SUPPORTING INFORMATION

for the
communication
entitled

Total Synthesis of (+)-Lepadin F.

authored by

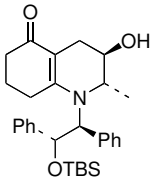
Gang Li, Richard P. Hsung*, Brian W. Slafer, and Irina K. Sagamanova

Division of Pharmaceutical Sciences and Department of Chemistry
7111 Rennebohm Hall, 777 Highland Avenue
University of Wisconsin, Madison, WI 53705

EXPERIMENTAL SECTION

Reagents were used as purchased (Aldrich, Acros, Alfa Aesar, TCI), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using a Bruker Equinox 55 FTIR Spectrometer. TLC analysis was performed using 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV, KMnO4 stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses performed at University of Wisconsin School of Pharmacy Mass Spectrometry Laboratory. X-Ray analysis performed at University of Minnesota Department of Chemistry X-Ray facility. All spectral data obtained for new compounds are reported here.

Synthesis of the Alcohol 6.



6

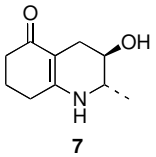
To a flame dried flask under N_2 was added **5** (0.30 g, 0.59 mmol) and anhyd CH_2Cl_2 (15 mL). The solution was cooled to -15 °C, then triethylsilane (3.00 mL, 18.6 mmol) and trifluoroacetic acid (0.55 mL, 7.11 mmol) were added dropwise. The resulting solution was sealed and kept in the freezer for 48 h at -20 to -10 °C, and then diluted with CH_2Cl_2 (8 mL) and worked-up with sat aq $NaHCO_3$ until basic. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: EtOAc) gave **6** (0.23 g, 80%) as a white solid.

6: R_f = 0.29 [100% EtOAc]; mp 206-208 °C; $[\alpha]_D^{23}$ = + 406.0 (*c* 0.29, $CHCl_3$);

^1H NMR (500 MHz, Toluene-d_8) δ -0.38 (s, 3H), 0.06 (d, 3H, *J* = 6.5 Hz), 0.10 (s, 3H), 0.73 (s, 9H), 1.20 (dtd, 1H, *J* = 4.5, 9.0, 18.0 Hz), 1.46 (ddd, 1H, J = 6.5, 11.5, 18.0 Hz), 1.79 (dt, 1H, *J* = 5.5, 15.5 Hz), 1.87-1.92 (m, 1H), 2.10-2.18 (m, 2H), 2.36 (dd, 1H, *J* = 4.5, 17.5 Hz), 2.80 (d, 1H, *J* = 17.5 Hz), 3.70 (brd, 1H, *J* = 3.5 Hz), 3.75 (brq, 1H, *J* = 6.5 Hz), 5.11 (d, 1H, *J* = 8.5 Hz), 5.39 (d, 1H, *J* = 8.5 Hz), 7.07-7.09 (m, 2H), 7.14 (q, 4H, *J* = 7.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, Toluene-d_8,) δ -4.7, -3.5, 17.8, 18.5, 22.3, 26.3, 26.6, 27.7, 36.7, 54.6, 66.9, 67.8, 74.6, 104.5, 128.6, 129.4, 131.5, 139.1, 143.8, 156.9, 194.4; IR (thin film) cm^{-1} 3353brs, 3063w, 2930s, 2889m, 2857s, 1591m,

1538m, 1436s, 857s; mass spectrum (ESI): m/e (% relative intensity) 514.3 (19) $(M+Na)^+$, 492.3 (100) $(M+H)^+$; m/e calcd for $C_{30}H_{42}NO_3Si^+$ 492.2928, found 492.2932.

Synthesis of Vinylogous Amide 7.



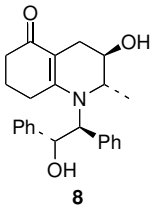
7

To a solution of **6** (1.08 g, 2.20 mmol) in MeO (15 mL), was added TFA (0.19 mL, 2.42 mmol) and $Pd(OH)_2/C$ (0.31 g, 20% Pd, 50% wet). The mixture was placed in a Lab-Crest® pressure reaction vessel at 15 *psi* for 2 d. When the reaction was completed (TLC with 9:1 MeOH/EtOAc as eluent), the reaction was filtered through Celite™ and concentrated under reduced pressure. Purification of the crude residue using silica gel flash column chromatography (isocratic eluent: 5:1 EtOAc/*i*-PrOH) provided **7** (0.39 g, 98%) as a tan solid.

7: R_f = 0.17 [10% MeOH/EtOAc]; mp 156-157 °C;

^{1}H NMR (500 MHz, Methanol-d_4) δ 1.19 (d, 3H, J = 7.0 Hz), 1.82-1.96 (m, 2H), 2.21 (dd, 1H, J = 7.0, 16.0 Hz), 2.28 (dd, 2H, J = 5.5, 7.0 Hz), 2.34-2.44 (m, 2H), 2.57 (dd, 1H, J = 5.0, 16.0 Hz), 3.18 (tt, 1H, J = 6.5, 6.5 Hz), 3.54 (dq, 1H, J =5.0, 6.5 Hz); ^{13}C NMR (125 MHz, Methanol-d_4) δ 19.2, 22.9, 27.7, 29.5, 36.8, 54.0, 69.3, 102.1, 163.9, 196.4; IR (thin film) cm^{-1} 3256brs, 3119brs, 2925s, 2854m, 1505s; mass spectrum (ESI): m/e (% relative intensity) 204.1 (100) $(M+Na)^+$, 197.0 (26), 182.1 (10) $(M+H)^+$; m/e calcd for $C_{10}H_{15}NO_2Na^+$ 204.1000, found 204.0991.

Synthesis of Diol 8.



8

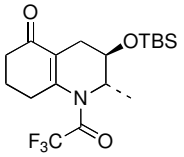
To a solution of **6** (1.72 g, 3.51 mmol) in anhyd THF (50 mL) was added TBAF (1.0 *M* in THF, 3.51 mL, 3.51mmol). The solution was stirred for 10 min at rt, and concentrated reduced under pressure. Purification of the crude residue using silica gel flash column chromatography (isocratic eluent: EtOAc) gave **8** (1.22 g, 92%) as a white solid.

8: R_f = 0.45 [10% MeOH/CH_2Cl_2]; mp 113-115 °C; $[\alpha]_D^{23}$ = + 456.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, Toluene-d_8) δ 0.17 (d, 3H, J = 6.0 Hz), 1.64-1.76 (m, 2H), 2.26-2.33 (m, 3H), 2.46 (dt, 1H, J = 4.5, 15.5 Hz), 2.60 (dt, 1H, J = 6.5, 16.5 Hz), 3.30 (d, 1H, J = 17.5 Hz), 3.94 (brs, 1H), 4.20 (dt, 1H, J = 3.0, 7.0) 5.28 (d, 1H, J = 2.5 Hz), 5.45 (s, 1H), 6.60 (s, 1H); 6.90-6.94 (m, 2H), 6.99 (t, 1H, J =

7.5 Hz), 7.10 (t, 1H, J = 7.5 Hz), 7.34 (d, 1H, J = 3.0 Hz), 7.57 (d, 2H, J = 7.5 Hz), 7.70 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, Toluene-d_8) δ 17.6, 22.6, 25.7, 28.0, 36.2, 54.0, 65.9, 66.6, 77.3, 106.0, 126.6, 127.2, 128.5, 128.6, 132.6, 136.3, 142.2, 157.6, 195.5.

Synthesis of Amide 9.



