

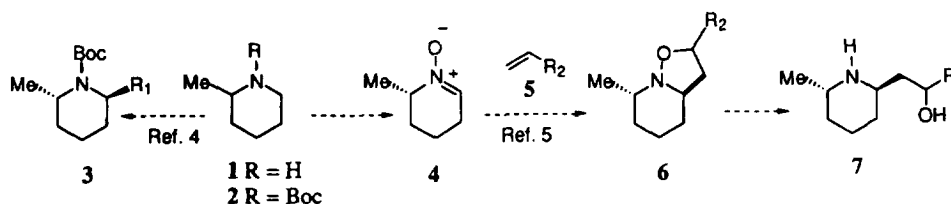
## A practical preparation of (*R*)- and (*S*)-*N*-Boc-2-methylpiperidines

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**Abstract:** The resolution of ( $\pm$ )-2-methylpiperidine using D- and L-tartaric acid followed by direct conversion of the intermediate tartrate salts to (*R*) and (*S*)-*N*-Boc-2-methylpiperidine is described. Also described is an NMR protocol for assessing the optical purity of the intermediate tartrate salts as well as the free bases. The resolved enantiomers showed an ee of >98% based on NMR integration. © 1997 Elsevier Science Ltd

Several biologically important natural products contain piperidine ring systems bearing a *trans*-2,6-disubstitution pattern.<sup>1–3</sup> Enantioselective syntheses of *trans*-2,6-disubstituted piperidine derivatives starting from 2-methylpiperidine of appropriate chirality could be achieved either *via* diastereoselective  $\alpha$ -alkylation<sup>4</sup> of *N*-Boc protected 2-methylpiperidine (**2**) or *via* a [3+2] nitron cycloaddition<sup>5</sup> of the chiral nitron **4** which could be generated from optically pure 2-methylpiperidine (Scheme 1).<sup>6</sup> However, investigation in this area is hindered by the paucity of optically pure 2-methylpiperidine.



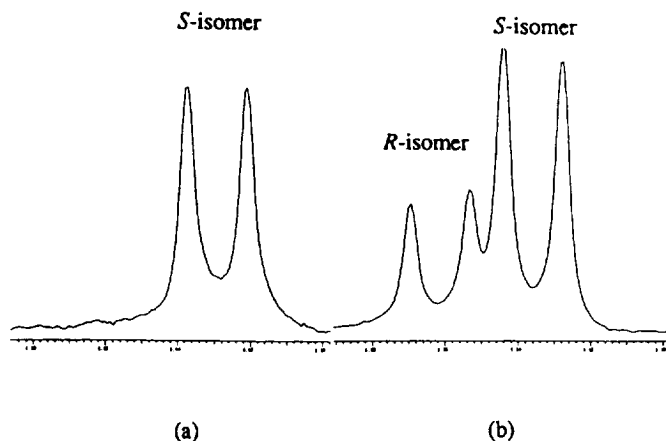
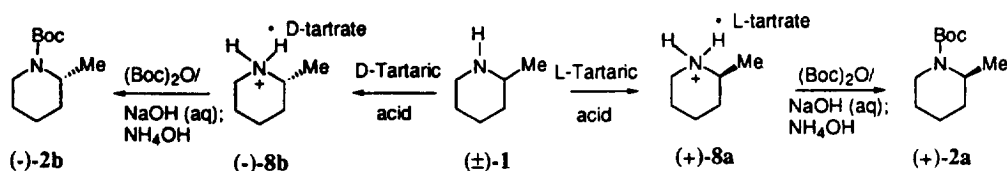
Scheme 1.

