SUPPORTING INFORMATION

FOR

Concise Formal Synthesis of (–)-Peduncularine via Ring Closing Metathesis

David G. Washburn, Richard W. Heidebrecht, Jr., and Stephen F. Martin^{*}

Department of Chemistry and Biochemistry, The University of Texas, Austin, TX 78712 USA

Experimental Procedures

General. Solvents and reagents were reagent-grade and used without purification unless otherwise noted. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and diisopropylamine were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. All reactions were done in flame-dried glassware under nitrogen unless otherwise indicated. ^1H nuclear magnetic resonance (NMR) spectra were obtained at either 500 MHz or 300 MHz as solutions in CDCl_3 or DMSO-d_6 . ^{13}C NMR were obtained at either 125 MHz or 75 MHz as solutions in CDCl_3 or DMSO-d_6 and chemical shifts are reported in parts per million (ppm, δ) and referenced from the solvent. ^{19}F NMR were obtained at 470 MHz as solutions in CDCl_3 and chemical shifts are reported in parts per million (ppm, δ) from an external reference (CFCl_3). Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, comp: complex, and br: broad. Infrared (IR) spectra were obtained using a Perkin-Elmer FTIR 1600 spectrophotometer using sodium chloride plates as indicated, and reported as wave numbers. Low resolution chemical ionization mass spectra were obtained with a Finnigan TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica gel plates. The plates were visualized with UV light, ninhydrin, phosphomolybdic acid, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) using ICN Silitech 32-63 D 60A silica gel.

7

4-Acetato-5-benzenesulfonyl-1-isopropylpyrrolidin-2-one (7). A solution of PhSO_2H (92 mg, 0.65 mmol), aminal **6** (137 mg, 0.53 mmol), CaCl_2 (0.2 mL, 0.79 mmol), and CH_2Cl_2 (1 mL) was stirred for 18 h at 25 °C. The solution was poured into a mixture of CHCl_3 (5 mL) and H_2O (2 mL). The layers were separated, and the organic layer was dried (MgSO_4) and concentrated to give a yellow oil that was purified by flash chromatography eluting with EtOAc/hexanes (50:50) to provide 58 mg (82%) of **7** as a white solid: mp 113–116 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.94 (dd, J = 9.0, 1.5 Hz, 2 H), 7.76–7.74 (m, 1 H), 7.62 (tt, J = 9.0, 1.5 Hz, 1 H), 5.22 (d, J = 6.5 Hz, 1 H), 4.65 (s, 1 H), 4.02 (septet, J = 6.5 Hz, 1 H), 2.49–2.44 (comp, 1 H), 2.13–2.10 (m, 1 H), 1.94 (s, 3 H), 1.46 (d, J = 6.5 Hz, 3 H), 1.39 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.5, 169.5, 135.8, 135.0, 129.9, 129.7, 129.5, 129.4, 83.6, 68.9, 48.9, 37.0, 20.6, 20.2, 19.1; mass spectrum (CI) m/z 326.1070 [$\text{C}_{15}\text{H}_{19}\text{NO}_6\text{S}$ (M+1) requires 326.1062], 311, 283, 251, 200, 184 (base).

8

4-Hydroxy-1-isopropyl-5-vinylpyrrolidin-2-one (8). A solution of THF (2.0 mL) and dry ZnCl_2 (195 mg, 1.43 mmol) was added to a solution of vinyl magnesium bromide in THF (9 mL, 0.26 M, 2.5 mmol) at 0 °C, and the mixture warmed to 25 °C over 1 h. A solution of the sulfone **7** (200 mg, 0.62 mmol) in THF (2.0 mL) was then added dropwise, and the reaction mixture was stirred for 18 h. Aqueous H_2SO_4 (3.8 M, 3.8 mL) was added, and the mixture was heated under reflux for 7 h. The reaction mixture was poured into Et_2O (20 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The organic layers were combined, dried (MgSO_4),