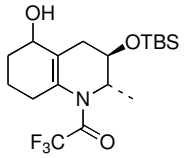
9

To a solution of **7** (393.0 mg, 2.17 mmol) in anhyd CH_3CN (60 mL) was added 2,6-lutidine (0.76 mL, 6.50 mmol). The resulting solution was then cooled to 0 °C and TBSOTf (1.5 mL, 6.50 mmol) was added dropwise via syringe. The solution was stirred for 12 h at rt, and diluted with CH_2Cl_2 and quenched with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with HCl 1.5%, H_2O, sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 50-100% EtOAc/Hexanes) afforded the pure silyl ether amide (640.0 mg, 100%), which was used for the following step.

To a solution of the above silyl ether amide (29.5 mg, 0.10 mmol) in anhyd CH_2Cl_2 (8 mL) were added pyridine (0.024 mL, 0.30 mmol), and DMAP (2.00 mg, 0.016 mmol). The solution was cooled to 0 ^{o}C and trifluoroacetic anhydride (31.5 mg, 0.021 mL, 0.15 mmol) were added dropwise via syringe. The solution was stirred for 12 h at rt, then diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 10-50% EtOAc/Hexanes) afforded **9** (39.0 mg, 100%).

9: R_f = 0.45 [50% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.77 (s, 9H), 1.07 (d, 3H, J = 6.8 Hz), 1.82-1.94 (m, 1H), 2.06 (ddt, 1H, J = 4.8, 9.2, 13.2 Hz), 2.13-2.21 (m, 1H), 2.25 (ddt, 1H, J = 2.4, 4.0, 18.8 Hz), 2.38 (d, 1H, J = 18.8 Hz), 2.46 (dd, 2H, J = 4.8, 8.4 Hz), 3.26 (dddt, 1H, J = 2.8, 4.4, 11.2, 17.2 Hz), 3.94 - 3.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.8, -4.7, 15.2, 18.0, 23.1, 25.7, 25.9, 29.4, 37.7, 55.6 (q, J = 2.3 Hz), 66.7, 116.4 (q, J = 287.2 Hz), 121.8, 151.4, 157.6 (q, J = 36.3 Hz), 198.6; IR (neat) cm^{-1} 2952m, 1709s, 1665s, 1419m, 1173s; mass spectrum (APCI): m/e (% relative intensity) 392.1 (100) $(M+H)^+$, 296.2 (35).

Synthesis of Alcohol 10.

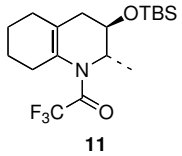


10

To a solution of **9** (11.0 mg, 0.028 mmol) in MeOH (2 mL) was added PtO_2 (6.00 mg). The mixture was placed in a high-pressure bomb at 200 *psi* for 4 h at rt. When the reaction was completed (TLC), the reaction solution was filtered through Celite^{TM} and concentrated under reduced pressure. Purification of the crude residue using silica gel flash column chromatography (gradient eluent: 10-50% EtOAc/Hexanes) provided **10** (10.0 mg, 90%).

10: R_f = 0.52 [50% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07(s, 3H), 0.84 (s, 9H), 1.08 (d, 3H, *J* = 6.8), 1.27 (d, 1H, *J* = 9.2), 1.49-1.60 (m, 1H), 1.65-1.73 (m, 2H), 1.85 (dddd, 1H, *J* = 2.4, 5.2, 10.8, 16.0), 1.98-2.05 (m, 1H), 2.10 (brd, 1H, *J* = 18.0), 2.48 (d, 1H, *J* = 18.8), 3.06 (brs, 1H), 3.84-3.98 (m, 2H), 4.03 (dd, 1H, *J* = 6.4, 14.8); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.7, 15.0, 18.2, 20.3, 25.8, 25.9, 27.8, 30.2, 32.9, 55.1, 68.4, 69.7, 116.9 (q, *J* = 288.9 Hz), 124.5, 131.8; IR (neat) cm^{-1} 3300brw, 2915s, 2830m, 1750m; mass spectrum (APCI): m/e (% relative intensity) 376.2 (100) $(M+H-H_2O)^+$.

Synthesis of Amide 11.

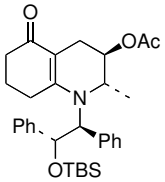


11

To a vial containing **9** (48.0 mg, 0.12 mmol) in MeOH (2 mL) was added PtO_2 (56.0 mg). The mixture was placed in a high-pressure bomb at 200 *psi* at rt. When the reaction was completed (TLC), the reaction solution was filtered through Celite^{TM} and concentrated reduced pressure. Purification of the crude residue using silica gel flash column chromatography provided **11** as an over hydrogenated product.

11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 1.09 (d, 3H, *J* = 6.8), 1.40-1.59 (m, 1H), 1.62-1.76 (m, 3H), 1.79-1.86 (m, 1H), 1.90 (d, 1H, *J* = 18.8), 1.97-2.04 (m, 2H), 2.15 (d, 1H, *J* = 18.0), 2.99 (brm, 1H), 3.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, 15.1, 18.2, 22.4, 23.4, 25.9, 27.7, 29.9, 33.8, 55.3, 68.5, 117.0 (q, *J* = 287.1 Hz), 121.8, 128.2, 153.8; IR (neat) cm^{-1} 2935m, 2861m, 1740m, 1703s, 1366m, 834m; mass spectrum (APCI): m/e (% relative intensity) 378.2 (70) $(M+H)^+$, 246.1 (100).

Synthesis of Acetate 15.



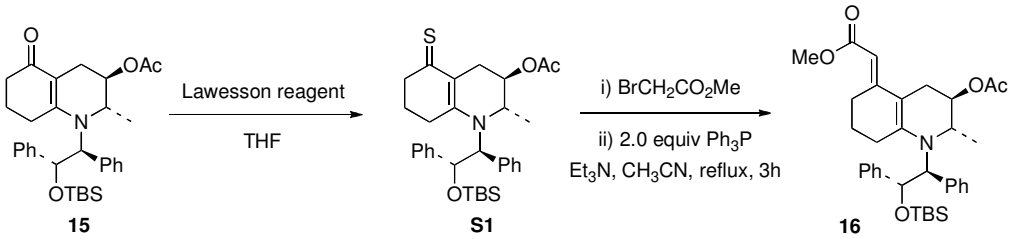
15

To a solution of **6** (401.0 mg, 0.813 mmol) in anhyd CH_2Cl_2 (20 mL) under N_2 was added Et_3N (0.34 mL, 2.44 mmol) and DMAP (10.0 mg, 0.080 mmol). The solution was cooled to 0 °C and acetic anhydride (0.16 mL, 1.22 mmol) was added dropwise via syringe. The solution was stirred for 12 h at rt, then diluted with CH_2Cl_2 and quenched with sat aq $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed sat aq NaCl, dried over Na_2SO_4, and concentrated in under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 50-100% EtOAc/Hexanes) gave **15** (412.0 mg, 95%) as a white foam.

15: R_f = 0.50 [100% EtOAc]; $[\alpha]_D^{23}$ = + 302.4 (*c* 0.19, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ -0.41 (s, 3H), 0.08 (s, 3H), 0.19 (d, 3H, *J* = 7.0 Hz), 0.65 (s, 9H), 1.25 (dtd, 1H, *J* = 4.5, 9.0, 18.0 Hz), 1.36-1.48 (brm, 1H), 1.58 (ddd, 1H, J = 6.5, 11.5, 18.0 Hz), 2.03-2.14 (m, 3H), 2.24 (s, 3H), 2.40 (dd, 1H, *J* = 5.5, 18.5 Hz), 2.59 (d, 1H, *J* = 18.5 Hz), 3.88 (q, 1H, *J* = 6.5 Hz), 4.98 (d, 1H, *J* = 9.0 Hz), 5.01 (dd, 1H, *J* = 2.5, 5.0 Hz), 5.18 (d, 1H, *J* = 9.5 Hz), 7.28-7.38 (m, 8H), 7.54 (dd, 2H, *J* = 1.5, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, -3.7, 17.4, 17.9, 21.4, 21.9, 22.8, 25.7, 27.1, 35.8, 52.0, 68.7, 69.9, 73.6, 103.9, 127,7, 128.0, 128.2, 128.3, 128.4, 131.0, 137.0, 143.6, 158.3, 170.4, 195.5; IR (neat) cm^{-1} 3035w, 2932m, 2859m, 1738s, 1618m, 1558s, 857m; mass spectrum (APCI): m/e (% relative intensity) 534.3 (100) $(M+H)^+$, 492.3(20), 474.3 (20); HRMS (MALDI): m/e calcd for $C_{32}H_{44}NO_4Si^+$ 534.3034, found 534.3043.