Munchhof and Meyers have reported a multistep enantioselective synthesis of (*S*)-2-methylpiperidine using (*S*)-phenylglycinol as a chiral auxiliary.<sup>7</sup> Racemic 2-methylpiperidine is inexpensive and readily available. The resolution of 2-methylpiperidine using tartaric acid was reported in 1896.<sup>8</sup> However, by virtue of its antiquity this report is devoid of experimental and analytical details needed to render itself readily reproducible. Additionally, the water solubility of 2-methylpiperidine makes extractive isolation difficult and the small magnitude of the specific rotation<sup>9</sup> of (*R*)- and (*S*)-2-methylpiperidines render assessment of their optical purity, based on specific rotation, unreliable. In our own hands, the resolution of 2-methylpiperidine using D- or L-tartaric acid yielded varying results in terms of optical purity and yield.

In the context of our total synthesis of the 2,6-disubstituted piperidine alkaloid himbacine,<sup>10</sup> an important structural lead in Alzheimer's disease therapy, and related natural products, we have developed an efficient procedure for the resolution of 2-methylpiperidine using D- as well as L-tartaric acid and the direct conversion of the intermediate tartrate salts to the corresponding, hitherto unreported (*R*)- and (*S*)-*N*-Boc-2-methylpiperidines. Also, we wish to report an efficient NMR protocol for the assessment of the optical purity of the intermediate tartrate salts **8a** and **8b** as well as the corresponding free amines (Scheme 2).

A concentrated, equimolar mixture of ( $\pm$ )-2-methylpiperidine and L-tartaric acid, upon standing at 0°C, gave an amorphous precipitate.<sup>8</sup> The precipitate was filtered and subjected to recrystallization from water. After a total of four crystallizations, the tartrate salt was directly converted to (*S*)-*N*-Boc-

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**Figure 1.** (a)  $^1\text{H}$  NMR spectrum of (*S*)-2-methylpiperidine-*L*-tartrate in the presence of (*R*)-*O*-acetylmandelic acid. The methyl doublet at  $\delta$  1.124 is shown. (b) Spectrum of the same sample with added ( $\pm$ )-2-methylpiperidine.<sup>16</sup>

2-methylpiperidine by treatment with an excess of di-*tert*-butyl dicarbonate in the presence of aqueous sodium hydroxide. The work-up procedure involved addition of an excess of aqueous ammonium hydroxide in order to convert the unreacted reagent, which co-eluted with the product, to the more polar *tert*-butyl urethane. Under identical conditions, (*R*)-*N*-Boc-2-methylpiperidine was generated by resolution of ( $\pm$ )-2-methylpiperidine using *D*-tartaric acid followed by *N*-protection.

The enantiomeric purity of the tartrate salt as well as the free base could be readily assessed from the  $^1\text{H}$  NMR spectrum using (*R*)-*O*-acetylmandelic acid as a chiral solvating agent.<sup>11</sup> In the presence of 1.5 equivalents of (*R*)-*O*-acetylmandelic acid, the methyl resonance of ( $\pm$ )-2-methylpiperidine-*L*-tartrate resolved into two well-defined doublets of equal intensity at  $\delta$  1.124 and 1.161.<sup>12,13</sup> Resolved (*S*)-2-methylpiperidine-*L*-tartrate, under identical conditions, showed only the upfield doublet which indicated >98% ee based on NMR integration.<sup>14</sup> Similarly, in the presence of 1.5 equivalents of (*R*)-*O*-acetylmandelic acid, the methyl resonance of ( $\pm$ )-2-methylpiperidine-*D*-tartrate resolved into two well-defined doublets at  $\delta$  1.132 and  $\delta$  1.160. The (*R*)-2-methylpiperidine-*D*-tartrate (**8b**), obtained after four recrystallizations, showed a single downfield methyl doublet corresponding to the (*R*)-isomer with no detectable upfield resonance corresponding to the (*S*)-isomer. As in the previous case, the NMR integration suggested >98% optical purity for (*R*)-2-methylpiperidine-*D*-tartrate.

