Supporting Information for

Network Analysis Guided Synthesis of Weisaconitine D and Liljestrandinine

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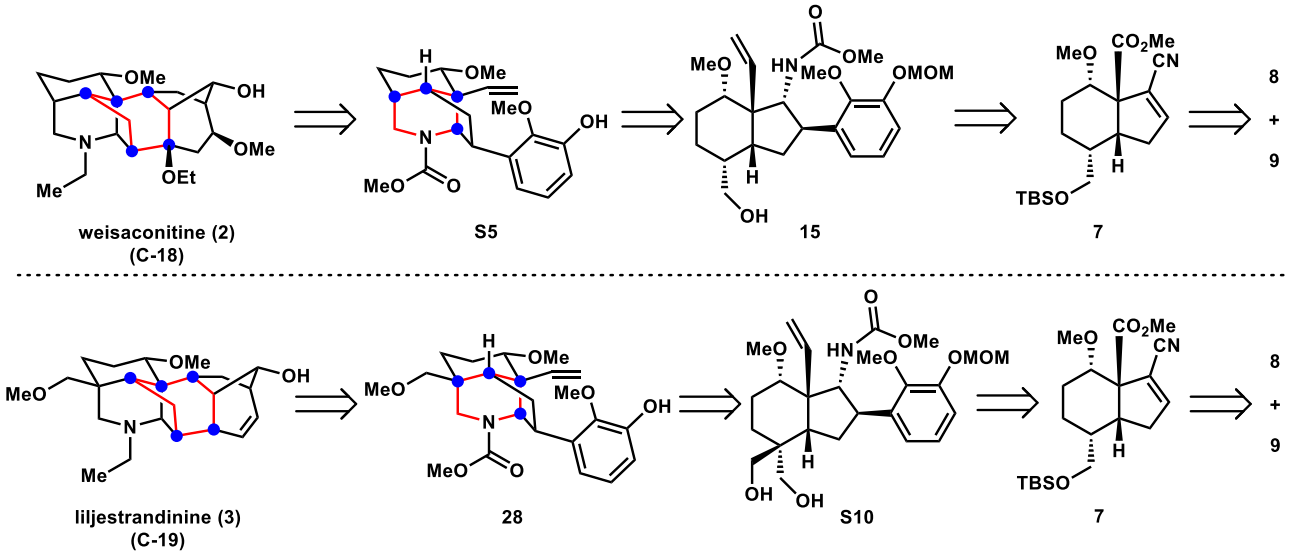
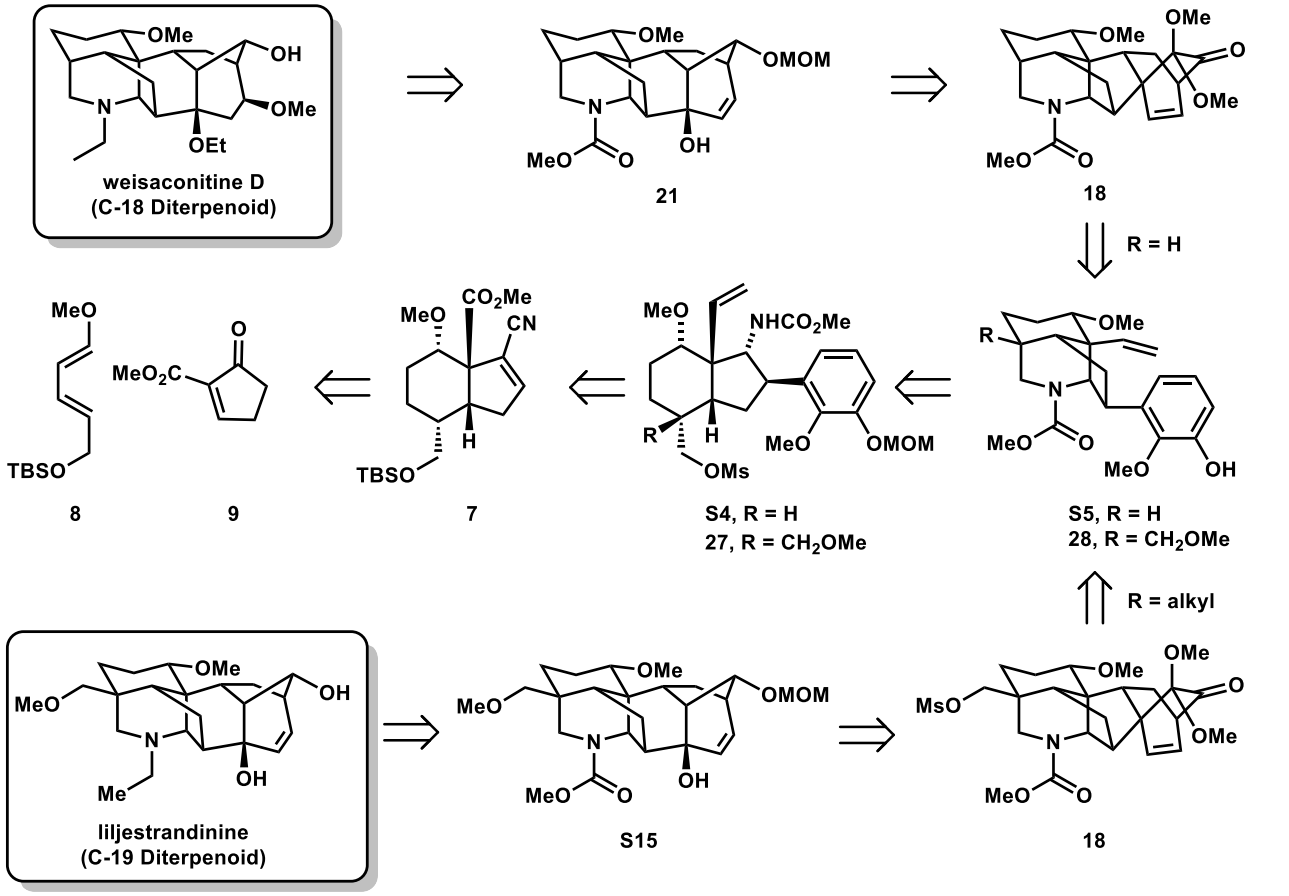
1. Figure S1. Retrosynthetic schemes for weisaconitine D, liljestrandinine

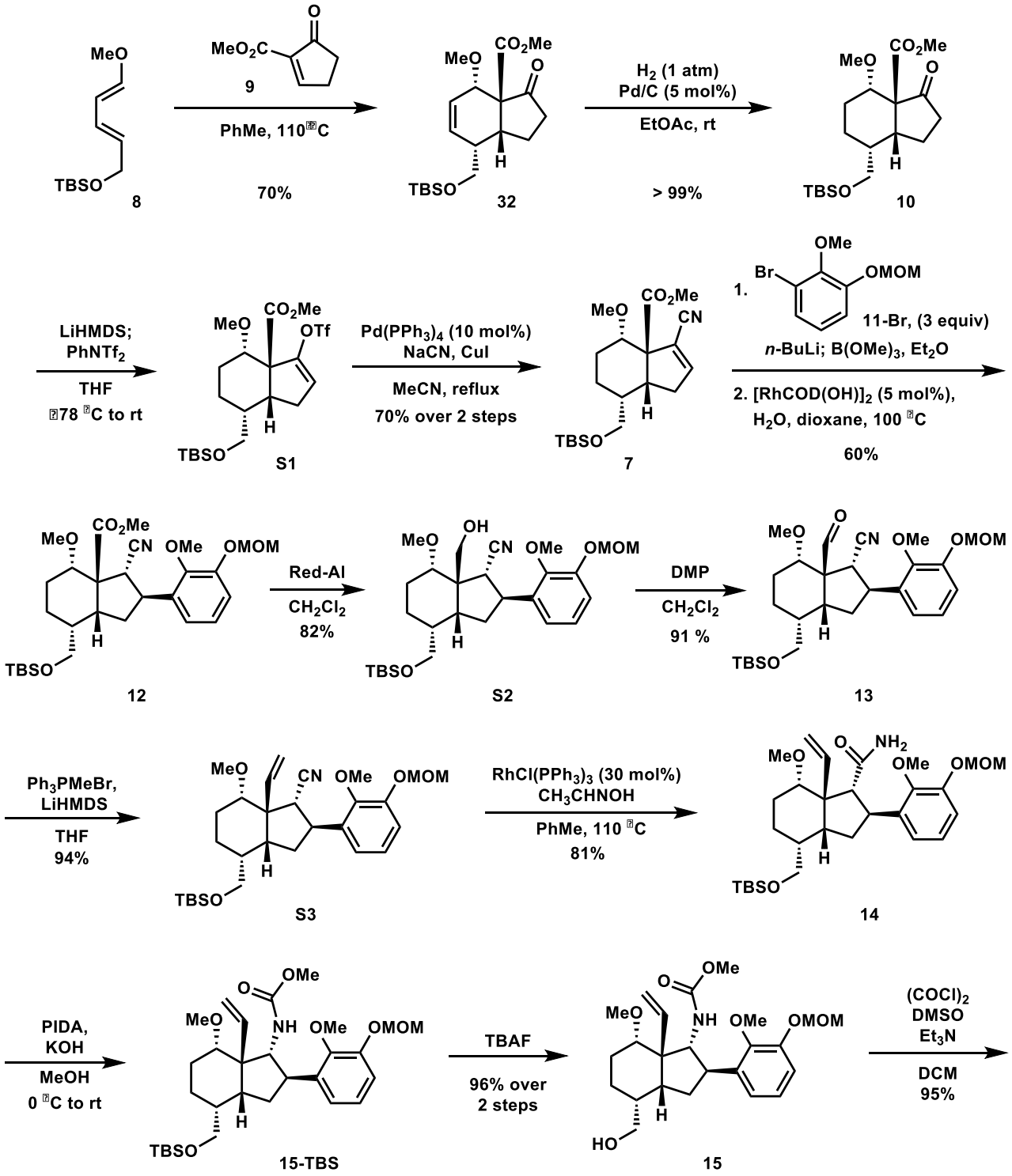
(a) Similar disconnections guided by network analysis can be imagined for liljestrandinine (**3**)

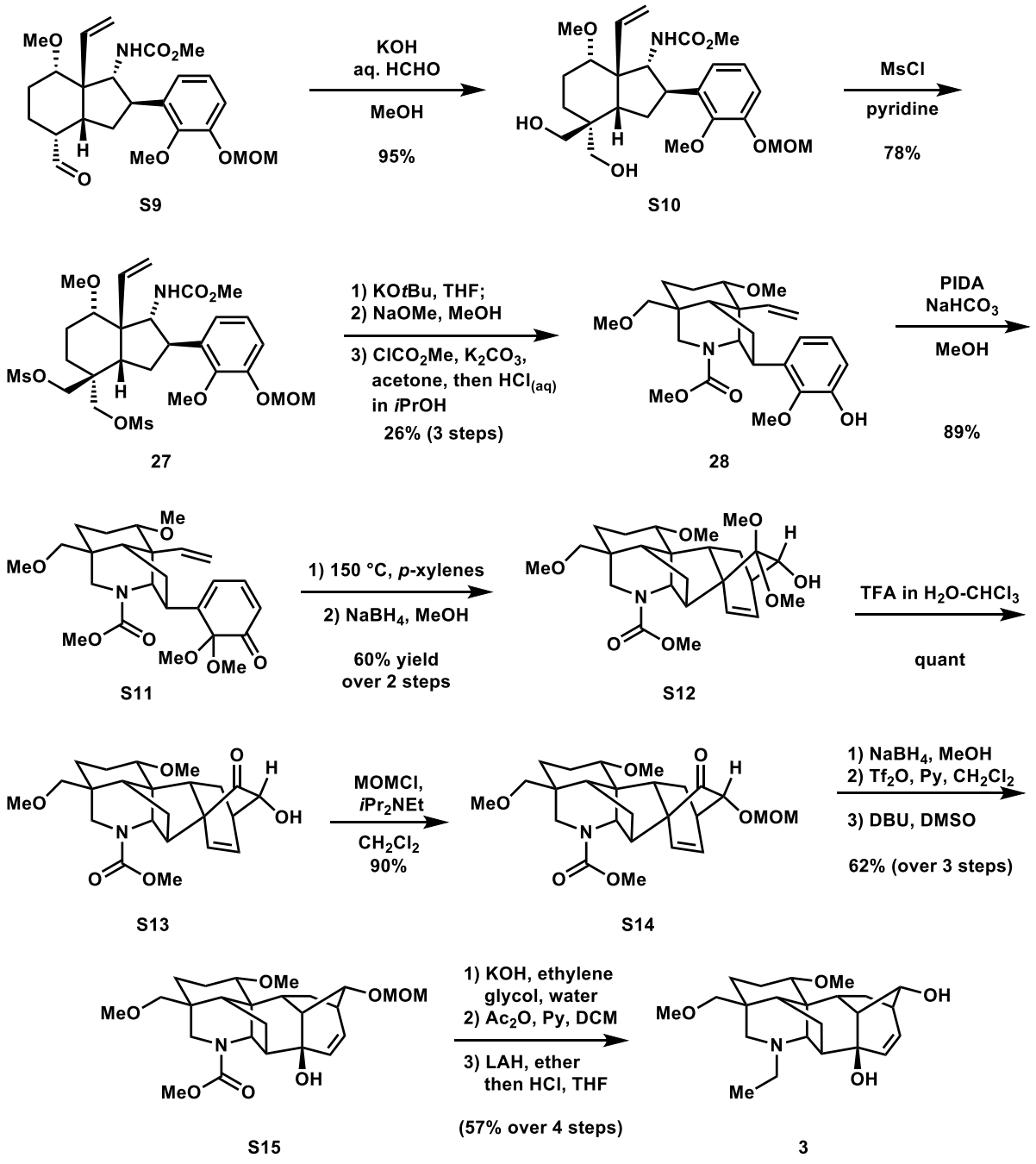


(b) Detailed retrosynthesis analyses of weisaconitine D (**2**) and liljestrandinine (**3**)



2. Figure S2. Detailed synthesis scheme for liljestrandinine



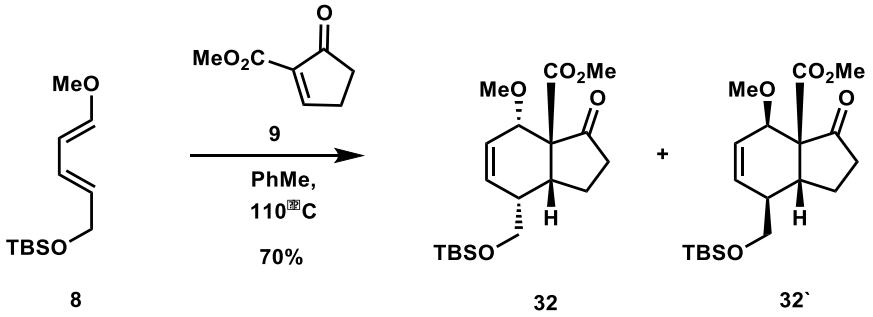

KOH
aq. HCHO
MeOH
95%
MsCl
pyridine
78%
S9
S10
1) KOtBu, THF;
2) NaOMe, MeOH
3) ClCO2Me, K2CO3,
acetone, then HCl(aq)
in iPrOH
26% (3 steps)
PIDA
NaHCO3
MeOH
89%
27
28
1) 150 °C, p-xylenes
2) NaBH4, MeOH
60% yield
over 2 steps
TFA in H2O-CHCl3
quant
S11
S12
MOMCl,
iPr2NEt
CH2Cl2
90%
1) NaBH4, MeOH
2) Tf2O, Py, CH2Cl2
3) DBU, DMSO
62% (over 3 steps)
S13
S14
1) KOH, ethylene
glycol, water
2) Ac2O, Py, DCM
3) LAH, ether
then HCl, THF
(57% over 4 steps)
S15
3

3. Experimental procedures

3.1. General experimental methods

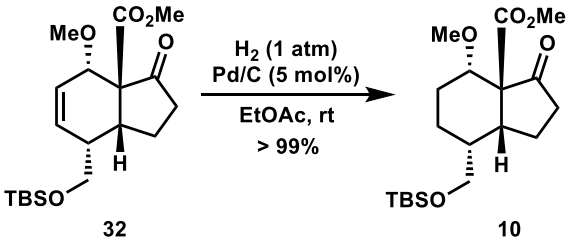
Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen, and all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in flame-dried glassware under a positive pressure of N_2 in dry solvents using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene, toluene (PhMe), methanol (MeOH) and triethylamine (Et_3N) were dried over alumina under an argon atmosphere in a GlassContour solvent system. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride under a nitrogen atmosphere. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above room temperature (r.t.), 23 °C, were controlled by an IKA® temperature modulator. Reaction progress was monitored by thin layer chromatography using SiliCycle silica gel 60 F254 precoated plates (0.25 mm) which were visualized using UV light (254 nm), *p*-anisaldehyde stain, $KMnO_4$ or CAM stain. Sorbtech and/or Silicycle silica gel (particle size 40-63 μm) was used for flash chromatography. Melting points were recorded on a Mel-Temp II Laboratory Devices, USA. Optical rotation was recorded on a Perkin Elmer Polarimeter 241 at the D line (1.0 dm path length). ^1H and ^{13}C NMR were recorded on Bruker AVB-400, AV-500, DRX-500 or AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125, and 150 MHz, respectively, in $CDCl_3$ or C_6D_6 at 23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$ δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR and C_6D_6 δ = 7.16 for ^1H NMR and δ = 128.06 for ^{13}C NMR). Data for ^1H NMR are reported as follows: chemical shift (multiplicity, coupling constant, number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. IR spectra were recorded on a Bruker Alpha FT-IR spectrophotometer using a diamond ATR accessory, or obtained as thin films on NaCl plates, and reported in frequency of absorption (cm^{-1}).

3.2. Synthesis of weisaconitine D



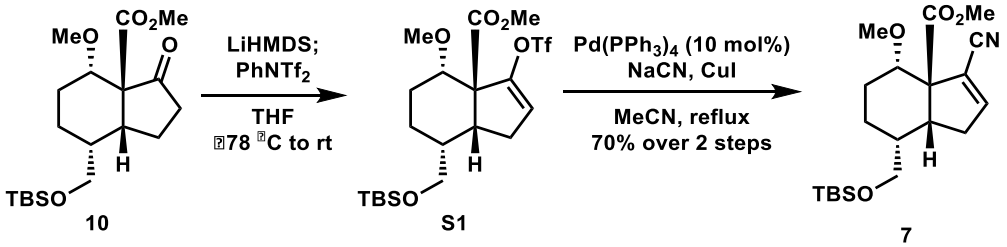
Hydrindenone 32 (Major, *endo* product): To a 250 mL round-bottomed Schlenk flask equipped with a magnetic stir bar, under a N_2 atmosphere, was added diene **8** (31.1 g, 136 mmol), dienophile **9** (9.43 g, 67.3 mmol), and PhMe (55 mL). The flask was sealed and the reaction mixture heated to 110 °C for 64 h, at which time TLC and NMR analyses indicated complete consumption of the starting material. The solvent was removed under reduced pressure. The crude mixture was purified by gradient flash chromatography (eluting with 98:2 to 88:12 hexanes/EtOAc) to deliver hydrindenone **32** as a yellow oil (17.4 g, 70% yield). R_f = 0.24 (95:5 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (dt, *J* = 11, 3.6 Hz, 1H), 5.71 (d, *J* = 10 Hz, 1H), 4.35 (s, 1H), 3.73 (s, 3H), 3.63 (dt, *J* = 20, 9.6 Hz, 2H), 3.31 (s, 3H), 2.99 (q, *J* = 6.6 Hz, 1H), 2.47 (d, *J* = 6.6 Hz, 1H), 2.38 (dd, *J* = 19, 8.4 Hz, 1H), 2.24 (q, *J* = 9.0 Hz, 1H), 1.96 – 1.87 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.9, 171.0, 128.0, 124.3, 73.7, 63.8, 63.3, 58.7, 52.7, 39.4, 38.6, 36.7, 25.8, 20.6, 18.2, -5.4, -5.5; IR (thin film) ν_{max} 2954, 2930, 2896, 2857, 1757, 1730, 1253, 1109, 1085, 838, 777 cm^{-1}; HRMS (ESI) calc'd for $[C_{19}H_{32}O_5NaSi]^+$: *m/z* 391.1911, found 391.1914.

Hydrindenone 32' (Minor, *exo* product): The *exo* diastereomer of hydrindenone **32`** was also isolated as a pale yellow solid with m.p. 61 – 65°C (2.66 g, 11% yield). R_f = 0.16 (95:5 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 – 5.89 (m, 2H), 4.28 (dd, *J* = 4.4, 1.4 Hz, 1H), 3.75 (s, 3H), 3.74 – 3.68 (m, 1H), 3.57 (dd, *J* = 9.6, 7.4 Hz, 1H), 3.31 (s, 3H), 2.77 (t, *J* = 5.8 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.20 – 2.08 (m, 1H), 1.96 – 1.85 (m, 2H), 0.90 (s, 9H), .06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 167.4, 132.2, 123.8, 72.4, 66.6, 66.0, 56.2, 52.5, 40.2, 35.3, 33.6, 25.9, 25.7, 18.1, -5.58, -5.62; IR (film) ν_{max} 2953, 1732, 1471 cm^{-1}; HRMS (EI) calc'd for $[C_{19}H_{32}O_5NaSi]^+$ *m/z* 391.1911, found 391.1916.

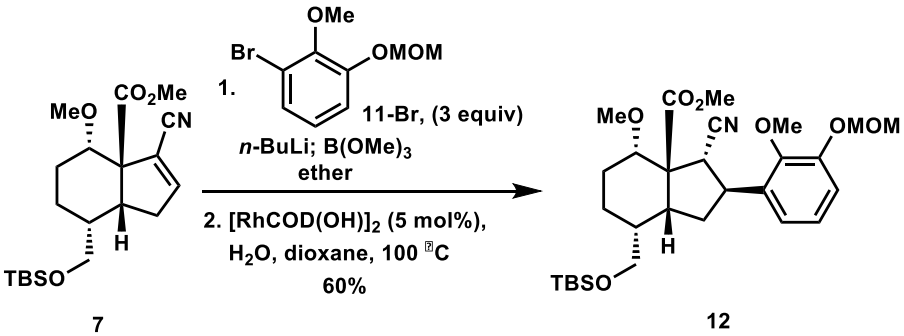


Hydrindanone 10: To a round-bottomed flask equipped with a magnetic stir bar was added hydrindenone **32** (19.6 g, 53.2 mmol), 10% Pd/C (3.00 g, 2.81 mmol) followed by careful addition of EtOAc (200 mL). The flask was carefully evacuated via gentle vacuum on the Schlenk line and backfilled with hydrogen (repeated 3 time). A balloon of H_2 was attached and the

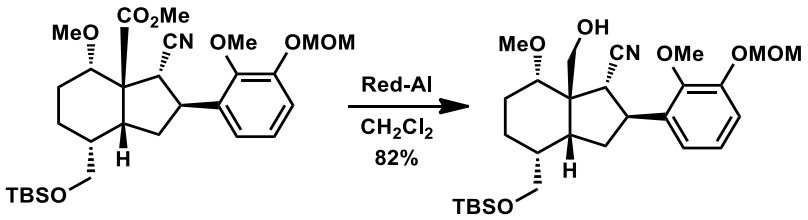
reaction mixture was stirred at r.t. for 12 h. After this time, the mixture was filtered through celite and concentrated under reduced pressure to deliver hydrindanone **10** (19.6 g, 99% yield) as a white solid with m.p. 37 – 39 °C. R_f = 0.42 (9:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.08 (s, 1H), 3.69 (s, 3H), 3.53 (dt, *J* = 24, 10 Hz, 2H), 3.17 (s, 3H), 3.02 (q, *J* = 6.6 Hz, 1H), 2.39 (dd, *J* = 19, 8.4 Hz, 1H), 2.25 (q, *J* = 9.0 Hz, 1H), 2.08 – 2.00 (m, 2H), 1.82 – 1.75 (m, 2H), 1.44 – 1.38 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.7, 170.9, 78.7, 65.6, 63.1, 57.2, 52.5, 41.2, 39.2, 38.2, 25.9, 25.4, 20.4, 18.3, 17.1, -5.36, -5.42; IR (thin film) ν_{max} 2953, 2930, 2896, 2857, 1755, 1728, 1252, 1092, 837, 776 cm^{-1}; HRMS (ESI) calc'd for $[C_{19}H_{34}O_5{}^{23}Na^{28}Si]^+$: *m/z* 393.2068, found 393.2070.



Vinyl Nitrile 7: To a 1 L round-bottomed flask equipped with a magnetic stir bar, under a N_2 atmosphere, was added hydrindanone **10** (20.0 g, 54.0 mmol) and THF (250 mL). The resulting solution was cooled to –78 °C and LiHMDS (1.0 M in THF, 70 mL, 70 mmol) was added dropwise via syringe. After the reaction mixture had been stirred for 1 h at –78 °C, *N*-phenyl-bis(trifluoromethanesulfonimide) (26.6 g, 75.6 mmol) was added as a solution in THF (120 mL). After being stirred for 12 h, during which time the dry ice/acetone bath was allowed to expire, the reaction mixture was cooled to 0 °C, quenched with a sat. solution of $NaHCO_{3(aq)}$ (250 mL), and extracted with EtOAc (3 × 70 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude vinyl triflate **S1**, which was purified by column chromatography (19:1 hexanes/EtOAc). A 1 L round-bottomed flask equipped with a magnetic stir bar and a reflux condenser under an N_2 atmosphere was added the vinyl triflate **S1** as a solution in MeCN (250 mL). NaCN (5.80 g, 119 mmol), $Pd(PPh_3)_4$ (3.70 g, 3.20 mmol) and CuI (1.20 g, 6.30 mmol) were then sequentially added to the reaction vessel. After being stirred for 2 h at the reflux temperature, the vessel was cooled to r.t. and the reaction mixture filtered through a pad of celite (rinsed 2 × 30 mL EtOAc), washed with water (2 × 40 mL) and brine (2 × 40 mL) and concentrated under reduced pressure. The crude mixture was purified by gradient flash column chromatography (eluting with 100:0 to 4:1 hexanes/EtOAc) to furnish vinyl nitrile **7** (14.3 g, 70% yield over two steps) as a yellow oil. R_f = 0.30 (9:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (t, *J* = 2.6 Hz, 1H), 3.88 (dd, *J* = 6.2, 2.5 Hz, 1H), 3.79 (s, 3H), 3.48 (dd, *J* = 10.1, 6.1 Hz, 1 H) 3.40 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.29 (s, 3H), 2.82 (td, *J* = 9.3, 5.1 Hz, 1H), 2.42 – 2.32 (m, 2H), 2.07 – 2.00 (m, 1H), 1.81 (dq, *J* = 14.1, 5.4 Hz, 1H), 1.66 – 1.60 (m, 1H), 1.49 – 1.42 (m, 1H), 1.32 (ddt, *J* = 13.1, 9.8, 6.5 Hz, 1H), 0.87 (s, 9H), 0.024 (s, 3H), 0.021 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 151.9, 116.0, 115.7, 66.0, 63.6, 57.6, 52.6, 43.4, 36.4, 33.2, 25.8, 24.1, 18.1, 17.8, -5.45, -5.51 (note: one sp^3 carbon signal missing, possibly due to signal overlap); IR (film) ν_{max} 2956, 2223, 1735 cm^{-1}; HRMS (ESI) calc'd for $[C_{20}H_{33}NO_4SiNa]^+$ *m/z* 402.2071, found 402.2075.

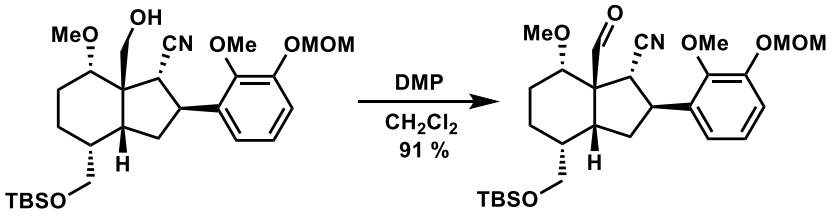


Alkyl Nitrile 12: To a 500 mL Schlenk flask equipped with a magnetic stir bar and placed under a N_2 atmosphere was added a solution of aryl bromide **11-Br** (10.2 g, 41.2 mmol) in Et_2O (40 mL). The flask was cooled to –78 °C and a solution of *n*-BuLi (2.5 M in hexanes, 18 mL, 45 mmol) was added. The resulting cloudy reaction mixture was stirred at –78 °C for 45 min, then at r.t. for 20 min, at which point a white slurry formed. This was cooled to –40 °C and $B(OMe)_3$ (5.0 mL, 45 mmol) was added via syringe. The dry ice/acetonitrile bath was allowed to expire over 20 min, during which time the temperature changed from –40 °C to –25 °C. The dry ice/acetonitrile bath was removed and the reaction mixture was stirred at r.t. for 60 min, producing a clear, colorless, solution. The majority of solvent was removed under gentle vacuum on a Schlenk manifold to give a white foam. While under a flow of N_2, $[RhCOD(OH)]_2$ (327 mg, 0.703 mmol) was added, followed by a solution of vinyl nitrile **7** (5.18 g, 13.6 mmol) in 1,4-dioxane (120 mL). The Schlenk flask was purged with N_2 for 15 min, then sealed and heated to 100 °C over 5 min, at which point H_2O (0.80 mL, 44 mmol) was added. The reaction mixture was heated at 100 °C for 16 h, then cooled to r.t., diluted with hexanes (100 mL), and filtered through a pad of celite (rinsed with 3 x 30 mL EtOAc). The filtrate was concentrated under reduced pressure to give a yellow liquid. Purification by gradient flash chromatography (eluting with 100:1 to 4:1 hexanes/EtOAc) allowed for the isolation of a light yellow liquid with two co-eluting compounds R_f = 0.23 (9:1 hexanes/EtOAc). A second column eluting with 79:20:1 CH_2Cl_2/hexanes/Et_2O selectively separates and removes the impurity. The column was then flushed with 9:1 CH_2Cl_2/Et_2O to give product **12** as a pale yellow liquid, which solidifies as an amorphous white solid in the fridge (4.46 g, 60%). R_f = 0.20 (79:20:1 CH_2Cl_2/hexanes/Et_2O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 6.88 Hz, 1H), 5.23 – 5.18 (m, 2H), 4.04 (t, *J* = 9.6 Hz, 1H), 3.98 (s, 1 H), 3.94 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 3.44 (s, 3H), 3.43 – 3.36 (m, 2H), 3.25 (d, *J* = 8.4 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.40 (q, *J* = 12.5 Hz, 1H), 2.09 (d, *J* = 14.4 Hz, 1H), 1.99 (bs, 1H), 1.62 (t, *J* = 10.4 Hz, 1H), 1.47 – 1.32 (m, 3H), 0.87 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 150.2, 147.8, 138.8, 124.2, 121.5, 120.2, 115.3, 95.1, 66.2, 61.3, 60.4, 56.9, 56.2, 52.6, 45.7, 43.6, 42.7, 38.1, 33.1, 25.8, 24.8, 18.2, 16.5, -5.4, -5.5 (note: one sp^3 carbon signal missing, possibly due to signal overlap); IR (film) ν_{max} 2952, 2239, 1732 cm^{-1}; HRMS (ESI) calc'd for $[C_{29}H_{45}NO_7SiNa]^+$ *m/z* 570.2858, found 570.2863



12 S2

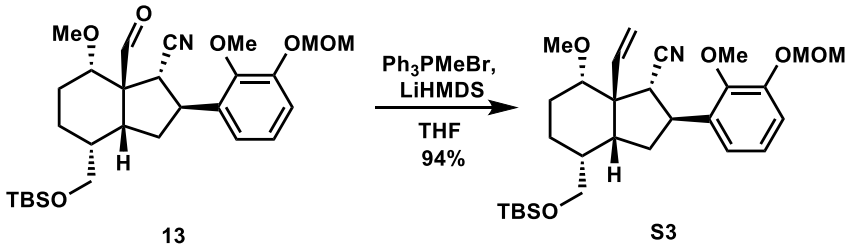
Primary Alcohol S2: To a 250 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added alkyl nitrile **12** (6.40 g, 11.7 mmol) and CH_2Cl_2 (100 mL). The reaction vessel was cooled to –78 °C and Red-Al® (65 wt% in toluene, 38 mL, 120 mmol) was added dropwise via syringe. The reaction mixture was warmed to r.t. and stirred for an additional 1 h, at which time the reaction was cooled to 0 °C and quenched with isopropanol (20 mL) and a sat. $NH_4Cl_{(aq)}$ solution (20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by gradient flash chromatography (20→33% EtOAc/hexanes) furnished primary alcohol **S2** (5.0 g, 82% yield) as a clear, viscous oil. R_f = 0.11 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.96 (t, = 7.9 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.23 – 5.18 (m, 2H), 4.01 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1 H), 3.92 (s, 3H), 3.62 (q, *J* = 11.3 Hz, 2H), 3.52 (s, 3H), 3.42 – 3.36 (m, 5H), 3.16 (d, *J* = 8.7 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.39 (q, *J* = 11.0 Hz, 1H), 2.09 (bs, 1H), 2.06 – 1.99 (m, 1H), 1.86 – 1.76 (m, 1H), 1.54 (ddd, *J* = 12.0, 8.4, 3.0 Hz, 1H), 1.45 – 1.32 (m, 3H), 0.87 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 147.7, 139.8, 124.2, 121.6, 121.4, 114.9, 95.0, 77.5, 66.5, 64.3, 61.4, 56.8, 56.2, 55.5, 43.8, 42.2, 39.7, 37.8, 33.9, 25.9, 24.1, 18.3, 17.0, -5.4; IR (film) ν_{max} 3475, 2932, 2237 cm^{-1}; HRMS (ESI) calc'd for $[C_{28}H_{45}NO_6SiNa]^+$ *m/z* 542.2908, found 542.2905.