Synthesis of α,β-Unsaturated Ester 16.



To a solution of **15** (762.5 mg, 1.43 mmol) in anhyd benzene (15 mL) was added Lawesson's reagent (289.0 mg, 0.715 mmol) at rt. When the reaction was completed as indicated by TLC analysis, the solvent was removed under reduced pressure and the residue was dissolved in CH_2C1_2 (20 mL), which was then treated with 1% aq NaOH (8 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat aq NaCl (30 mL),

dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via Al_2O_3 gel flash column chromatography (gradient eluent: 10-50% EtOAc/Hexanes) gave **S1** (713.0 mg, 91%) as yellow solid.

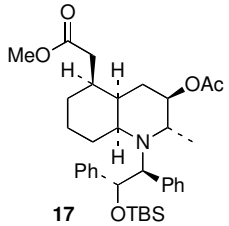
S1: R_f = 0.40 [20% EtOAc/Hexanes], 1H NMR (400 MHz, CDCl3) δ -0.41 (s, 3H), 0.09 (s, 3H), 0.25 (d, 3H, *J* = 6.4 Hz), 0.66 (s, 9H), 1.12-1.24 (m 1H), 1.50-1.66 (m, 2H), 2.06-2.18 (m, 1H), 2.25 (s, 3H), 2.57-2.68 (m, 1H), 2.77 (dd, 1H, *J* = 6.0, 18.8 Hz), 2.83 (dt, 1H, *J* = 4.8, 16.8 Hz), 3.08 (d, 1H, *J* = 18.4 Hz), 3.99 (brq, 1H, *J* = 6.0 Hz), 5.00 (d, 1H, *J* = 9.2 Hz), 5.07-5.13 (brm, 1H), 5.25 (d, 1H, *J* = 9.2 Hz), 7.28-7.42 (m, 8H), 7.58-7.63 (dd, 2H, *J* = 1.5, 7.0 Hz).

To a solution of **S1** (713.0 mg, 1.30 mmol) in anhyd THF (10 mL) was added methyl bromoacetate (269.0 mg, 0.16 mL, 1.78 mmol) and the solution was stirred at rt for 11 h. Then the volatiles were removed under reduced pressure. The residue was then dissolved in CH_3CN (20 mL), and triphenylphosphine (689.0 mg, 2.63 mmol) and triethylamine (0.27 mL, 1.95 mmol) were added at rt. The solution was refluxed for 3 h under N_2, and then the volatiles were removed under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0-20% EtOAc/Hexanes) gave **16** (538.0 mg, 70%) as a yellow foam.

16: R_f = 0.30 [20% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 499.4 (*c* 0.16, $CHCl_3$);

^{1}H NMR (400 MHz, CDCl3) δ -0.42 (s, 3H), 0.06 (s, 3H), 0.18 (d, 3H, J = 6.8 Hz), 0.65 (s, 9H), 1.00-1.11 (m, 1H), 1.38-1.50 (m, 2H), 1.86-1.98 (m, 1H), 2.16-2.30 (m, 4H), 2.37 (dd, 1H, *J* = 6.0, 18.0 Hz), 2.47-2.58 (m, 1H), 3.02 (dt, 1H, *J* = 4.8, 15.6 Hz), 3.61 (s, 3H), 3.79 (brq, 1H, *J* = 6.4 Hz), 4,96-5.00 (m, 1H), 5.00 (d, 1H, *J* = 8.8 Hz), 5.07 (d, 1H, *J* = 8.8 Hz), 5.14 (s, 1H), 7.23-7.36 (m, 8H), 7.56-7.60 (dd, 2H, *J* = 2.0, 9.5 Hz); ^{13}C NMR (125 MHz, CDCl3) δ -4.9, -3.6, 16.9, 18.0, 21.8, 21.9, 25.7, 25.8, 26.4, 27.7, 50.4, 51.4, 68.2, 70.7, 74.0, 99.7, 100.0, 127.6, 127.7, 128.0, 128.1, 128.2, 131.0, 137.8, 143.9, 148.9, 158.7, 168.8, 170.5; IR (neat) cm^{-1} 2933m, 2887m, 2859m, 1739m, 1699m, 1544s, 1433m, 839m; mass spectrum (APCI): m/e (% relative intensity) 590.4 (100) (M+H)+, 558.3 (10); HRMS (MALDI): m/e calcd for $C_{35}H_{48}NO_5Si^+$ 590.3296, found 590.3305.

Synthesis of Ester 17.



17

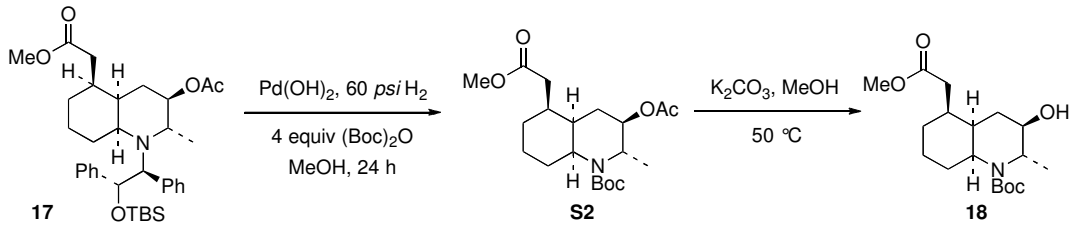
To a solution of **16** (29.4 mg, 0.050 mmol) in anhyd MeOH (1.5 mL) was added PtO_2 (14.0 mg, 80% Pt). The mixture was placed in a Lab-Crest® pressure reaction vessel at 15 *psi* for 30 min. When the reaction was completed as indicated by TLC (20% EtOAc/Hexanes) or use LCMS, the reaction was filtered

through Celite™ and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: 20% EtOAc/Hexanes) afforded **17** and its diastereomer at C5 (26.9 mg, 91%) as colorless oil, which were further separated by MPLC (median pressure liquid chromatography).

