Facile entry to substituted decahydroquinoline alkaloids.

Total synthesis of lepadins A-E and H

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Experimental

(2*S*,3*R*)-3-(*tert*-Butyloxycarbonyl)amino-2-(*tert*-butyldimethylsilyloxy)-

butyl bromide 8. To a solution of **9** (8.2 g, 30.6 mmol) in dry DMF (15 mL) were added TBSCl (5.6 g, 37 mmol) and imidazole (6.4 g, 94 mmol). The mixture was stirred at room temperature for about 20 h before it was diluted with CH₂Cl₂. The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated. The residue was purified by chromatography eluting with 1:90 ethyl acetate/petroleum ether to give 9.3 g (80%) of **8** as a colorless oil. $[\alpha]_D^{19}$ -6.5 (*c* 1.8, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.41 (s, 9H) 3.2-3.4 (m, *J* = 6.3, 7.5, 4.2 Hz, 2H), 3.90 (br t, *J* = 6.0 Hz, 2H), 4.91 (br d, *J* = 6.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.96, -4.32, 12.9, 18, 25.8, 28.4, 32.8, 48.2, 73.6, 79.3, 154.8; IR (neat) 3457, 3354, 1708, 1500, 1172 cm⁻¹; ESI-MS *m/z* 404 (M + Na)⁺; ESI-HRMS calcd for C₁₅H₃₂NO₃BrSiNa(M + Na)⁺ requires 404.1225, found 404.1227.

Wittig olefination of 7. To an ice cooled suspension of Ph₃P⁺CH₂OMeCl⁻ (1.3 g, 3.8 mmol) in 6 mL of THF was added NaHMDS (2 M in THF, 2 mL). The resultant mixture was maintained at this temperature for 0.5 h with vigorous stirring. After the reaction mixture was put into a dry ice bath, a solution of ketone **7** (300 mg, 0.76 mmol) in 4 mL of THF was added dropwise via syringe. After addition, the reaction mixture was maintained at -78 °C for 1 h and then allowed to warm to room temperature overnight. The resultant solution was diluted with ether before saturated aqueous ammonium chloride was added. The organic layer was separated and the

aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by chromatography eluting with 1:60 ethyl acetate/petroleum ether to give 242 mg (75%) of enol ether **16** as a mixture of E- and Z-isomers, which was used without further purification.

Olefination of the aldehyde 18 with phosphonate 26. To a stirred solution of phosphonate **26** (276 mg, 0.94 mmol) in 3 mL of DME was added KHMDS (1M in THF, 1.0 mL) dropwise by a syringe at $-78\text{ }^\circ\text{C}$ over 20 min. The resultant solution was stirred for 0.5 h before a solution of the aldehyde **18** (70 mg, 0.24 mmol) in 2 mL of DME was added dropwise via syringe over 10 min. The reaction mixture was maintained at $-78\text{ }^\circ\text{C}$ for 6 h and then allowed to slowly warm to room temperature. The resultant solution was partitioned between ether and saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by chromatography eluting with 1:10 ethyl acetate/petroleum ether to give 98 mg (92%) of diene **27**. $[\alpha]_{\text{D}}^{30} -1.9$ (c 0.6, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ -0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.14 (d, $J = 5.7$ Hz, 3H), 1.25 (q like, $J = 7.2, 11.4$ Hz, 1H), 1.33 (s, 3H), 1.43-1.75 (m, 10H), 1.97 (dt, $J = 1.8, 2.1, 9.0$ Hz, 1H), 2.17 (dd like, $J = 7.5, 7.2$ Hz, 2H), 2.40 (q, $J = 12$ Hz, 1H), 2.53 (dq, $J = 2.7, 6.0$ Hz, 1H), 3.0 (br d, $J = 1.1$ Hz, 1H), 3.27 (ddd, $J = 2.4, 6.0, 6.7$ Hz, 1H), 3.96 (dd like, $J = 4.2, 3.3$ Hz, 4H), 5.31 (dd, $J = 8.2, 14.1$ Hz, 1H), 5.57 (dt, $J = 7.2, 14.2$ Hz, 1H), 5.98 (dd, $J = 7.2, 14.4$ Hz, 1H), 6.06 (dd, $J = 6.9, 14.6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ -4.7, -4.11, 17.9, 19.5, 20.4, 23.9, 25.8, 27.2, 32.2, 33.8, 37.4, 38.8, 39.4, 41.9, 54.8, 59.8,

64.6, 70.9, 109.8, 130.2, 130.5, 131.9, 136.6; IR (neat) 2930, 1473, 1376 cm^{-1} ; ESI-MS m/z 450 ($\text{M} + \text{H}$)⁺; HRMS calcd for $\text{C}_{26}\text{H}_{47}\text{NO}_3\text{Si}$ ($\text{M} + \text{H}$)⁺ requires 450.3398, found 450.3397.