S2 13

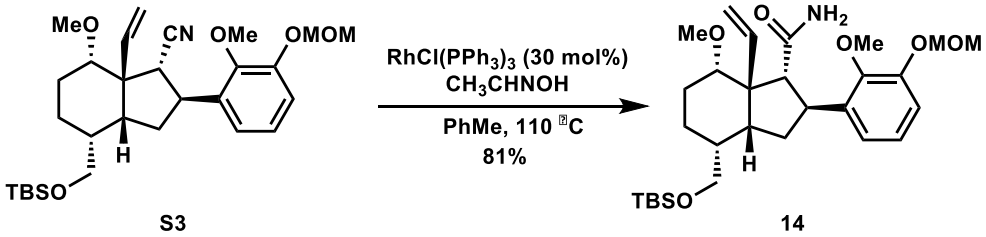
Aldehyde 13: To a 100 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added primary alcohol **S2** (2.16, 4.16 mmol), CH_2Cl_2 (40 mL) and $NaHCO_3$ (1.75 g, 20.8 mmol). The reaction vessel was cooled to 0 °C and Dess-Martin periodinane (3.52 g, 8.30 mmol) was added portion-wise. The reaction mixture was allowed to stir at this temperature for 1.5 h, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by slow sequential addition of sat. $NaHCO_{3(aq)}$ solution (10 mL) and sat. $Na_2S_2O_{3(aq)}$ solution (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (4:1 hexanes/EtOAc) to furnish aldehyde **13** as a colorless liquid (1.95 g, 91% yield). R_f = 0.41 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.06 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.24 –

5.20 (m, 2H), 4.04 (ddd, *J* = 11.9, 8.7, 3.2 Hz, 1H), 3.96 (s, 3H), 3.87 (bs, 1H), 3.52 (s, 3H), 3.47 – 3.35 (m, 5H), 3.16 (d, 8.7 Hz, 1H), 2.93 (ddd, *J* = 13.1, 8.7, 4.9 Hz, 1H), 2.44 (q, *J* = 12.3 Hz, 1H), 2.19 – 2.12 (m, 1H), 1.80 – 1.67 (m, 2H), 1.49 – 1.23 (m, 3H), 0.87 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 150.4, 147.7, 137.9, 124.2, 121.9, 119.3, 115.6, 95.1, 77.2, 75.3, 66.0, 63.9, 61.3, 56.9, 56.3, 44.9, 42.2, 41.8, 38.7, 33.0, 25.9, 24.7, 18.3, 16.3, -5.4, -5.5; IR (film) ν_{max} 2932, 2239, 1727 cm^{-1}; HRMS (ESI) calc'd for $[C_{28}H_{43}NO_6NaSi]^+$ *m/z* 540.2752, found 540.2751.



13 S3

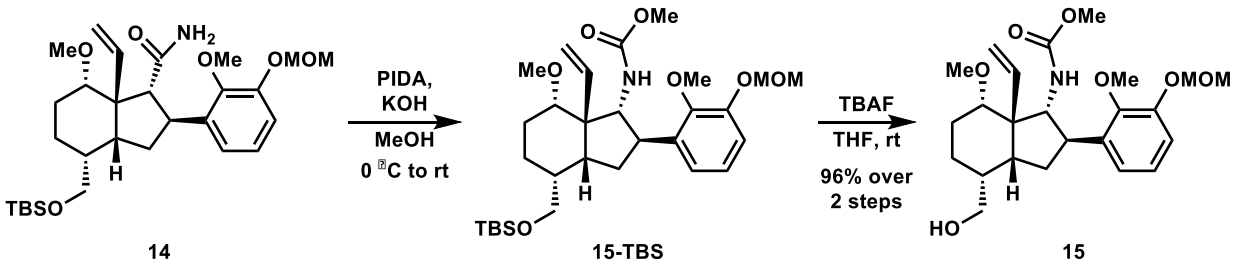
Olefin S3: To a 250 mL two-neck round-bottomed flask fitted with a reflux condenser and a magnetic stir bar under a N_2 atmosphere was added methyltriphenylphosphonium bromide (6.60 g, 18.5 mmol) and THF (60 mL). The reaction vessel was cooled to 0 °C and LiHMDS (1.0 M in THF, 15.5 mL, 16 mmol) was added dropwise to produce a yellow solution which was heated to reflux for 30 min. After this time, the vessel was cooled to 0 °C and aldehyde **13** (3.20 g, 6.18 mmol) was added as a solution in THF (20 mL). Following addition, the reaction vessel was allowed to warm to r.t. and stirred at that temperature for 1 h before being cooled to 0 °C and quenched by the addition of sat. $NH_4Cl_{(aq)}$ solution (20 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by gradient flash chromatography (eluting with 9:1 to 4:1 hexanes/EtOAc) to furnish olefin **S3** as a colorless liquid (3.00 g, 94% yield). R_f = 0.50 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.91 (dd, *J* = 17.9, 11.1 Hz, 1H), 5.29 (d, *J* = 17.7 Hz, 1H), 5.24 – 5.18 (m, 3H), 4.02 (ddd, *J* = 11.7, 8.8, 3.1 Hz, 1H), 3.93 (s, 3H), 3.52 (as, 4H), 3.45 – 3.36 (m, 5H), 2.85 (d, *J* = 8.9 Hz, 1H), 2.64 – 2.56 (m ,1H), 2.41 (q, *J* = 12.3 Hz, 1H), 2.03 – 1.88 (m, 2H), 1.64 – 1.56 (m, 1H), 1.48 – 1.22 (m, 3H), 0.88 (s, 9H), 0.20 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.0, 141.5, 139.7, 124.3, 121.8, 121.3, 115.3, 95.3, 80.1, 66.6, 61.6, 56.9, 56.4, 55.6, 48.8, 44.2, 43.3, 37.9, 33.7, 26.1, 23.9, 18.5, 17.1, -5.21, -5.24; IR (film) ν_{max} 2931, 2235, 1479 cm^{-1}; HRMS (ESI) calc'd for $[C_{29}H_{45}NO_5SiNa]^+$ *m/z* 538.2959, found 538.2955.



S3 14

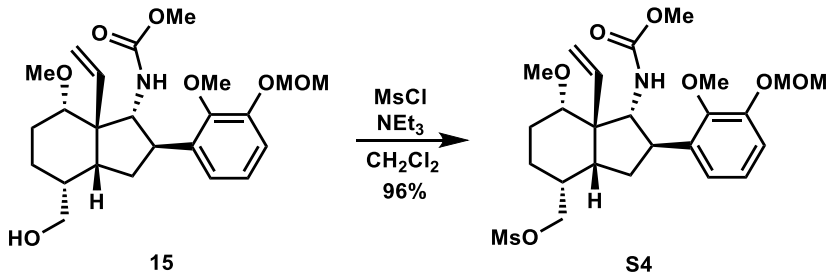
Amide 14: To a 25 mL round-bottomed flask equipped with a magnetic stir bar, under a N_2 atmosphere, was added olefin **S3** (1.74 g, 3.37 mmol), PhMe (3.5 mL), and acetaldoxime (6.2

mL, 110 mmol). Wilkinson's catalyst (620 mg, 0.670 mmol) was added and the reaction vessel was fitted with a reflux condenser and heated to reflux for 12 h. The vessel was charged with a second addition of Wilkinson's catalyst (310 mg, 0.335 mmol) and heating was continued for an additional 3 h, at which time NMR analysis indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and purified using column chromatography (9:1 to 4:1 hexanes/EtOAc) to produce amide **14** (1.50 g, 81% yield) as a white solid. R_f = 0.38 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.93 (m, 2H), 6.90 (br. s, 1H), 6.20 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.27 – 5.09 (m, 5H), 5.13 (d, *J* = 11.4 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.90 (s, 3H), 3.70 (br. s, 1H), 3.51 (s, 3H), 3.44 – 3.36 (m, 2H), 3.25 (s, 3H), 2.79 – 2.72 (m, 1H), 2.70 (d, *J* = 8.7 Hz, 1H), 2.45 (q, *J* = 12.3 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.58 (ddd, *J* = 11.9, 8.9, 2.6 Hz, 1H), 1.44 – 1.21 (m, 3H), 0.90 (s, 9H), 0.027 (s, 3H), 0.001 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 149.7, 145.8, 144.7, 142.5, 125.1, 121.1, 113.5, 112.4, 94.9, 79.3, 66.2, 61.3, 56.3, 56.1, 55.2, 3.1, 38.2, 37.4, 34.4, 25.8, 23.7, 18.1, 17.1, -5.5, -5.6; IR (film) ν_{max} 3427, 3188, 2929, 1668 cm^{-1}; HRMS (ESI) calc'd for $[C_{29}H_{48}NO_6Si]^+$ *m/z* 534.3245, found 534.3253.



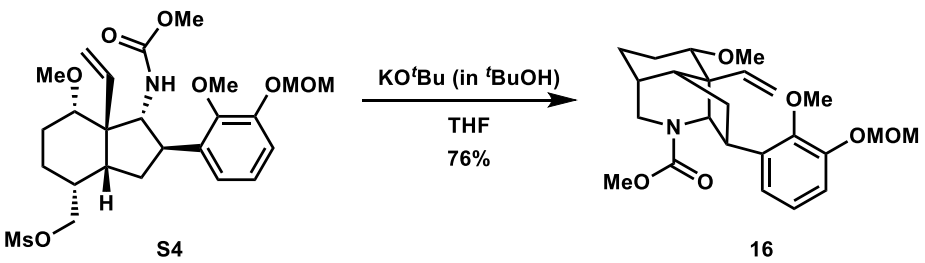
Carbamate 15: To a 25-mL round-bottomed flask was added primary amide **14** (296 mg, 0.554 mmol) and methanol (5.5 mL). The resulting suspension was stirred at r.t. for 10 min until all substrate had dissolved. Powdered KOH (105 mg, 1.87 mmol) was subsequently added and this mixture was stirred at r.t. until a transparent solution was obtained. The reaction flask was cooled 0 °C in an ice/water bath and PIDA (232 mg, 0.720 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h, then at r.t. for 80 min, at which point TLC analysis indicated full consumption of starting material. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and carefully concentrated under reduced pressure to remove methanol. The residue obtained was diluted with sat. $NH_4Cl_{(aq)}$ and extracted with with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **15-TBS** as a viscous, orange liquid. In a 25 mL round-bottomed flask **15-TBS** was dissolved in THF under N_2, and added a solution of TBAF (1.0 M in THF, 1.6 mL, 1.6 mmol). The reaction mixture was stirred at r.t. for 5 h, at which point TLC analysis indicated full consumption of starting material. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ solution (2 mL), then carefully concentrated under reduced pressure to remove THF. The residue obtained was diluted with sat. $NH_4Cl_{(aq)}$ solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as a yellow liquid. Purification via Yamazen® automated chromatography (medium column, small inject, eluting with 7:3 to 3:2 hexanes/EtOAc) gave carbamate **15** as a colourless liquid (230 mg, 96% over two steps); R_f = 0.30 (1:1 hexanes/EtOAc); ratio of rotamers 1:2 ($CDCl_3$, 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) both

rotamers: δ 6.96 – 6.79 (m, 3H), 5.85 – 5.69 (m, 1H), 5.20 – 5.05 (m, 4H), 5.01 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H, minor rotamer), 4.22 (t, *J* = 9.6 Hz, 1H), 4.06 (t, *J* = 9.6 Hz, 1H, minor rotamer), 3.82 (s, 3H), 3.53 – 3.35 (m, 10H), 3.33 (s, 3H), 2.62 – 2.50 (m, 1H), 2.28 (q, *J* = 12.4 Hz, 1H), 2.16 (s, 1H), 2.00 (app. d, *J* = 11.1, 1H), 1.94 – 1.83 (br. s, 1H), 1.47 – 1.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 156.6, 149.9, 147.6, 142.5, 140.2, 124.0, 121.6, 114.2, 113.7, , 94.9, 78.6, 67.6, 65.8, 60.8, 56.0, 55.3, 53.8, 51.7, 45.4, 41.5, 37.7, 32.1, 22.9, 17.0; minor rotamer δ 157.3, 147.8, 142.7, 140.3, 123.7, 122.0, 114.4, 113.5, 78.2, 68.6, 53.5, 51.8, 46.3, 41.8, 31.6; IR (film) ν_{max} 3446, 2940, 1716 cm^{-1}; HRMS (ESI) calc'd for $[C_{24}H_{36}NO_7]^+$ *m/z* 450.2486, found 450.2495.



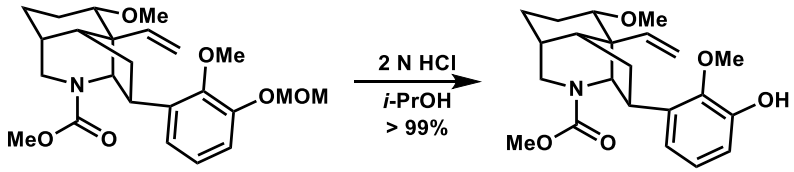
15 S4

Mesylate S4: To a 25 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added carbamate **15** (230 mg, 0.530 mmol), CH_2Cl_2 (5.5 mL), and Et_3N (0.37 mL). The reaction vessel was cooled to 0 °C and methanesulfonyl chloride (62 µL, 0.80 mmol) was added. The mixture was held at this temperature for 45 min, at which time TLC analysis indicated full consumption of starting material. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extract was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by Yamazen® automated chromatography (medium column, small inject, eluting with 55:45 to 35:65 hexanes/EtOAc) provided mesylate **S4** (270 mg, 96% yield) as a clear, colorless oil. R_f = 0.35 (1:1 hexanes/EtOAc); ratio of rotamers 1:4 (C_6D_6, 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) both rotamers: δ 6.98 – 6.76 (m, 3H), 5.86 – 5.68 (m, 1H), 5.20 – 4.82 (m 5H), 4.24 (t, *J* = 9.7 Hz, 1H), 4.09 (t, *J* = 10 Hz, 1H, minor rotamer), 4.01 (d, *J* = 7.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H, minor rotamer), 3.54 – 3.31 (m, 12H), 3.07 (s, 3H, minor rotamer), 2.94 (s, 3H), 2.67 – 2.53 (m, 1H), 2.31 (q, *J* = 12.2 Hz, 1H), 2.23 – 2.10 (m 1H), 2.09 – 1.96 (m 1H), 1.52 – 1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 156.5, 150.0, 147.7, 141.9, 139.6, 123.86, 114.5, 114.0, 94.9, 78.0, 72.7, 67.5, 60.7, 56.0, 55.4, 53.8, 51.74, 45.7, 40.8, 37.0, 34.9, 31.9, 31.4, 22.5, 16.8; minor rotamer δ 157.1, 149.9, 142.5, 140.2, 123.92, 123.6, 114.2, 113.9, 113.6, 78.5, 77.7, 67.6, 65.9, 60.8, 55.3, 51.68, 46.7, 45.3, 41.5, 37.7, 32.1, 22.9, 17.0; IR (film) ν_{max} 3447, 2943, 1724, 1354, 1175, 835, 776 cm^{-1}; HRMS (ESI) calc'd for $[C_{25}H_{37}NO_9SNa]^+$ *m/z* 550.2081, found 550.2092.



S4 16

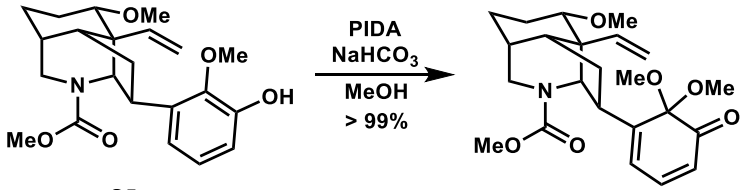
Tricycle 16: To a 25 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added mesylate **S4** (260 mg, 0.493 mmol) and THF (4.5 mL). KO^{t}Bu (1.0 M in ^{t}BuOH, 1.5 mL, 1.5 mmol) was added and the resulting yellow solution was stirred at 30 °C for 7 h, at which time LC/MS analysis indicated full consumption of starting material. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and concentrated under reduced pressure to remove THF. The residue obtained was diluted with sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product mixture was purified by Yamazen® automated chromatography (medium column, small inject, eluting with 7:3 to 1:1 hexanes/EtOAc) to afford tricycle **16** (162 mg, 76% yield) as a clear, colorless liquid. R_f = 0.43 (1:1 hexanes/EtOAc); ratio of rotamers 1:2.7 (C_6D_6, 25 °C). ^{1}H NMR (400 MHz, C_6D_6) both rotamers: 7.12 (d, *J* = 7.9 Hz, minor rotamer), 7.03 (dd, *J* = 8.0, 4.7 Hz, 2H), 6.84 (t, *J* = 8.2 Hz, 1H), 6.11 (dd, *J* = 17.8, 10.9 Hz, minor rotamer), 5.95 (dd, *J* = 17.8, 10.9 Hz, 1H), 5.57 (s, minor rotamer), 5.19 (s, 1H), 4.96 – 4.83 (m, 6H), 4.13 (d, *J* = 13.8 Hz, 1H), 3.98 (s, 1H), 3.76 (s, 3H), 3.63 (s, 4H), 3.55 (s, 1H), 3.31 – 3.22 (m, 1H), 3.16 (s, 3H), 3.13 (d, *J* = 11.3 Hz, 2H), 3.09 (s, 3H), 3.08 – 3.02 (m, 1H), 2.21 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.89 – 1.56 (m, 6H), 1.38 – 1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 155.2, 150.0, 148.4, 145.1, 136.6, 122.33, 121.8, 114.6, 113.4, 95.2, 85.7, 63.7, 59.9, 57.1, 56.2, 52.8, 52.5, 44.1, 43.12, 43.07, 33.11, 31.8, 29.8, 24.8; minor rotamer: δ 149.94, 145.2, 122.25, 122.2, 113.1, 85.9, 62.3, 60.3, 57.7, 52.9, 52.4, 43.6, 43.4, 43.2, 33.2, 33.15, 30.0, 25.0; IR (film) ν_{max} 2932, 1691, 1470 cm^{-1}; HRMS (ESI) calc'd for $[C_{24}H_{34}NO_6]^+$ *m/z* 432.2381, found 432.2386.



16 S5

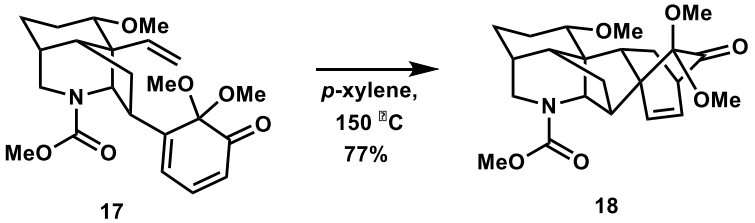
Phenol S5: To a 10 mL round-bottomed flask was added tricycle **16** (110 mg, 0.13 mmol) and a cooled (0 °C) solution of 2 N HCl/*i*-PrOH (2 mL). The resulting solution was stirred for 3.5 h with warming to r.t. The reaction mixture was then cooled to 0 °C, quenched with a sat. $NaHCO_{3(aq)}$ solution (3 mL), and extracted with EtOAc (3 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (50% EtOAc/hexanes) to furnish phenol **S5** as a white foam (52 mg, 99% yield). R_f = 0.33 (1:1 hexanes/EtOAc); ratio of rotamers 1:4 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 6.91 – 6.76 (m, 3H), 5.81 (dd, *J* = 17.9, 11.0 Hz, 1H, minor rotamer), 5.73 (dd, *J* = 17.8, 10.9 Hz, 1H), 6.18 (br. s, 1H), 5.11 – 4.89 (m, 3H), 3.91 (d, *J* =

13.8 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H, minor rotamer), 3.72 (s, 3H, minor rotamer), 3.70 (s, 3H), 3.47 – 3.30 (m, 2H), 3.28 – 3.21 (m, 4H), 2.40 – 2.29 (m, 2H), 2.02 – 1.86 (m, 3H), 1.83 (br. s, 1H), 1.63 – 1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 155.2, 149.1, 145.7, 144.7, 123.3, 119.7, 113.8, 113.3, 85.5, 63.6, 59.6, 57.0, 52.63, 52.56, 43.9, 43.1, 43.0, 32.9, 29.6, 24.6 (note: 2 sp^3 carbons missing, possibly due to signal overlap); minor rotamer: δ 154.0, 149.0, 145.6, 144.8, 119.9, 113.7, 113.1, 85.7, 62.6, 59.7, 57.7, 52.5, 43.5, 43.3, 43.2, 33.0, 32.2, 31.5, 29.9, 24.9; IR (film) ν_{max} 3306, 2933, 1674, 1586 cm^{-1}; HRMS (ESI) calc'd for $[C_{22}H_{28}NO_5]^+$ *m/z* 386.1973, found 386.1969.



S5 17

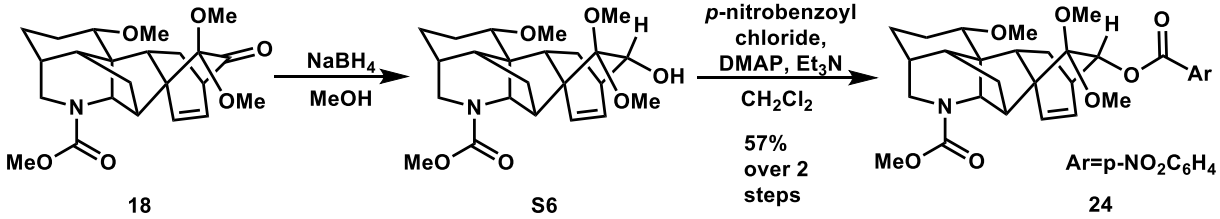
***Ortho*-Quinone Dimethyl Ketal 17:** To a 25 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added phenol **S5** (160 mg, 0.41 mmol) and MeOH (4 mL). The resulting solution was cooled to 0 °C. To this mixture was added $NaHCO_3$ (173 mg, 2.06 mmol) followed by PIDA (200 mg, 0.621 mmol) to produce a bright green solution. The reaction mixture was allowed to stir for at 0 °C for 1 h and then concentrated under reduced pressure. The crude mixture was purified by gradient flash chromatography (eluting with 4:1 to 1:1 hexanes/EtOAc) to furnish *ortho*-quinone dimethyl ketal **17** (170 mg, 99% yield) as a pale yellow solid with m.p. 73 – 76 °C. R_f = 0.38 (1:1 hexanes/EtOAc); ratio of rotamers 1:1.5 ($CDCl_3$, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 6.92 – 6.86 (m, 1H), 6.40 (d, *J* = 6.5 Hz, 1H, minor rotamer), 6.28 (d, *J* = 6.4 Hz, 1H), 6.11 (dd, *J* = 17.9, 10.9 Hz, 1H, minor rotamer), 6.01 (dd, *J* = 17.9, 10.9 Hz, 1H), 5.94 (d, *J* = 5.94 Hz, 1H), 5.18 – 5.10 (m, 2H), 5.03 (s, 1H, minor rotamer), 4.98 (s, 1H), 3.83 (d, *J* = 13.9 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H, minor rotamer), 3.66 (d, *J* = 13.9 Hz, 1H, minor rotamer), 3.30 – 3.19 (m, 8H), 3.14 (s, 3H, minor rotamer), 3.07 (s, 3H, minor rotamer), 3.04 (t, *J* = 8.6 Hz, 1H), 2.99 (t, *J* = 8.6 Hz, 1H, minor rotamer), 2.30 – 2.25 (m, 1H), 2.22 – 2.08 (m, 1H), 1.99 – 1.93 (m, 1H), 1.92 – 1.84 (m, 1H), 1.81 – 1.75 (m, 2H), 1.68 – 1.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: δ 197.0, 154.9, 152.6, 145.4, 140.7, 123.9, 123.4, 113.3, 94.8, 85.7, 62.2, 57.0, 53.1, 52.4, 50.9, 49.9, 43.6, 43.4, 42.6, 32.8, 31.8, 29.7, 24.6; minor rotamer: δ 153.1, 145.1, 141.0, 124.0, 123.3, 61.8, 52.9, 52.3, 50.3, 43.1, 43.0, 29.9, 24.7; IR (film) ν_{max} 2937, 1683, 1575, 1450 cm^{-1}; HRMS (ESI) calc'd for $[C_{23}H_{32}NO_6]^+$ *m/z* 418.2224, found 418.2230.



17 18

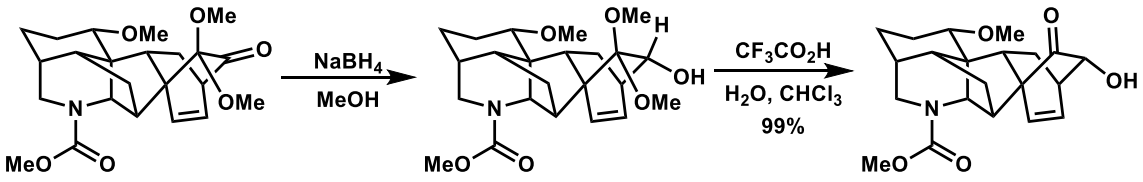
Hexacycle 18: A 100 mL Schlenk flask equipped with a magnetic stir bar was added a solution of *ortho*-quinone dimethyl ketal **17** (202 mg, 0.484 mmol) in *p*-xylene (24 mL) via

cannula. The resulting solution was subjected to three cycles of 'freeze-pump-thaw'. The sealed vessel was heated at 150 °C for 24 h. The reaction mixture was cooled to r.t., and the solvent removed under reduced pressure. The crude material was purified by Yamazen® automated chromatography (large column, small inject, eluting with 2:1 to 2:3 hexanes/EtOAc) to furnish hexacycle **18** (156 mg, 77% yield) as a white foam. R_f = 0.39 (1:1 hexanes/EtOAc); ratio of rotamers 1:2.7 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 6.39 (dd, *J* = 8.0, 6.5 Hz, 1H), 6.35 (dd, *J* = 8.1, 6.5 Hz, 1H, minor rotamer), 6.11 (d, *J* = 6.6 Hz, 1H, minor rotamer), 5.99 (d, *J* = 6.5 Hz, 1H), 4.38 (bs, 1H, minor rotamer), 4.20 (bs, 1H), 3.73 (s, 3H), 3.70 (s, 3H, minor rotamer), 3.45 (s, 3H), 3.40 – 3.37 (m, 1H), 3.29 – 3.24 (m, 4H), 3.21 (s, 3H), 3.18 (s, 3H, minor rotamer), 3.02 – 2.95 (m, 1H), 2.88 (ddd, *J* = 13.6, 6.9, 2.8 Hz, 1H), 2.57 (d, *J* = 5.2 Hz, 1H, minor rotamer), 2.50 (d, *J* = 5.3 Hz, 1H), 2.36 (q, *J* = 10.2 Hz, 1H), 2.16 – 1.99 (m, 3H), 1.94 – 1.73 (m, 3H), 1.48 – 1.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 206.6, 164.5, 156.25, 135.7, 129.8, 99.4, 77.8, 62.3, 55.3, 52.8, 51.66, 50.9, 50.5, 49.1, 48.84, 45.94, 45.6, 45.2, 44.5, 32.6, 30.0, 29.43, 25.1, 24.3; minor rotamer: 206.9, 156.32, 135.9, 129.4, 99.5, 77.4, 62.5, 55.2, 52.4, 51.70, 50.8, 50.3, 48.82, 48.5, 45.91, 45.7, 45.3, 44.0, 32.8, 30.1, 29.36, 25.12, 24.4; IR (film) ν_{max} 2940, 1731, 1696, 1448 cm^{-1}; HRMS (ESI) calc'd for $[C_{23}H_{31}NO_6Na]^+$ *m/z* 440.2044, found 440.2051.