The NMR experiment was repeated on the free base. Racemic 2-methylpiperidine, in the presence of 1.5 equivalents of (*R*)-*O*-acetylmandelic acid, showed a pair of methyl doublets at  $\delta$  1.091 and  $\delta$  1.121 corresponding to the (*R*) and (*S*) enantiomers respectively, as determined from the  $^1\text{H}$  NMR spectrum of the resolved free amines. Either the (*R*)- or (*S*)-2-methylpiperidine, generated from the corresponding tartrate salts mentioned above,<sup>15</sup> showed no detectable trace of its enantiomer in the  $^1\text{H}$  NMR spectrum (Figure 1).<sup>16</sup>

In conclusion, we have achieved an efficient synthesis of the hitherto unreported (*R*)- and (*S*)-*N*-Boc-2-methylpiperidines starting from commercially available and inexpensive ( $\pm$ )-2-methylpiperidine.

This resolution protocol obviates the difficult isolation and purification of the volatile and water soluble free base and affords both enantiomers of *N*-Boc-2-methylpiperidine, which are valuable synthetic intermediates, in >98% optical purity.

## Experimental

### General procedures

NMR spectra were recorded on a Varian Gemini 300, or Gemini 400 spectrometer. Mass spectra were obtained on a VG-ZAB-SE, HP-MS-Engine, or JEOL-HX-110 mass spectrometer. HRMS (FAB) were obtained on a VG-ZAB-SE spectrometer by peak matching against appropriate standards. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Genesis Series FT IR spectrophotometer. Optical rotations were measured on a Perkin Elmer 243 B or a Jasco DIP-140 polarimeter. L-Tartaric acid (99% ee) and D-tartaric acid (98% ee) were used as purchased from Aldrich.

### (S)-2-Methylpiperidine-L-tartrate (**8a**)

To a solution of L-tartaric acid (200 g, 1.3 mol) in water (133 ml), cooled in an ice bath, was added ( $\pm$ )-2-methylpiperidine (156 g, 1.3 mol) in portions, keeping the temperature of the solution below 30°C. The solution was concentrated on a rotary evaporator (bath temperature: 70°C) to give a syrup. The residue was dissolved in water (135 ml), heating on a steam bath as needed, and the solution was cooled in an ice bath. The amorphous solid was collected by filtration, and the residue washed with cold water (100 ml). The precipitate was dissolved in water (80 ml) and cooled in an ice bath. The crystalline tartrate salt was collected by filtration and recrystallized from 30 ml of water. The final recrystallization was carried out from 16 ml of water. The product was collected by filtration and dried to a constant weight under high vacuum to give (*S*)-2-methylpiperidine-L-tartrate·2H<sub>2</sub>O as a white crystalline solid (43 g). MP 65–66°C, lit.<sup>8a</sup>, 65–66°C;  $[\alpha]_D^{24} +13.7$  (*c* 0.10, CH<sub>3</sub>OH); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.19 (d, *J*=6.4 Hz, 3 H), 1.32–1.70 (m, 3 H), 1.75–1.88 (m, 3 H), 2.90 (t, *J*=8 Hz, 1 H), 3.15 (m, 1 H), 3.30 (d, *J*=8 Hz, 1 H), 3.52 (m, 1 H), 3.59 (m, 1 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 18.7, 21.4, 21.7, 29.8, 43.2, 51.3, 72.0, 174.6. Anal. Calcd for C<sub>10</sub>H<sub>19</sub>NO<sub>6</sub>·2H<sub>2</sub>O: C 42.10, H 8.13, N 4.91. Found: C 42.34, H 8.53, N 4.94.

