A Formal Synthesis of Porantheridine and an Epimer

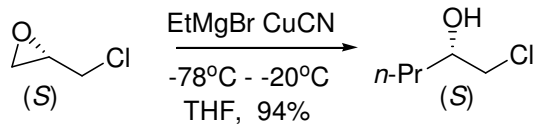
Roderick W. Bates and Yongna Lu

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, 21 Nanyang Link, Nanyang Technological University, Singapore 637371

General Information:

Tetrahydrofuran was distilled from sodium/benzophenone; dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use. Methanol was distilled from activated magnesium. All other solvents and reagents were used as received.

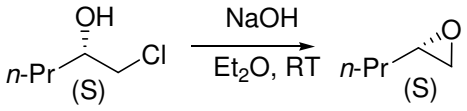
IR spectra were recorded either neat or as nujol mulls using NaCl plates. ^1H NMR spectra were recorded at 300, 400 or 500 MHz with residual protic solvent as the reference. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instrument at 75, 100 or 125 MHz. Chemical shifts are in ppm and coupling constants, *J*, are in Hz. Specific rotations, $[\alpha]_D$ are given with units of $10^{-1}degcm^2g^{-1}$. Enantiomeric excess was determined by chiral HPLC analysis, performed on a Chiralcel OD-H column, eluting with IPA/hexane.



(*S*)-1-Chloropentan-2-ol.[1]

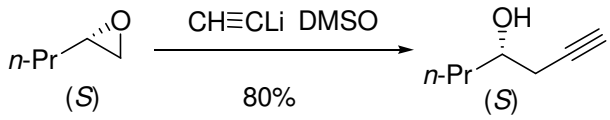
A trace of I_2 was added to a suspension of magnesium (0.77 g, 32.3 mmol) in Et_2O (16 mL).The mixture was heated at reflux until the color disappeared. Bromoethane was added dropwise over 0.5 h. After completion of addition, the mixture was heated

at reflux for 1 h. The resulting solution of ethylmagnesium bromide was added dropwise to a solution of (*R*)-epichlorohydrin (2.0 g, 21.6 mmol) and CuCN (0.19 g, 2.16 mmol) in dry THF (30 mL) at –78 °C. The mixture was warmed to -20 °C over 3 h and poured into a saturated NH_4Cl solution. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through celite and concentrated *in vacuo* to afford (*S*)-1-chloro-pentan-2-ol as a yellowish oil (2.5 g, 94%) which was used without further purification. $[\alpha]_D^{22.1}$ +1.0 (*c* 2.7, $CHCl_3$), $[\alpha]_D^{24}$ -19.7 (*c* 1.5, MeOH), (ref.2 $[\alpha]_D^{20}$ +1.1 (*c* 2.9, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84–3.80 (1H, m), 3.64 (1H, dd, *J* = 11.1, 3.2 Hz), 3.48 (1H, dd, *J* = 11.1, 7.2 Hz), 2.12 (bs, 1H), 1.58–1.39 (4H, m), 0.95 (3H, t, *J* = 7.0 Hz).



(*S*)-1,2-epoxypentane.[1]

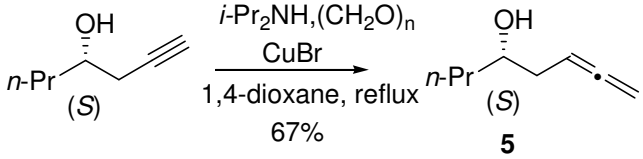
Powdered NaOH (2.7 g, 68.6 mmol) was added to a solution of (*S*)-1-chloropentan-2-ol (1.5 g, 12.2 mmol) in Et_2O (20 mL). The mixture was stirred vigorously for 24 h and poured into water (20 mL). After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and filtered through celite. Removal of the solvent by distillation through a 10 cm Vigreux-column afforded (*S*)-1,2-epoxypentane (1.8 g) as a light yellow oil, which was used without further purification.



