SUPPORTING INFORMATION

FOR

**Cascade Iminium Ion Reactions for the Facile Synthesis of Quinolizidines.
Concise Syntheses of ($\pm$)-Epilupinine and (-)-Epimyrine.**

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EXPERIMENTAL PROCEDURES

General. Unless otherwise indicated, all starting materials and solvents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by passage through two columns of activated neutral alumina, acetonitrile (CH₃CN) was dried by passage through two columns of activated molecular sieves, and methylene chloride (CH₂Cl₂) was distilled from calcium hydride. All solvents contained less than 50 ppm H₂O by Karl Fisher coulometric moisture analysis. Reactions involving air- or moisture-sensitive reagents or intermediates were performed in flame-dried glassware under an atmosphere of dry nitrogen or argon. Flash chromatography was performed following the Still¹ protocol with ICN Biomedical ICN-SILITech 32-63d silica gel with the indicated solvents. Proton (¹H) and carbon (¹³C) NMR spectra were obtained using a Varian Unity Plus (400 MHz) or Varian Unity Plus (500MHz) spectrometer as solutions in CD₃CN unless otherwise noted. Chemical shifts are reported as parts per million (ppm, δ) and referenced to the residual protic solvent unless otherwise noted. Coupling constants are reported in hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, multiplet; comp, complex multiplet, app, apparent. Low-resolution chemical ionization mass spectra (CI) were obtained on a Finnigan TSQ-70 instrument. High-resolution mass spectra (HRMS) were obtained on a VG Analytical ZAB-2E instrument. IR spectra were recorded as films or solutions (with solvent indicated) on sodium chloride plates on a Perkin-Elmer 1600 series FTIR.

12

(5R*, 6S*)-5-(Vinyl)-1-azabicyclo[4.4.0]decane (12). Freshly prepared amine² **9** (363 mg, 2.12 mmol) was added dropwise to a suspension of freshly prepared aldehyde³ **10** (310 mg, 2.12 mmol) and molecular sieves (4 Å, 0.50 mg) in CH₃CN (2.0 mL) at 0 °C. The ice bath was removed, and the reaction was stirred for 2 h at which time the solution was transferred via syringe to a flame dried round-bottom flask. Additional CH₃CN (30 mL) was added, and the mixture was cooled to 0 °C with stirring. Freshly distilled CF₃CO₂H (2.4 g, 1.6 mL, 21.2 mmol) was added dropwise, and the reaction mixture was stirred for 2 h. The ice bath was removed, and the solution was stirred at rt for

12 h. Neat Et_3SiH (2.5 g, 3.2 mL, 21.2 mmol) was added dropwise, and the mixture was heated under reflux for 24 h. The reaction mixture was cooled to rt, and the solvents were removed under reduced pressure. The crude residue was dissolved in Et_2O (15 mL), and a solution of 2 N HCl (15 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with Et_2O (3 X 15 mL). The aqueous layer was made basic with a solution of 5% NaOH saturated with NaCl (15 mL) and extracted with Et_2O (3 X 15 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure (300 mm Hg). The crude residue was purified by flash chromatography eluting with pentane/EtOH (60:1). An aliquot of the fractions containing pure **12** was concentrated under reduced pressure (300 mm Hg) to give an analytical sample for characterization. The remaining fractions containing pure **12** were combined, $\text{CF}_3\text{CO}_2\text{H}$ (1.5 mL) was added, and the mixture was concentrated under reduced pressure to give 444 mg (75%) of the trifluoroacetate salt of **12** as a pale yellow oil. ^1H (500 MHz) δ 5.60 (ddd, $J = 17.5, 10.0, 9.0$ Hz, 1 H), 4.99 (ddd, $J = 17.5, 2.0, 1.0$ Hz, 1 H), 4.94 (dd, $J = 10.0, 2.0$ Hz, 1 H), 2.76-2.69 (comp, 2 H), 2.00-1.93 (comp, 2 H), 1.85 (app tdd, $J = 11.0, 9.0, 3.0$ Hz, 1 H), 1.74 (app dp, $J = 13.0, 2.5$ Hz, 1 H), 1.74-1.64 (comp, 2 H), 1.63-1.54 (comp, 4 H), 1.54-1.46 (m, 1 H), 1.23-1.13 (comp, 2 H), 1.04 (app dq, $J = 10.5, 3.5$ Hz, 1 H); ^{13}C (125 MHz) δ 142.2, 114.8, 66.5, 57.2, 56.9, 48.3, 32.5, 31.3, 26.4, 25.6, 25.2; IR (neat) 3400, 3079, 2953, 2869 (Bohlmann Bands), 2723, 2627, 2584, 1738, 1671, 1448, 1201; mass spectrum (CI) m/z 166.1591 [$\text{C}_{11}\text{H}_{20}\text{N}$, (M+1) requires 166.1596], 164, 194, 248, 327, 329, 341, 399, 401.