***p*-Nitrobenzoate 24:** Hexacycle **18** (29 mg, 0.069 mmol) was diluted in MeOH (1 mL) in a 5 mL round-bottomed flask and cooled to 0 °C. Sodium borohydride (5.3 mg, 0.14 mmol) was then added and the reaction mixture was allowed to stir at this temperature for 2 h, at which time it was diluted with water (1 mL) and then methanol was removed under reduced pressure. The resulting aqueous solution was extracted with EtOAc (3 x 2 mL) and the combined organic phases dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude alcohol **S6** was diluted with CH_2Cl_2 (0.5 mL). Et_3N (0.1 mL) and DMAP (8.4 mg, 0.069 mmol) were subsequently added, followed by *p*-nitrobenzoyl chloride (64 mg, 0.34 mmol) and the resulting mixture stirred at r.t. for 12 h at which point, a sat. NH_4Cl solution (0.5 mL) was added and the mixture extracted with EtOAc (3 × 1 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (20→30% EtOAc/hexanes) to furnish *p*-nitrobenzoate **24** (22 mg, 57%) as a viscous oil, which precipitates upon exposure to hexanes. R_f = 0.61 (1:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, *p*-xylene-*d*10) δ 7.84 (t, *J* = 9.0 Hz, 2H), 7.52 (dd, *J* = 11.0, 8.3 Hz, 2H), 6.29 (t, *J* = 7.0 Hz, 1H), 6.23 (t, *J* = 7.1 Hz, 1H, minor rotamer), 6.12 (d, *J* = 7.9 Hz, 1H, minor rotamer), 5.28 (d, *J* = 5.4 Hz, 1H), 4.64 (s, 1H, minor rotamer), 4.40 (s, 1H), 3.56 – 3.49 (m, 4H), 3.43 (dt, *J* = 12.1, 6.0, 1H), 3.29 (br. s, 1H), 3.15 (s, 3H), 3.13 (s, 3H, minor rotamer), 3.10 – 3.07 (m, 3H), 2.97 (s, 3H), 2.51 (d, 5.1 Hz, 1H, minor rotamer), 2.41 (s, 1H), 2.38 (d, *J* = 5.3 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.80 – 1.71 (m, 3H), 1.56 – 1.45 (m, 5H), 0.88 – 0.99 (m, 3H); ^{13}C NMR

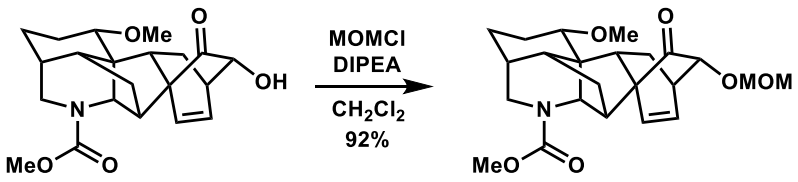
(125 MHz, $CDCl_3$) major rotamer: δ 163.8, 156.4, 150.5, 135.9, 132.4, 130.91, 123.4, 108.0, 78.3, 77.9, 61.7, 60.4, 55.3, 52.8, 50.70, 50.03, 49.7, 46.2, 45.3, 43.5, 37.91, 32.6, 30.1, 29.7, 28.61, 25.11, 24.3, 14.2; minor rotamer: δ 163.9, 135.8, 132.6, 132.3, 131.8, 130.93, 108.1, 78.5, 77.5, 61.9, 55.2, 52.4, 50.75, 50.67, 49.6, 49.4, 46.1, 45.4, 44.6, 44.1, 43.6, 37.88, 32.8, 30.2, 28.65, 25.13, 24.5; IR (film) ν_{max} 2938, 1721, 1693, 1606, 1529, 1345 cm^{-1}; HRMS (ESI) calc'd for $[C_{30}H_{36}N_2O_9]^+$ *m/z* 568.2426, found 568.2421.



18 **S6** **19**

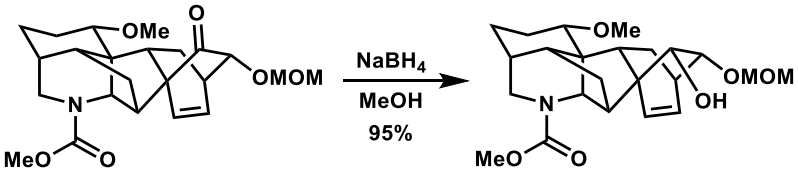
*α-Ketol **19***. Ketone **18** (248 mg, 0.593 mmol) was dissolved in MeOH (3.5 mL), in a 25 mL round bottom flask under a N_2 atmosphere, and cooled to 0 °C in an ice/water bath. $NaBH_4$ (67 mg, 1.8 mmol) was added in one portion. The reaction stirred for 3 h, during which time the ice bath was allowed to expire. The reaction was quenched by dropwise addition of a solution of sat. $NH_4Cl_{(aq)}$ (0.5 mL), and the resulting mixture concentrated under reduced pressure to remove THF. The residue obtained in this manner was diluted with sat. $NH_4Cl_{(aq)}$ solution (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extract was washed with $NH_4Cl_{(aq)}$ solution (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude alcohol **S6** as an amorphous pale yellow foam (271 mg). This material was used in the subsequent hydrolysis step without purification.

To a 25 mL round-bottomed flask equipped with a magnetic stir bar, under a N_2 atmosphere, was added crude alcohol **S6** (271 mg) and $CHCl_3$ (7 mL). The solution was cooled to 0 °C in an ice/water bath and a 1:1 CF_3CO_2H/H_2O solution (2.2 mL, precooled in an ice/water bath) was then added dropwise. After being stirred for 13 h, during which time the ice bath was allowed to expire, the reaction mixture was diluted with CH_2Cl_2 (7 mL), and washed with a solution of 10% $NaOH_{(aq)}$ (3 x 5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, yielding *α-ketol **19*** (220 mg, 99% over two steps) as a yellow oil. R_f = 0.14 (1:1 hexanes/EtOAc); The product obtained was pure by ^1H and ^{13}C NMR analyses; ratio of rotamers 5:4 ($CDCl_3$, 25 °C); ^1H NMR (500 MHz, $CDCl_3$): major rotamer: δ 6.66 (t, *J* = 7.0 Hz, 1H), 5.65 (d, *J* = 7.6 Hz, 1H), 4.24 (s, 1H), 3.93 (s, 1H), 3.73 (s, 3H), 3.51 (d, *J* = 13.5 Hz, 1H), 3.36 (dd, *J* = 13.6, 6.3 Hz, 2H), 3.26 (s, 3H), 2.97 (s, 1H), 2.62 (d, *J* = 2.0 Hz, 1H), 2.44 (d, *J* = 5.4 Hz, 1H), 2.16 – 1.59 (m, 11H); minor rotamer: δ 6.63 (t, *J* = 7.0 Hz, 1H), 5.75 (d, *J* = 7.6 Hz, 1H), 4.44 (s, 1H), 3.71 (s, 3H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.23 (s, 3H), 2.59 (d, *J* = 2.2 Hz, 1H), 2.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) both rotamers: δ 207.3, 207.1, 156.3, 156.2, 139.1, 138.7, 126.2, 126.0, 78.2, 78.0, 71.5, 71.4, 59.9, 59.8, 57.2, 57.1, 55.67, 55.62, 53.0, 52.7, 46.9, 46.83, 46.80, 44.15, 44.07, 43.9, 43.5, 42.8, 42.3, 40.1, 34.2, 32.6, 32.4, 30.3, 30.2, 27.7, 27.6, 27.0, 24.6, 24.5, 22.4, 14.2; IR (thin film) ν_{max} 3443, 2940, 2360, 2340, 1727, 1693, 1450, 1093, 730 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{21}H_{28}NO_5]^+$: *m/z* 374.1962, found 374.1962.



19 **S7**

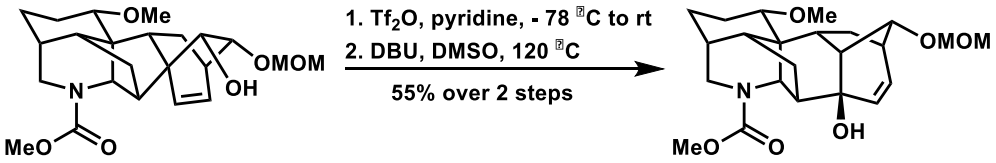
MOM-ether **S7**. To a 10 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added keto alcohol **19** (0.048 g, 0.13 mmol) and CH_2Cl_2 (2 mL). The solution was cooled to 4 °C and DIPEA (0.25 mL, 1.3 mmol) was added, followed by MOMCl (0.050 mL, 0.64 mmol). The ice bath was allowed to slowly expire over 16 h, during which time the solution slowly turned orange in color. The reaction mixture was then quenched by the addition of H_2O. The aqueous layer was extracted with CH_2Cl_2 (5 × 1 mL) and the organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, yielding an orange oil. Purification by Yamazen® automated chromatography (medium column, small inject) provided MOM-ether **S7** in a clear, colorless, oil (49 mg, 92%). R_f = 0.35 (1:1 hexanes/EtOAc), purple by anisaldehyde stain; ratio of rotamers 5:4 ($CDCl_3$, 25 °C) ^{1}H NMR (600 MHz, $CDCl_3$): major rotamer δ 6.65 (t, *J* = 7.9 Hz, 1H), 5.65 (d, *J* = 7.7 Hz, 1H), 4.85 (dd, *J* = 6.7, 1.6 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.22 (s, 1H), 3.92 (s, 1H), 3.71 (s, 3H), 3.49 (d, *J* = 13.6 Hz, 1H), 3.40 (s, 3H), 3.37 – 3.30 (m, 2H), 3.23 (s, 3H), 2.91 (s, 1H), 2.40 (d, *J* = 5.4 Hz, 1H), 1.90 (dd, *J* = 12.1, 10.0 Hz, 1H), 1.87 – 1.70 (m, 5H), 1.68 (t, *J* = 5.6 Hz, 1H), 1.60 (ddd, *J* = 22.0, 14.2, 5.3 Hz, 1H), 1.46 – 1.42 (m, 2H), 1.24 (t, *J* = 4.3 Hz, 1H); minor rotamer: δ 6.62 (t, *J* = 6.6 Hz, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 4.41 (s, 1H), 3.69 (s, 3H), 3.21 (s, 3H), 2.45 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): both rotamers δ 204.3, 104.1, 156.3, 156.2, 138.4, 138.0, 126.3, 126.1, 96.8, 78.3, 78.1, 74.6, 74.5, 60.5, 60.1, 59.9, 57.4, 57.3, 55.7, 55.65, 55.6, 53.0, 52.7, 46.9, 46.85, 46.8, 44.6, 44.5, 44.0, 43.6, 43.1, 42.6, 39.2, 32.7, 32.5, 30.4, 30.3, 27.4, 27.3, 26.6, 24.6, 24.5, 21.2, 14.3 ; IR (thin film) ν_{max} 2943, 1731, 1694, 1448, 1094, 728 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{23}H_{31}NO_6]^+$: *m/z* 418.2224, found 418.2223.



S7 **20**

[2.2.2] bicyclic alcohol **20**. To a 4 mL vial equipped with a magnetic stir bar in a 4 °C bath, was added a solution of keto MOM ether **S7** (49 mg, 0.12 mmol) in MeOH (0.5 mL). $NaBH_4$ (0.015 g, 0.40 mmol) was then added, leading to the evolution of gas and the clear solution turning a turbid white. After being stirred for 2 h at 4 °C, the reaction mixture was quenched by the sequential addition of a sat. NH_4Cl solution (1 mL) and sat. $NaCl_{(aq)}$ solution (0.5 mL). The aqueous layer was extracted with EtOAc (5 × 1 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure, yielding alcohol MOM ether **20** (48 mg, 95%) as a white gum. Ratio of rotamers 2:1 ($CDCl_3$, 25 °C); ^{1}H NMR (600 MHz, $CDCl_3$): major rotamer: δ 6.49 (t, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 8.2 Hz, 1H), 4.63 (s, 2H), 4.17 (s, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.37 (s, 3H), 3.26 – 3.18 (m, 1H), 3.19 (s,

3H), 2.62 (s, 1H), 2.34 (d, *J* = 5.2 Hz, 1H), 1.97 (d, *J* = 9.8 Hz, 1H), 1.91 – 1.69 (m, 3H). 1.67 – 1.55 (m, 2H), 1.56 – 1.34 (m, 3H), 1.32 – 1.17 (m, 2H), 1.00 (t, *J* = 9.6 Hz, 1H), 0.86 (t, *J* = 6.6 Hz, 1H); minor rotamer: δ 6.46 (t, *J* = 6.6 Hz, 1H), 5.88 (d, *J* = 8.1 Hz, 1H), 4.37 (s, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.39 (d, *J* = 3.9 Hz, 1H), 0.97 (t, *J* = 9.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): both rotamers δ 156.6, 156.3, 134.3, 134.1, 132.0, 96.2, 78.4, 78.2, 76.5, 69.8, 60.8, 60.5, 55.9, 55.8, 55.6, 55.5, 52.8, 52.5, 49.4, 49.3, 46.9, 46.2, 46.1, 45.2, 45.1, 44.6, 44.3, 43.8, 38.1, 32.9, 32.7, 30.5, 30.4, 28.8. 28.7, 25.1, 24.6, 24.5, 22.5, 21.2, 14.3, 14.2; IR (thin film) ν_{max} 3233, 2942, 1693, 1448, 1095, 730 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{23}H_{34}NO_6]^+$: *m/z* 420.2381, found 420.2379.

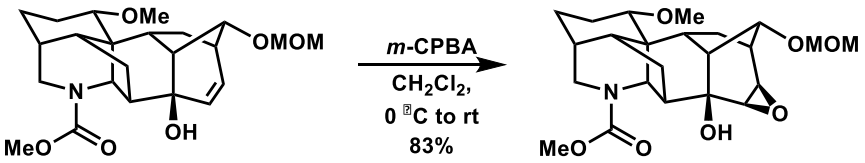


20 **21**

[3.2.1] bicyclic alcohol **21**. To a 4 mL vial equipped with a magnetic stir bar under a N_2 atmosphere was added alcohol **20** (50 mg, 0.12 mmol) as a solution in CH_2Cl_2 (1 mL). The resulting solution was cooled to –78 °C, and then pyridine (0.50 mL, 6.2 mmol) and triflic anhydride (0.20 mL, 1.2 mmol) were added sequentially via syringe. The reaction mixture was stirred for 16 h, during which time the bath was allowed to expire, and then the reaction mixture was quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 0.5 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure, yielding the crude triflate as a red oil.

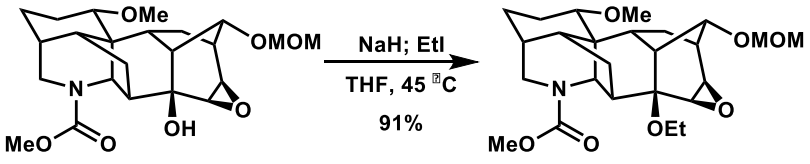
To a solution of the crude triflate in DMSO (1 mL), in a 4 mL vial equipped with a magnetic stir bar under a N_2 atmosphere, was added DBU (60 μL, 0.40 mmol). The solution turned from an initial red color to a darker purple once DBU was added. The vial was sealed and heated at 120 °C for 1 h. The reaction mixture was then quenched with H_2O (0.5 mL), and the aqueous layer was extracted with Et_2O (5 × 0.5 mL). The organic layers were combined, washed sequentially with H_2O (5 × 0.5 mL) and sat. $NaCl_{(aq)}$ solution (2 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure, yielding a black oil. Gradient flash chromatography (eluting with 1:1 to 1:4 hexanes/EtOAc) gave [3.2.1] bicyclic alcohol **21** (28 mg, 55% over two steps) as an amorphous white foam. R_f = 0.15 (1:1 hexanes/EtOAc), purple by *p*-anisaldehyde stain; ratio of rotamers 1:1 ($CDCl_3$, 25 °C); ^{1}H NMR (600 MHz, $CDCl_3$) both rotamers: δ 5.95 (t, *J* = 9.0, 1H), 5.93 (t, *J* = 7.8 Hz, 1H), 5.75 (d, *J* = 9.5 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 4.59 (s, 2H), 4.39 (s, 1H), 4.20 (s, 1H), 3.90 (t, *J* = 4.8 Hz, 1H), 3.68 (s, 3H), 3.56 (d, *J* = 13.6 Hz, 1H), 3.45 (d, *J* = 13.7 Hz, 1H), 3.35 (s, 3H), 3.33 – 3.24 (m, 1H), 3.19 (s, 3H), 3.15 (d, *J* = 8.3 Hz, 1H), 3.11 (t, *J* = 8.4 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.48 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.41 (dd, *J* = 14.1, 5.3 Hz, 1H), 2.29 (t, *J* = 5.6 Hz, 1H), 2.24 (td, *J* = 17.1, 12.9 Hz, 1H), 2.05 – 1.90 (m. 2H), 1.88 – 1.74 (m, 3H), 1.51 (ddd, *J* = 23.9, 14.7, 8.0 Hz, 2H), 1.42 – 1.39 (m, 2H), 1.34 – 1.17 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) both rotamers: δ 156.2, 155.8, 131.4, 131.4, 130.0, 129.9, 95.9, 95.8, 84.1, 84.0, 79.7, 79.6, 74.1, 74.1, 57.2, 57.1, 56.4, 56.2, 55.9, 52.8, 52.6, 49.3, 49.1, 47.4, 47.4, 45.5, 45.4, 45.3, 45.2, 44.1, 44.0, 43.8, 43.6, 36.4, 35.2, 35.0, 32.6, 29.7, 29.5, 27.9, 27.9, 25.3, 25.1; IR (thin film) ν_{max}

3233, 2942, 1693, 1448, 1095, 730 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{23}H_{34}NO_6]^+$: *m/z* 420.2381, found 420.2379.



21 25

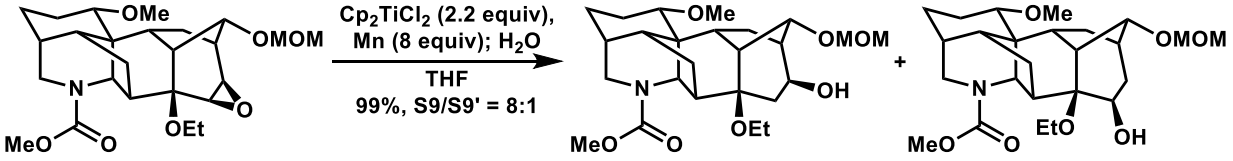
[3.2.1] epoxide **25***.* To a 4 mL vial, in a 4 °C bath, equipped with a magnetic stir bar under a N_2 atmosphere, was added allylic alcohol **21** (20 mg, 0.050 mmol) and CH_2Cl_2 (0.5 mL). *m*-CPBA (45 mg, 0.26 mmol) was then added in one portion. After being stirred for 16 h, during which time the bath was allowed to expire, the reaction mixture was quenched by the sequential addition of sat. $Na_2S_2O_{3(aq)}$ solution (0.5 mL) along with 10% NaOH solution (0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 0.5 mL). The organic layers were combined, washed with 10% NaOH (5 × 0.5 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*, yielding a white foam. Purification by gradient flash chromatography (1:1 to 1:2 hexanes/EtOAc) furnished [3.2.1] epoxide **25** (19 mg, 83%) as a white solid with m.p. 171.0 – 172.5 °C. Ratio of rotamers 1:1 ($CDCl_3$, 25 °C); ^{1}H NMR (600 MHz, $CDCl_3$) both rotamers: δ 4.74 – 4.68 (m, 3H), 4.61 (t, *J* = 6.7 Hz, 2H), 4.53 (s, 1H), 3.77 (q, *J* = 4.8, 2H), 3.702 (s, 3H), 3.700 (s, 3H), 3.54 (d, *J* = 13.6 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 1H), 3.40 (s, 6H), 3.39 – 3.25 (m, 6H), 3.25 – 3.19 (m, 6H), 3.18 – 3.10 (m, 3H), 2.58 (dq, *J* = 8.4, 4.4 Hz, 2H), 2.41 (ddd, *J* = 29.0, 14.5, 5.9 Hz, 2H), 2.22 (m, 2H), 2.18 – 2.10 (m, 4H), 2.08 – 1.97 (m, 3H), 1.93 – 1.76 (m, 8H), 1.76 – 1.65 (m, 2H), 1.54 (ddd, *J* = 19.5, 14.7, 7.8 Hz, 2H), 1.48 – 1.33 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) both rotamers: δ 156.07, 156.04, 96.13, 96.10, 83.7, 78.8, 78.7, 73.24, 73.15, 56.84, 56.79, 56.3, 56.2, 55.8, 55.49, 55.45, 55.33, 55.29, 52.9, 52.7, 50.7, 50.4, 47.6, 47.5, 45.6, 45.5, 44.7, 44.6, 44.0, 43.8, 43.61, 43.59, 35.0, 34.9, 33.07, 33.02, 29.6, 29.4, 28.81, 28.78, 25.71, 25.66, 25.0; IR (ATR) ν_{max} 3530, 2930, 1694, 1447, 1115, 1091, 1048 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{23}H_{33}NO_7Na]^+$: *m/z* 458.2141, found 458.2149.



25 22

Tertiary ethoxy epoxide **22**. To a 4 mL vial, equipped with a magnetic stir bar under a N2 atmosphere, was added hydroxy epoxide **25** (0.017 g, 0.038 mmol) as a solution in THF (0.5 mL). The solution was cooled to 4 °C and NaH (60% in mineral oil, washed 5× with hexanes, 0.014 g, 0.57 mmol) was then added to the solution, generating a cloudy white mixture. After being stirred for 30 min at 4 °C, EtI (45 µL, 0.57 mmol) was added by microsyringe. After the vial was sealed and heated to 40 °C for 16 h, the reaction mixture was quenched by the addition of sat.

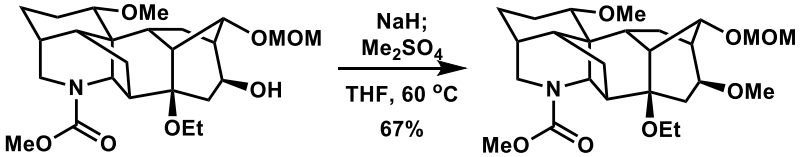
$NH_4Cl_{(aq)}$ (1 mL). The aqueous layer was extracted with EtOAc (5 × 0.5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in *vacuo*, yielding ethoxy epoxide **22** (0.016 g, 91%) as a white foam. R_f = 0.11 (1:1 hexanes/EtOAc), green by p-anisaldehyde stain; ratio of rotamers 1:1 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 4.77 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.63 – 4.56 (m, 2H), 4.43 (s, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.69 – 3.63 (m, 3H), 3.58 – 3.43 (m, 2H), 3.40 (s, 3H), 3.38 – 3.29 (m, 2H), 3.27 (td, *J* = 3.9, 1.2 Hz, 1H), 3.22 (s, 3H), 3.15 – 3.06 (m, 2H), 2.54 (dq, *J* = 8.6, 4.4 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.18 (ddd, *J* = 14.5, 11.3, 7.4 Hz, 1H), 2.11 (dq, *J* = 7.3, 4.8, 3.8 Hz, 1H), 1.90 – 1.62 (m, 4H), 1.49 – 1.34 (m, 3H), 1.13 (td, *J* = 6.9, 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) both rotamers: δ 156.1, 96.0, 95.9, 84.0, 83.9, 57.4, 56.3, 56.2, 55.7, 55.6, 55.5, 55.3, 52.9, 52.6, 51.8, 51.6, 47.7, 46.8, 46.4, 46.2, 46.1, 44.42, 44.36, 43.7, 40.5, 40.2, 35.2, 35.1, 34.7, 34.6, 29.6, 29.5, 28.4, 25.3, 25.1, 24.8, 22.5, 16.1, 16.0, 14.2, 7.9; IR (ATR) ν_{max} 2928, 1694, 1445, 1092, 916 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{25}H_{37}NO_7Na]^+$: *m/z* 486.2462, found 486.2456.



22 **S8** **S8'**

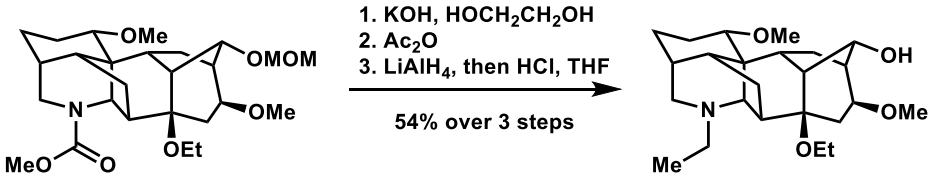
Secondary alcohol **S9**. An oven-dried 4 mL vial equipped with a magnetic stir bar was charged with Cp_2TiCl_2 (18.6 mg, 0.0747 mmol) and manganese powder (14.2 mg, 0.258 mmol). The vial was brought into a nitrogen-filled glove-box and THF (0.5 mL; degassed via 3 cycles of 'freeze-pump-thaw') was added. The resulting mixture was stirred at ambient temperature (30 °C) for 40 min, during which time the solution changed color from red to dark green. Tertiary ethoxy epoxide **22** (16 mg, 0.034 mmol) and H_2O (23 µL, 1.3 mmol, sparged with N_2 for 45 min.) were then added to the reaction vial together as a solution in degassed THF (0.5 mL). The reaction mixture was stirred for 11 h at ambient temperature (30 °C) in the glovebox, then quenched by exposure to air and adding sat. $NaH_2PO_{4(aq)}$ (1 mL). The reaction mixture changed color from blue to yellow. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 1 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, to give a yellow oil. Purification by gradient flash chromatography (eluting with 1:2 to 0:100 hexanes/EtOAc) yielded the product as an 8:1 mixture of regioisomers in favor of secondary alcohol **S8** (16 mg, 99%) as a colorless film. Some pure fractions can be obtained through chromatography, and these were used for the purpose of characterization. R_f = 0.23 (1:3 hexanes/EtOAc), purple by *p*-anisaldehyde stain; ratio of rotamers 1:1 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 4.93 (dd, *J* = 8.6, 6.8 Hz, 1H), 4.56 (dd, *J* = 6.8, 1.9 Hz, 1H), 4.49 (s, 1H), 4.26 (s, 1H), 4.09 (t, *J* = 4.9 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.55 – 3.40 (m, 1H), 3.39 (s, 3H), 3.37 – 3.27 (m, 2H), 3.22 (s, 3H), 3.11 – 3.06 (m, 1H), 2.46 (dd, *J* = 16.7, 8.7 Hz, 1H), 2.38 – 2.21 (m, 2H), 2.21 – 2.02 (m, 3H), 1.94 – 1.70 (m, 6H), 1.50 – 1.22 (m, 3H), 1.05 (td, J = 6.9, 5.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) both rotamers: δ 156.2, 95.1, 95.0, 84.4, 84.4, 77.6, 76.4, 72.7, 56.5, 56.3, 55.7, 55.7, 52.9, 52.7, 49.5, 49.1, 47.8, 47.7, 46.1, 46.0, 44.2, 44.0, 43.9, 41.8, 41.4, 41.3, 36.7, 35.9, 35.0, 34.9, 29.6,

29.5, 27.9, 27.8, 27.3, 27.0, 25.0, 24.9, 22.5, 16.2, 14.2; IR (ATR) ν_{max} 2924, 2820, 1693, 1445, 1113, 1091 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{25}H_{39}NO_7Na]^+$: *m/z* 488.2619, found 488.2617.



S8 **23**

Secondary methyl ether **23**. A 4 mL vial equipped with a magnetic stir bar under a N_2 atmosphere was charged with secondary alcohol **S9** (16 mg, 0.034 mmol, **S8**/**S8'** = 8:1) in THF (0.78 mL). The resulting solution was cooled to 0 °C, and NaH (60% in mineral oil, washed 5× hexanes, 10 mg, 0.41 mmol) was added, resulting in a cloudy white solution. After being stirred for 30 min at 0 °C, Me_2SO_4 (24 µL, 0.25 mmol) was added via microsyringe. The vial was sealed and heated at 60 °C for 2 h. The resulting white suspension was cooled to r.t. and quenched by the addition of sat. aqueous $NH_4Cl_{(aq)}$ (0.5 mL). The biphasic mixture was separated and the aqueous layer was extracted with EtOAc (3 × 0.5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, to give the crude product as a yellow oil. Gradient flash chromatography (eluting with 97:3 to 4:1 CH_2Cl_2/acetone) furnished secondary methyl ether **23** (11 mg, 67%, 14:1 isomeric mixture) as a colorless film. R_f = 0.45 (9:1 CH_2Cl_2/acetone); ratio of rotamers 1:1 ($CDCl_3$, 25 °C); 1H NMR (500 MHz, $CDCl_3$) both rotamers: δ 4.91 (d, *J* = 5.5 Hz, 2H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.27 (s, 1H), 4.09 (s, 1H), 3.95 (q, *J* = 4.3 Hz, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.57 (d, *J* = 13.6 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.41 – 3.35 (m, 13H), 3.35 – 3.25 (m, 7H), 3.24 – 3.19 (m, 6H), 3.14 – 3.05 (m, 2H), 2.41 – 2.28 (m, 3H), 2.26 – 2.15 (m, 9H), 2.15 – 2.06 (m, 2H), 2.06 – 1.97 (m, 2H), 1.88 – 1.71 (m, 10H), 1.47 – 1.28 (m, 6H), 1.05 (t, *J* = 6.9 Hz, 3H), 1.04 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) both rotamers: δ 156.05, 155.99, 95.00, 94.96, 83.9, 83.8, 83.6, 77.2, 76.9, 56.7, 56.6, 56.4, 56.2, 55.8, 55.8, 55.76 , 55.73 , 55.53, 55.51, 52.9, 52.6, 49.2, 49.0, 48.2, 48.1, 46.1, 45.9, 43.84, 43.80, 43.7, 43.5, 41.8, 41.6, 40.2, 40.0, 36.0, 35.9, 35.3, 35.2, 29.4, 29.3, 29.1, 29.0, 28.7, 25.7, 25.5, 16.21, 16.17; IR (ATR): 2924, 2818, 1696, 1446, 1366, 1339, 1298, 1240, 1190, 1149, 1092, 1073, 1047 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{26}H_{41}NO_7Na]^+$: *m/z* 502.2775, found 502.2763.



23 **2**

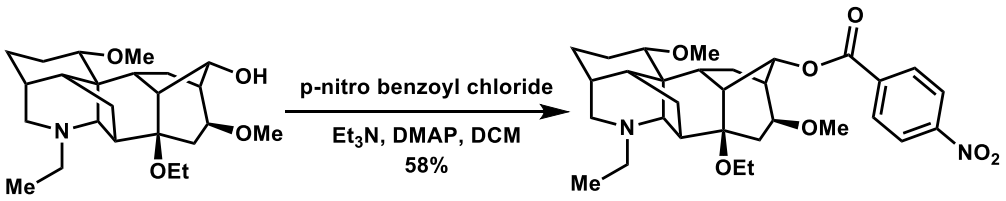
Weisaconitine D (**2**). To a 4 mL vial equipped with a magnetic stir bar, containing secondary methyl ether **23** (8.7 mg, 0.018 mmol), was added ethylene glycol (0.4 mL) and 4 M KOH (0.4 mL). The vial was sealed heated at 100 °C for 96–120 h. H_2O (1 mL) was added and the

aqueous layer was extracted with EtOAc (5 × 0.5 mL). The organic layers were combined, washed with H_2O (5 × 0.3 mL), dried over $MgSO_4$, and concentrated under reduced pressure, yielding the crude secondary amine as a white oil.

In a 4 mL vial the crude secondary amine was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C in an ice/water bath. Pyridine (40 µL, 0.5 mmol) and Ac_2O (16 µL, 0.17 mmol) were subsequently added and the reaction mixture was stirred for 16 h, during which time the ice bath was allowed to expire. The reaction mixture was quenched by addition of H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 0.5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure, yielding the crude acetamide as a white oil.

A 4 mL vial containing a solution of the crude acetamide in Et_2O (0.8 mL), was cooled to 0 °C in an ice/water bath. $LiAlH_4$ (7.0 mg, 0.18 mmol) was then added in one portion. The vial was sealed and heated at 40 °C for 2 h. The reaction mixture was quenched by slow addition of a solution of 10% $NaOH_{(aq)}$ (1 mL). The aqueous layer was extracted with EtOAc (10 × 0.5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to yield the crude tertiary amine as a yellow-tinted oil.