### (S)-N-tert-Butoxycarbonyl-2-methylpiperidine (**2a**)

To a solution of (*S*)-2-methylpiperidine-L-tartrate·2H<sub>2</sub>O (13.021 g, 45.64 mmol) in aqueous sodium hydroxide (10%, 40 ml), cooled in an ice bath, was added a solution of di-*tert*-butyl dicarbonate (58.103 g, 266 mmol) in THF (35 ml). Cooling was discontinued and the reaction mixture was stirred at room temperature for 18 h. Saturated aqueous ammonium hydroxide (30%, 400 ml) was added to the reaction mixture slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (500 ml). The organic phase was extracted with ethyl acetate (2×100 ml). The combined organic phase was washed with 1N HCl (200 ml) and water (2×200 ml), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with 7% ethyl acetate in hexane to give the product as an oil (8.30 g, 91%).  $[\alpha]_D^{20} +50.9$  (*c* 0.83, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (d, *J*=7.0 Hz, 3 H), 1.43 (s, 9 H), 1.20–2.20 (m, 6 H), 2.77 (dt, *J*=13.0 Hz, 2.4 Hz, 1 H), 3.88 (d, *J*=14.5 Hz, 1 H), 4.34 (m, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  15.4, 18.4, 25.4, 28.20, 29.8, 38.4, 45.7, 78.7, 154.4. MS (FAB) *m/e* 200 (M+H)<sup>+</sup>; IR (KBr) 1695 cm<sup>-1</sup>.

### (R)-2-Methylpiperidine-D-tartrate (**8b**)

The resolution of ( $\pm$ )-2-methylpiperidine (148 g, 1.5 mol) using D-tartaric acid (224 g, 1.5 mol) was carried out according to the above procedure to give (*R*)-2-methylpiperidine-D-tartrate·2H<sub>2</sub>O as a white crystalline solid (50.0 g). MP 65–66°C, lit.<sup>8a</sup>, 65–66°C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.19 (d, *J*=6.4 Hz, 3 H), 1.30–1.60 (m, 3 H), 1.70–1.83 (m, 3 H), 2.90 (t, *J*=8 Hz), 3.05 (m, 1 H), 3.25 (d, *J*=8 Hz, 1 H), 3.42 (m, 1 H), 3.49 (m, 1 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 18.7, 21.4, 21.7,

29.8, 43.2, 51.3, 72.0, 174.6. Anal. Calcd for  $C_{10}H_{19}NO_6 \cdot 2H_2O$ : C 42.10, H 8.13, N 4.91. Found: C 42.11, H 8.54, N 4.92.

**(R)-N-tert-Butoxycarbonyl-2-methylpiperidine (2b)**

Conversion of (*R*)-2-methylpiperidine-D-tartrate  $\cdot 2H_2O$  (12.50 g, 43.82 mmol) to (*R*)-*N*-Boc-2-methylpiperidine (8.08 g, 93%) was carried out according to the procedure given above.  $[\alpha]_D^{20} -46.4$  (*c* 0.83,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.11 (d,  $J=7.0$  Hz, 3 H), 1.45 (s, 9 H), 1.20–2.20 (m, 6 H), 2.80 (dt,  $J=13.0$  Hz, 2.4 Hz, 1 H), 3.90 (d,  $J=14.5$  Hz, 1 H), 4.37 (m, 1 H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  15.1, 18.1, 25.1, 27.9, 29.5, 38.1, 45.5, 78.4, 154.1. MS (FAB)  $m/e$  200 (M+H)<sup>+</sup>; IR (KBr) 1695  $cm^{-1}$ .

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12. The tartrate salts are only sparingly soluble in  $CDCl_3$ . However, upon addition of (*R*)-*O*-acetylmandelic acid, a homogeneous solution was obtained.
13. The absolute value of chemical shifts, given here for comparison, varied somewhat depending on concentration.
14. After a total of three recrystallizations, the ee of (*S*)-2-methyl-L-tartrate was about 92%.
15. The free base was generated from the tartrate salt by dissolving it in 5% aqueous sodium hydroxide followed by extracting with dichloromethane.  $^1H$  NMR experiments were conducted on the crude product without further purification.
16. The  $^1H$  NMR experiment was repeated in each case by addition of about 15 molar percent of racemic 2-methylpiperidine to the sample. As expected, this gave rise to an additional methyl doublet corresponding to the opposite enantiomer.

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