and concentrated to give a yellow oil that was purified by flash chromatography eluting with *i*PrOH/hexanes (1:9) to provide 64 mg (61%) of **8** as a yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 5.70 (ddd, $J = 17.0, 10.0, 8.5$ Hz, 1 H), 5.31 (dt, $J = 17.0, 0.75$ Hz, 1 H), 5.20 (dt, $J = 10.0, 0.75$ Hz, 1 H), 4.19 (septet, $J = 7.0$ Hz, 1 H), 4.06-4.04 (m, 1 H), 4.01-3.90 (m, 1 H), 2.76 (s, 1 H), 2.72 (dd, $J = 17.0, 6.0$ Hz, 1 H), 2.26 (dd, $J = 17.0, 2.0$ Hz, 1 H), 1.20 (d, $J = 7.0$ Hz, 3 H), 1.15 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 137.0, 117.8, 71.4, 68.6, 44.2, 40.0, 21.7, 19.7; IR (neat) 3369, 2976, 2934, 1667, 1434, 1367, 1278, 1130, 1057, 933 cm^{-1} ; mass spectrum (CI) m/z 170.1184 [$\text{C}_9\text{H}_{15}\text{NO}_2$ (M+1) requires 170.1181], 154, 152, 115, 103, 75 (base).

9

3-Allyl-4-hydroxy-1-isopropyl-5-vinylpyrrolidin-2-one (9). A solution of **8** (50 mg, 0.30 mmol) in THF (1 mL) was added to LDA (2.5 mmol) in THF (3 mL) at 0 °C. The reaction was cooled to -78 °C, and a solution of allyl bromide (0.25 mL, 10 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred for 1.5 h at -78 °C and then 18 h at -20 °C. The mixture was poured into 10% aqueous HCl (3 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to give a yellow oil that was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to provide 51 mg (83%) of **9** as a yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 5.85-5.77 (m, 1 H), 5.67 (ddd, $J = 17.1, 10.1, 9.0$ Hz, 1 H), 5.35 (dd, $J = 17.1, 1.15$ Hz, 1 H), 5.24 (dd, $J = 10.1, 1.15$ Hz, 1 H), 5.11 (dd, $J = 17.5, 3.3$ Hz, 1 H), 5.05 (dd, $J = 10.1, 3.3$ Hz, 1 H), 4.08 (septet, $J = 7.0$ Hz, 1 H), 3.81 (dd, $J = 9.0, 5.2$ Hz, 1 H), 3.74 (dd, $J = 6.5, 5.2$ Hz, 1 H), 2.65 (br, 1 H), 2.64-2.56 (m, 1 H), 2.38 (ddd, $J = 8.85, 6.5, 4.4$ Hz, 1 H), 2.27 (m, 1 H), 1.20 (d, $J = 7.0$ Hz, 3 H), 1.15 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 138.1, 135.4, 118.9, 117.3, 75.8, 67.7, 49.9, 44.5, 33.5, 21.3, 19.4; IR (neat) 3400, 2976, 2929, 1667, 1432, 1366, 1221, 1091, 995 cm^{-1} ; mass spectrum (CI) m/z 210.1490 [$\text{C}_{15}\text{H}_{19}\text{NO}_6\text{S}$ (M+1) requires 326.1062] (base), 209, 208, 194, 192.

2

(1*S*, 5*R*, 8*R*)-8-Hydroxy-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-7-one (2). A solution of diene **9** (21 mg, 0.10 mmol) in degassed CH₂Cl₂ (10 mL) containing (PCy₃)₂(I-MESH₂)(Cl)₂Ru=CHPh (**11**) (4 mg, 0.0046 mmol), and was stirred for 3 h at 40 °C. The solution was concentrated to give a brown oil that was purified by flash chromatography eluting with EtOAc to provide 20 mg (99%) of **2** as a white solid: mp 85–88 °C; [α]_D –79.5 (c 0.6, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.09 (ddt, *J* = 9.5, 5.5, 2.0 Hz, 1 H), 5.59 (dt, *J* = 9.5, 3.5 Hz, 1 H), 4.30 (sept, *J* = 6.7 Hz, 1 H), 4.20 (s, 1 H), 3.63 (d, *J* = 5.5 Hz, 1 H), 2.64 (s, 1 H), 2.44–2.42 (m, 2 H), 2.31 (br s, 1 H), 1.14 (d, *J* = 11.0 Hz, 3 H), 1.12 (d, *J* = 11.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 174.3, 130.9, 128.1, 74.8, 56.6, 48.4, 42.8, 28.4, 22.1, 20.4; IR (neat) 3336, 2970, 1663, 1438, 1211, 1027, 751 cm^{–1}; mass spectrum (CI) *m/z* 182.1182 [C₁₀H₁₅NO₂ (M+1) requires 182.1181] (base), 154, 149.