The crude tertiary amine was dissolved in THF (0.3 mL) in a 4 mL vial. 2 N HCl (0.3 mL) was subsequently added and the reaction mixture was stirred at r.t. for 16 h, after which the reaction mixture was quenched by the addition of a solution of 10% $NaOH_{(aq)}$ (1 mL). The aqueous layer was extracted with EtOAc (10 × 0.5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a colorless film. Purification by preparative TLC (eluting with 87.5:10:2.5 petroleum ether/acetone/Et_3N) gave weisaconitine D **2** as a colorless film (4 mg, 54% over three steps). R_f = 0.29 (87.5:10:2.5 petroleum ether/acetone/Et_3N); ^{1}H NMR (500 MHz, C_6D_6) δ 4.16 (q, *J* = 5.4 Hz, 1H), 3.61 (d, *J* = 6.6 Hz, 1H), 3.31 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.20 (s, 3H), 3.16 (q, *J* = 6.9 Hz, 2H), 3.08 (s, 3H), 3.00 (s, 1H), 2.81 (dd, *J* = 10.5, 6.7 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.42 – 2.21 (m, 7H), 2.21 – 2.08 (m, 3 H), 1.94 – 1.85 (m, 1H), 1.66 (ddd, *J* = 15.0, 11.4, 7.8 Hz, 2H), 1.46 – 1.36 (m, 3H), 1.32 – 1.23 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 1.09 – 1.03 (overlapping m, 1H), 0.99 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 85.7, 83.2, 78.8, 75.7, 62.7, 55.95, 55.93, 50.7, 49.6, 49.0, 46.4, 45.9, 45.7, 41.0, 39.7, 37.1, 36.1, 30.2, 29.0, 26.9, 23.2, 16.3, 13.8 (one carbon signal is likely overlapping with another in this solvent; all 24 carbon signals are observed in $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.4, 82.9, 78.6, 75.4, 63.2, 56.7, 56.5, 56.1, 50.4, 49.8, 49.0, 46.1, 45.8, 45.6, 41.0, 39.4, 36.9, 36.0, 30.1, 29.3, 28.6, 26.7, 16.3, 13.7. IR (ATR): 3531 (weak, broad), 2922, 2854, 2814, 1457, 1096, 1068 cm^{-1}, HRMS (ESI) calc'd for $[^{12}C_{24}H_{40}NO_4]^+$: *m/z* 406.2952, found 406.2946.

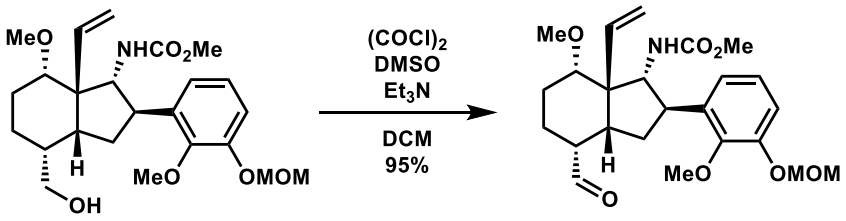


2 **26**

p-nitrobenzoyl weisaconitine D **26**. A 4 mL vial equipped with a magnetic stir bar under a N_2 atmosphere, containing weisaconitine D (**2**) (10 mg, 0.032 mmol) was added CH_2Cl_2 (0.8 mL)

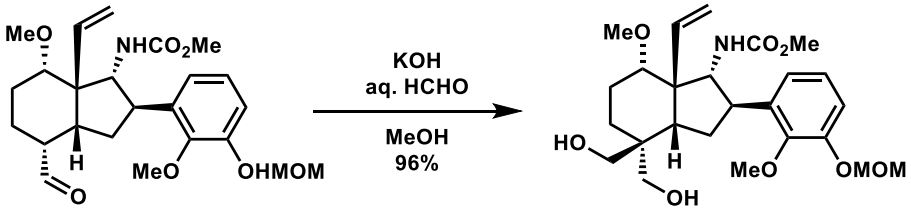
which was then cooled to 4 °C. To the solution was added NEt_3 (35 µL, 0.25 mmol), DMAP (2 crystals), and *p*-nitro benzoyl chloride (0.014 g, 0.075 mmol). After being stirred for 16 h, during which time the initially yellow colored solution had turned a deep red color, LC/MS analysis indicated incomplete conversion so an additional amount of NEt_3 (52 µL, 0.37 mmol) and *p*-nitrobenzoyl chloride (0.028 g, 0.15 mmol) was added. After being stirred for an additional 24 h, LC/MS analysis indicated remaining starting material so an additional amount of *p*-nitro benzoyl chloride (0.007 g, 0.04 mmol) was added. After another 24 h of being stirred, the reaction mixture was quenched by the addition of H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 0.5 mL). The organics were combined, dried with $MgSO_4$, and concentrated in *vacuo* yielding a brown solid. Column chromatography (eluting with 87.5:10:2.5 petroleum ether/acetone/Et_3N) yielded 13 mg of material, which upon recrystallization by slow vapor diffusion of hexanes into a solution of **26** in EtOAc (approx. 0.3 mL), provided yellow crystals (8 mg, 58%) with m.p. 161 – 165 °C. R_f = 0.27 (9:1 CH_2Cl_2/MeOH), blue by *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 5.07 (t, *J* = 5.0 Hz, 1H), 3.28 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.16 (s, 3H), 3.15 – 3.12 (m, 1H), 3.09 (s, 3H), 3.06 (dd, *J* = 8.5, 6.9 Hz, 1H), 2.88 (s, 1H), 2.82 (dd, *J* = 10.5, 6.7 Hz, 1H), 2.66 (dd, *J* = 7.1, 4.9 Hz, 1H), 2.53 (dd, *J* = 7.8, 5.0 Hz, 1H), 2.49 – 2.08 (m, 9H), 1.92 (dt, *J* = 11.9, 5.6 Hz, 1H), 1.66 (ddd, *J* = 14.7, 7.6, 4.8 Hz, 2H), 1.45 (dt, *J* = 12.2, 6.3 Hz, 1H), 1.41 – 1.23 (m, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.07 – 1.00 (m, 1H), 0.67 (t, *J* = 6.9 Hz, 3H), 0.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 150.5, 136.7, 130.9, 123.5, 85.7, 83.4, 78.0, 77.2, 62.1, 56.2, 56.0, 55.7, 50.7, 49.6, 49.2, 45.3, 45.2, 43.7, 41.3, 34.5, 37.2, 37.2, 30.2, 29.1, 27.1, 16.0, 13.8; IR (thin film) ν_{max} 2968, 2923, 1725, 1527, 1278, 1094, 721 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{31}H_{43}N_2O_7]^+$: *m/z* 555.3065, found 555.3055.

3.3. Synthesis of liljestrandinine.



15 **S9**

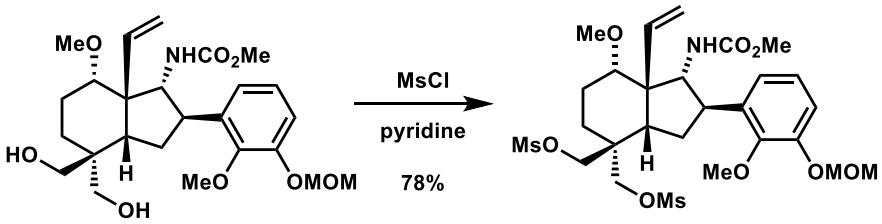
*Aldehyde **S9**. To* a 50 mL round-bottomed flask equipped with a magnetic stir bar was added oxalyl chloride (0.28 mL, 3.2 mmol) and CH_2Cl_2 (5 mL), and the resulting solution was cooled to –78 °C. Primary alcohol **15** (0.50 g, 1.1 mmol) was then added as a solution in CH_2Cl_2 (6 mL) containing DMSO (0.48 mL, 6.8 mmol). After the reaction mixture had been stirred for 30 min at –78 °C, NEt_3 (1.87 mL, 13.4 mmol) was added dropwise, resulting in a yellow slurry. The reaction mixture was then warmed to r.t. and stirred for 1 h. After diluting with H_2O (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, yielding a yellow oil. Purification using an automated Yamazen® chromatography system (L universal column, M inject column, eluting with 87:13 to 66:34 hexanes/EtOAc) provided **S9** (470 mg, 95%) as a white foam. R_f = 0.51 (2 : 1 hexanes/EtOAc); ratio of rotamers 4 : 1 ($CDCl_3$, 25 °C); major rotamer*:* ^{1}H NMR (500MHz) δ 9.66 (s, 1H), 6.97 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.85 (dd, *J* = 11.1, 17.8 Hz, 1H), 5.24-5.18 (m, 2H), 5.19 (s, 2H), 4.98 (d, *J* = 10.7 Hz, NH), 4.31 (dd, *J* = 10.7, 9.6 Hz, 1H), 3.86 (s, 3H), 3.83 (m, 1H), 3.55 (s, 3H), 3.50 (s, 3H), 3.48-3.49 (m, 2H), 3.37 (s, 3H). 3.00 (m, 1H), 2.61 (dt, *J* = 12.5, 4.3 Hz, 1H), 2.27 (ddd, *J* = 12.5, 12.4, 12.2, 1H), 2.10 (m, 1H), 1.78 (dddd, *J* = 12.6, 12.5, 12.2, 1,8 Hz, 1H); 1.57 (m, 1H), 1.42 (dd, *J* = 12.6, 12.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 156.8, 150.3, 147. 9, 142.0, 139.6, 124.1, 122.0, 114.8, 114.4, 95.2, 78.1, 67.5, 61.0, 56.3, 55.7, 54.2, 52.1, 48.8, 46.4, 39.8, 33.1, 22.4, 14.1 ppm; IR (ATR): ν_{max} 3448, 2952, 2826, 2703, 1708, 1582, 1502, 1474, 1256, 1209, 1152, 1005, 920 cm^{-1}; HRMS (ESI) calc'd for $[C_{24}H_{33}NO_7Na]^+$: *m/z* 470.2149, found 470.2149.



S9 **S10**

*Diol **S10**.* A 50 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere was added aldehyde **S9** (0.47 g, 1.1 mmol), MeOH (10 mL), followed by aq. formaldehyde (37%, 1.66 mL, 22 mmol) and 2.0 N KOH (4.47 mL, 8.9 mmol). The reaction mixture was stirred at r.t. for 15 h and then diluted with sat. $NaCl_{(aq)}$ solution (7 mL). The MeOH

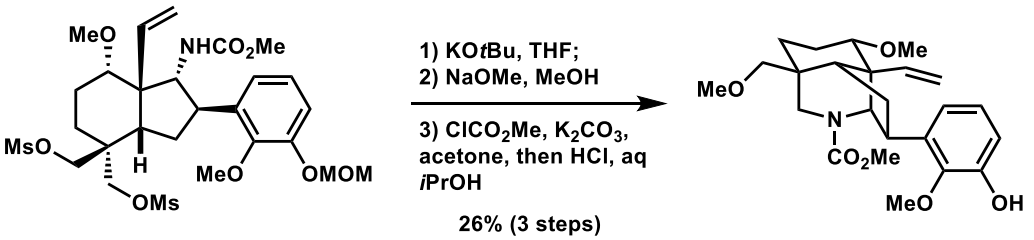
was removed by concentration under reduced pressure. The residual aqueous mixture was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic was dried over anhydrous Na_2SO_4, filtered, and concentrated to provide a colorless oil. Purification using a Yamazen® automated chromatography (L universal column, M inject column, eluting with 35:65 to 1:99 hexanes/EtOAc) afforded diol **S10** (480 mg, 96%) as a white foam. R_f = 0.36 (4:1 EtOAc/hexanes); ratio of rotamers 4:1 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz) δ major rotamer: 6.99 - 6.91 (m, 3H), 5.89 (dd, *J* = 18.0, 11.4 Hz, 1H), 5.18 (s, 2H), 5.06 (d, *J* = 11.4 Hz, 1H), 5.02 (d, *J* = 18.0 Hz, 1H), 4.90 (d, J = 10.7 Hz, 1H), 4.24 (dd, *J* = 10.7, 9.6 Hz, 1H), 3.85 (s, 3H), 3.83 (m, 1H), 7.74-3.66 (m, 2H), 3.50-3.35 (m, 3H), 3.51 (s, 3H), 3.49 (s, 3H), 3.38 (s, 3H), 3.00 (s br, OH), 2.78 (s br, OH), 2.52 (d, *J* = 12.7, 9.1 Hz, 1H), 2.39 (m, 1H), 1.90 (dq, *J* = 15.1, 3.0 Hz), 1.63 (m, 1H), 1.55 (m, 1H), 1.41 (td, *J* = 13.8, 3.0 Hz), 1.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 150.2, 147.9, 145.1, 140.4, 124.3, 121.8, 114.7, 112.9, 95.2, 71.1, 67.8, 67.3, 61.1, 56.3, 55.7, 53.2, 52.0, 45.1, 44.1, 40.5, 40.4, 34.6, 19.3, 18.9; IR (ATR): ν_{max} 3448 (br), 2950, 2896, 2826, 1710, 1632, 1583, 1505, 1474, 1265, 1040 cm^{-1}; HRMS (ESI) calc'd for $[C_{25}H_{37}NO_8Na]^+$: *m/z* 502.2411, found 502.2416.



S10 **27**

*Bis-mesylate **27**.* To a 50 mL round-bottomed flask, in a 4 °C, equipped with a magnetic stir bar was added diol **S10** (0.205 g, 0.427 mmol), pyridine (5 mL), and then MsCl (115 µL, 1.48 mmol). The reaction mixture was warmed to r.t. over 20 min and then stirred for 2 h resulting in a bright orange cloudy mixture. Upon complete conversion to the product (as judged by LC/MS analysis), the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with sat. $NaCl_{(aq)}$ solution (15 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent *in vacuo* yielded a yellowish solid residue which was purified using an automated Yamazen® chromatography system on silica gel (L universal column, M inject column, eluting with 45:55 to 20:80 hexanes/EtOAc) to give **27** (210 mg, 78%) as a white solid with m.p. 144 – 145 °C. R_f = 0.50 (4 : 1 EtOAc/hexanes); ratio of rotamers 3 : 1 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) major rotamer: δ 7.02 – 6.91 (m, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 5.80 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.21 (m, 1H), 5.20 (s, 2H), 5.09 (d, *J* = 17.9 Hz, 1H), 4.82 (d, *J* = 10.5 Hz, 1H), 4.47 (d, *J* = 9.9 Hz, 1H), 4.30 (t, *J* = 10.5 Hz, 1H), 4.20 (d, *J* = 9.9 Hz, 1H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.90 (s, 3H), 3.73 (s, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 3.44 – 3.35 (m, 2H), 3.05 (s, 3H), 2.99 (s, 3H), 2.45 – 2.33 (m, 2H), 2.05 – 1.99 (m, 1H), 1.68 (m, 1H), 1.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) major rotamer*:* δ 156.7, 150.4, 148.0, 144.1, 139.1, 124.1, 122.0, 115.2, 114.5, 95.3, 76.1, 71.4, 68.4, 67.5, 61.0, 56.4, 55.9, 53.0, 52.1, 45.9, 44.4, 40.2, 37.4, 37.3, 33.8, 18.5, 17.9; IR (neat): ν_{max} 3447, 2952, 2937, 2827, 1727, 1633, 1583,

1505, 1476, 1355, 1170, 961 cm^{-1}; HRMS (ESI) calc'd for $[C_{27}H_{41}NO_{12}NaS_2]^+$: *m/z* 658.1962, found 658.1978



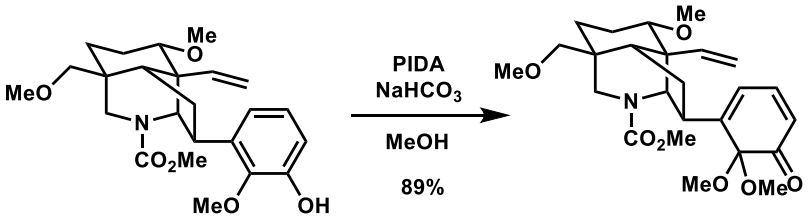
27 **28**

Phenol *28.* To a 25 mL round-bottomed flask equipped with a magnetic stir bar and reflux condenser was added *bis*-mesylate **27** (388 mg, 0.610 mmol) and THF (9 mL). The vessel was then heated to 50 °C and held at this temperature until all the *bis*-mesylate dissolved. A solution of KO^{t}Bu (1.0 M in ^{t}BuOH, 3.05 mL, 3.1 mmol) was added to the reaction mixture and the resulting yellowish solution was stirred at 50 °C for 4 h until complete consumption of the starting material (as judged by LC/MS analysis). The reaction mixture was then cooled to r.t. and quenched with sat. $NaHCO_{3(aq)}$ solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to yield the crude product (350 mg) as yellow oil. This material was used in the next step without further purification.

To a 100 mL round-bottomed flask was added the crude product from the previous step and a methanolic solution of 0.50 M NaOMe (43 mL, 22 mmol). The resulting reaction mixture was equally divided between three 20 mL microwave vials, sealed, and degassed by sparging with N_2 (30 min). The sealed vials were each heated to 120 °C in a microwave and held at this temperature for 24 h. The combined reaction mixtures were concentrated and treated with sat. $NaHCO_{3(aq)}$ solution (15 mL). The resulting mixture was extracted with EtOAc (5 x 20 mL) and organic layers were dried over anhydrous Na_2SO_4 and concentrated to yield a mixture of carbamate and secondary amine as a yellow foam (263 mg). The crude mixture was used directly in the next step.

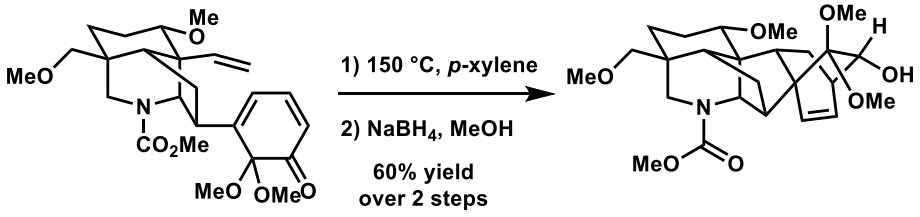
To a 50 mL round-bottomed flask equipped with a reflux condenser and magnetic stir bar was added the crude material from the previous step and dry acetone (15 mL). K_2CO_3 (3.37 g, 24.2 mmol) was then added, followed by methyl chloroformate (0.94 mL, 12 mmol). The reaction mixture was stirred and heated at reflux for 20 h. Following this time, the mixture was cooled to r.t. and diluted with H_2O (20 mL). The acetone was removed *in vacuo* and the resulting aqueous residue was extracted with EtOAc (5 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to yield a dark brown oil which was immediately dissolved in 2 N aqueous HCl/^{i}PrOH (18 mL). The resulting mixture was stirred until the reaction was judged complete by LC/MS analysis (4.5 h), then diluted with sat. $NaHCO_{3(aq)}$ solution (15 mL) and partially concentrated *in vacuo.* The residual aqueous mixture was extracted with EtOAc (5 x 20 mL) and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a crude product that was purified using an automated Yamazen® chromatography system on silica gel (L universal column, M inject column, eluting with 60:40 to 38:62 hexanes/EtOAc) to give phenol **29** (69 mg, 26% over three steps) as a white

foam. R_f = 0.31 (4 : 1 EtOAc/hexanes); ratio of rotamers 3 : 1 ($CDCl_3$, 25 °C); ^{1}H NMR (500MHz, $CDCl_3$) major rotamer: δ 6.81 – 6.75 (m, Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.61 (dd, *J* = 17.8, 10.9 Hz, 1H), 5.58 (s, OH), 4.95 (d, *J* = 17.8 Hz, 1H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.83 (s, 1H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.65 (s, 3H) 3.66-3.57 (m, 2H), 3.59 (s, 3H), 3.26 (s, 3H), 3.25 – 3.11 (m, 2H), 3.14 – 3.04 (m, 2H), 3.13 (s, 3H), 2.81 (dd, *J* = 13.5, 1.8 Hz, 1H), 2.15 – 0.02 (m, 3H), 1.96 – 1.82 (m, 1H), 1.77 (dd, *J* = 8.4, 2.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) major rotamer: δ 155.3, 149.2, 145.8, 144.7, 135.6, 123.9, 119.9, 113.8, 113.8, 113.8, 85.6, 78.8, 63.4, 59.9, 59.7, 57.2, 53.0, 52.8, 46.0, 45.2, 43.0, 36.2, 32.9, 27.2, 25.0; IR (neat): ν_{max} 3300 br, 2927, 2876, 2826, 1751, 1660, 1586, 1448, 1098 cm^{-1}; HRMS (ESI) calc'd for $[C_{24}H_{33}NO_6Na]^+$: *m/z* 454.2200, found 454.2198.



28 **S11**

*Dimethylacetal dienone **S11**.* To a 25 mL round-bottomed flask, in a 4 °C bath, was added phenol **28** (74 mg, 0.17 mmol) and MeOH (2 mL). To the resulting vigorously stirred solution was added $NaHCO_3$ (72 mg, 0.86 mmol) followed by PIDA (83 mg, 0.26 mmol). The reaction mixture turned a bright yellowish-green color within a few seconds after addition was complete. After being stirred for 1 h at 0 °C, the mixture was concentrated and dry-loaded on a silica gel column. Elution with hexanes/EtOAc (3:1 to 1:1 gradient) afforded **S11** (70 mg, 89%) as a yellow foam. R_f = 0.35 (1:1 EtOAc/hexanes); ratio of rotamers 3 : 1 ($CDCl_3$, 25 °C); ^{1}H NMR (500MHz, $CDCl_3$) major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 9.9, 6.5 Hz, 1H), 6.27 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 17.9, 10.9 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 5.21 – 5.09 (m, 2H), 5.01 (s, 1H), 3.80 – 3.75 (m, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 3.27 (s, 3H), 3.29 – 3.22 (m, 1H), 3.24 (s, 3H), 3.18 – 3.09 (m, 2H), 3.07 (s, 3H), 2.92 (t, *J* = 8.9 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.02 – 1.93 (m, 4H), 1.85 – 1.76 (m, 1H) 1.58-1.55 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) major rotamer: δ 197.2, 155.2, 152.7, 145.4, 141.0, 124.2, 123.4, 113.7, 95.1, 85.9, 78.6, 61.8, 59.7, 57.2, 53.5, 52.8, 51.2, 50.2, 45.7, 44.5, 43.7, 36.1, 33.0, 27.8, 25.0; IR (neat): ν_{max} 2925, 2875, 2829, 1751, 1673, 1642, 1575, 1447, 1256, 1098, 1070 cm^{-1}; HRMS (ESI) calc'd for $[C_{25}H_{35}NO_7Na]^+$: *m/z* 484.2306, found 484.2304.

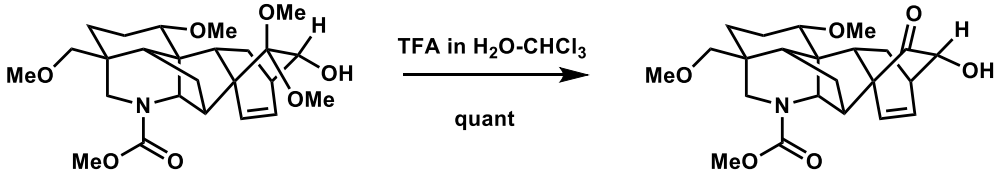


S11 **S12**

*Dimethylketal alcohol **S12**.* A 50 mL pressure tube equipped with a magnetic stir bar was charged with dienone **S11** (70 mg, 0.15 mmol), *p*-xylene (20 mL) and dibutylhydroxytoluene (40 mg, 0.18 mmol). The solution was then degassed using 3 cycles of freeze-pump-thaw. The

reaction mixture was then heated at 150 °C for 14 h. After cooling to r.t., the resulting mixture was concentrated and used immediately in the next step.

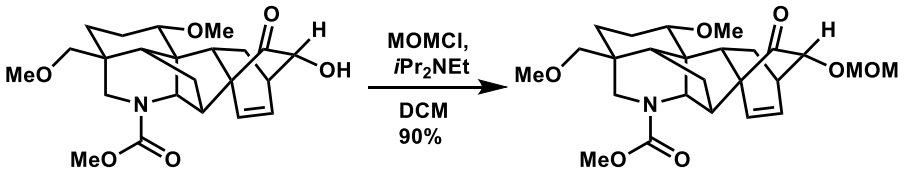
To a 25 mL round-bottomed flask equipped with a magnetic stir bar, in a 4 °C bath, was added the crude Diels–Alder adduct and MeOH (3 mL). $NaBH_4$ (60 mg, 1.6 mmol) was added and the reaction mixture was warmed to r.t. over 1 h. After this time, H_2O (4 mL) was added and the resulting mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified using an automated Yamazen® chromatography system on silica gel (M universal column, S inject column, eluting with (65:35 to 45:55 hexanes/EtOAc) to give **S12** (42 mg, 60% yield over two steps) as a white foam. R_f = 0.51 (1:2 hexanes/EtOAc); ratio of rotamers 5:4 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 6.37 (t, *J* = 7.1 Hz, 1H), 6.33 (t, *J* = 7.1 Hz, 1H), 5.85 (d, *J* = 7.1 Hz, 1H), 5.74 (d, *J* = 7.1 Hz, 1H), 4.33 (s, 1H), 4.14 (s, 1H), 3.75 – 3.71 (m, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 3.29 (s, 6H), 3.28 – 3.21 (m, 2H), 3.20 (s, 3H), 3.19 (s, 6H), 3.17 (s, 3H), 3.13 – 2.98 (m, 6H), 2.95 (dd, *J* = 13.3, 1.7 Hz, 1H), 2.90 (d, *J* = 13.5 Hz, 1H), 2.79 (dd, *J* = 13.9, 8.0 Hz, 2H), 2.54 – 2.46 (m, 2H), 2.44 (d, *J* = 5.4 Hz, 1H), 2.35 (d, *J* = 5.4 Hz, 1H), 2.14 – 2.02 (m, 4H), 1.85 – 1.68 (m, 6H), 1.62 (d, *J* = 7.8 Hz, 1H), 1.54 (d, *J* = 7.8 Hz, 1H), 1.41 – 1.21 (m, 6H); ^{13}C NMR (126 MHz,) both rotamers: δ 156.53, 156.44, 133.68, 133.16, 131.65, 131.44, 106.60, 106.52, 79.48, 78.83, 77.83, 77.47, 75.77, 75.68, 62.24, 61.96, 59.65, 59.62, 55.37, 55.24, 52.95, 52.53, 50.67, 50.62, 50.28, 50.23, 50.10, 50.04, 49.14, 48.45, 47.94, 47.73, 47.45, 47.34, 45.97, 45.95, 44.31, 44.25, 40.75, 40.73, 37.46, 37.33, 33.26, 33.13, 28.32, 28.26, 24.71, 24.66, 22.94, 22.81; IR (neat): ν_{max} 3530, 2941, 2874, 2824, 2245, 1684, 1445, 1346, 1336, 1089, 1060, 726 cm^{-1}; HRMS (ESI) calc'd for $[C_{25}H_{37}NO_7Na]^+$: *m/z* 486.2462, found 486.2455.



S12 **S13**

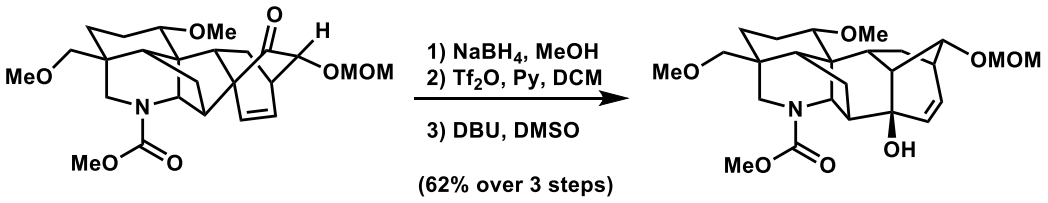
*Hydroxyketone **S13**.* To a 20 mL vial equipped with a magnetic stir bar, in a 4 °C bath, was added acetal **S12** (42 mg, 0.091 mmol) and $CHCl_3$ (2 mL). A cold (0 °C) mixture of TFA and water (1:1 by volume) was then added to the reaction mixture. The reaction was judged complete by TLC after stirring for 1 h. At this time, the mixture was diluted with sat. $NaHCO_{3(aq)}$ solution (6 mL). The aqueous layer was extracted with $CHCl_3$ (5 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give **S13** (38 mg, quant) as white foam. R_f = 0.28 (2 : 1 EtOAc/hexanes); ratio of rotamers 5:4 ($CDCl_3$, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$) both rotamers: δ 6.69 – 6.57 (m, 2H), 5.73 (d, *J* = 7.7 Hz, 1H), 4.44 (s, 1H), 7.26 (s, 1H), 5.63 (d, *J* = 7.6 Hz, 1H), 4.24 (s, 1H), 3.89 (s, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.38 (dd, *J* = 19.4, 13.4 Hz, 2H), 3.33 – 3.27 (m, 2H), 3.27 (s, 3H), 3.27 (s, 3H), 3.23 (s, 3H), 3.22 (s, 3H), 3.11 – 2.89 (m, 7H), 2.87 (d, *J* = 13.5 Hz, 1H), 2.79 (d, *J* = 14.4 Hz, 2H), 2.42 (d, *J* = 5.4 Hz, 1H), 2.36 (d, *J* = 5.4 Hz, 1H), 2.11 – 2.01 (m, 4H), 2.00 – 1.90 (m, 2H), 1.89 – 1.76 (m, 3H), 1.76 – 1.64 (m, 3H), 1.56 (dd, *J* = 19.0, 7.0 Hz, 2H), 1.49 – 1.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) both rotamers: δ 207.26, 207.12, 156.29, 156.18, 139.12, 138.74, 126.11, 125.88, 78.78, 78.17, 78.03, 77.78, 71.47,

71.37, 68.11, 60.04, 59.90, 59.65, 59.60, 57.12, 56.97, 55.65, 55.57, 53.11, 52.75, 48.08, 47.68, 47.28, 47.05, 46.65, 44.27, 44.20, 42.36, 41.86, 40.07, 36.99, 36.86, 33.30, 33.15, 27.53, 27.44, 25.74, 24.64, 24.62, 24.30, 24.25; IR (neat): ν_{max} 3434, 2947, 2876, 2624, 2247, 1725, 1684, 1447, 1348, 1191, 1094, 728 cm^{-1}; HRMS (ESI) calc'd for $[C_{23}H_{31}NO_6Na]^+$: *m/z* 440.2044, found 440.2037.



S13 **S14**

*Methylene-methoxy Keto MOM ether **S14***. To a 4 ml vial equipped with a magnetic stir bar under a N_2 atmosphere in a 4 °C bath, was added a solution of keto alcohol **S13** (11 mg, 0.027 mmol) in CH_2Cl_2 (0.5 mL). DIPEA (0.2 ml, 1 mmol) was then added, followed by MOMCl (0.060 ml, 0.79 mmol). After being stirred for 16 h, during which time the bath expired, the reaction mixture was quenched by addition of H_2O (1 mL). The aqueous layer was extracted CH_2Cl_2 (5 × 0.5 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo* to yield an orange oil. Keto MOM ether **S14** (10 mg, 90%) was of sufficient purity to be used in the next step without further purification. R_f = 0.25 (1:1 hexanes/EtOAc); ratio of rotamers 5:4 ($CDCl_3$, 25 °C); ^{1}H NMR (600 MHz, $CDCl_3$): both rotamers; δ 6.66 (t, *J* = 7.0 Hz, 1H), 6.63 (t, J = 7.0 Hz, 1H, minor rotamer), 5.77 (d, J = 7.8 Hz, 1H), 5.67 (d, J = 7.7 Hz, 1H, minor rotamer), 4.44 (s, 1H), 4.24 (s, 1H, minor rotamer), 3.90 (s, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.40 – 3.29 (m, 2H), 3.29 (s, 3H), 3.28 (s, 3H, minor rotamer), 3.24 (s, 3H), 3.22 (s, 3H, minor rotamer), 3.10 – 2.98 (m, 2H), 2.97 – 2.85 (m, 2H), 2.42 (d, J = 4.5 Hz, 1H), 2.35 (s, 1H), 2.11 – 2.01 (m, 2H), 1.93 (td, J = 11.9, 5.2 Hz), 1.87 – 1.74 (m, 2H), 1.69 (br s, 1H), 1.61 (t, J = 4.6 Hz, 1H), 1.56 – 1.50 (m, 2H), 1.49 – 1.34 (m, 3H), 1.33 – 1.20 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): both rotamers; δ 204.1, 156.3, 156.2, 138.4, 126.2, 126.0, 96.8, 78.9, 78.3, 78.1, 77.9, 74.6, 74.5, 60.2, 60.1, 59.6, 59.6, 57.2, 57.1, 55.7, 55.6, 55.5, 53.1, 52.7, 48.2, 47.8, 47.4, 47.2, 46.8, 44.8, 44.7, 42.7, 42.2, 39.2, 39.2, 37.1, 36.9, 34.3, 33.3, 33.2, 27.3, 27.2, 24.7, 23.9, 22.5, 14.2 ; IR (thin film) ν_{max} 2947, 2885, 2823, 1730, 1693, 1446, 1107, 1091 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{25}H_{35}NO_7Na]^+$: *m/z* 484.2306, found 484.2302.