14

(±)-Epilupinine. The trifluoroacetate salt of **12** (75 mg, 0.27 mmol) was dissolved in Et_2O (3 mL) in a two neck round-bottom flask fitted with a drying tube (CaCl_2) and an ozone inlet. The mixture was cooled to $-78\text{ }^\circ\text{C}$, and ozone was passed through the stirred solution until the solution turned blue. Air was passed through the reaction mixture for 5 min, and the ozone bubbler and drying tube were replaced with septa. A solution of LiAlH_4 (51 mg, 1.5 mmol) in THF (2 mL) was added, the dry ice bath was removed, and the suspension was stirred at rt for 12 h. H_2O (0.05 mL), 5% NaOH (0.05 mL), and H_2O (0.15 mL) were added dropwise sequentially with stirring, and the mixture was stirred until the suspension turned white. The solids were removed by vacuum filtration

and washed with Et₂O. The combined filtrate and washings were concentrated under reduced pressure to give 40 mg (88%) of **14** as a colorless oil. Recrystallization with pentane provided a white solid; (mp 79-80 °C; lit. 78-79 °C⁴).

¹ H NMR (500 MHz, CDCl ₃)	¹ H NMR (lit. ⁴)	¹³ C NMR	¹³ C NMR (lit. ⁴)
δ 3.67 (dd, <i>J</i> = 10.8, 3.6 Hz, 1 H)	δ 3.64 (dd, <i>J</i> = 10.9, 3.5 Hz, 1 H)	δ 64.8	δ 64.5
3.58 (dd, <i>J</i> = 11.2, 6.0 Hz, 1 H)	3.54 (dd, <i>J</i> = 10.9, 5.9 Hz, 1 H)	64.5	64.3
2.85–2.77 (comp, 2 H)	2.80 (t, <i>J</i> = 12.3 Hz, 2 H)	57.1	56.8
2.06–1.98 (comp, 2 H)	2.30–1.52 (m, 12 H)	56.9	56.5
1.91–1.58 (comp, 9 H)	1.48–1.34 (m, 1 H)	44.2	43.8
1.41 (m, 1 H)	1.32–1.10 (m, 2 H)	30.1	29.6
1.31–1.13 (comp, 3 H)		28.4	28.1
		25.8	25.5
		25.3	24.9
		24.8	24.5

16a,b

21

(4R)-2-Methylenyl-4-methyl-6-cyanoquinolizidine (21). Freshly prepared amine **20**⁷ (217 mg, 1.26 mmol) was added dropwise to a suspension of freshly prepared aldehyde **10**³ (185 mg, 1.26 mmol) in CH₃CN (2.0 mL) containing molecular sieves (4 Å, 0.5 g) at 0 °C. The suspension was stirred for 2 h, at which time the ice bath was removed and the suspension was stirred at rt for 12 h. The solution was transferred via syringe to a round-bottom flask charged with CH₃CN (15 mL), and the solution was cooled to 0 °C with an ice bath. Freshly distilled CF₃CO₂H (718 mg, 0.5 mL, 6.30 mmol) was added dropwise, and the mixture was stirred for 2 h. The ice bath was removed, and the reaction mixture stirred for 4 h at rt. The mixture was concentrated under reduced pressure, and the