17: R_f = 0.35 [20% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 27.5 (*c* 0.16, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ -0.42 (s, 3H), -0.12 -0.00 (m, 1H), -0.07 (s, 3H), 0.56 (s, 9H), 0.82-0.94 (m, 1H), 0.89 (d, 3H, *J* = 6.5 Hz), 1.00 (qt, 1H, *J* = 3.5, 12.5 Hz), 1.18-1.32 (m, 3H), 1.38 (dtt, 1H, *J* = 2.5, 12.5 Hz), 1.53 (dtt , 1H, *J* = 5.0, 12.0 Hz), 1.71 (m, 1H), 1.93 (s, 3H), 2.03-2.12 (m, 2H), 2.15 (dd, 1H, *J* = 5.0, 12.5 Hz), 2.87 (dq, 1H, *J* = 6.5, 9.5 Hz), 2.94 (dt, 1H, *J* = 3.5, 12.0 Hz), 3.51 (ddd, 1H, *J* = 5.5, 10.0, 10.5 Hz), 3.70 (s, 3H), 4.28 (d, 1H, *J* = 9.5 Hz), 5.11 ((d, 1H, *J* = 9.0 Hz), 7.18-7.32 (m, 10H); ^{1}H NMR (500 MHz, C_6D_6) δ -0.25 (s, 3H), -0.02 (s, 3H), 0.08-0.14 (m, 1H), 0.67 (qd, 1H, *J* = 4.0, 13.0 Hz), 0.76 (s, 9H), 0.89-0.97 (m, 1H), 0.99 (d, 1H, *J* = 6.0 Hz), 1.16-1.24 (m, 3H), 1.27 (dq, 1H, *J* = 3.0, 13.0 Hz), 1.63 (s, 3H), 1.69 (dt, 1H, *J* = 5.0, 12.5 Hz), 1.85-1.94 (m, 1H), 1.90 (dd, 1H, *J* = 8.0, 15.0 Hz), 1.98 (dd, 1H, *J* = 7.0, 15.0 Hz), 2.14-2.23 (m, 1H), 2.92-3.02 (m, 2H), 3.43 (s, 3H), 3.80 (ddd, 1H, *J* = 5.5, 9.0, 10.5 Hz), 4.43 (d, 1H, *J* = 9.0 Hz), 5.25 ((d, 1H, *J* = 9.0 Hz), 7.10-7.18 (m, 2H), 7.22 (t, 2H, *J* = 7.5 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.36 (d, 2H, *J* = 7.0 Hz), 7.45 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.0, -4.0, 16.4, 17.9, 19.7, 21.4, 24.9, 25.1, 25.7, 26.5, 37.8, 38.4, 38.5, 51.1, 51.6, 56.1, 65.8, 75.1, 76.8, 126.6, 127.6, 127.7, 128.0, 128.1, 128.9, 141.8, 144.6, 170.3, 173.7; IR (neat) cm^{-1} 3063w, 3028m, 2855m, 1732s, 834s; mass spectrum (APCI): m/e (% relative intensity) 594.4 (95) $(M+H)^+$, 534.3 (100); HRMS (MALDI): m/e calcd for $C_{35}H_{52}NO_5Si^+$ 594.3609, found 594.3586.

Synthesis of Alcohol 18.



To a solution of **17** (40.5 mg, 0.068 mmol) and di-tert-butyl dicarbonate (60.0 mg, 0.275 mmol) in anhyd methanol (2 mL) was added $Pd(OH)_2$/C (38.4 mg, 20% Pd, 50% wet). The mixture was placed in a Lab-Crest® pressure reaction vessel at 60 *psi* for 24 h. When the reaction was completed as indicated by TLC (20% EtOAc/Hexanes), the reaction was filtered through Celite™ after a few drops of NEt_3 were added and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 10-30% EtOAc/Hexanes)) afforded **S2** (21.4 mg, 82%) as a colorless oil.

S2: R_f = 0.15 [20% EtOAc/Hexanes], ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (qd, 1H, *J* = 3.5, 13.0 Hz), 1.23 (d, 3H, *J* = 7.0 Hz), 1.29-1.39 (m, 1H), 1.40-1.54 (m, 11H), 1.54-1.68 (m, 3H), 1.71 (dt, 1H, *J* = 3.0, 13.5

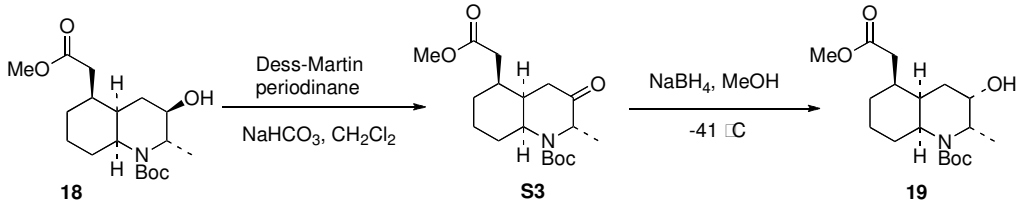
Hz), 1.84 (brdd, 1H, J = 2.5, 13.0 Hz), 2.02-2.13 (m, 1H), 2.06 (s, 3H), 2.19 (brd, 1H, J = 8.5 Hz), 2.26-2.34 (m, 1H), 3.67 (s, 3H), 3.82 (dq, 1H, J = 4.5, 12.0 Hz), 3.96 (qd, 1H, J = 2.5, 7.0 Hz), 4.98 (dt, 1H, J = 2.5, 8.5 Hz); m/e (% relative intensity) 284.2 (100) $(M+H\text{-}Boc)^+$, 224.1 (15).

To a solution of **S2** (9.10 mg, 0.015 mmol) in MeOH (1.5 mL) was added K_2CO_3 (2.60 mg, 0.018 mmol). The reaction solution was then sealed and heated at 50 °C for overnight. After which, the reaction was quenched with sat aq NaCl (0.5 mL), and CH_2Cl_2 (10 mL) was added to the mixture and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: 50% EtOAc/Hexanes)gave **18** (8.20 mg, 97%) as colorless oil.

18: R_f = 0.26 [50% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 16.7 (c 0.12, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (qd, 1H, J = 3.5, 13.0 Hz), 1.26 (d, 3H, J = 7.0 Hz), 1.33 (qt, 1H, J = 3.5, 13.0 Hz), 1.40-1.46 (m, 1H), 1.46 (s, 9H), 1.50-1.59 (m, 1H), 1.69-1.79 (m, 2H), 1.84 (qd, 1H, J = 4.0, 12.5 Hz), 1.91 (dt, 1H, J = 7.0, 14.5 Hz), 2.08 (ttd, 1H, J = 4.0, 7.5, 7.5 Hz), 2.18-2.25 (m, 3H), 3.67 (s, 3H), 3.80 (qd, 1H, J = 4.0, 6.5 Hz), 3.85 (dt, 1H, J = 4.5, 12.0 Hz), 3.90 (dt, 1H, J = 4.0, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 24.7, 25.1, 25.9, 26.3, 28.7, 34.1, 37.4, 38.4, 51.8, 53.8, 55.4, 70.2, 79.6, 155.9, 173.3; IR (neat) cm^{-1} 3450brs, 2972m, 2927s, 1736s, 1682s, 1660s, 1365s; mass spectrum (APCI): m/e (% relative intensity) 242.1 (100) $(M\text{-}Boc+H)^+$, 224.2 (10); HRMS (MALDI): m/e calcd for $C_{18}H_{31}NO_5Na^+$ 364.2094, found 364.2097.

Synthesis of Alcohol 19.



To a solution of **18** (23.3 mg, 0.068 mmol) and $NaHCO_3$ (40.0 mg, 0.48 mmol) in CH_2Cl_2 (3 mL) was added self-made Dess-Martin periodinane (43.0 mg, 0.10 mmol). The reaction solution was stirred at rt. When the reaction was completed (TLC analysis), the reaction was quenched with a few drops of isopropyl alcohol. The reaction was filtered through Celite^{TM} and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: 30% EtOAc/Hexanes) afforded **S3** (21.9 mg, 95%) as colorless oil. **S3:** R_f = 0.65 [50% EtOAc/Hexanes], ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97-1.23 (m, 2H), 1.36 (d, 3H, J = 6.8 Hz), 1.42-1.53 (m, 11H), 1.73 (dt, 1H, J = 2.8, 13.6 Hz), 1.78-1.95 (brm, 1H), 2.17-2.27 (m, 3H), 2.35 (dd, 1H, J = 12.0, 19.2 Hz), 2.46 (dd, 1H, J = 7.2, 19.2 Hz), 2.60-2.68 (m, 1H), 3.69 (s, 3H), 3.92-4.10 (brm, 1H), 4.22 (brs, 1H); m/e (% relative intensity) 240.2 (100)

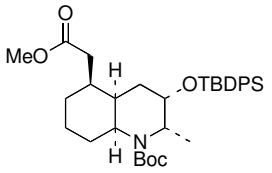
$(M+H\text{-}Boc)^+$.