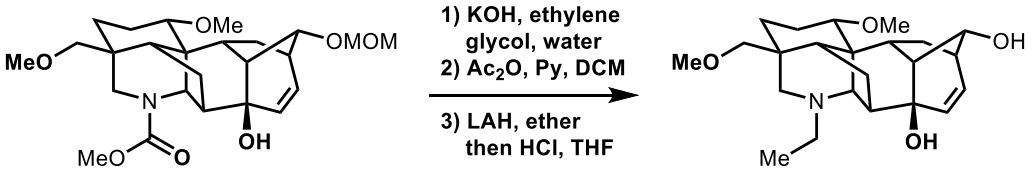
S14 **S15**

*Methylene-methoxy [3.2.1] bicyclic alcohol **S15***. To a 4 mL vial equipped with a magnetic stir bar in a 4 °C bath was added a solution of methylene-methoxy keto MOM ether **S14** (10 mg, 0.022 mmol) in MeOH (0.5 ml). $NaBH_4$ (15 mg, 0.40 mmol) was then added, leading to gas evolution and generation of a turbid white solution. After being stirred for 2 h at 4 °C, the reaction mixture was quenched by the sequential addition of sat. NH_4Cl solution (1 ml) and sat.

NaCl solution (0.5 ml). The aqueous layer was extracted with EtOAc (5 x 1 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo* to yield alcohol MOM ether (9.5 mg) as a white gum.

To a 4 mL vial equipped with a magnetic stir bar under a N_2 atmosphere in a -78 °C bath was added a solution of the resulting alcohol (9.5 mg, 0.021 mmol) in CH_2Cl_2 (1 mL). Pyridine (0.10 ml, 1.2 mmol) was then added, followed by triflic anhydride (0.040 ml, 0.24 mmol). After being stirred for 16 h, during which time the bath was allowed to expire, the reaction mixture was quenched with addition of H_2O (1 mL). The aqueous layer was extracted CH_2Cl_2 (5 × 0.5 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo*, to yield the triflate as a red/black oil.

To a 4 mL vial equipped with a magnetic stir bar, was added a solution of the crude triflate in DMSO (1 ml). DBU (0.020 ml, 0.12 mmol) was then added. The vial was sealed and heated to 120 °C and held at this temperature for 1 h. The reaction mixture was then cooled to r.t. and quenched with H_2O (0.5 ml). The aqueous layer was extracted with Et_2O (5 × 0.5 mL). The organic layers were combined, washed with H_2O (5 × 0.5 mL) then with sat. aqueous NaCl solution (0.3 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to yield a black oil. Gradient flash chromatography (eluting with 1:1 to 1:4 hexanes/EtOAc) furnished methylene-methoxy [3.2.1] bicyclic alcohol **S15** (6 mg, 62% yield over 3 steps) as a white foam. R_f = 0.11 (1 : 1 hexanes/EtOAc), purple by *p*-anisaldehyde stain; ratio of rotamers 1:1 ($CDCl_3$, 25 °C); ^{1}H NMR (600 MHz, $CDCl_3$) both rotamers: δ5.96 (t, *J* = 7.8, 1H), 5.94 (t, *J* = 7.8 Hz, 1H), 5.75 (dd, *J* = 9.3, 1.2 Hz, 1H), 5.63 (dd, *J* = 9.3, 1.8 Hz, 1H), 4.60 (q, J = 3.5 Hz, 2H), 4.41 (s, 1H), 4.21 (s, 1H), 3.91 (t, *J* = 4.2 Hz, 1H), 3.69 (s, 3H), 3.69 (s, 3H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H, minor rotamer), 3.32 (s, 3H), 3.31 (s, 3H), 3.20 (s, 3H), 3.20 (s, 3H), 3.11 (quint, *J* = 9 Hz, 3H), 3.09 (d, J = 7.8 Hz, 1H), 3.03 (d, *J* = 9 Hz, 1H), 2.86 (d, *J* = 13.4 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.48 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.31 (s, 1H), 2.09 – 2.03 (m, 3H), 1.99 – 1.94 (m, 3H), 1.90 (d, *J* = 7.7 Hz, 1H), 1.87 – 1.64 (m, 4H), 1.46 – 1.34 (m, 2H), 1.31 – 1.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ156.4, 155.9, 131.2, 130.1, 96.0, 95.9, 89.8, 79.7, 79.7, 79.4, 79.4, 78.9. 73.4, 59.7, 59.7, 57.3, 56.2, 56.0, 55.9, 52.9, 52.6, 49.2, 48.9, 47.6, 47.1, 46.7, 45.7, 45.6, 45.3, 45.2, 44.6, 38.0, 37.8, 36.4, 32.6, 32.5, 32.5, 25.6, 25.5, 23.8; IR (ATR) ν_{max} 2949, 2929, 2882, 2820, 1693, 1446, 1111, 1094, 1039 cm^{-1}; HRMS (ESI) calc'd for $[^{12}C_{25}H_{37}NO_7Na]^+$: *m/z* 48602452, found 486.2462.



S15 **3**

*Liljestrandinine **3***. To a 20 mL vial was added carbamate **S15** (13 mg, 0.028 mmol), ethylene glycol (2.5 mL), and 10% KOH (6.0 mL). After the vial was sealed and heated to 100 °C and held at this temperature until complete consumption of the starting material as judged by LCMS analysis (67 h), the contents of the vial were diluted with H_2O (5 mL). The aqueous layer was extracted with EtOAc (7 × 5 mL). The organic layers were combined, dried over anhydrous

Na_2SO_4, and concentrated in vacuo. The residue was dried with vigorous stirring at 35 °C at reduced pressure (0.3 torr) for 14 h yielding the crude secondary amine as a yellowish oil.
To a 4 mL vial equipped with a magnetic stir bar, in a 4 °C bath, was added the crude amine and CH_2Cl_2 (2 mL). Pyridine (0.12 mL, 1.4 mmol) was then added, followed by Ac_2O (0.14 mL, 1.4 mmol). After being stirred for 13 h at r.t., the reaction mixture was diluted with CH_2Cl_2 (3 mL) and quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 2 mL). The organic layers were combined, dried with anhydrous Na_2SO_4 and concentrated. The yellow oil residue was dissolved in CH_2Cl_2 (0.5 mL) and passed through a plug of silica gel (the desired product was eluted with EtOAc (15 mL)). The fractions were concentrated and used directly in the next step.

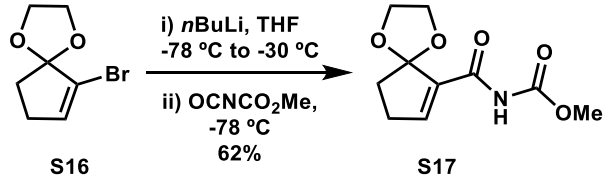
To a 10 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere, in a 4 °C ice/water bath, was added the crude acetamide and Et_2O (4 mL). $LiAlH_4$ (22 mg, 0.56 mmol) was then added portion-wise. The reaction mixture was heated to 40 °C for 1.5 h (judged complete by LCMS analysis). After this time, the reaction mixture was cooled to 0 °C and quenched by slow addition of a solution of 2 N $NaOH_{(aq)}$ (1 mL). The aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude tertiary amine as a yellow oil. The resulting oily crude material (liljestrandinine MOM ether) was dissolved in THF (2 mL) and treated r.t. with 12 N HCl (0.25 mL). The reaction mixture was stirred for 2 h (at which time LC/MS analysis indicated complete consumption of starting material) and then, quenched by the addition of sat. $NaHCO_{3(aq)}$ solution (3 mL). The aqueous layer was extracted with EtOAc (10 × 2 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated to furnish 10.4 mg of the crude natural product (~10-15% of impurities). The crude product can be further purified by column chromatography using CH_2Cl_2 and then 97:3:1 DCM/MeOH/NH_4OH as eluent to afford analytically pure liljestrandinine (**3**) (6.2 mg, 57% over four steps). R_f = 0.09 (95:5:1 DCM/MeOH/NH_4OH); ^{1}H NMR (500 MHz, C_6D_6) δ 5.71 (dd, *J* = 9.5, 6.7 Hz, 1H), 5.63 (d, *J* = 9.5 Hz, 1H), 3.79 (d, *J* = 4.7 Hz, 1H), 3.12 (s, 3H), 3.12 – 3.08 (m, 1H), 3.06 (s, 3H), 2.96 (d, *J* = 8.7 Hz, 1H), 2.87 (dd, *J* = 10.6, 6.7 Hz, 1H), 2.84 (d, *J* = 8.7 Hz, 1H), 2.64 (s, OH), 2.58 – 2.49 (m, 2H), 2.49 – 2.35 (m, 2H), 2.34 – 2.24 (m, 1H), 2.21 – 2.12 (m, 2H), 2.10 (d, *J* = 6.7, 4.7 Hz, 1H), 2.02 (dd, *J* = 14.8, 7.5 Hz, 1H), 1.99 – 1.95 (m, 2H), 1.94 – 1.89 (m, 1H), 1.82 (s, OH), 1.66 – 1.58 (m, 1H), 1.57 – 1.47 (m, 4H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, C_6D_6) δ 132.4, 129.7, 85.6, 80.0, 74.9, 74.5, 63.0, 59.1, 55.6, 53.9, 49.5, 48.6, 46.8, 46.3, 46.0, 42.7, 39.6, 38.9, 33.4, 33.2, 26.7, 24.2, 13.7; IR (neat): ν_{max} 3314 br, 2923, 2854, 1724, 1667, 1459, 1093, 730 cm^{-1}; HRMS (ESI) calc'd for $[C_{23}H_{36}NO_4]^+$: *m/z* 390.2639, found 390.2632.

Note: Due to rapid protonation and other dynamic effects, the ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ are inconsistent and often display broadened and poorly resolved resonances and extra peaks arising from the protonated material. Characterization data was therefore obtained in benzene-d_6. Data collected in chloroform was only of satisfactory resolution and used only to compare to the reported tabulated data for isolated liljestrandinine.[1]

^{1}H NMR in $CDCl_3$ comparison of the tabulated data:

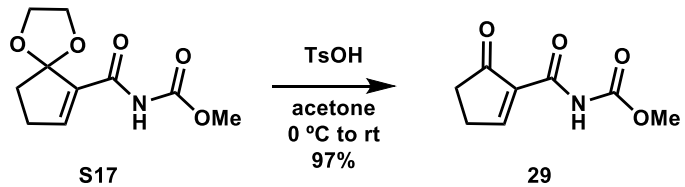
# of proton	Isolated liljestrandinine	Synthetic liljestrandinine
CH (16)	5.89 (dd *J* = 9.2, 6.8 Hz)	5.89 (dd, *J* = 9.3, 7.6 Hz)
CH (15)	5.63 (dd, *J* = 9.6, 1.6 Hz)	5.64 (d, *J* = 9.4 Hz)
CH (14)	4.05 (t, *J* = 4.4 Hz)	4.06 (d, *J* = 4.1 Hz, 1H)
OCH_3 (18)	3.30 (s)	3.31 (s)
OCH_3 (1`)	3.24 (s)	3.24 (s)
CH_2 (18)	3. 13 (ABq *J* = 8.0 Hz)	3. 14 (ABq *J* = 9.0 Hz)
CH (1)	3.09 (dd, *J* = 10.8, 6.8 Hz)	3.09 (dd, *J* = 10.0, 6.8 Hz)
CH_2 (18)	3.00 (ABq *J* = 8.0 Hz)	3. 00 (ABq *J* = 9.0 Hz)
CH (17)	2.94 (s)	2.93 (s)
OH		2.68 (s)
CH_2 (19)	2.51	2.50
CH_2 (21) and CH (13)	2.41 (m, 3H)	2.48-2.40 (m, 3H)
CH_2 (12) (ß)	2.39 (m)	2.35 (m)
CH (9)	2.27 (m)	2.28 (m)
CH_2 (2) (ß)	2.24 (m)	2.20 (m)
CH (7)	2.09 (d, *J* = 8.0 Hz)	2.09 (d, *J* = 7.9 Hz)
CH_2 (19)	1.98 (m)	1.99-1.90 (m, 4H)
CH_2 (2) (α)	1.97 (m)	
CH_2 (6) (ß)	1.92(m)	
CH (10)	1.92 (m)	
CH_2 (12) (α)	1.86 (m)	1.86 (m)
CH_2 (3) (α)	1.76 (m)	1.76 (m)
CH (5)	1.64 (d, *J* = 7.2 Hz)	1.63 (d, *J* = 7.2 Hz)
CH_2 (6) (α)	1.54 (dd, *J* = 14.8, 8.0 Hz	1.55 (dd, *J* = 14.8, 8.0 Hz)
CH_2 (3) (ß)	1.43 (td, *J* = 12.2, 2.8 Hz,)	1.42 (t, *J* = 14.1 Hz,)
CH_3 (22)	1.02 (t, *J* = 7.6 Hz)	1.01 (t, *J* = 7.1 Hz)

3.4. Enantioselective Diels-Alder cycloaddition



S16 S17

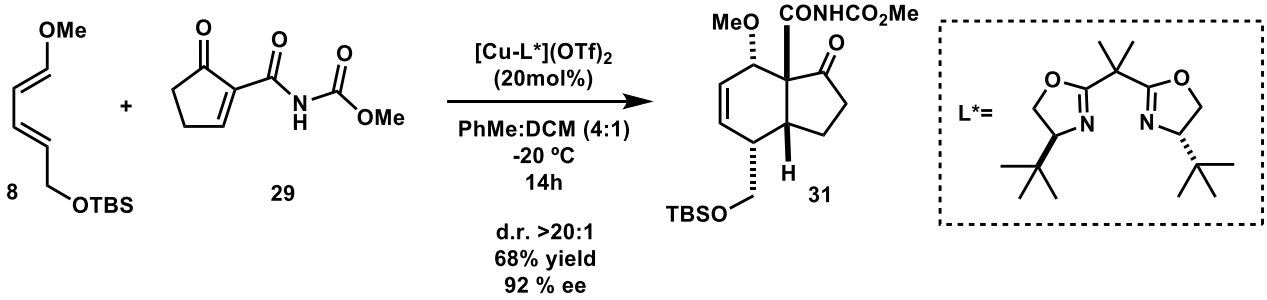
Acetal N-acyl carbamate **S19**. To a 25 mL round-bottomed flask equipped with a magnetic stir bar, under a N_2 atmosphere, in a -78 °C bath, was added vinyl bromide **S16**[2] (300 mg, 1.46 mmol) and THF (7 mL). *n*-BuLi (2.26 M in hexanes, 0.85 mL, 1.90 mmol) was then added dropwise to the solution via syringe. The resulting yellow mixture was stirred and slowly brought to –30 °C over 3 h (the progress of bromine-lithium exchange was monitored by GCMS). At that time the reaction mixture was re-cooled to –78 °C and $OCNCO_2Me$ (0.24 mL, 2.9 mmol) was added, which resulted in the formation of deep-orange colored slurry. After stirring at the same temperature for an additional hour, the mixture was quenched with sat. $NH_4Cl_{(aq)}$ solution (6 mL) and the resulting solution was warmed to r.t. The resulting two-layer mixture was separated and the aqueous layer was extracted with EtOAc (6 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. Column chromatography of the crude mixture using an automated Yamazen® chromatography system on silica gel (L universal column, M inject column, eluting with 50:50 to 45:65 hexanes/EtOAc) afforded **S17** (191 mg, 62%) as a white solid with m.p. 112 – 113 °C. R_f = 0.30 (1 : 2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s br, NH), 7.25 (t, *J* = 2.5 Hz, 1H), 4.21 – 4.08 (m, 2H), 4.10 – 3.99 (m, 2H), 3.79 (s, 3H), 2.49 (td, *J* = 6.4, 2.5 Hz, 2H), 2.15 (td, *J* = 6.4, 1.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.5, 151.8, 151.5, 135.3, 118.0, 64.5, 53.04, 35.7, 28.2 ppm; IR (neat): ν_{max} cm^{-1} 3427, 3264, 2958, 2897, 2851, 1774, 1692, 1634, 1505, 1206; HRMS (ESI) calc'd for $[C_{10}H_{14}NO_5]^+$: *m/z* 228.0866, found 228.0866.



S17 29

N-acyl carbamate **29**. To a 25 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere, in a 0 °C ice/water bath, was added acetal **S17** (250 mg, 1.10 mmol) and acetone (10 mL). TsOH•H_2O (30 mg, 0.16 mmol) was then added. The resulting mixture was stirred for 1.5 h with warming to r.t., at which point TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (15 mL) and then filtered through a short plug of silica gel. The product was eluted with EtOAc (150 mL). The combined filtrate was concentrated to give >97% of **29** (200 mg, 97%) as a white solid with m.p. 96 – 98°C. R_f = 0.24 (1:2 hexanes/EtOAc). The product is thermally unstable and must be stored at –20 °C in a frozen benzene matrix. The spectral data that was obtained is in agreement with that previously reported.[3] ^{1}H NMR (500MHz) δ 10.15 (s br, NH), 8.77 (t, *J* = 2.7 Hz, 1H), 3.82 (s, 3H), 2.82 (td, *J* =

4.3, 2.7 Hz, 2H), 2.69 (t, *J* = 4.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.2, 176.3, 158.1, 151.3, 136.9, 53.0, 36.1, 27.0 ppm;



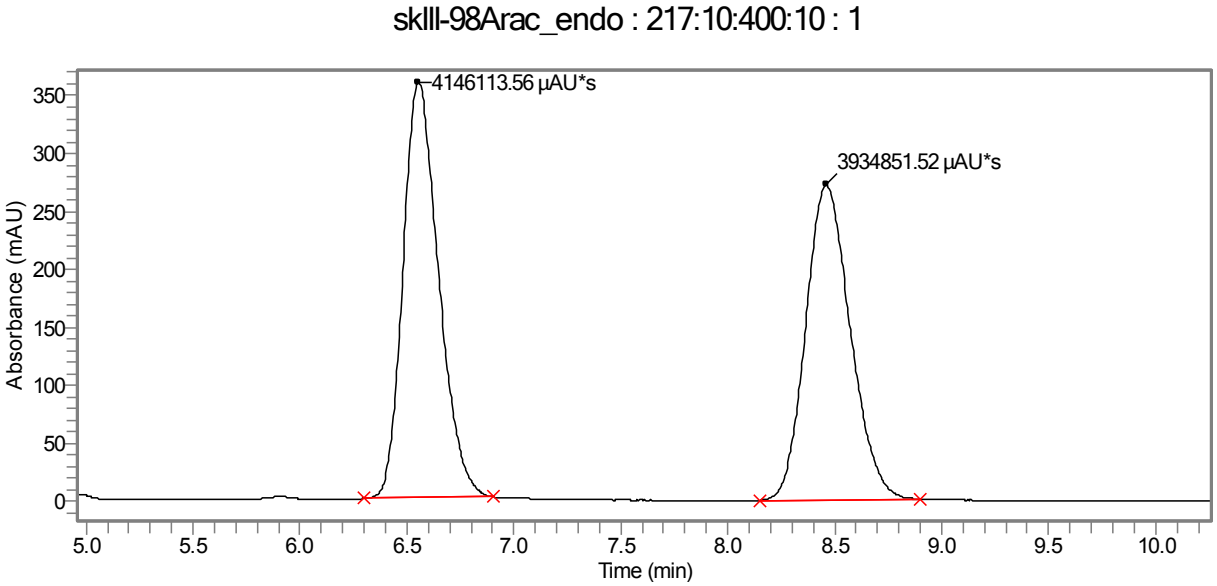
Part I: Synthesis of the racemic products.
A mixture of diene **8** (225 mg, 0.984 mmol) and dienophile **29** (90.0 mg, 0.492 mmol) in 0.3 mL of benzene was heated to 50 °C and held at this temperature for 14 h. The resulting mixture was concentrated in *vacuo* and purified using an automated Yamazen® chromatography system on silica gel (L universal column, S inject column, eluting with 9:1 to 1:1 hexanes/ethyl acetate) to yield *endo* product **31** (154 mg, 76%) as a white solid (m.p. 101.0 – 102.5 °C) and exo product **31`** (11 mg, 5%) as a white solid (m.p. 107.0 – 108.0 °C).

Part II: Enantioselective Diels-Alder cycloaddition.
Chiral BOX-Cu complex preparation: To a white slurry of $Cu(OTf)_2$ (50.0 mg, 0.138 mmol) in dry CH_2Cl_2 (1.75 mL) was added a solution of (S,S)-2,2′-Isopropylidene-bis(4-tert-butyl-2-oxazoline (40.7 mg, 0.138 mmol) in CH_2Cl_2 (0.7 mL). The light-blue mixture was stirred under inert atmosphere for 28 h to give a stock solution of the desired complex.

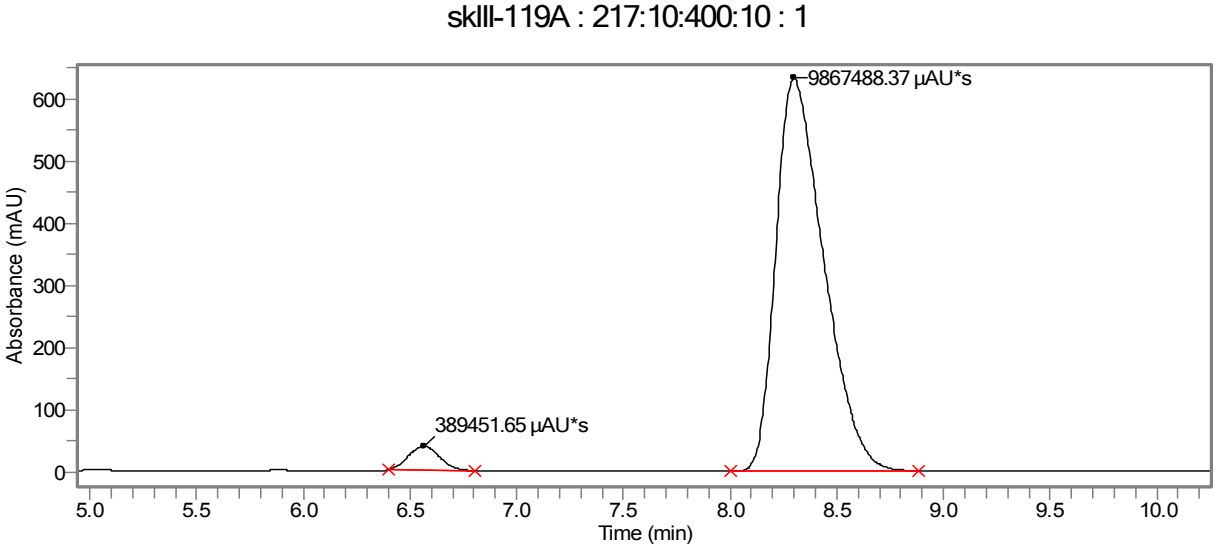
Enantioselective cycloaddition: A solution of dienophile **29** (50.0 mg, 0.272 mmol) in PhMe (2.4 mL) was added to a vial containing flame-dried 4Å powdered molecular sieves at r.t. After 5 min, 1.1 mL (0.054 mmol) of the stock solution of the chiral Cu complex was introduced by dropwise addition (via syringe) and the resulting mixture was stirred at r.t. for 10 min and then cooled to –20 °C. At that time, the solution of diene **8** (125 mg, 0.545 mmol) in PhMe (2 mL) was added and the resulting mixture was stirred at –20 °C for 14 h. At that time, sat. $NaHCO_{3(aq)}$ (5 mL) was added and the mixture was allowed to warm to r.t. The blue aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The yellow residue (>20:1 dr by NMR) was purified using an automated Yamazen® chromatography system on silica gel (L universal column, M inject column, eluting with 9:1 to 1:1 hexanes/EtOAc) to give *endo*-**31** as a white solid (76.2 mg, 68% yield, 92% ee) and *exo*-**31`** as a white solid (3.1 mg, 3% yield).

Enantiomeric excess was determined by HPLC analysis on chiral stationary phase (Chiralcel OD-H 25 cm, 20% i-PrOH/Hexanes, 1 mL/min, 25°C, 217 nm, t_r (minor) = 6.6 min, t_r (major) = 8.4 min.

*Racemic endo-**31***



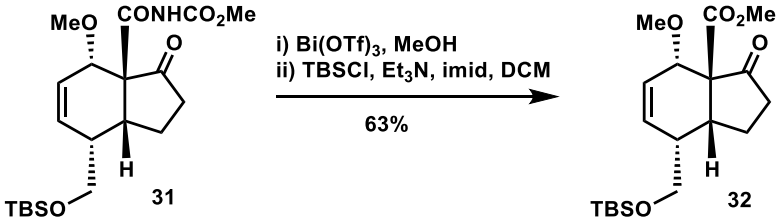
*Enantioenriched endo-**31***



Endo-**31**: R_f = 0.31 (3 : 1 hexanes/EtOAc); $[\alpha]^{20}_D$ +25.8 (c 1.00, DCM) for the sample with 92% ee and > 95:5 d.r; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (s br, NH), 5.89 (dt, *J* = 10.5, 4.3, 2.6 Hz, 1H), 5.81 (dd, *J* = 10.5, 2.2 Hz, 1H), 3.84 (d, *J* = 4.3 Hz, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 8.0 Hz, 2H), 3.30 (s, 3H), 3.20 – 3.11 (m, 1H), 2.78 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.44 (ddd, *J* = 19.2, 8.1, 1.3 Hz, 1H), 2.20 (ddd, *J* = 19.2, 10.8, 8.7 Hz, 1H), 1.98 – 1.83 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 216.2, 167.7, 151.5, 130.8, 121.7, 76.4, 63.8, 62.2, 58.5, 53.1, 39.0, 37.9, 37.7, 26.0, 20.0, 18.3, -5.2, -5.3. IR (neat): ν_{max} cm^{-1} 3293, 2953, 2929, 2890, 2856, 1789, 1729, 1504, 1082, 837 cm^{-1}. HRMS (ESI) calc'd for $[C_{20}H_{33}NNaO_6Si]^+$: *m/z* 234.1969, found 234.1965

Exo-**31**`: R_f = 0.25 (3 : 1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (s, 1H), 5.89 (dd, *J* = 10.1, 2.2 Hz, 1H), 5.85 – 5.80 (m, 1H), 3.94 (q, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 3.74 (dd, *J* = 9.8, 8.4 Hz, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.41 (s, 3H), 3.02 – 2.97 (m, 1H), 2.51 – 2.38 (m, 1H), 2.38 – 2.28

(m, 1H), 2.28 – 2.17 (m, 1H), 2.13 – 2.09 (m, 1H), 1.72 (dt, *J* = 21.8, 8.4 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 212.64, 165.29, 151.11, 132.49, 124.98, 74.76, 66.51, 64.95, 58.08, 52.92, 42.20, 38.38, 36.74, 27.51, 26.05, 18.40, -5.16, -5.20; IR (neat): ν_{max} cm^{-1} 3300, 2953, 2927, 2855, 1776, 1728, 1506, 1090, 835 cm^{-1}; HRMS (ESI) calc'd for $[C_{20}H_{33}NNaO_6Si]^+$: *m/z* 234.1969, found 234.1964.



Conversion of **31** into **32**. To a solution of **31** (50 mg, 0.12 mmol) in MeOH (1.5 mL) was added $Bi(OTf)_3$ (28 mg, 0.042 mmol) as a solution in MeOH (1 mL) at r.t.. The reaction mixture was stirred for 12 h and then treated with NEt_3 (1 mL). The resulting solution was concentrated to dryness under reduced pressure and further concentrated at 0.3 torr for 1 h on a Schlenk manifold. The resulting yellow oil was dissolved in CH_2Cl_2 (1 mL), cooled to 0 °C and treated with NEt_3 (30 µL), imidazole (41 mg, 0.60 mmol), and TBS-chloride (74 mg, 0.49 mmol). The reaction mixture was allowed to warm to r.t. and stirred until judged complete by TLC (2 h). After this time, a sat. $NaHCO_{3(aq)}$ solution (2 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The yellow oily residue was purified using an automated Yamazen® chromatography system on silica gel (S universal column, 2S inject column) with hexanes/ethyl acetate (95:5 to 85:1 gradient) to yield **32** (28.3 mg, 63%) as a colorless viscous oil. R_f = 0.32 (4:1 hexanes/EtOAc). The product has identical in all respects to **32** prepared by the cycloaddition of diene **8** and dienophile **9.**

4. Supporting Information for graphing program to determine the maximally bridging ring

A graphing program that is deterministic and permits the identification of the maximally bridging ring (or rings) for any molecule has been developed. The algorithm is guaranteed to identify the maximally bridging ring or rings each time it is run.

Algorithm:

The developed algorithm is guaranteed to identify all maximally bridging rings each time it is run. The program allows control of several criteria (e.g., the number of atoms that comprise the maximally bridging ring or that span bridging atoms in the maximally bridging ring). The program will output the maximally bridging ring or in the case of ties, all maximally bridging rings." When more than one ring has the same number of bridging atoms, ties are broken by the ring size. To use the program, the user specifies the minimum size (x) and maximum size (y) for rings to consider as maximally bridging as well as the maximum bridge length including the bridgehead atoms (k). Our graphing program first identifies all rings with at least x and no more than y atoms (using the Chemistry Development Kit (CDK) software library). Then every pair of atoms in the ring is examined to determine if it constitutes a bridging pair by searching for a secondary path (sequence of bonds and atoms) between the two atoms that must not contain any atoms of the original ring (except for the two bridgehead atoms). Should a secondary path be identified with a path length of at least 3 but no more than k atoms (including the bridgehead atoms), then the atoms of the original pair are marked as bridging. After considering all pairs of atoms in a ring, the number of bridging atoms is used to output identified rings in order of their bridging atom count.

We have employed x=3, y=8 and k=7. However, these can be varied.