crude residue was cooled to 0 °C. A solution of NaCN (114 mg, 2.30 mmol) in H₂O (2 mL) was added dropwise with stirring. The ice bath was removed, and the solution stirred at rt for 4 h. The reaction mixture was diluted with CH₂Cl₂ (10 mL) and a solution of 5% NaOH saturated with NaCl (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were dried (K₂CO₃) and concentrated under reduced pressure (300 mm Hg). The crude residue was purified by flash chromatography eluting with petane/Et₂O (60:1) to give 213 mg (89%) of **21** as a pale yellow oil; ¹H (500 MHz) δ 4.70 (app t, *J* = 2.0 Hz, 2 H), 4.35 (app t, *J* = 3.5 Hz, 1 H), 2.35-2.18 (comp, 4 H), 2.07-1.95 (comp, 3 H), 1.82-1.70 (comp, 3 H), 1.59 (app qt, *J* = 12.0, 1.5 Hz, 1 H), 1.31-1.23 (m, 1 H), 1.14 (d, *J* = 6.0, 1 H); ¹³C (125 MHz) δ 146.3, 117.4, 107.8, 59.3, 58.3, 50.7, 43.7, 42.8, 33.9, 29.6, 21.3, 20.3; IR (neat) 3074, 2939 2868, 2825 (Bohlmann Bands), 2736, 2221, 1778, 1726, 1659, 1444, 1379, 1328, 1182; mass spectrum (CI) *m/z* 191.1541 [C₁₅H₂₃N₁, (M+1) requires 191.1548], 220, 191, 164 (base).

23

(-)-Epimyrtiline (23). The trifluoroacetate salt of **22** (115 mg, 0.41 mmol) was dissolved in a mixture of CH₂Cl₂ (3 mL) and MeOH (0.5 mL) in a two-neck round-bottom flask fitted with a drying tube (CaCl₂) and an ozone inlet. The solution was cooled to -78 °C, and ozone was bubbled through the solution until a blue color persisted (5 min). Air was then passed through the reaction mixture until the blue color disappeared. The ozone bubbler and drying tube were replaced with septa, and methyl sulfide (128 mg, 0.15 mL, 2.06 mmol) was added to the solution dropwise. The dry ice bath was removed and the reaction mixture stirred at rt for 12 h. A solution of 5% NaOH saturated with NaCl (1 mL) was added dropwise with stirring. The layers were separated, and the aqueous layer was extracted with Et₂O (3 X 15 mL). The combined organic layers were dried (K₂CO₃) and concentrated under reduced pressure (300 mmHg). The crude residue was purified by flash chromatography eluting with hexanes/EtOH (10:1) to give 40 mg (60%) of a mixture (95:5) of **23**⁸ and **24** as a pale yellow oil; [α]_D²³ -18 (*c* 0.4, CDCl₃); [lit.⁸ ([α]_D²⁰ -17.4 (*c* 0.7, CHCl₃); [α]_D²³ -19 (*c* 0.4, CHCl₃)].

¹ H NMR (500 MHz, CDCl ₃)	¹ H NMR (lit. ⁸)	¹³ C NMR	¹³ C NMR (lit. ⁸)
δ 3.30-3.26 (m, 1 H)	δ 3.34 (br d, <i>J</i> = 11.0 Hz, 1 H)	δ 208.4	δ 208.7
2.40-2.12 (comp, 6 H)	2.50-2.25 (m, 4 H)	62.1	62.4
1.83-1.52 (comp, 5 H)	2.24-2.12 (m, 1 H)	59.3	59.6
1.41-1.33 (m, 1 H)	1.90-1.55 (m, 6 H)	51	51.3
1.30-1.20 (m, 1 H)	1.50-1.25 (m, 2 H)	49.8	50
1.17 (d, <i>J</i> = 5.5 Hz, 3 H)	1.20 (d, <i>J</i> = 5.7 Hz, 3 H)	48.7	49
		34.2	34.4
		25.9	26.2
		23.9	24.2
		20.7	21

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