To a solution of **S3** (21.9 mg, 0.065 mmol) in anhyd MeOH (2 mL) under N_2 at -41 °C - -45 °C was added $NaBH_4$ (5.10 mg, 0.129 mmol). The reaction solution was stirred at same temperature for 40 min (TLC analysis). Then the reaction was quenched with a few drops of acetone and filtered through Celite™ and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: 50% EtOAc/Hexanes) gave **19** (21.9 mg, 100%) as colorless oil.

19: R_f = 0.31 [50% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 31.0 (*c* 0.14, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (qd, 1H, *J* = 3.5, 12.5 Hz), 1.14-1.22 (m, 1H), 1.18 (d, 3H, *J* = 7.0 Hz), 1.32 (qt, 1H, *J* = 3.5, 13.0 Hz), 1.39-1.55 (m, 11H), 1.69 (dtt, 1H, *J* = 3.5, 3.5, 13.5 Hz), 1.82-1.93 (m, 2H), 2.08 (ttd, 1H, *J* = 3.5, 7.5, 7.5 Hz), 2.20 (dd, 1H, *J* = 7.0, 15.0 Hz), 2.25 (dd, 1H, *J* = 8.0, 15.0 Hz), 2.37 (dq, 1H, *J* = 4.5, 14.0 Hz), 3.67 (s, 3H), 3.72 (dt, 1H, *J* = 4.5, 12.5 Hz), 4.00 (qd, 1H, *J* = 5.0, 7.0Hz), 4.22 (td, 1H, *J* = 5.0, 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 24.4, 24.8, 26.2, 28.7, 29.8, 33.6, 37.2, 38.1, 51.8, 54.6, 66.79 66.81, 79.6, 155.0, 173.3; IR (neat) cm^{-1} 3455brs, 2977m, 2940s, 1737s, 1686s, 1664s, 1366s; mass spectrum (APCI): m/e (% relative intensity) 242.1 (100) $(M\text{-}Boc+H)^+$, 224.1 (10); HRMS (MALDI): m/e calcd for $C_{18}H_{31}NO_5Na^+$ 364.2094, found 364.2102.

Synthesis of Silyl Ether 20.



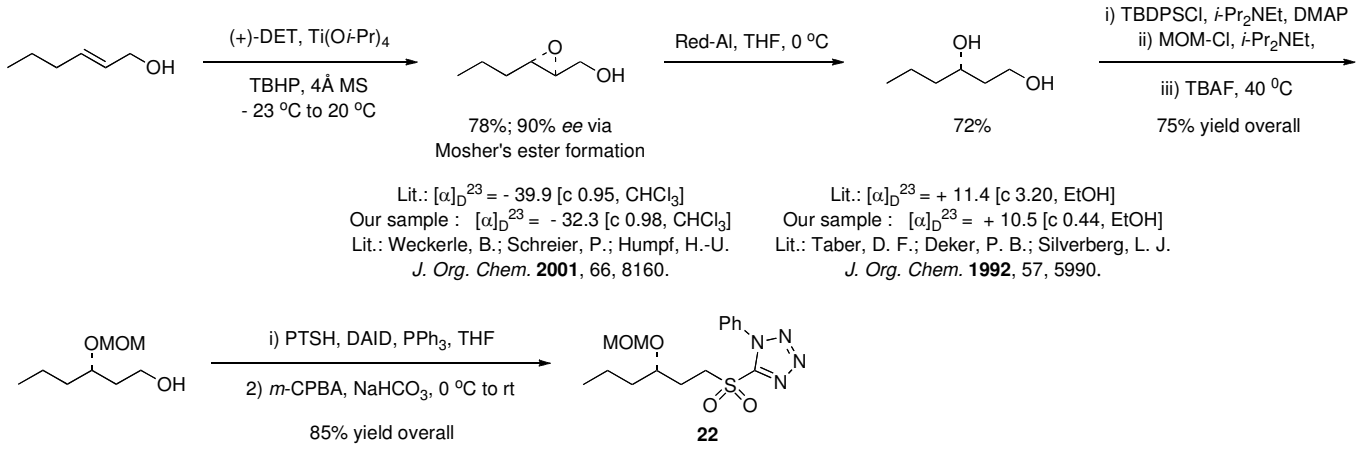
20

To a solution of **19** (21.1 mg, 0.062 mmol) in anhyd CH_2Cl_2 (2 mL) was added imidazole (42.1 mg, 0.62 mmol). Then the reaction was stirred for 2 min and TBDPSCl (174.0 mg, 0.162 mL, 0.62 mmol) was added dropwise to the reaction solution. The reaction was sealed and heated to 40 °C for 12 h. At the time when the TLC analysis showed the reaction was completed, the reaction mixture was diluted with hexanes (15 mL) and washed with water (15 mL), sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0-10% of EtOAc/hexanes) afforded **20** (34.3 mg, 96%) as colorless oil.

20: R_f = 0.18 [10% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.44-0.62 (m, 1H), 0.64-0.92 (m, 1H), 1.08 (s, 9H), 1.12-1.33 (m, 5H), 1.34-1.54 (m, 12H), 1.61-1.80 (brm, 1H), 1.86-2.18 (brm, 3H), 2.26 (dq, 1H, *J* = 4.5, 14.0Hz), 3.30-3.70 (brm, 1H), 3.62-3.92 (m, 1H), 3.66 (s, 3H), 3.93-4.25 (brs, 1H), 7.33-7.47 (m, 6H), 7.67 (dd, 4H, *J* = 7.5, 13.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 19.4, 24.3, 25.2, 26.0, 27.2, 28.7, 29.7, 33.8, 37.3, 38.2, 51.8, 54.1, 67.9, 77.4, 79.3, 127.90, 127.94, 130.1, 136.0, 136.1, 154.7, 173.4; mass spectrum (APCI): m/e (% relative intensity) 580.3 (10) $(M+H)^+$, 480.3 (100).

Synthesis of Sulfone 22.

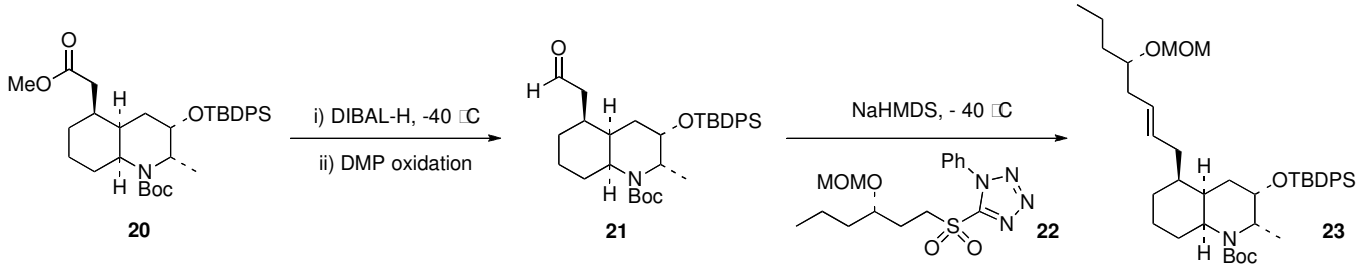
For the synthesis see of **22**, see the scheme below and also: For the synthesis of **22**, see. (a) D'Souza, L. J.; Sinha, S. C.; Lu, S.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255. (b) Blackemore, P. A.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (c) Pu, X.; Ma, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4222.