Libraries:

GNU Lesser Public General License: https://github.com/cdk/cdk/blob/master/doc/lgpl.license
CDK: http://sourceforge.net/projects/cdk/.[4,5]

Test Sets and Graphing Program Outputs

3D representations of the test set are located at: http://www.cadrerl.com/ring/
Visualization program: 3Dmol.[6] For 3Dmol license please see:
https://github.com/dkoes/3Dmol.js/blob/master/LICENSE

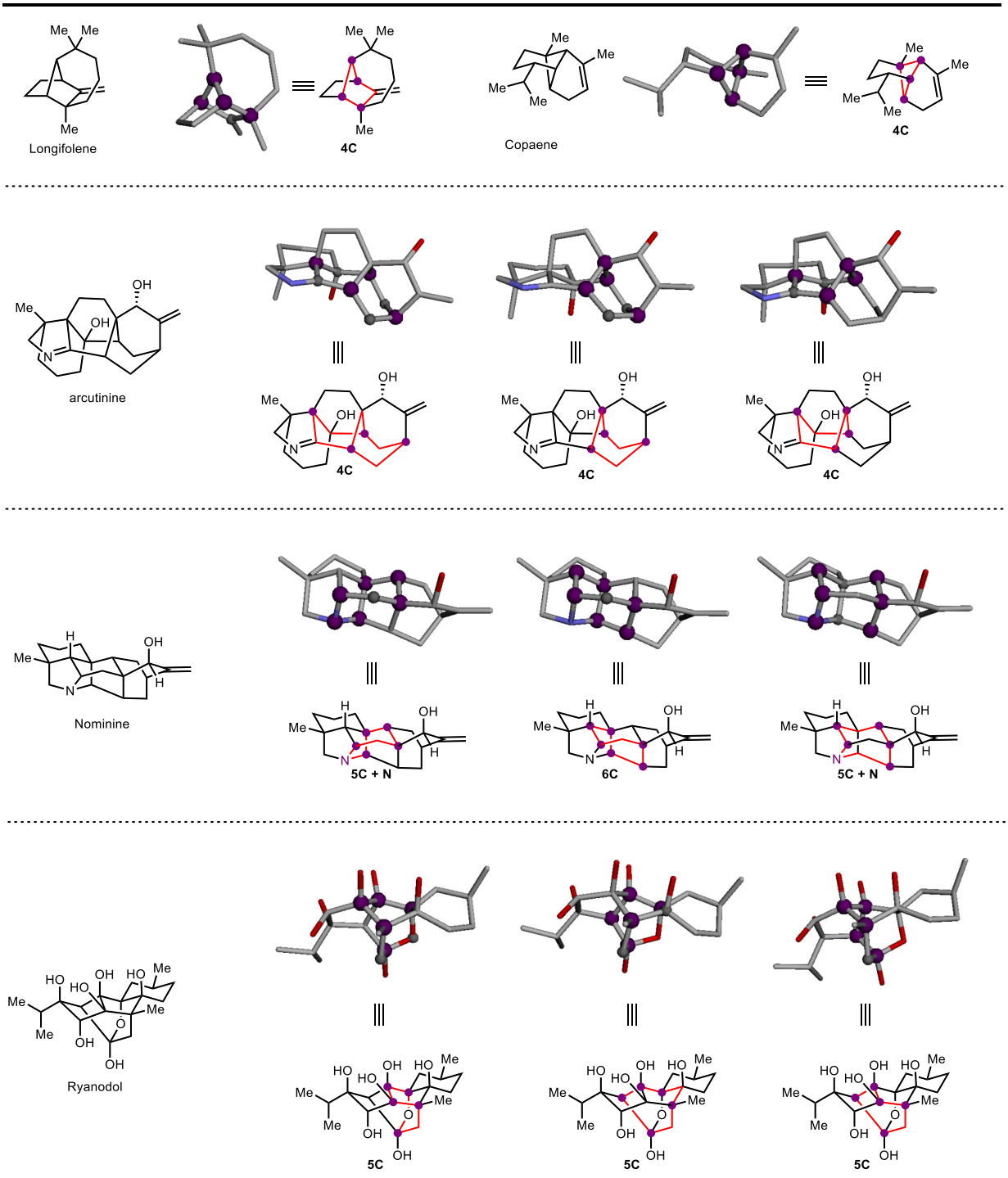


Figure S3. Expanded test set for the maximally bridging ring graphing program.
nC (where **n** = integer) represents the count of carbon bridgehead atoms and **nN** (where **n**=integer) represents the count of nitrogen bridgehead atoms.

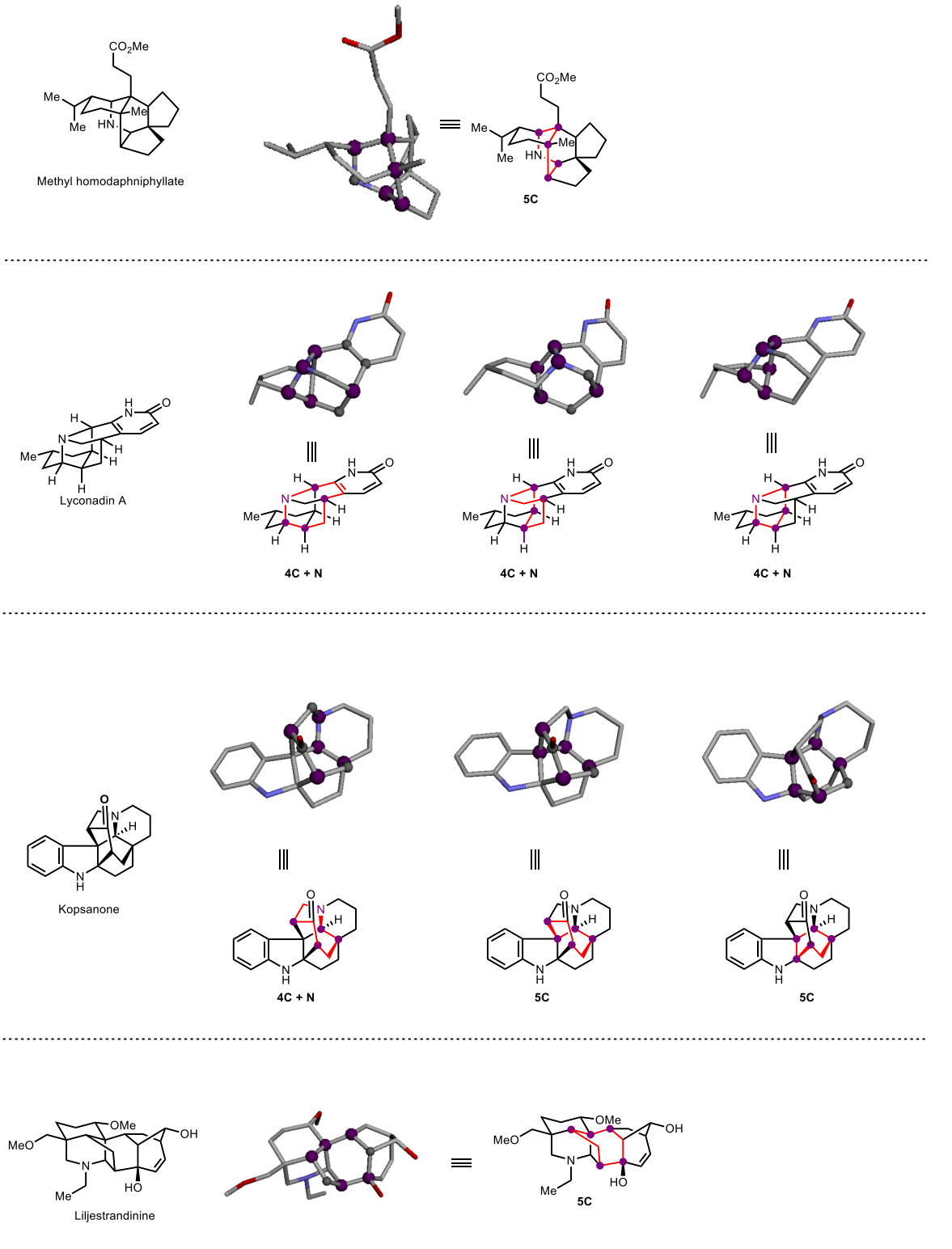


Figure S3(cont.). Expanded test set for the maximally bridging ring graphing program.
nC (where **n** = integer) represents the count of carbon bridgehead atoms and **nN** (where **n**=integer) represents the count of nitrogen bridgehead atoms.

5. References

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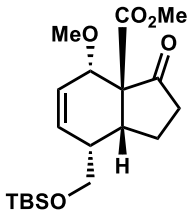
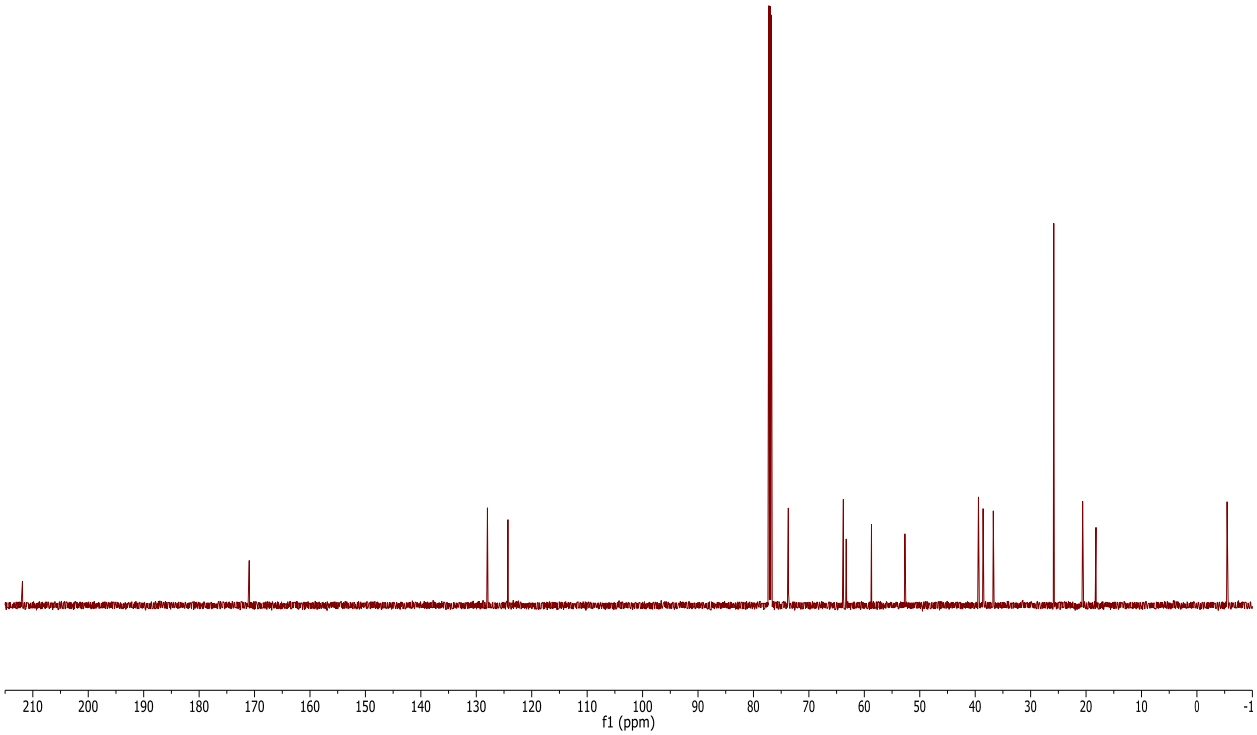
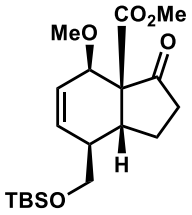
5. C. Steinbeck, C. Hoppe, S. Kuhn, M. Floris, R. Guha, E. L. Willighagen, *Curr. Pharm. Des.* **12**, 2111 (2006).
6. N. Rego, D. Koes, *Bioinformatics* **31,** 1322 (2015).

6. Spectral data



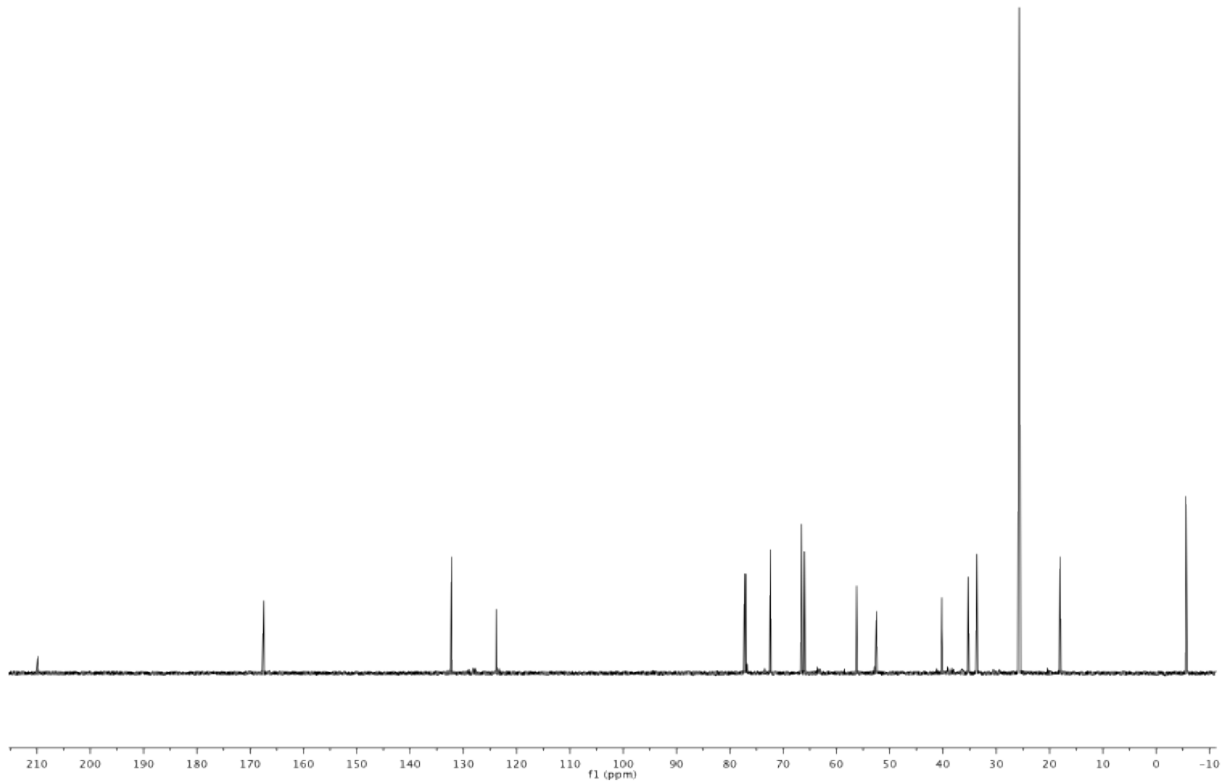
32

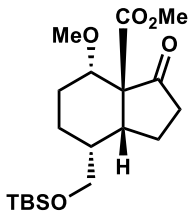



MeO
CO2Me
O
H
TBSO

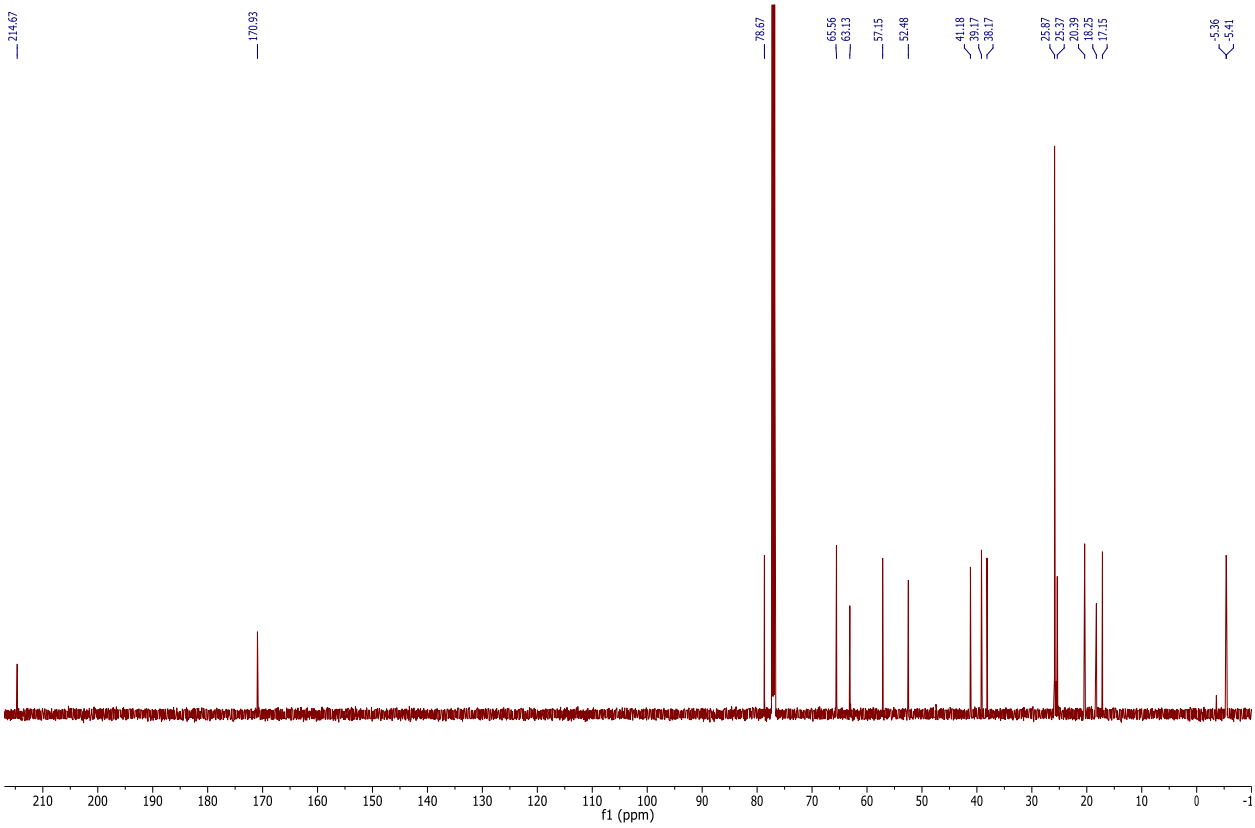
32`

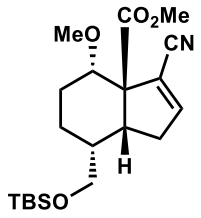
2.00
0.95
2.94
1.20
1.03
3.01
0.94
1.16
2.01
2.13
9.98
6.43
f1 (ppm)


f1 (ppm)



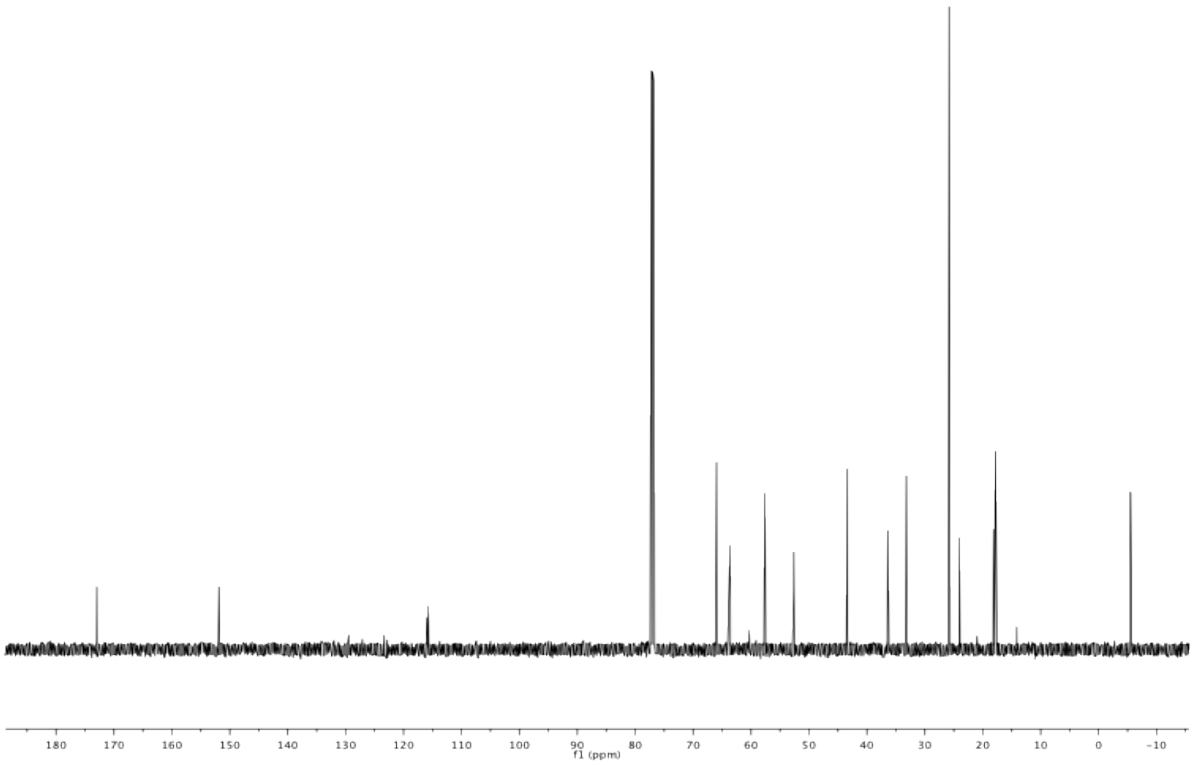
10

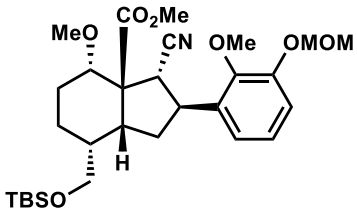



MeO
CO2Me
CN
H
TBSO

7

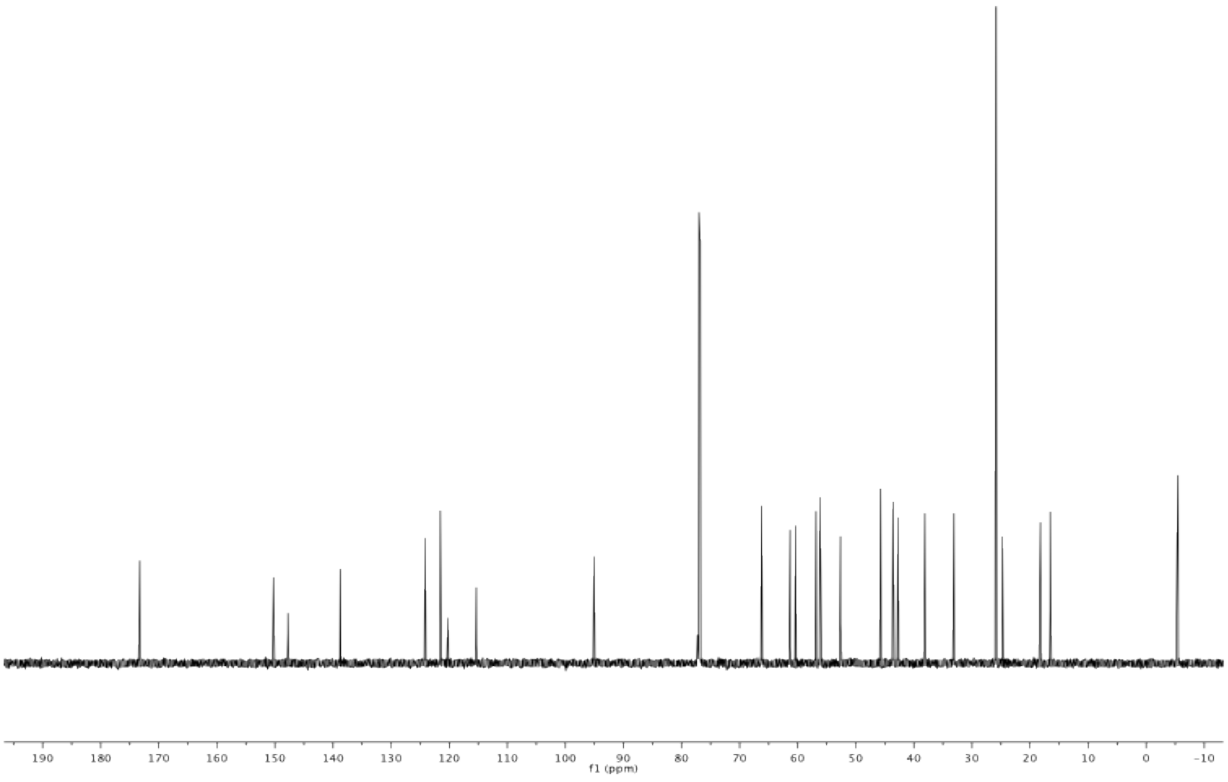
1.00
1.03
3.03
1.06
1.07
3.06
1.03
2.11
0.61
1.07
1.06
0.99
0.96
0.63
9.12
6.01
f1 (ppm)

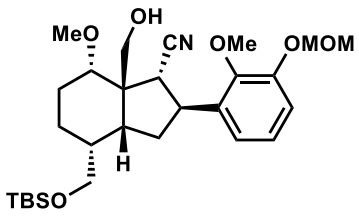

f1 (ppm)


MeO
CO2Me
CN
OMe
OMOM
H
TBSO

12

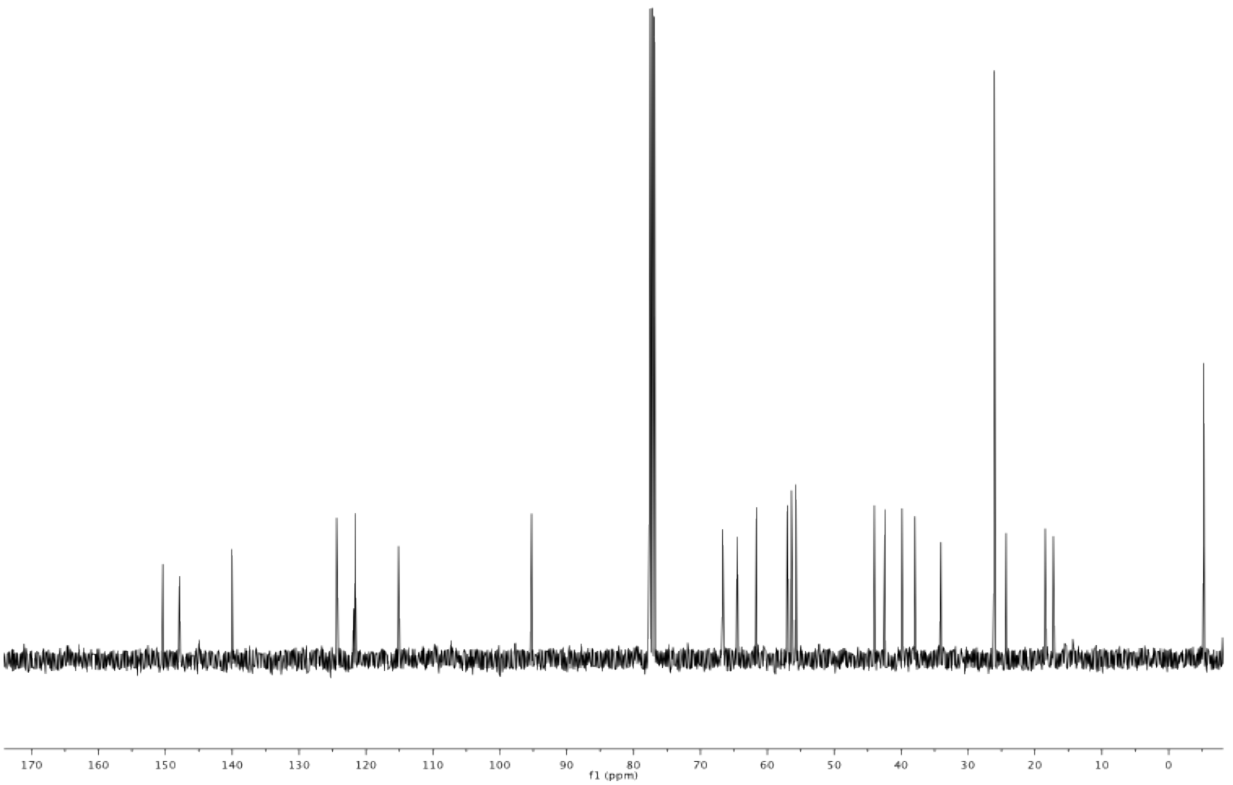
0.98
0.99
1.00
1.99
1.00
1.00
2.98
2.93
2.91
3.00
1.98
0.97
0.99
0.97
1.03
0.97
1.00
3.06
9.18
5.83
f1 (ppm)

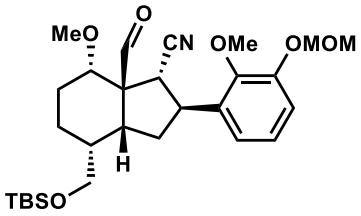

f1 (ppm)


MeO
OH
CN
OMe
OMOM
H
TBSO

S2

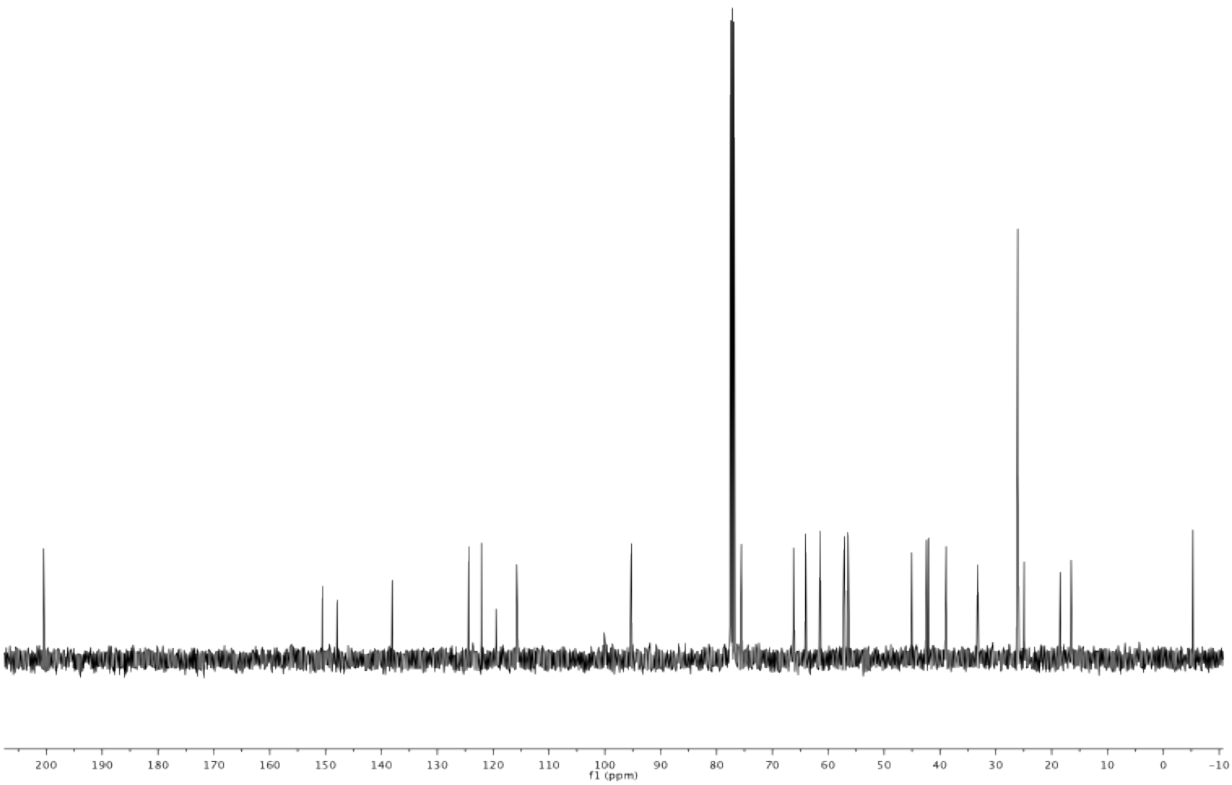
2.04
1.00
2.06
1.01
2.95
2.04
3.04
5.96
1.02
0.98
1.02
0.96
1.50
1.04
1.05
2.96
9.45
6.00
f1 (ppm)

