane was added and basification with potassium hydroxide gave a single isomer of (*1S,2S*)-**4** in 42% yield (98.3% ee). To the filtrate in the above step was added 0.5 equiv. (D)-TA and reflux for 1h, followed by filtration and basification with potassium hydroxide gave the other isomer (*1R,2R*)-**4** in 41% yield (98.5% ee).

In conclusion, we have developed a practical method for the preparation of enantiomerically pure *trans-N¹,N²*-dimethylcyclohexane-1,2-diamine from an inexpensive starting material through four simple steps. In the whole procedure, the product of every step was used directly for the next step without purification. The advantages of our procedure include mild reaction conditions, easy work-up and good yields.

Experimental

The starting material and other reagent were purchased from common commercial suppliers and were used without further purification. IR spectra were recorded on a Spectrum RX IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DMX 400 MHz spectrometer using $CDCl_3$ as solvent, and TMS as the internal standard. High resolution mass spectra were recorded on an Applied Biosystems Mariner System 5303. Enantiomeric excess (ee) determinations were carried out using HPLC with a Chiralcel AD-H column on an Agilent 1200 Series.

trans-*2-(Methylamino)cyclohexanol* (**2**): Cyclohexene oxide **1** (29.4 g, 0.3 mol) was added into 25% aqueous methylamine (55.8 g, 0.45 mol) with stirring in an ice bath, and the resulting mixture was set up in a sealed reactor, which was maintained at 80 °C for 5h. Then, it was cooled to room temperature and excess aqueous methylamine was removed under *in vacuo*. Toluene (300 mL) was added to the residue and evaporated to remove the residual water. The residue was dried *in vacuo* to afford a light yellow oil (38.6 g, 97%). ^{1}H NMR (δ, $CDCl_3$): 3.27–3.18 (m, 3H), 2.40 (s, 3H), 2.15 (m, 1H), 2.07 (s, 1H), 2.01–1.92 (m, 1H), 1.74–1.69 (m, 2H), 1.33–1.16 (m, 3H), 1.01–0.92 (m, 1H). HRMS cald for $C_7H_{16}NO$ (M+1) 130.1232, found 130.1219.

7-*Methyl-7-azabicyclo[4.1.0]-heptane* (**3**): The solution of DEAD (22 mL, 0.12 mol) in CH_2Cl_2 (80 mL) was added dropwise into a solution of PPh_3 (31.44 g, 0.12 mol) and *trans*-2-(methylamino)cyclohexanol **2** (13 g, 0.1 mol) in CH_2Cl_2 (180 mL) in an ice bath. The reaction mixture was stirred at room temperature for 6h. 2N HCl (100 mL) was added and the resulting mixture was added to a separating funnel. After separation, the aqueous solution was neutralised using 2N KOH until pH=9–10 and extracted with CH_2Cl_2 (200 mL×2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvents were removed under reduced pressure to afford the crude product **3**, which was distilled at atmospheric pressure and the fraction of 118–126 °C was collected as a light yellow oil (9.2 g, 83%). ^{1}H NMR (δ, $CDCl_3$): 2.23 (s, 3H), 1.75–1.71 (m, 2H), 1.70–1.66 (m, 2H), 1.36–1.34 (m, 2H), 1.23–1.18 (m, 2H), 1.16–1.05 (m, 2H). HRMS calcd for $C_7H_{14}N$ (M+1) 112.1126, found 112.1141.

rac-trans-*N¹,N²-Dimethylcyclohexane-1,2-diamine* (**4**): A mixture of 7-methyl-7-azabicyclo[4.1.0]-heptane **3** (11.1 g, 0.1 mol) and 25% aqueous methylamine (18.6 g, 0.15 mol) and NH_4Cl (0.27 g, 0.005 mol) was added into the sealed reactor and stirred for 5 h at 110 °C. The solution was cooled and evaporated to dryness under reduced pressure to give the pale yellow oil: 12.4 g, yield 85%. The crude product was used directly in the resolution without further purification. (purity≥95% by GC). ^{1}H NMR (δ, $CDCl_3$): 2.35 (s, 6H), 2.08–1.97 (m, 6H), 1.68–1.64 (m, 2H), 1.20–1.15 (m, 2H), 0.96–0.87 (m, 2H). IR (film) ν_{max} 3300, 2930, 2852, 1550, 1438, 1150, 1098, 1040. HRMS Calculated for $C_8H_{19}N_2$ (M+1) 143.1458, found 143.1452.

(1S,2S)-N¹,N²-*Dimethylcyclohexane-1,2-diamine (*1S,2S*)*-(**4**): (L)-TA (45 g, 0.3 mol) was added to the solution of *rac-trans- N¹,N²*-dimethylcyclohexane-1,2-diamine **4** (85.2 g, 0.6 mol) in absolute EtOH (300 mL) at room temperature and the mixture was heated to reflux with agitation for 1 h. After cooling to room temperature, the mixture was filtered and the collected solid was washed with absolute EtOH. The filtrate was put aside for next step. The solid was suspended in CH_2Cl_2 (180 mL) and 2 N KOH (300 mL) was added into the mixture until pH=9–10. The mixture was stirred at room temperature to give a clear heterogeneous solution when stirring ceased. After separation, the aqueous phase was extracted additionally two times with the same amount of CH_2Cl_2 and the combined organic phases were dried with Na_2SO_4, filtered, and then concentrated to afford *(1S,2S)*-**4** as a waxy solid upon standing: 35.7 g, yield 42% (98.3% ee by HPLC). $[\alpha]_D^{20}$ = +130.3 (c 1.6, CH_2Cl_2). ^{1}H NMR (δ, CDCl3): 2.38 (s, 6H), 2.08–1.97 (m, 6H), 1.70–1.67 (m, 2H), 1.20–1.16 (m, 2H), 0.93–0.90 (m, 2H). HRMS calcd for $C_8H_{19}N_2$ (M+1) 143.1458, found 143.1450.

(1R,2R)-N¹,N²-*Dimethylcyclohexane-1,2-diamine* (1R,2R)-(**4**): (D)-TA (45 g, 0.3 mol) was added to the filtrate in the above step and the mixture was heated to reflux with agitation for 1h. The subsequent work-up was performed as described above. *(1R,2R)*-**4** was obtained as a waxy solid: 36.4 g, yield 43% (99.0% ee by HPLC). $[\alpha]_D^{20}$ = –130.9 (c 1.6, CH_2Cl_2) [cf. lit.[13] $[\alpha]_D^{20}$ = –136.2 (c 1.9, $CHCl_3$)]. ^{1}H NMR (δ, CDCl3): 2.39 (s, 6H), 2.09–1.97 (m, 6H), 1.69–1.64 (m, 2H), 1.20–1.15 (m, 2H), 0.96–0.89 (m, 2H). HRMS calcd for $C_8H_{19}N_2$ (M+1) 143.1458, found 143.1462.

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