R_f = 0.25 [20% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 8.60 (*c* 0.91, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.0 Hz), 1.30-1.50 (m, 3H), 1.56-1.64 (m, 1H), 2.02-2.12 (m, 1H), 2.20-2.28 (m, 1H), 3.39 (s, 3H), 3.74 (qd, 1H, *J* = 4.0, 6.5 Hz), 3.82 (ddd, 1H, *J* = 5.0, 11.0, 15.0 Hz), 3.90 (ddd, 1H, *J* = 5.0, 11.0, 14.5 Hz), 4.64 (d, 1H, *J* = 7.0 Hz), 4.66 (d, 1H, *J* = 7.0 Hz), 7.58-7.65 (m, 3H), 7.68-7.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 18.7, 26.9, 36.6, 52.9, 56.1, 75.5, 96.0, 125.4, 130.0, 131.7, 133.3, 153.8; mass spectrum (APCI): m/e (% relative intensity) 323.1 (100) $(M\text{-}OMe)^+$, 311.1 (20), 293.1(55).

Synthesis of Alkene 23.



To a solution of **20** (34.3 mg, 0.059 mmol) in anhyd THF (1.5 mL) was added DIBAL-H (1.0 *M* in hexanes, 0.237 mL, 0.237 mmol) dropwise at − 40 °C. When the reaction was completed (about 2 h via TLC analysis or LCMS), methanol was added at the same temperature followed by sat aq potassium sodium tartrate solution and the reaction was stirred vigorously. When two phases of the solution were clear after a few hours, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography afforded (gradient eluent: 20-50% of EtOAc/hexanes) an alcohol intermediate (30.1 mg,

92%) as a colorless oil: R_f = 0.45 [50% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45-0.64 (brm, 1H), 0.64-0.92 (brm, 1H), 1.04-1.15 (m, 10H), 1.15-1.32 (m, 7H), 1.30-1.52 (m, 13H), 1.63-1.77 (m, 1H), 2.17-2.27 (m, 1H), 3.30-3.70 (brm, 3.5H), 3.70-3.85 (m, 0.5H), 4.04-4.22 (brm, 1H), 7.35-7.47 (m, 6H), 7.68 (t, 4H, *J* = 8.0 Hz); mass spectrum (APCI): m/e (% relative intensity) 452.3 (100) M+H-Boc)$^+$, 418.2 (65), 374.3 (30). *This alcohol was oxidized by DMP directly.*

To a solution of the above alcohol (30.1 mg, 0.055 mmol) and $NaHCO_3$ (37.0 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) was added self-made Dess-Martin periodinane (35.0 mg, 0.0825 mmol). The reaction solution was then stirred at rt for about 30 min. When the reaction was completed as indicated by TLC analysis (30% EtOAc/Hexanes) or LCMS, the reaction was quenched with a few drops of isopropyl alcohol. The reaction was filtered through Celite™ and concentrated under reduced pressure. Purification of the crude residue via a short silica gel column (isocratic eluent: 30% EtOAc) afforded **21** (28.8 mg, 96%) as colorless oil.

21: R_f = 0.65 [30% EtOAc/Hexanes]; R_f = 0.65 [30% EtOAc/Hexanes]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46-0.66 (brm, 1H), 0.66-1.00 (brm, 1H), 1.05-1.11 (m, 10H), 1.17-1.24 (m, 5H), 1.30-1.45 (m, 10H), 1.49 (dt, 1H, *J* = 2.8, 13.2 Hz), 1.65-1.80 (m, 1H), 1.96-2.30 (m, 3H), 2.50 (dd, 1H, *J* = 1.6, 6.8 Hz), 3.40-3.70 (brs, 1H), 3.70-3.94 (brm, 1H), 4.06-4.19 (brm, 1H), 7.36-7.48 (m, 6H), 7.64-7.71 (m, 4H), 9.70 (s, 1H). *Aldehyde **21** was immediately used for the following step.*

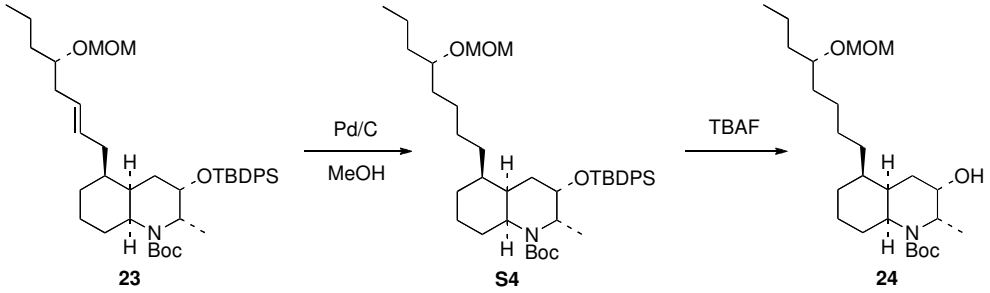
To a solution of sulfone **22** (43.4 mg, 0.123 mmol) in THF (2 mL) at -78 °C was dropwise added NaHMDS (1.0 *M* in THF, 0.123 mL, 0.123 mmol). After the reaction mixture was stirred for 30 min, a solution of **21** (28.8 mg, 0.0525 mmol) in THF (1.5 mL) was dropwise added, and additional THF (0.5 mL) was used to rinse the vial containing **21**, which was also added to the reaction solution. After the reaction was stirred for 1 h at -78 °C, the reaction mixture was allowed to warm to rt overnight. Then sat aq NaCl was added to quench the reaction, and the solution was diluted by EtOAc (6 mL) and H_2O (6 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 10-30% of EtOAc/hexanes) afforded **23** (32.0 mg, 90%) as a colorless oil.

23: R_f = 0.50 [20% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = - 1.80 (*c* 0.17, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.45-0.60 (brm, 1H), 0.60-0.80 (brm, 1H), 0.92 (t, 3H, *J* = 7.0 Hz), 1.00-1.12 (m, 10H), 1.15-1.30 (brm, 5H), 1.30-1.53 (m, 17H), 1.60-1.930 (brm, 3H), 2.16-2.28 (brm, 3H), 3.38 (s, 3H), 3.48-3.62 (m, 1.5H), 3.70-3.82 (m, 0.5H), 4.12 (brs, 1H), 4.64 (d, 1H, *J* = 7.0 Hz), 4.69 (d, 1H, *J* = 7.0 Hz), 5.32-5.46 (m, 2H), 7.35-7.47 (m, 6H), 7.68 (q, 4H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 15.5, 18.8, 19.3, 24.5, 24.9, 26.0, 27.2, 28.7, 30.3, 33.5, 36.5, 36.6, 37.8, 40.6, 51.9, 54.4, 55.6, 68.1, 77.1, 79.1, 95.5, 127.6, 127.79, 127.84, 129.9, 131.3, 135.9, 136..0, 154.7; IR (neat) cm^{-1} 2940s, 2860m,

1689s, 1394m, 1367m, 1041s; mass spectrum (APCI): m/e (% relative intensity) 678.4 (30) $(M+H)^+$, 578.4 (60) $(M+H\text{-}Boc)^+$, 546.3 (100); HRMS (MALDI): m/e calcd for $C_{41}H_{63}NO_5SiNa^+$ 700.4368, found 700.4378.

Synthesis of Alcohol 24.



To a solution of **23** (30.4 mg, 0.045 mmol) in anhyd methanol (2 mL) was added Pd/C (4.80 mg, 10% Pd/C). The mixture was placed in a Lab-Crest® pressure reaction vessel at 20 *psi* for 2 h. When the reaction was completed (LCMS analysis), the reaction was filtered through Celite™ and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: 20% EtOAc) afforded **S4** (30.1 mg, 99%) as a light yellow colorless oil. **S4:** R_f = 0.4 [15% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.44-0.64 (brm, 1H), 0.64-0.82 (brm, 1H), 0.93 (t, 3H, *J* = 7.2 Hz), 1.00-1.13 (m, 10H), 1.16-1.29 (brm, 9H), 1.29-1.55 (m, 21H), 1.60-1.80 (brm, 1H), 2.17-2.26 (m, 1H), 3.40 (s, 3H), 3.54 (quint, 1H, *J* = 5.6 Hz), 3.62-3.92 (brm, 1H), 4.06-4.20 (brm, 1H), 4.64 (s, 0.5H), 4.66 (s, 1.5H), 7.35-7.46 (m, 6H), 7.64-7.72 (m, 4H); m/e (% relative intensity) 680.4 (35) $(M+H)^+$, 580.4 (100) $(M+H\text{-}Boc)^+$.