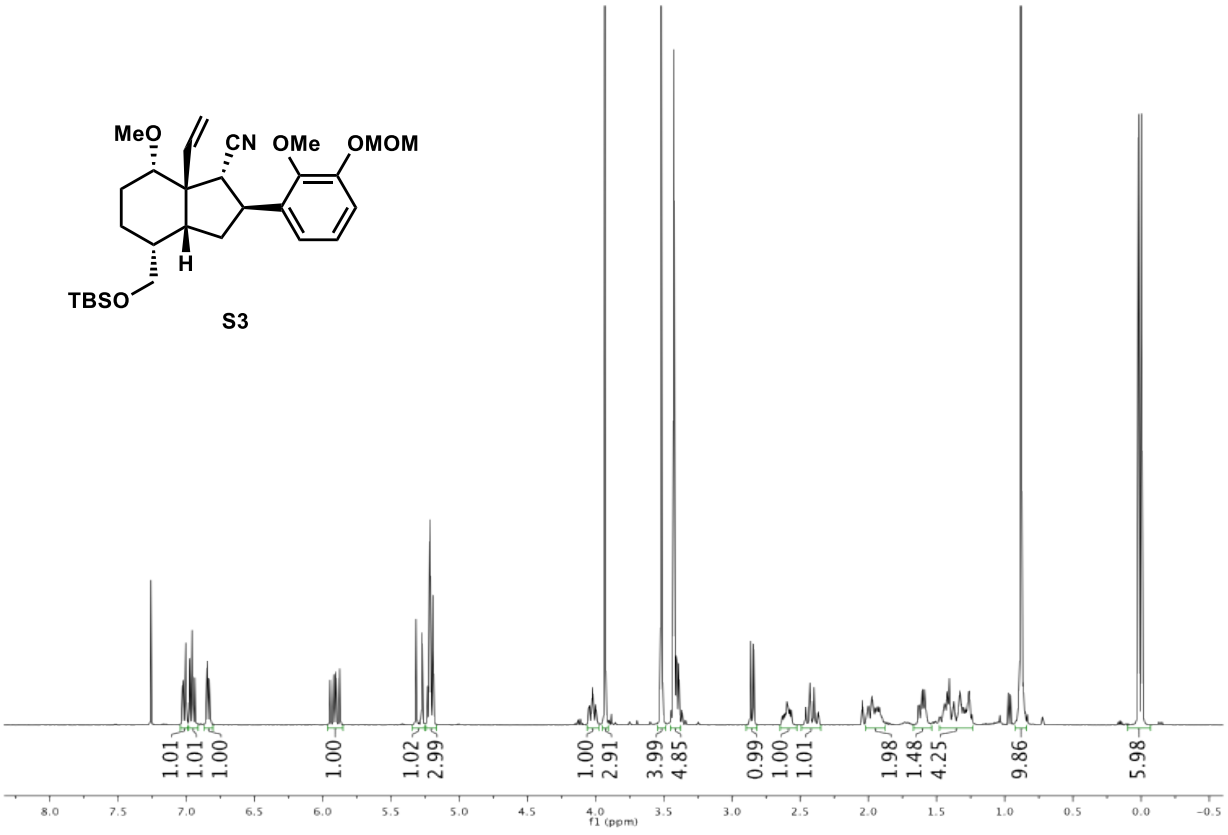

f1 (ppm)

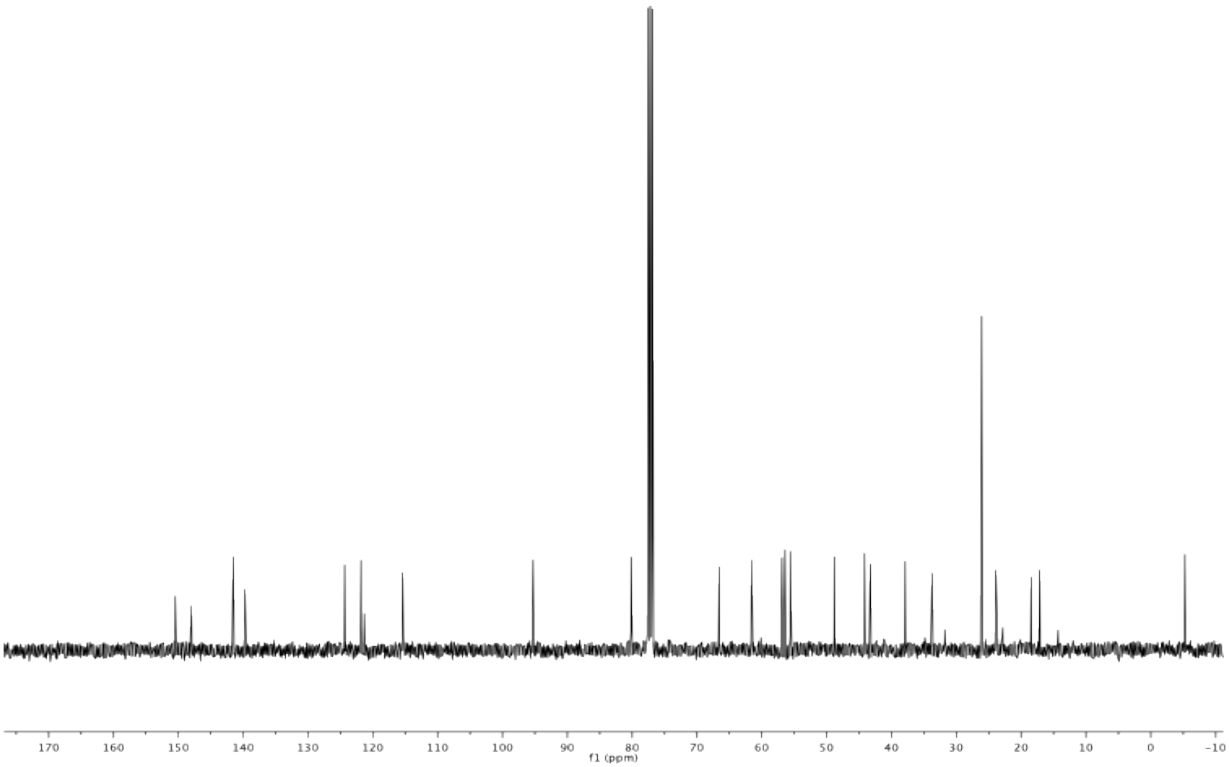

MeO
O
CN
OMe
OMOM
H
TBSO

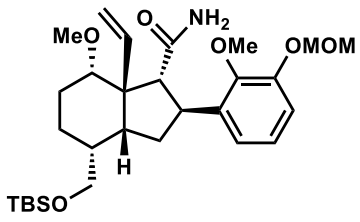
13

1.00
1.03
1.08
1.03
2.11
0.94
3.13
1.11
3.27
5.30
1.04
1.05
1.06
1.07
2.12
2.01
9.62
6.31
f1 (ppm)


f1 (ppm)

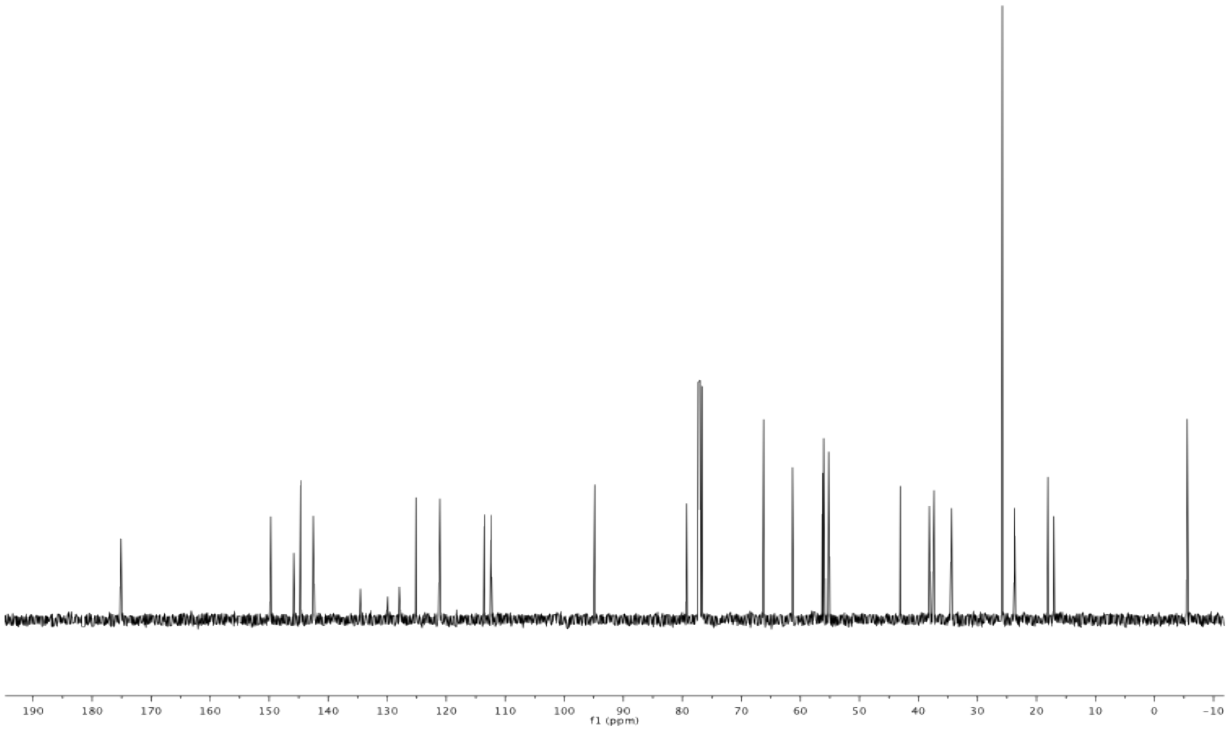

MeO
CN
OMe
OMOM
H
TBSO
S3
1.01
1.01
1.00
1.00
1.02
2.99
1.00
2.91
3.99
4.85
0.99
1.00
1.01
1.98
1.48
4.25
9.86
5.98
f1 (ppm)

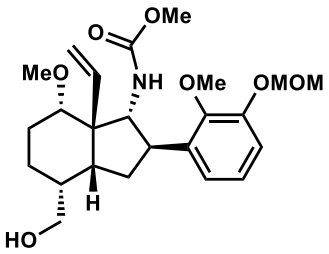

f1 (ppm)


MeO
O
NH2
OMe
OMOM
H
TBSO

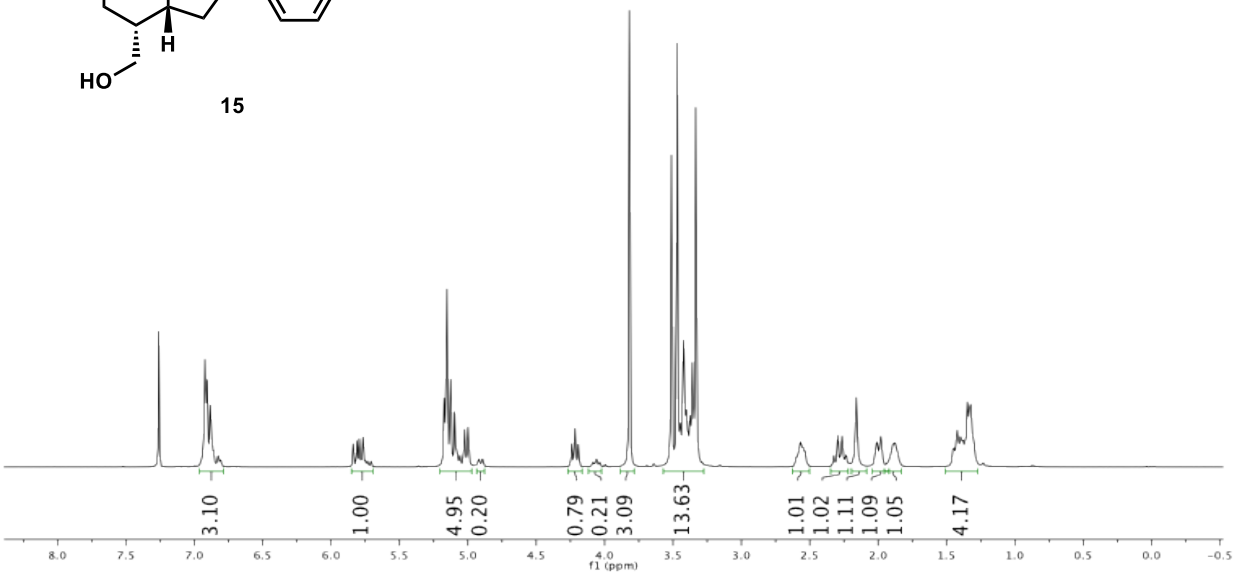
14

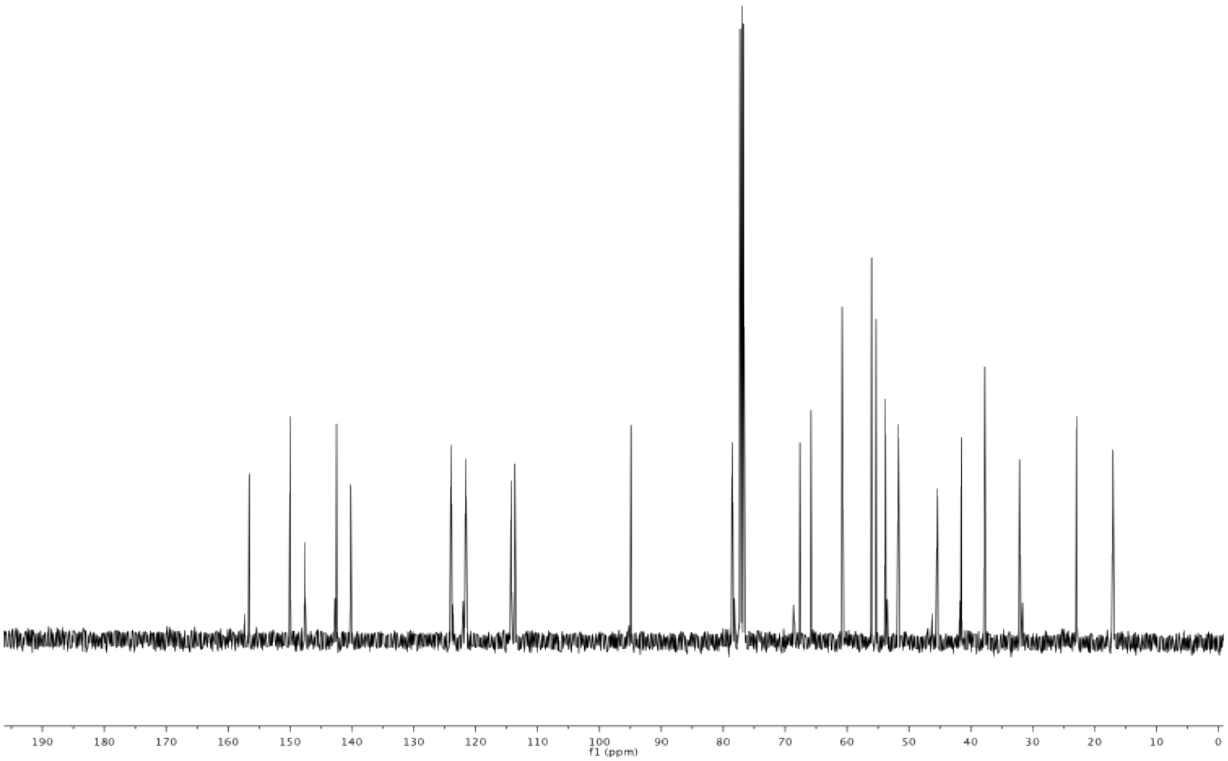
1.02
2.01
0.89
0.95
2.51
1.03
1.38
1.05
2.92
0.97
3.00
2.05
2.97
0.96
0.98
0.95
1.98
1.01
2.09
1.06
9.09
2.95
2.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

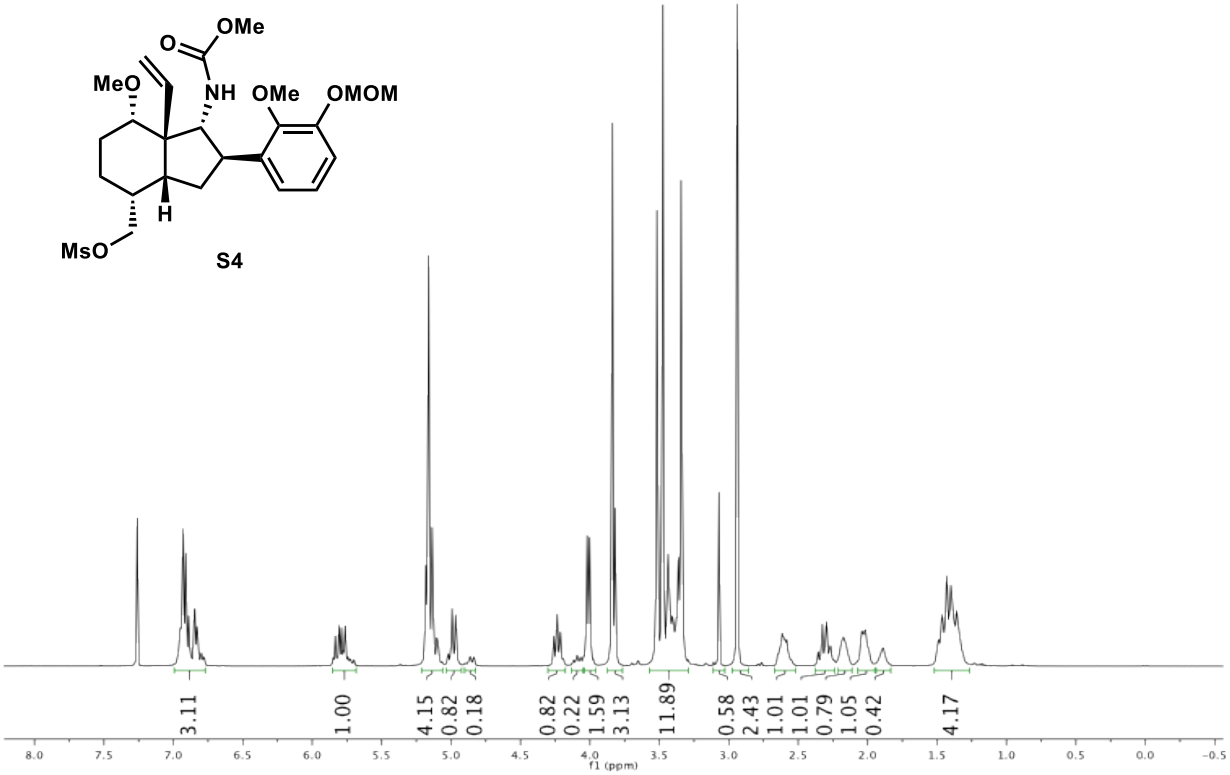

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OMe
O
NH
OMe
OMOM
MeO
H
HO

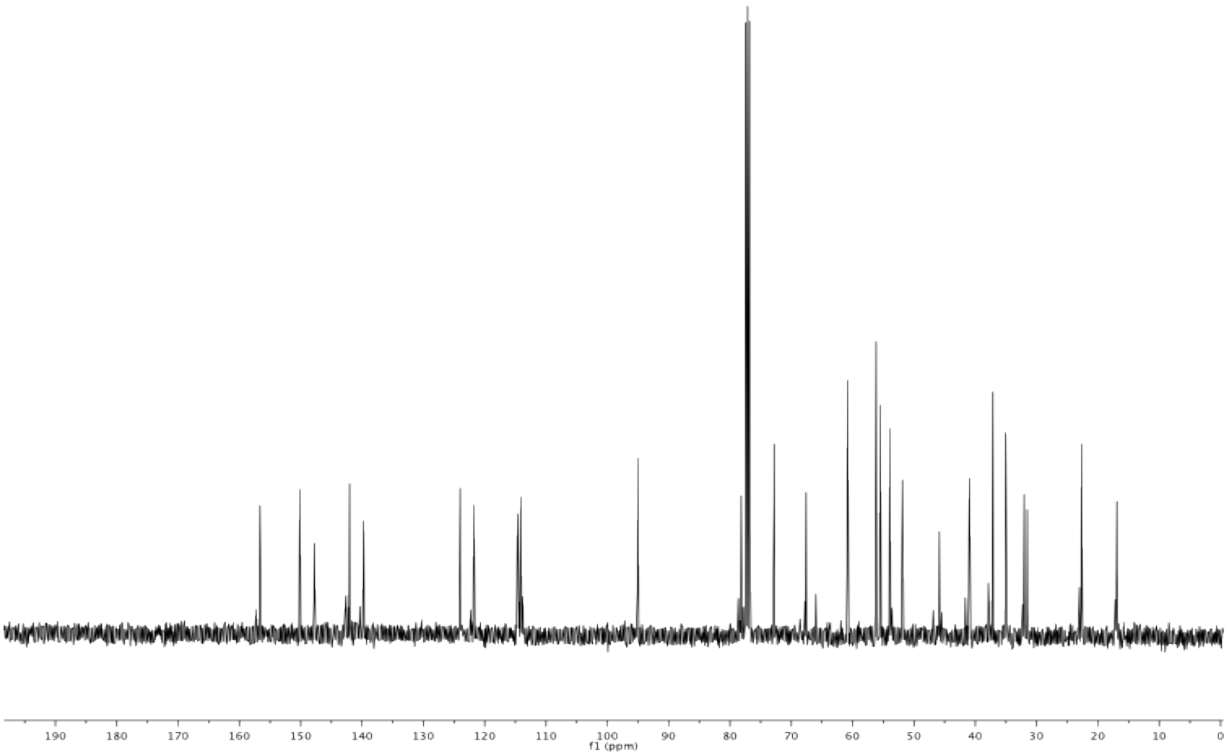
15

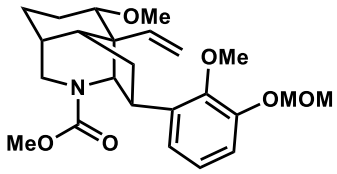

3.10
1.00
4.95
0.20
0.79
0.21
3.09
13.63
1.01
1.02
1.11
1.09
1.05
4.17
f1 (ppm)


f1 (ppm)

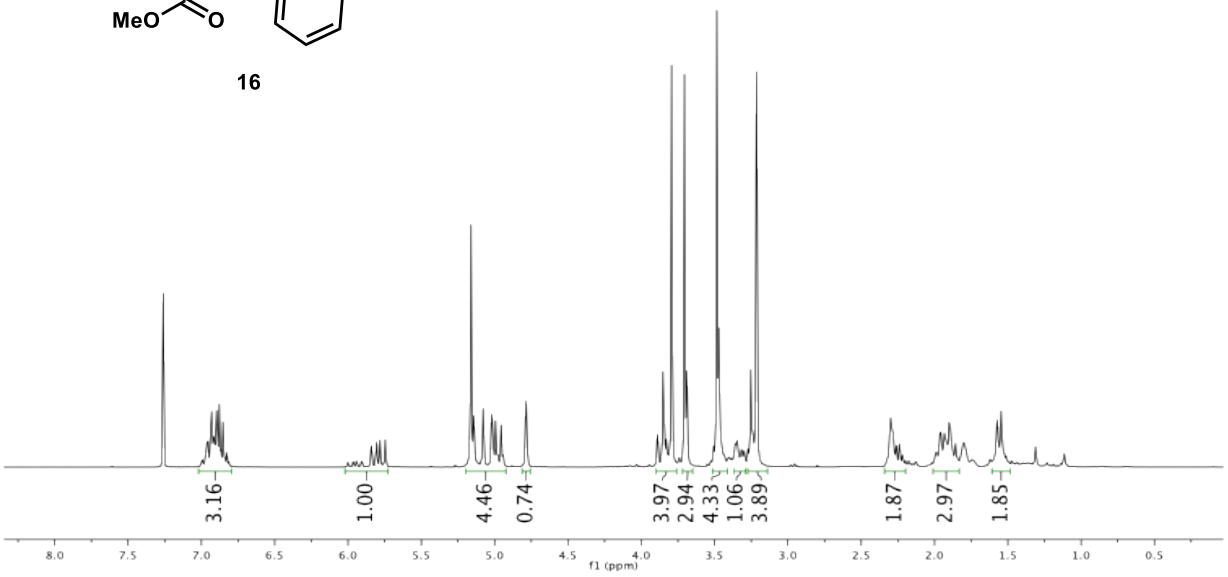

OMe
O
MeO
NH
OMe
OMOM
H
MsO
3.11
1.00
4.15
0.82
0.18
0.82
0.22
1.59
3.13
11.89
0.58
2.43
1.01
1.01
0.79
1.05
0.42
4.17
f1 (ppm)

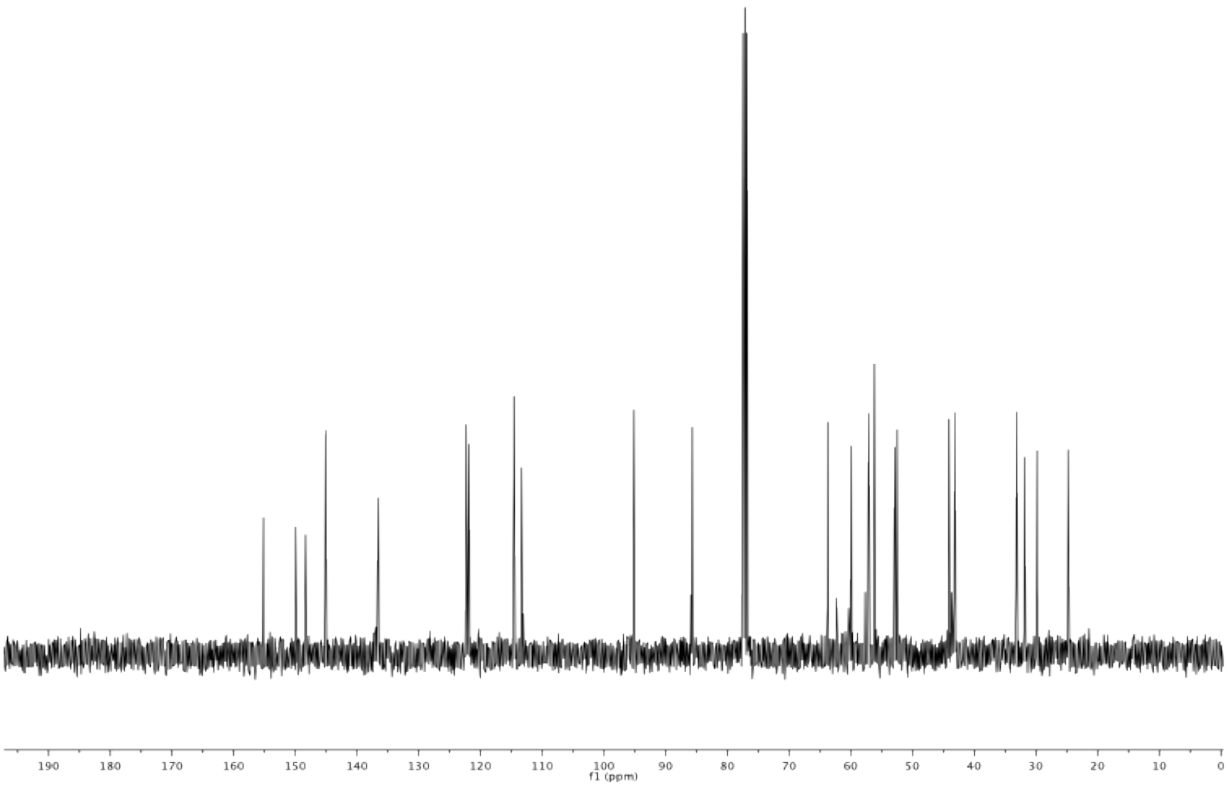
S4

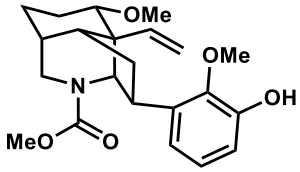

f1 (ppm)


OMe
OMe
OMOM
N
MeO
O

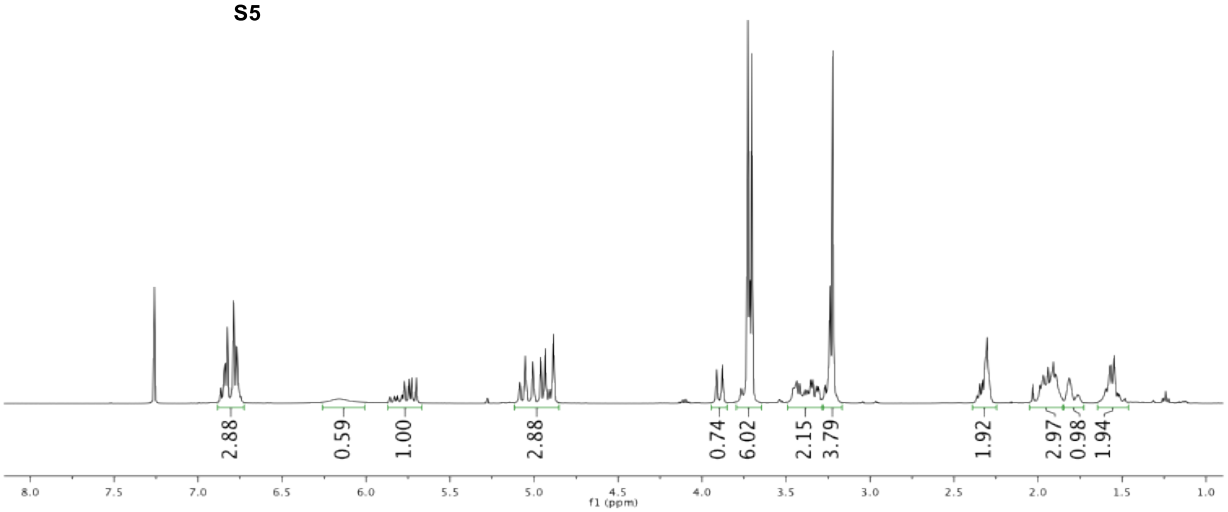
16

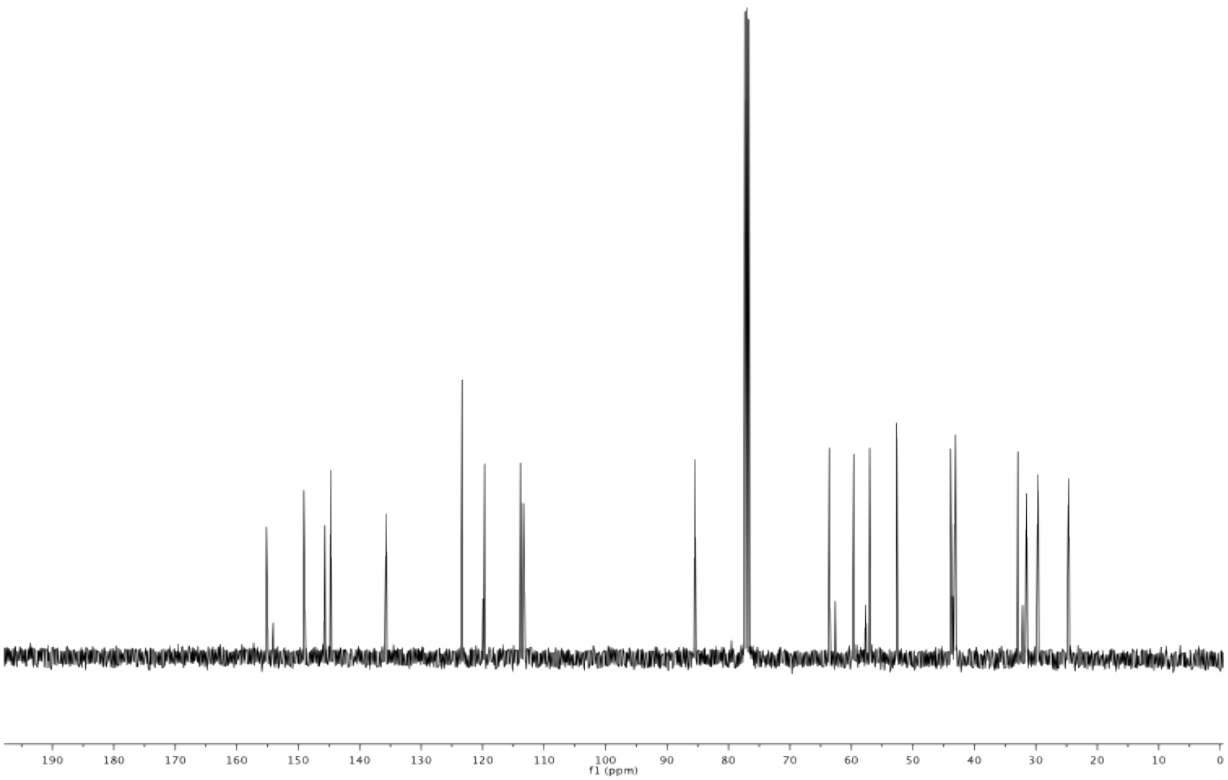

3.16
1.00
4.46
0.74
3.97
2.94
4.33
1.06
3.89
1.87
2.97
1.85
f1 (ppm)