(2*S*,3*R*,4*aS*,5*R*,8*aR*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-hydroxy-5-((1'*E*,3'*E*)-7-ethylenedioxy-octadien-1-yl)decahydroquinoline **28.** To a solution of the diene **27** (80 mg, 0.178 mmol) in anhydrous benzene were sequentially added (Boc)₂O (201 mg, 0.92 mmol) and K₂CO₃ (2 mg, 0.015 mmol). The resultant mixture was heated to gently reflux under argon for 72 h. After water was added to quench the reaction, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and evaporated *in vacuo*. The residue was purified via chromatography eluting with 1:50 ethyl acetate/petroleum ether to give a crude carbamate. This product was dissolved in anhydrous 2 mL of THF before TBAF (2 M in THF, 0.55 mL) was added via syringe at room temperature. The reaction mixture was stirred for 36 h, and then partitioned between ether and saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether, and dried over MgSO₄. After the solution was concentrated *in vacuo*, the residue was purified by chromatography eluting with 1:5 ethyl acetate/petroleum ether to give 65 mg (85% for two steps) of **28**. $[\alpha]_{\text{D}}^{20} +9.8$ (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃, amide rotamer) δ 1.17 (d, J = 7.8 Hz, 3H), 1.33 (s, 3H), 1.46 (s, 9H), 1.45-1.55 (m, 5H), 1.67-1.75 (m, 5H), 2.07 (dt, J = 1.5, 12.0 Hz, 1H), 2.13 (m, 1H), 2.17(m, 2H), 2.21(m, 1H), 3.83 (br d, J = 1.1 Hz, 1H) 3.94 (q like, J = 2.9, 4.0 Hz, 4H), 4.12 (dq, J = 2.9, 6.4 Hz, 1H), 4.15 (br s, 1H), 5.60 (dt, J = 6.9, 14.2 Hz,

1H), 5.82 (dd, $J = 7.2, 14.4$ Hz, 1H), 6.01 (dd, $J = 6.5, 14.5$ Hz, 1H), 6.05 (dd, $J = 5.9, 14.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3 , amide rotamer) δ 20.1, 21.1, 23.9, 25.8, 27.2, 27.87, 28.1, 28.5, 29.6, 32.6, 38.7, 42.1, 49.9, 53.4, 64.6, 69.5, 79.5, 109.8, 130.1, 130.5, 132.4, 135.0, 155.7; IR (neat) 3426, 1681 cm^{-1} ; ESI-MS m/z 436 ($\text{M} + \text{H}$) $^{+}$; HRMS calcd for $\text{C}_{25}\text{H}_{42}\text{NO}_5$ ($\text{M} + \text{H}$) $^{+}$ requires 436.3063, found 436.3079.

Peterson reaction of the ketone 7 with $\text{TMSCH}_2\text{CO}_2\text{Et}$. To a solution of $\text{TMSCH}_2\text{COOEt}$ (324.8 mg, 2.03 mmol) in 2 mL THF was added LDA (2 M in THF, 1.04 mL) at -78°C . After the mixture was maintained at this temperature for 0.5 h with vigorous stirring, a solution of **7** (403 mg, 1.02 mmol) in 2 mL THF was added dropwise via syringe. After addition, the reaction mixture was stirred at -78°C for 1 h and then allowed to warm to room temperature overnight. The resultant solution was partitioned between ether and saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by chromatography eluting with 1:30 ethyl acetate/petroleum ether to give 461 mg (98%, E/Z = 15:1) of olefin **33**. $[\alpha]_{\text{D}}^{20}$ -7.5 (c 0.15, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , major isomer) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.21-1.35 (t and m, $J = 7.2$ Hz, 6H), 1.44 (s, 9H), 1.61-1.80 (m, 4H), 2.12 (ddd, $J = 1.8, 12.6, 12.8$ Hz, 1H), 2.91 (br d, $J = 5.1$ Hz, 1H), 3.75 and 3.78 (s, 1H in 1:2 ratio due to rotamer), 4.03-4.18 (q and m, 3H), 5.67 and 5.72 (s, 1H in 1:2 ratio due to rotamer); IR (neat) 1729, 1647 cm^{-1} ; ESI-MS m/z 468 ($\text{M} + \text{H}$) $^{+}$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{45}\text{NO}_5\text{SiNa}$ ($\text{M} + \text{Na}$) $^{+}$ requires 490.2951, found 490.2959.

Olefin 35. To a solution of **33** (446 mg, 1.02 mmol) in 20 mL of dry CH₂Cl₂ was added trifluoroacetic acid (0.8 mL) dropwise at room temperature. The reaction was carefully monitored by TLC, and quenched with methanolic K₂CO₃. After removal of solvent, the residue was chromatographed eluting with 1:1:0.01 petroleum ether/ethyl acetate/methanol to afford 370 mg (100%) of **35**. [α]_D¹⁸ +21.5 (*c* 0.37, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.48-1.80 (m, 7H), 2.21 (dq, *J* = 2.0, 14.0 Hz, 1H), 2.56 (m, 2H), 3.21 (q like, *J* = 3.3 Hz 1H), 3.44 (ddd, *J* = 4.3, 5.4, 11.0 Hz, 1H), 3.96 (dd like, *J* = 1.5, 13.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.74 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.5, -4.0, 14.3, 18.0, 19.3, 21.8, 25.9, 29.5, 31.7, 36.0, 43.9, 57.7, 59.6, 59.9, 70.1, 115.1, 161.1, 166.6; IR (neat) 1719, 1643 cm⁻¹; EI-MS *m/z* 367 (M⁺), 352, 322, 310, 220, 209, 166, 138; HRMS calcd for C₂₀H₃₇NO₃Si (M⁺) requires 367.2562, found 367.2581.

No title

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PL1 -5.00 dB
SFO1 75.4752953 MHz

CHANNEL f2

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Compound 1a

Compound 27

Compound 27

Compound 28

S25

Compound 29

Compound 29

Compound **1c**

Compound 1c

MPW1126

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NUV1229

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