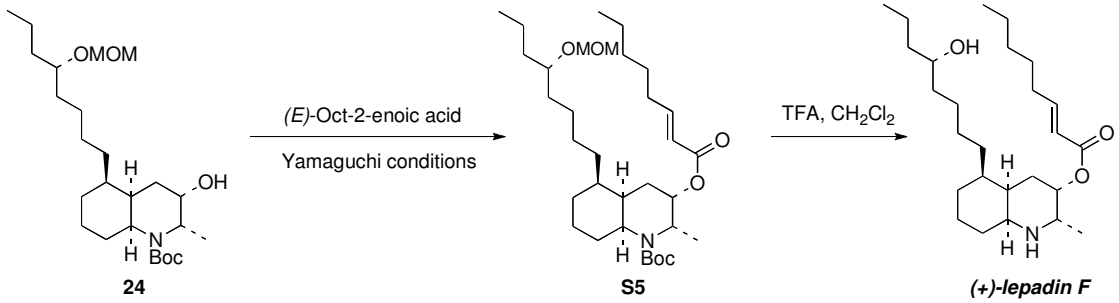
To a solution of **S4** (30.1 mg, 0.044 mmol) in anhyd THF (2 mL) was dropwise added TBAF (1.0 *M* in THF, 0.22 mL). Then the vial was sealed and heated to 50 °C overnight. Then the solution was poured into water and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with sat aq NaCl (45 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 10-30% of EtOAc/hexanes) gave **24** (19.4 mg, 99%) as a colorless oil.

24: R_f = 0.35 [40% EtOAc/Hexanes]; $[\alpha]_D^{23}$ = + 5.20 (*c* 0.11, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz), 0.98-1.12 (m, 2H), 1.20 (d, 3H, *J* = 6.5Hz), 1.15-1.23 (m, 2H), 1.23-1.53 (m, 14H), 1.47 (s, 9H), 1.57-1.61 (m, 1H), 1.63-1.70 (m, 1H), 1.82-1.90 (m, 2H), 2.31 (dq, 1H, *J* = 4.5, 14.0 Hz), 3.38 (s, 3H), 3.53 (tt, 1H, *J* = 6.0, 6.5 Hz), 3.67 (dt, 1H, *J* = 4.0, 12.0 Hz), 3.99 (qd, 1H, *J* = 5.0, 6.5 Hz), 4.21 (ddd, 1H, *J* = 4.5, 9.0, 13.0 Hz), 4.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 15.5, 18.8, 24.69, 24.71, 25.7, 26.6, 27.4, 28.7, 30.3, 33.2, 33.6, 34.5, 36.8, 40.1, 51.9, 55.1, 55.7, 67.1, 77.4, 79.5, 95.6, 155.1; IR (neat) cm^{-1} 3452brm, 2927s, 2854m, 1727m, 1687s, 1666s, 1457s,

1399s, 1377s 1040s; mass spectrum (APCI): m/e (% relative intensity) 442.3 (10) $(M+H)^+$, 342.3 (100) $(M+H\text{-}Boc)^+$, 324.3 (50); HRMS (MALDI): m/e calcd for $C_{25}H_{47}NO_5Na^+$ 464.3346, found 464.3340.

Synthesis of (+)-Lepadin F.



To a solution of *(E)*-Oct-2-enoic acid (6.00 μL, 0.040 mmol), $^i Pr_2NEt$ (0.010 mL, 0.059 mmol) and trichlorobenzoylchloride (9.00 μL, 0.058 mmol) in toluene (1 mL) was added a solution of **24** (8.50 mg, 0.019 mmol) in toluene (1 mL). An additional toluene (0.5 mL) was used to rinse the vial that contained the **24** solution, and the rinse was also added to the reaction solution. After the reaction solution was stirred for 1 h at rt, a solution of of DMAP (5.90 mg, 0.048 mmol) in toluene (1 mL) was added over 30 min (during the addition of DMAP solution, a white suspension was formed). The resulting solution was stirred for 18 h at rt before it was completed (TLC analysis). Then water was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with MTBE (3 × 8 mL). The combined organic layers were washed with sat aq NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0-10% of EtOAc/hexanes) gave **S5** (10.4 mg, 95%) as a colorless oil. **S5:** R_f = 0.7 [20% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86-0.96 (m, 1H), 0.90 (t, 3H, *J* = 7.0 Hz), 0.92 (t, 3H, *J* = 7.0 Hz), 1.22 (d, 3H, *J* = 6.5 Hz), 1.06-1.38 (m, 20H), 1.38-1.58 (m, 11H), 1.68 (dt, 1H, *J* = 3.0, 13.0 Hz), 1.86-2.12 (m, 3H), 2.21 (q, 1H, *J* = 7.0 Hz), 2.32-2.44 (m, 1H), 3.38 (s, 3H), 3.52 (quint, 1H, *J* = 6.0 Hz), 3.69 (brm, 1H), 4.08 (brm, 1H), 4.64 (d, 1H, *J* = 7.0 Hz), 4.66 (d, 1H, *J* = 7.0 Hz), 5.27 (m, 1H), 5.82 (d, 1H, *J* = 16 Hz), 6.99 (dt, 1H, *J* = 7.0, 16 Hz); m/e (% relative intensity) 466.4 (100) $(M+H\text{-}Boc)^+$, 434.4 (40), 404.4 (25).

To a solution of **S5** (14.0 mg, 0.025 mmol) in CH_2Cl_2 (1.1 mL) was added TFA (0.11 mL) carefully dropwise. The resulting reaction mixture was stirred for 1 h at rt. After which 5% aq NH_3 (0.30 mL) was added in 5 portions to quench the reaction over 20 min. Then the solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (isocratic eluent: CH_2Cl_2/MeOH/conc NH_3: 30:1:0.1) gave (+)-lepadin F (7.80 mg, 75%) as a colorless oil.

(+)-Lepadin F: R_f = 0.23 [10% MeOH/CH_2Cl_2], R_f = 0.16 [CH_2Cl_2/MeOH/con NH_3 = 15:1:0.1];

$[\alpha]_D^{23}$ = + 7.04 (*c* 0.27, $CHCl_3$); $[\alpha]_D^{23}$ = + 1.56 (*c* 0.16, CH_2Cl_2);

^{1}H NMR (500 MHz, C_6D_6) δ 0.76-0.84 (m, 1H), 0.81 (t, 3H, *J* = 7.0 Hz), 0.91 (t, 3H, *J* = 7.0 Hz), 1.08 (d, 3H, *J* = 6.5 Hz), 1.10-1.50 (m, 23H), 1.59 (qd like, 1H, *J* = 3.5, 13.0 Hz), 1.63-1.69 (m, 1H), 1.81 (dt, 1H, *J* = 3.0, 14.5 Hz), 1.88 (brq, 2H, *J* = 7.0 Hz), 2.16 (m, 1H), 2.79 (m, 1H), 2.84 (q, 1H, *J* = 6.5 Hz), 3.43 (quint, 1H, *J* = 5.0 Hz), 5.03 (brs, 1H), 6.00 (d, 1H, *J* = 15.5 Hz), 7.12-7.22 (m, 1H);