(*S*)-Hept-1-yn-4-ol.[2]

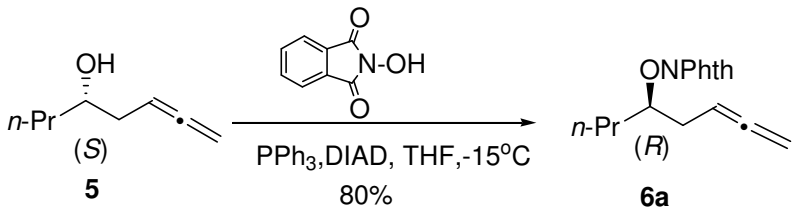
Lithium acetylide-EDA complex (4.8 g, 52.3 mmol) was added to a solution of (*S*)-1,2-epoxypentane (1.8 g, 20.9 mmol) in dry DMSO (25 mL), and the mixture was stirred overnight at room temperature. After quenching with ice, 0.5 M H_2SO_4 was used to neutralize the basic solution. The solution was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered

through celite and concentrated *in vacuo* to give (*S*)-hept-1-yn-4-ol (2.34 g, 80%) as a colorless oil. $[\alpha]_D^{25.2}$ -25.4 (*c* 2.0, MeOH), (ref.3 $[\alpha]_D$ -27.2 (*c* 1.1, MeOH)). ^{1}H NMR (300 MHz, CDCl3) δ 3.78-3.75 (1H, m), 2.43 (1H, ddd, *J* = 16.7, 4.7, 2.7 Hz), 2.31 (1H, ddd, *J* = 16.7, 6.8, 2.7 Hz), 2.05 (1H, t, *J* = 2.7 Hz), 1.92 (1H, brd, *J* = 4.7 Hz), 1.63-1.22 (4H, m), 0.94 (t, *J* = 7.1 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.9, 70.7, 69.6, 38.3, 27.3, 18.8, 13.9



(*S*)-Octa-6,7-dien-4-ol 5.

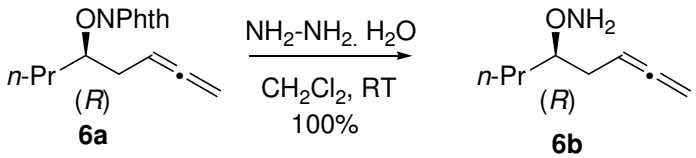
Diisopropylamine (6.8 mL, 48.6 mmol) was added to a mixture of (*S*)-hept-1-yn-4-ol (2.72 g, 24.3 mmol), paraformaldehyde (1.46 g, 48.6 mmol) and copper (I) bromide (1.15 g, 8.0 mmol) in dioxane (80 mL). The reaction was heated at reflux overnight and then cooled to room temperature. Air was bubbled through the reaction mixture for 0.5 h. The reaction mixture was then filtered through celite, washing with Et_2O (3 x 15 mL). The filtrate was concentrated *in vacuo* to give a brown oil. The crude product was purified by distillation under reduced pressure to give (*S*)-octa-6,7-dien-4-ol **5** (2.05g, 67%) as a colorless oil. $[\alpha]_D^{24.4}$ -5.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (1H, tt, *J* = 7.0, 7.0 Hz), 4.67 (2H, dt, *J* = 7.0, 2.8 Hz), 3.67-3.65 (1H, m), 2.23-2.15 (1H, m), 2.12-2.03 (1H, m), 1.97 (1H, d, *J* = 3.4 Hz), 1.47-1.27 (4H, m), 0.90 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 86.3, 74.6, 70.8, 38.8, 36.4, 18.8, 14.0; IR (neat) 3401, 2959, 1956 cm^{-1}; MS (m/z) 149 $[M+Na]^+$; HRMS *m/z calcd.* for $C_8H_{15}O$ $[M+H]^+$ 127.1123, found 127.1117.



2-((*R*)-Octa-6,7-dien-4-yloxy)isoindoline-1,3-dione 6a.

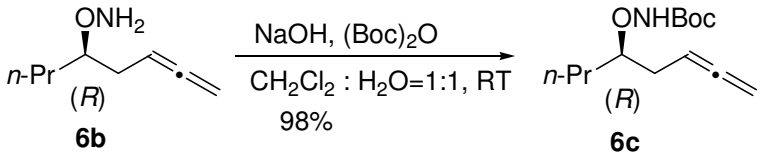
A solution of diisopropyl azodicarboxylate (0.89 mL, 4.48 mmol) in THF (2 mL) was

