Synthesis of N-Methyl Coniine

(±)-Coniine (502.6 mg, 3.95 mmol) and (-)-mandelic acid (605.5 mg, 3.98 mmol), were added to a 16 mL screw top glass test tube (Note 1). To the (±)-coniine and (-)-mandelic acid mixture was added 1.6 mL of MeOH and the mixture warmed until all (±)-coniine and (-)-mandelic acid was dissolved, then anhydrous diethylether (4.00 mL) was added and the mixture put on ice. Crystals of (+)-coniine (-)-mandelate began to form within 60 min of adding the diethyl ether. After 16 h at -20 °C, the solvent was filtered from the crystals, the crystals collected, and dried in vacuo. The crystals were recrystallized (3×) by dissolving the crystals in MeOH (1.6 mL), adding diethyl ether (4 mL), and then allowing them to crystallize at -20 °C. The (+)-coniine (-)-mandelate crystals were filtered for a final time, collected, and dried in vacuo (314.7 mg, 1.13 mmol, 57% yield): feathery needles, mp 115 °C; [R]25.1 D ) -47.8° (c ) 0.52, MeOH). This same procedure was used with (±)-coniine (513.7 mg, 4.04 mmol) and (+)-mandelic acid (635.1 mg, 4.17 mmol). The (-)-coniine (+)-mandelate crystals were collected and dried in vacuo (364.0 mg, 1.30 mmol, 65% yield): feathery needles, mp 117-119 °C; [R]24.7 D ) +49.0° (c ) 0.60, MeOH).

Note 1: Amounts to be used:

250 mg coniine free base  
300 mg + or – mandelic acid  
0.8 mL MeOH  
2.0 mL Diethyl ether (reagent grade)  
A way to heat a solution to 60°C

Do not discard filtrate from recrystallization!

N-Methylation of coniine

A solution of coniine/mandelic complex (50 mg) and catalytic amount of Pd/C was stirred under hydrogen atmosphere in 3 mL HOAc/H2O/HCHO (1/1/1) for 2 days. The
reaction mixture was filtered through Celite and the residue was washed with little (ca. 1 mL) MeOH (Note 1). The combined solution was added to a 125 mL Erlenmeyer flask containing solids of Na$_2$SO$_4$ (ca. 5 g) and NaHCO$_3$ (ca. 5 g). After the complete neutralization of acetic acid (Note 2), 50 mL Et$_2$O was added and the slurry of reaction mixture was filtered through glass wool. The reaction mixture was extracted again with another 50 mL of Et$_2$O. The organic solution was added with 1 drop of 6 M H$_2$SO$_4$ and the solvents were evaporated to dryness using compressed air. Water (ca. 2 mL) was added to the resulting white solid and the solution was filtered through 0.2 μm syringe filter into a 20 mL vial (Note 3). This water extraction process was repeated twice and the combine aqueous solution (ca. 6 mL) was evaporated to dryness with compressed air. The resulting N-methylconiine sulfate should be checked with NMR to confirm the complete methylation. The aqueous solution of N-methylconiine, which may contain little mandelic acid, was loaded to a column packed with Dowex 1X-8 (OH$^-$ form) and the column was eluted with more water (ca. 10 mL). To this aqueous solution, precisely 0.4 equivalent of 6 M H$_2$SO$_4$ (12.0 μL based on 80% yield) was added. The aqueous solution was evaporated to dryness. After examining the quality of N-methylconiine sulfate salt with NMR, the product was distributed into 2 pre-weighted 2 mL vials (Note 4). The water was evaporated and the samples of N-methylconiine are ready for toxicity study.

Note 1: Pd/C is a fire hazard reagent. Disposal as instructed.
Note 2: This, which usually takes 20 min, can be judged by the cease of bubbling.
Note 3: Pressure needs to be applied for the filtration. Hold the syringe and filter firmly.
Note 4: The vial without caps needs to be pre-weighted using analytical balance.