^{1}H NMR (500 MHz, using K_2CO_3 pretreated $CDCl_3$) δ 0.87-0.96 (m, 1H), 0.90 (t, 3H, *J* = 7.0 Hz), 0.92 (t, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 6.5 Hz), 1.11-1.51 (m, 23H), 1.64 (ABq-dd, 1H, *J* = 14.5, 14.0, 2.5 Hz), 1.71 (ABq-brt, 1H, *J* = 14.5, 3.5 Hz), 1.75-1.89 (m, 2H), 2.05-2.11 (m, 1H), 2.18-2.24 (m, 2H), 2.87 (dt, 1H, *J* = 4.5, 12.5 Hz), 3.08 (brq, 1H, *J* = 6.0 Hz), 3.52-3.62 (m, 1H), 4.93 (brs, 1H), 5.91 (dt, 1H, *J* = 1.5, 16.0 Hz), 7.01 (dt, 1H, *J* = 7.0, 15.5 Hz);

^{13}C NMR (100 MHz, C_6D_6) δ 14.1, 14.4, 18.5, 19.2, 22.7, 24.0, 25.4, 25.8, 26.1, 26.9, 27.4, 27.9, 31.6, 32.3, 33.4, 33.5, 38.0, 39.8, 40.3, 47.5, 55.7, 71.2, 71.3, 121.9, 149.4, 166.0;

^{13}C NMR (100 MHz, using K_2CO_3 pretreated $CDCl_3$) δ 14.0, 14.2, 18.5, 18.9, 22.5, 23.8, 25.3, 25.4, 25.8, 26.6, 27.0, 27.7, 31.4, 32.2, 33.1, 33.1, 37.5, 39.5, 39.8, 47.1, 55.5, 71.3, 71.7, 121.3, 149.8, 166.6;

IR (neat) cm^{-1} 3314brw, 2956m, 2929s, 2857m, 1718s, 1654m, 1463m, 1266s; mass spectrum (APCI): m/e (% relative intensity) 422.3 (100) $(M+H)^+$; HRMS (MALDI): m/e calcd for $C_{26}H_{48}NO_3^+$ 422.3629, found 422.3635.

MATCHING OF OPTICAL ROTATIONS

OUR SYNTHETIC (+)-LEPADIN F VERSUS BLECHERT'S SYNTHETIC (+)-LEPADIN F; CARROLL'S ISOLATED (+)-LEPADIN F, AND WRIGHT'S ISOLATED (-)-LEPADIN F.

Blechert	*Our Sample*	Isolation Data
$[\alpha]_D^{20}$ = + 8.80 ° (*c* 0.25, $CHCl_3$)	$[\alpha]_D^{23}$ = + 7.04 ° (*c* 0.27, $CHCl_3$)	**Carroll:** $[\alpha]_D^{22}$ = + 5.50 ° (*c* 0.12, CH_2Cl_2)
$[\alpha]_D^{20}$ = + 1.50 ° (*c* 0.27, CH_2Cl_2)	$[\alpha]_D^{23}$ = + 1.56 ° (*c* 0.16, CH_2Cl_2)	**Wright:** $[\alpha]_D^{22}$ = - 1.50 ° (*c* 0.10, $CHCl_3$)

MATCHING OF PROTON NMR

OUR SYNTHETIC (+)-LEPADIN F VERSUS CARROLL'S ISOLATED (+)-LEPADIN F IN C_6D_6.

^{1}H NMR (500 MHz, C_6D_6) The internal standard is set at δ = 7.16 ppm.[1]

Carroll	*Our Sample*	Δδ
0.80	0.76-0.84	0.00 ppm
0.81	0.81	0.00
0.90	0.91	0.01
1.08	1.08	0.00
1.08-1.48	1.10-1.50	0.02
1.58	1.59	0.01
1.65	1.63-1.69	0.01
1.82	1.81	-0.01
1.89	1.88	-0.01
2.17	2.16	-0.01
2.81	2.79	-0.02
2.84	2.84	0.00
3.42	3.43	0.01
5.00	5.03	0.03
6.00	6.00	0.00
7.19	7.12-7.22	0.02

---

1. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

MATCHING OF CARBON NMR

OUR SYNTHETIC (+)-LEPADIN F VERSUS CARROLL'S ISOLATED (+)-LEPADIN F IN C_6D_6.

^{13}C NMR (100 MHz, C_6D_6) The internal standard is set at δ = 128.04 ppm.[1]

Carroll	*Our Sample*	Δδ
14.1 ppm	14.1 ppm	0.0 ppm
14.4	14.4	0.0
18.3	18.5	0.2
19.2	19.2	0.0
22.7	22.7	0.0
23.9	24.0	0.1
25.3	25.4	0.1
25.7	25.8	0.1
26.2	26.1	-0.1
26.9	26.9	0.0
27.4	27.4	0.0
27.9	27.9	0.0
31.6	31.6	0.0
32.3	32.3	0.0
33.2 [C4a]	33.4*	0.2
33.5 [C1']	33.5*	0.0
38.1	38.0	-0.1
39.8	39.8	0.0
40.3	40.3	0.0
47.6	47.5	-0.1
55.8	55.7	-0.1
71.2	71.2	0.0
71.2	71.3	0.1
121.9	121.9	0.0
149.5	149.4	0.1
166.0	166.0	0.0

** These two assignments were confirmed using HSQC.*

MATCHING OF PROTON NMR

OUR SYNTHETIC (+)-LEPADIN F VERSUS WRIGHT'S ISOLATED (-)-LEPADIN F IN $CDCl_3$.

$CDCl_3$ HAS BEEN TREATED WITH K_2CO_3.

^{1}H NMR (500 MHz, $CDCl_3$) The internal standard is set at δ = 7.26 ppm.[1]

Wright	*Our Sample*	Δδ
0.90 ppm	0.90 ppm	0.00 ppm
0.90	0.92	0.02
0.93	0.87-0.96	-0.01
1.01	1.00	-0.01
1.15-1.48	1.11-1.51	-0.01
1.62	1.64	0.02
1.72	1.71	-0.01
1.78	1.75-1.89	0.04
2.05	2.05-2.11	0.03
2.20	2.18-2.24	0.01
2.89	2.87	-0.02
3.09	3.08	-0.01
3.54	3.52-3.62	0.03
4.92	4.93	0.01
5.89	5.91	0.02
7.01	7.01	0.00

MATCHING OF CARBON NMR

OUR SYNTHETIC (+)-LEPADIN F VERSUS WRIGHT'S ISOLATED (-)-LEPADIN F IN $CDCl_3$.

$CDCl_3$ HAS BEEN TREATED WITH K_2CO_3.

^{13}C NMR (100 MHz, $CDCl_3$) The internal standard is set at δ = 77.10 ppm.[1]

Wright	*Our Sample*	Δδ
14.0 ppm	14.0 ppm	0.0 ppm
14.2	14.2	0.0
18.4	18.5	0.1
18.9	18.9	0.0
22.5	22.5	0.0
23.7	23.8	0.1
25.2	25.3	0.1
25.4	25.4	0.0
25.8	25.8	0.0
26.6	26.6	0.0
27.0	27.0	0.0
27.7	27.7	0.0
31.4	31.4	0.0
32.2	32.2	0.0
33.0 [C4a]	33.1*	0.1
33.1 [C1']	33.1*	0.0
37.5	37.5	0.0
39.5	39.5	0.0
39.8	39.8	0.0
47.1	47.1	0.0
55.4	55.5	0.1
71.3	71.3	0.0
71.6	71.7	0.1
121.2	121.3	0.1
149.9	149.8	-0.1
166.6	166.6	0.0

** Overlapping peaks correspond to C4a and C1', and this has been confirmed using HSQC. While unlike Wright's data, these two peaks overlapped in our ^{13}C NMR, they are resolved in C_6D_6.*