added to a solution of (*S*)-octa-6,7-dien-4-ol (0.47 g, 3.73 mmol), triphenylphosphine (1.17 g, 4.48 mmol) and *N*-hydroxyphthalimide (0.73 g, 4.48 mmol) in THF (8 mL) dropwise at -15 °C. The reaction mixture was stirred at -15 °C for 1 h. After evaporation of the solvent, the residue was subjected to purification by flash chromatography (EtOAc : Hexane = 1 : 9) to afford the *N*-phthaloyl hydroxylamine **6a** (0.81 g, 80%) as a colorless oil. $[\alpha]_D^{23.8}$ +48.4 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.79 (2H, m), 7.76-7.71 (2H, m), 5.24 (1H, tt, *J* = 7.0, 7.0 Hz,), 4.65 (2H, dt, *J* = 7.0, 2.9 Hz), 4.30 (1H, tt, *J* = 5.7, 5.7 Hz), 2.44-2.24 (2H, m,), 1.80-1.50 (4H, m), 0.96 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 164.2 (2C), 134.3 (2C), 129.0 (2C), 123.4 (2C), 87.1, 85.3, 74.8, 34.3, 31.9, 18.3, 14.0; IR (neat) 2961, 2936, 2872, 1956, 1789, 1732, 1468 cm^{-1}; MS (m/z) 272 $[M+H]^+$; HRMS *m/z calcd*. for $C_{16}H_{18}O_3N$ $[M+H]^+$ 272.1287, found 272.1286. Chiral HPLC: Chiralcel OD-H (hexane / *i*-PrOH = 99 / 1, flow rate 0.30 mL / min, λ = 230 nm), t_R(minor)= 45.6 min, t_R(major)= 48.6 min; 99% ee.



(*R*)-Octa-6,7-dien-4-hydroxylamine 6b.

Hydrazine monohydrate (0.54 mL, 11.1 mmol) was added to a solution of the *N*-phthaloyl hydroxylamine (0.75 g, 2.77 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and was filtered through celite, washing with Et_2O. The filtrate was concentrated *in vacuo* to give hydroxylamine **6b** (0.39 g, 100%) as a colorless oil, which was used without further purification. $[\alpha]_D^{24}$ +29.2 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (2H, br), 5.10 (1H, tt, *J* = 7.0, 7.0 Hz), 4.67 (2H, dt, *J* = 7.0, 2.8 Hz), 3.59 (1H, tt, *J* = 6.0, 6.0 Hz), 2.30-2.24 (2H, m), 1.47-1.23 (4H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 86.1, 83.0, 74.2, 34.4, 31.7, 18.7, 14.1; IR (neat) 3316, 2959, 2934, 1956 cm^{-1}; MS (m/z) 142 $[M+H]^+$; HRMS *m/z calcd*. for $C_8H_{16}ON$ $[M+H]^+$ 142.1232, found 142.1239.



***N-tert*-Butoxycarbonyl (*R*)-octa-6,7-dien-4-hydroxylamine 6c.**

Powered sodium hydroxide (0.41 g, 10.20 mmol) was added to a solution of the hydroxylamine (0.60 g, 4.26 mmol) and di-*tert*-butyl dicarbonate (1.17 mL, 5.10 mmol) in dichloromethane-water (15 mL-15 mL) at room temperature. The reaction mixture was stirred at room temperature overnight and extracted with ethyl acetate (3 x 8 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. Purification by flash chromatography (EtOAc : Hexane = 1 : 9) provided *N*-protected hydroxylamine **6c** as a colorless oil (1.0 g, 98%). $[\alpha]_D^{24.1}$ +40.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, brs), 5.12 (1H, tt, *J* = 7.0, 7.0), 4.63 (2H, dt, *J* = 7.0, 2.8 Hz), 3.77 (1H, tt, *J* = 5.6, 5.6 Hz), 2.31-2.24 (2H, m), 1.57-1.22 (4H, m), 1.45 (9H, s), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 157.1, 85.7, 84.7, 81.3, 74.4, 34.1, 31.5, 28.1 (3C), 18.5, 14.1; IR (neat) 3319, 2980, 2961, 2934, 2873, 1956, 1748 cm^{-1}; MS (m/z) 264 $[M+Na]^+$; HRMS *m/z calcd.* for $C_{13}H_{23}O_3NNa$ $[M+Na]^+$ 264.1576, found 264.1568.

References

1. Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227.

2. Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; Voss, J. J. D. *J. Org. Chem.* **2005**, *70*, 3054.