General Procedure for Preparing Mosher Esters of (–)-2 and *rac*-2. To a solution of (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (3.0 eq, 99+% ee) and hexanes (0.033 M) was added oxalyl chloride (30 eq.) and a drop of dimethylformamide. The reaction was stirred for 1 h, and the supernatant was carefully transferred to a new flask by pipette. The resulting clear, colorless solution was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ to give a concentration of 0.30 M, and Et₃N (9.0 eq), dimethylaminopyridine (1 crystal) and alcohol (–)-**2** or *rac*-**2** (1 eq) were added. When the reaction was complete as judged by TLC (10% acetone in EtOAc), the reaction was diluted with EtOAc (5 mL) and washed with saturated aqueous NH₄Cl (5 mL), water (5 mL), saturated aqueous NaHCO₃ (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give a residue that was purified by flash chromatography eluting with EtOAc/hexanes (3:7) to provide the Mosher esters as clear, colorless oils. The (*R*)- and (*S*)-Mosher esters were prepared from (–)-**2**, whereas the (*S*)-Mosher ester was prepared from *rac*-**2**.

(1S, 2S', 5R, 8R)-6-isopropyl-8-[2'-phenyl-2'-methoxy-2'-(trifluoromethyl)propionato]-6-azabicyclo[3.2.1]oct-3-en-7-one. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.49 (m, 2 H), 7.43-7.37 (comp, 3 H), 6.16 (ddt, $J = 9.3, 5.8, 2.2$ Hz, 1 H), 5.71 (dt, $J = 9.3, 3.3$ Hz, 1 H), 5.31 (s, 1 H), 4.24 (sept, $J = 6.8$ Hz, 1 H), 3.90 (d, $J = 5.6$ Hz, 1 H), 3.49 (s, 3 H), 2.80-2.78 (m, 1 H), 2.57-2.55 (m, 2 H), 1.13 (d, $J = 6.8$ Hz, 3 H), 1.02 (d, $J = 6.8$ Hz, 3 H); ^{19}F NMR (470 MHz, CDCl_3) δ -72.2; mass spectrum (CI) m/z 398.1574 [(M+H) requires 398.1579] (base), 316, 164.

(1S, 2R', 5R, 8R)-6-isopropyl-8-[2'-phenyl-2'-methoxy-2'-(trifluoromethyl)propionato]-6-azabicyclo[3.2.1]oct-3-en-7-one. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.49 (m, 2H), 7.42-7.38 (comp, 3 H), 6.14 (ddt, $J = 9.4, 5.8, 2.1$ Hz, 1 H), 5.71 (dt, $J = 9.4, 3.3$ Hz, 1 H), 5.34 (s, 1 H), 4.24 (sept, $J = 6.8$ Hz, 1 H), 3.76 (d, $J = 5.8$ Hz, 1 H), 3.53 (s, 3 H), 2.85-2.83 (m, 1 H), 2.59-2.56 (m, 2 H), 1.08 (d, $J = 6.8$ Hz, 3 H), 0.86 (d, $J = 6.8$ Hz, 3 H); ^{19}F NMR (470 MHz, CDCl_3) δ -71.8; mass spectrum (CI) m/z 398.1579 [(M+H) requires 398.1579] (base), 316, 164.