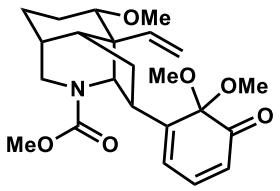

f1 (ppm)


OMe
OMe
OH
N
MeO
O

S5

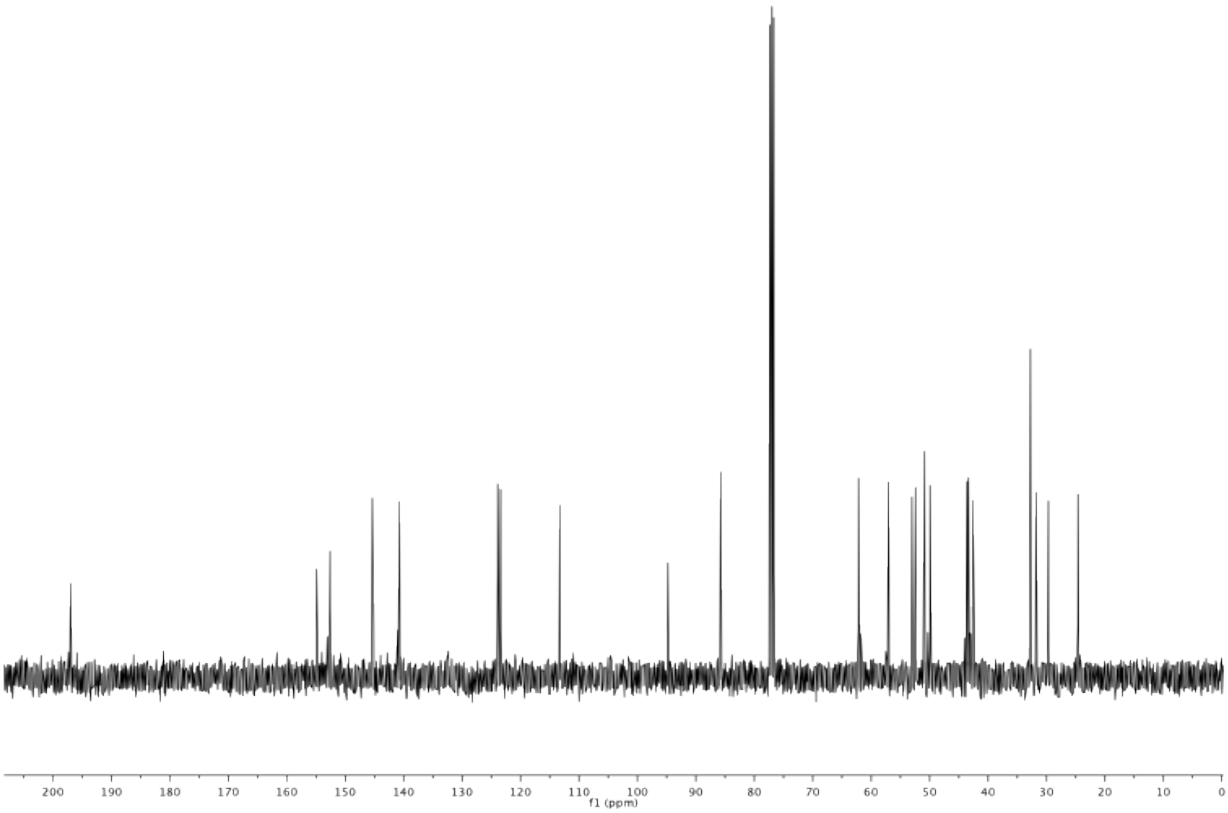

2.88
0.59
1.00
2.88
0.74
6.02
2.15
3.79
1.92
2.97
0.98
1.94
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

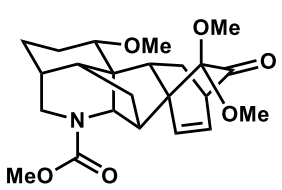

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
MeO
OMe
N
MeO
O
O

17

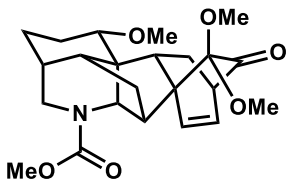
1.00
0.23
0.77
2.01
3.04
0.82
3.31
12.38
1.00
1.19
4.14
2.11
f1 (ppm)


f1 (ppm)



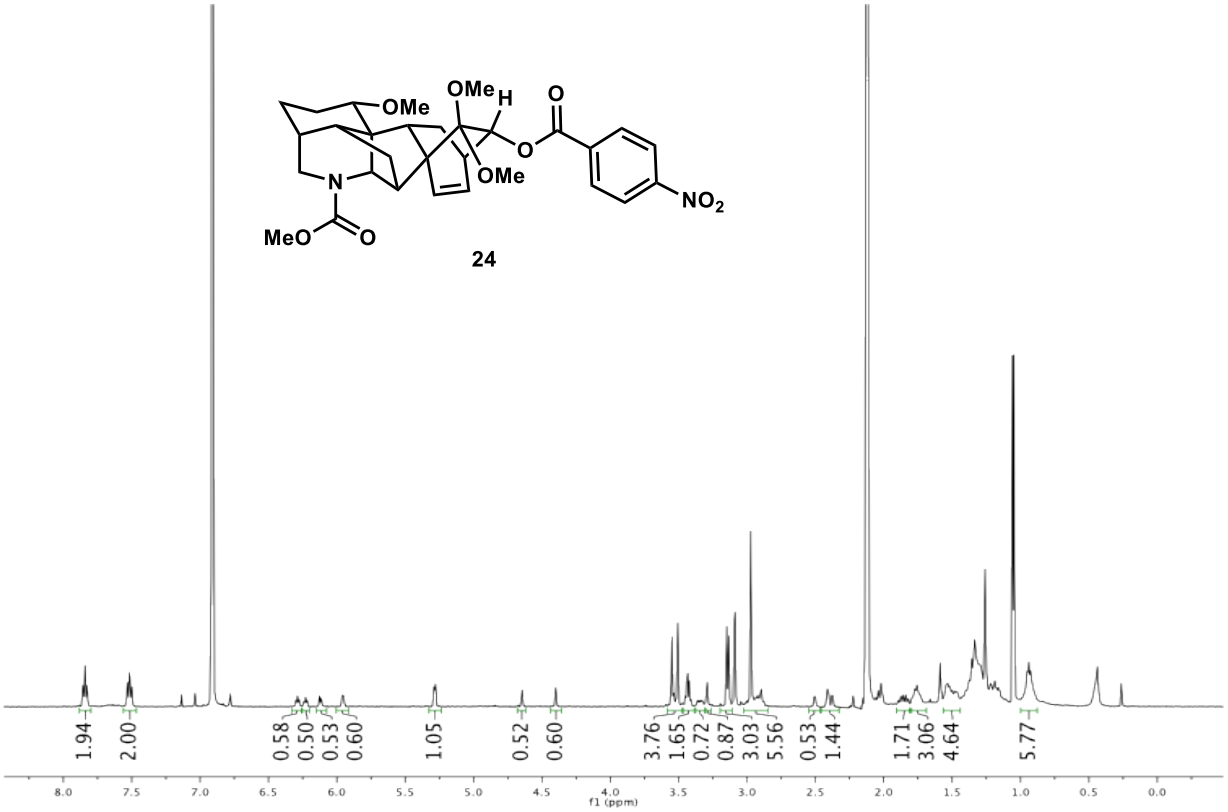
18

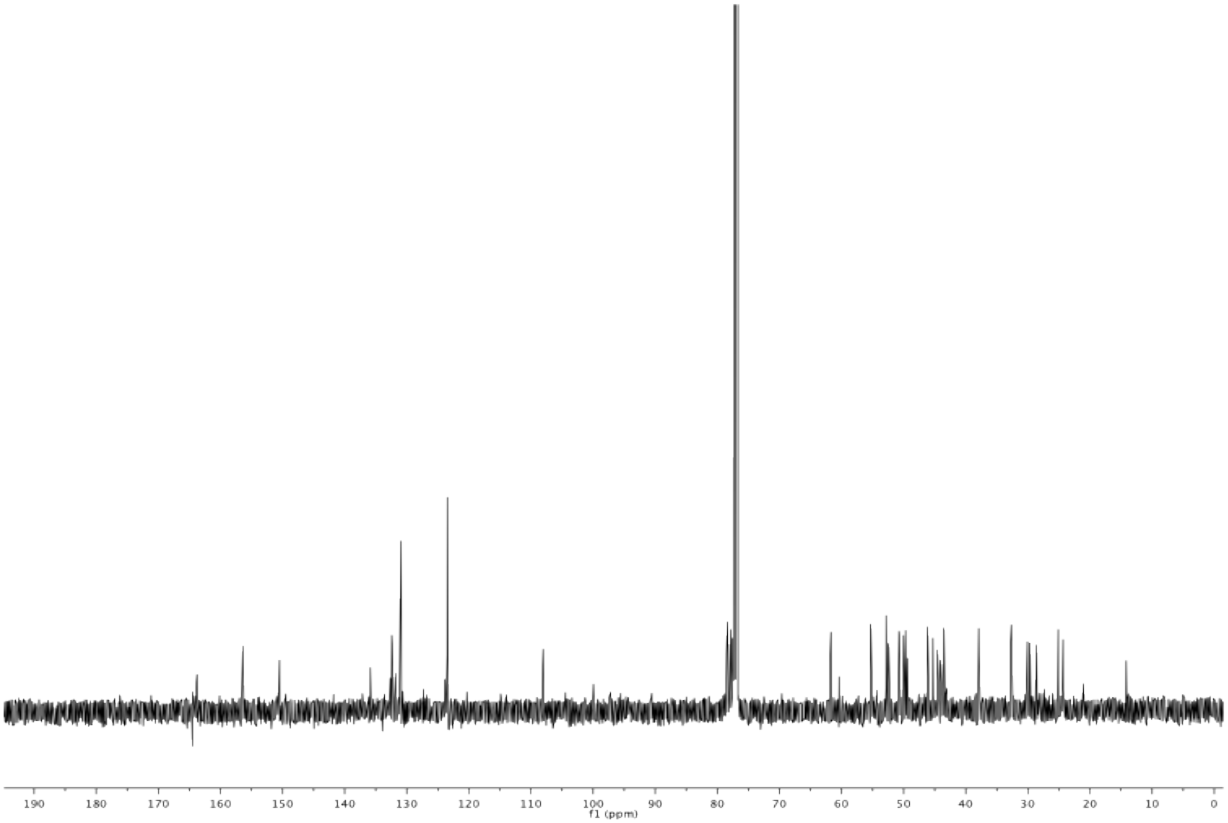
^{1}H NMR in C_6D_6

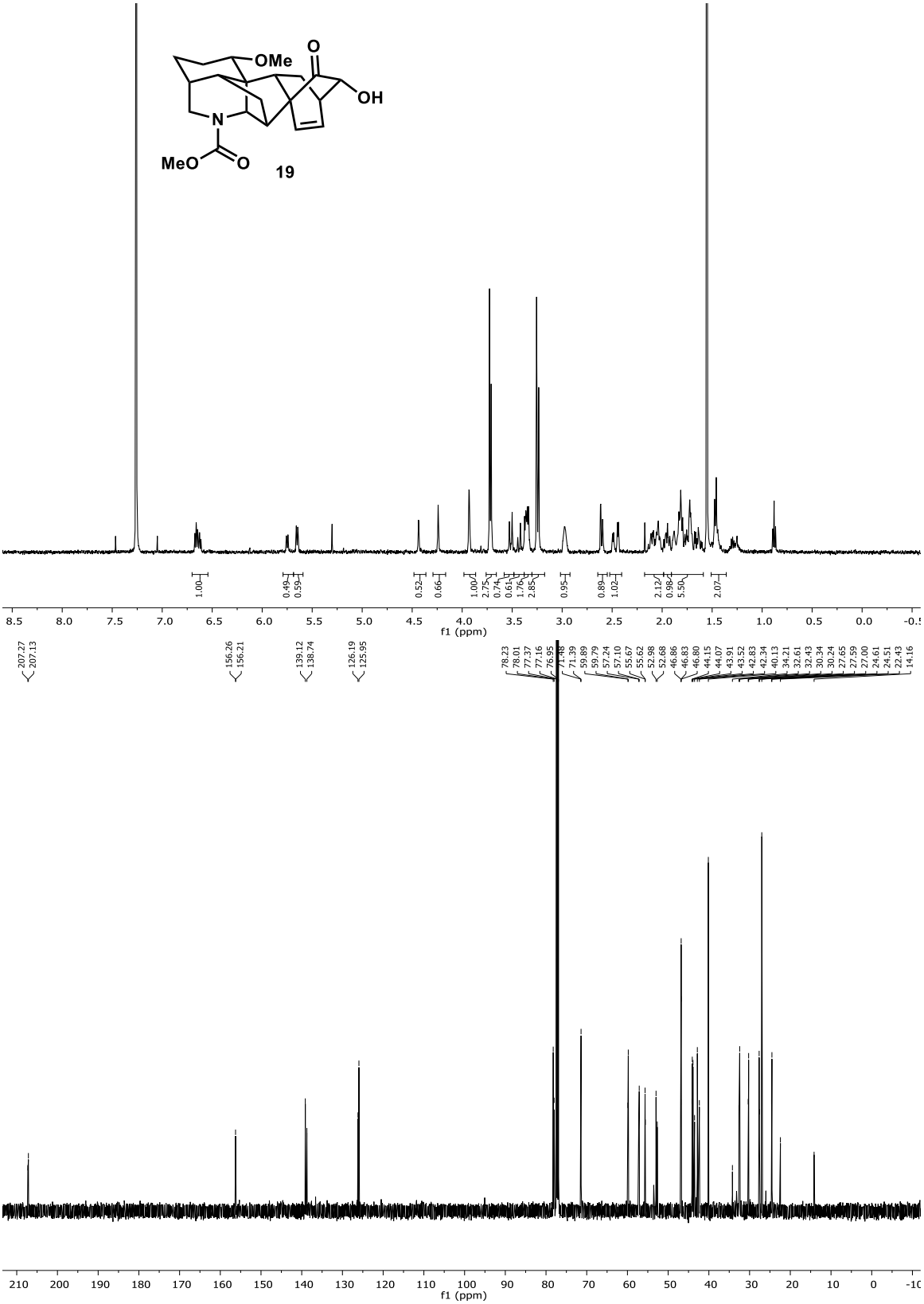


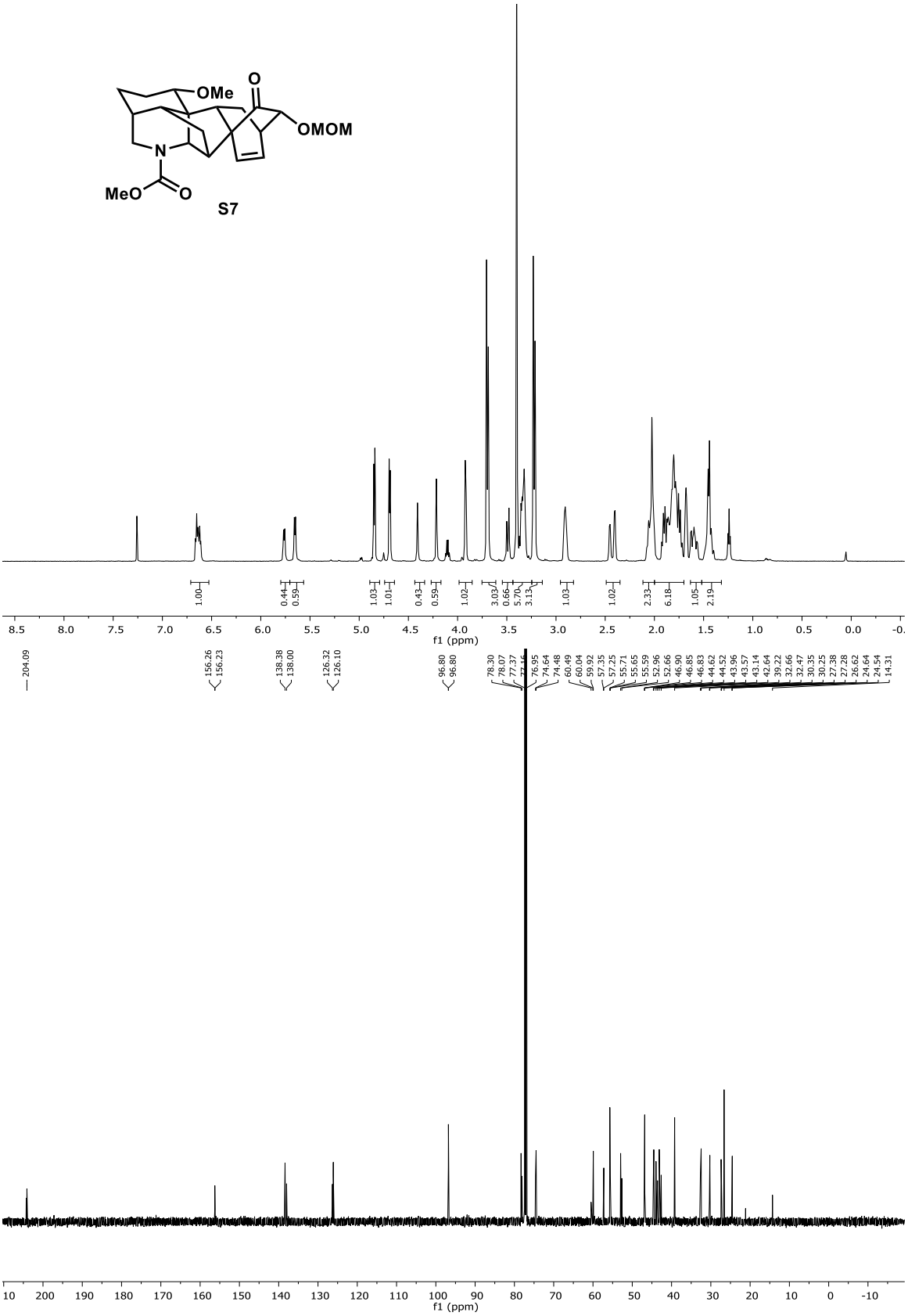
18

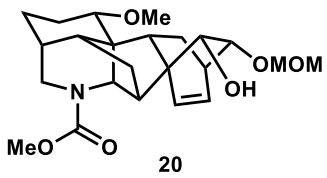
^{13}C NMR in $CDCl_3$


OMe
OMe
H
O
O
OMe
N
MeO
O
NO2
24
1.94
2.00
0.58
0.50
0.53
0.60
1.05
0.52
0.60
3.76
1.65
0.72
0.87
3.03
5.56
0.53
1.44
1.71
3.06
4.64
5.77
f1 (ppm)


f1 (ppm)


OMe
O
OH
N
MeO
O
19
f1 (ppm)
f1 (ppm)

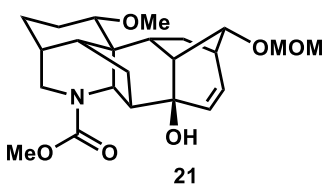

OMe
O
OMOM
N
MeO
O
S7
f1 (ppm)
f1 (ppm)


OMe
OMOM
OH
N
MeO
O

20

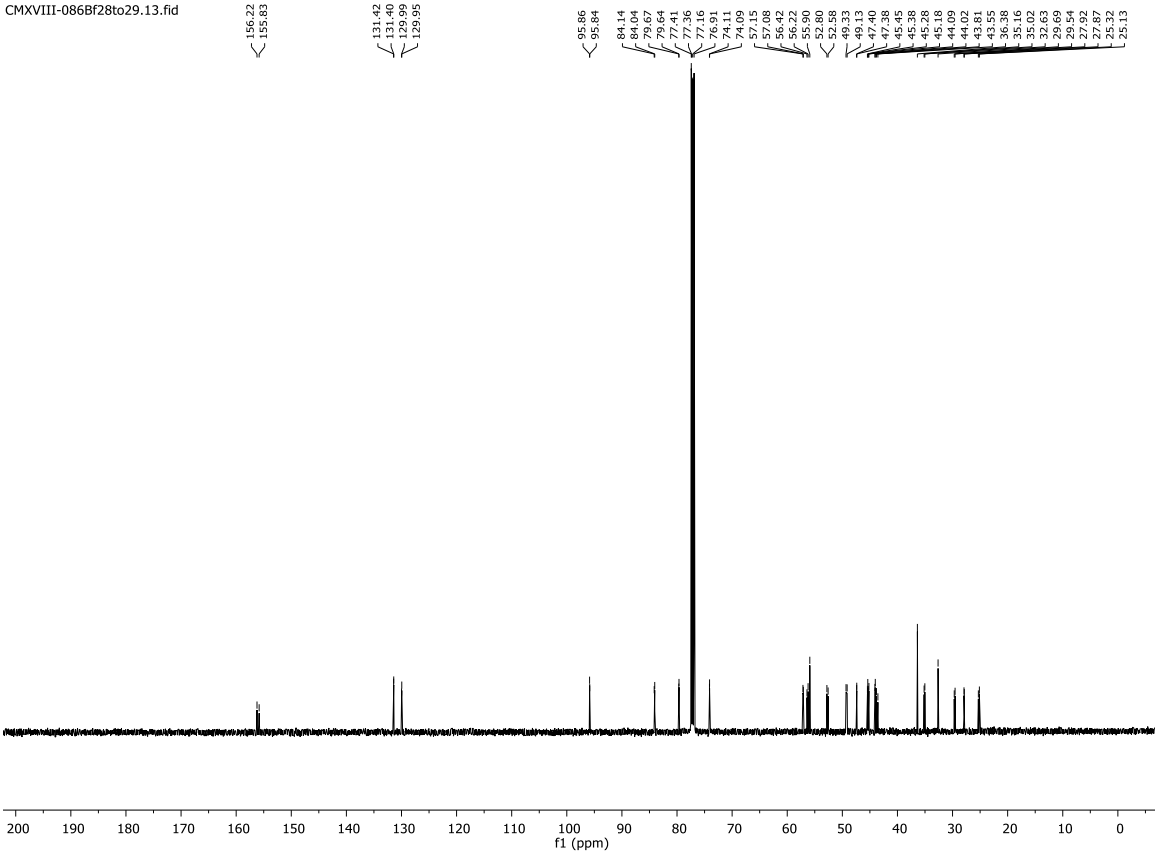
1.00
1.02
2.02
0.33
0.70
1.97
3.13
0.73
4.59
4.40
1.95
1.03
1.05
4.41
2.16
3.35
1.93
1.11
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
156.59
156.26
134.32
134.05
132.48
132.30
96.24
78.45
78.17
77.37
77.16
76.95
76.46
69.85
69.77
60.87
60.78
60.49
55.87
55.59
55.50
52.84
52.54
49.39
49.29
46.89
46.20
46.11
45.15
45.08
45.03
44.56
44.27
43.76
38.11
34.23
32.87
32.66
30.52
30.41
28.76
28.65
25.10
24.60
24.48
22.45
21.16
14.32
14.17
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

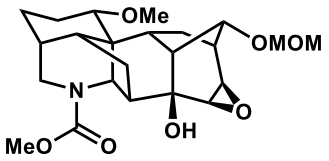
CMXVIII-086Bf28to29.1.fid



21

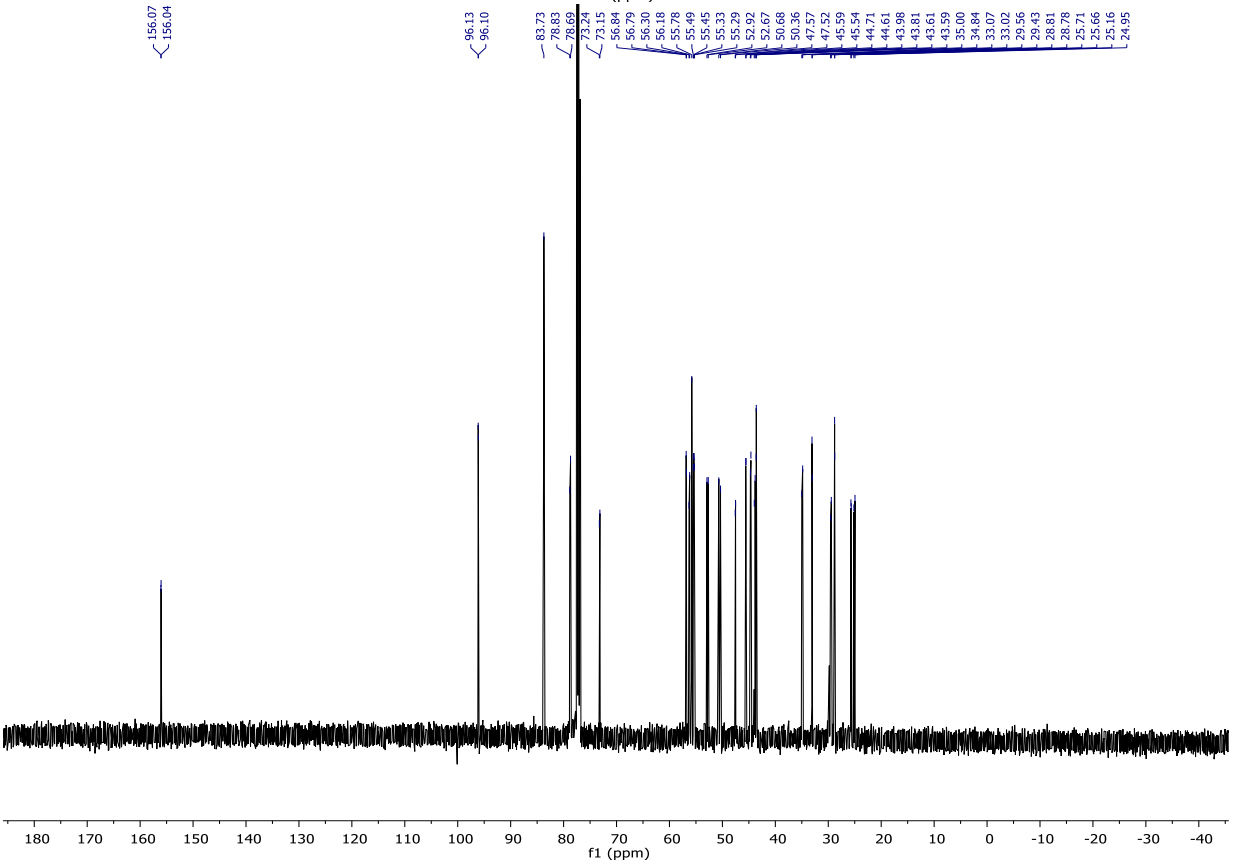
CMXVIII-086Bf28to29.13.fid



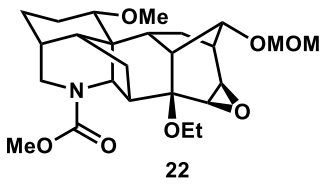

OMe
OMOM
N
O
OH
MeO
O

25

2.97
2.19
0.90
2.15
5.72
1.00
0.94
5.98
5.90
6.31
3.16
2.01
2.41
2.49
4.00
2.75
8.10
2.15
2.28
4.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

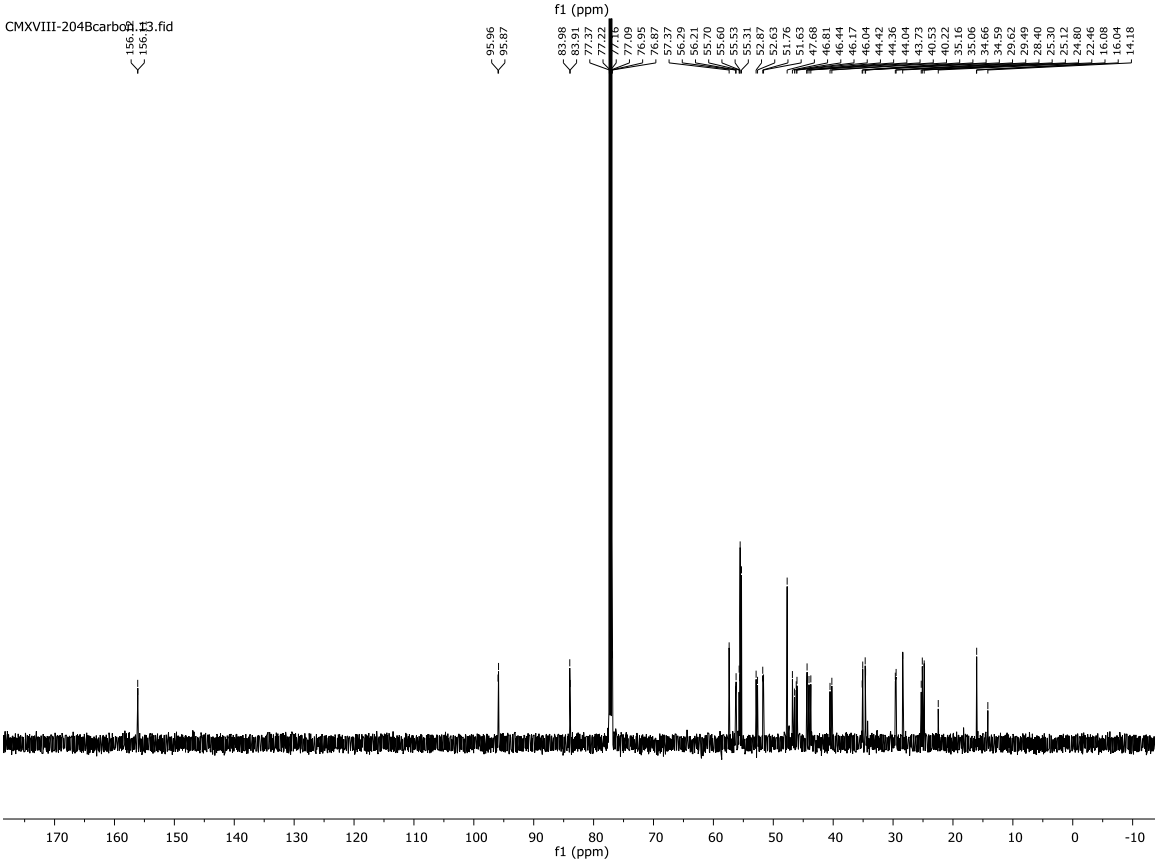

156.07
156.04
96.13
96.10
83.73
78.83
78.69
73.24
73.15
56.84
56.79
56.30
56.18
55.78
55.49
55.45
55.33
55.29
52.92
52.67
50.68
50.36
47.57
47.52
45.59
45.54
44.71
44.61
43.98
43.81
43.61
43.59
35.00
34.84
33.07
33.02
29.56
29.43
28.81
28.78
25.71
25.66
25.16
24.95
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

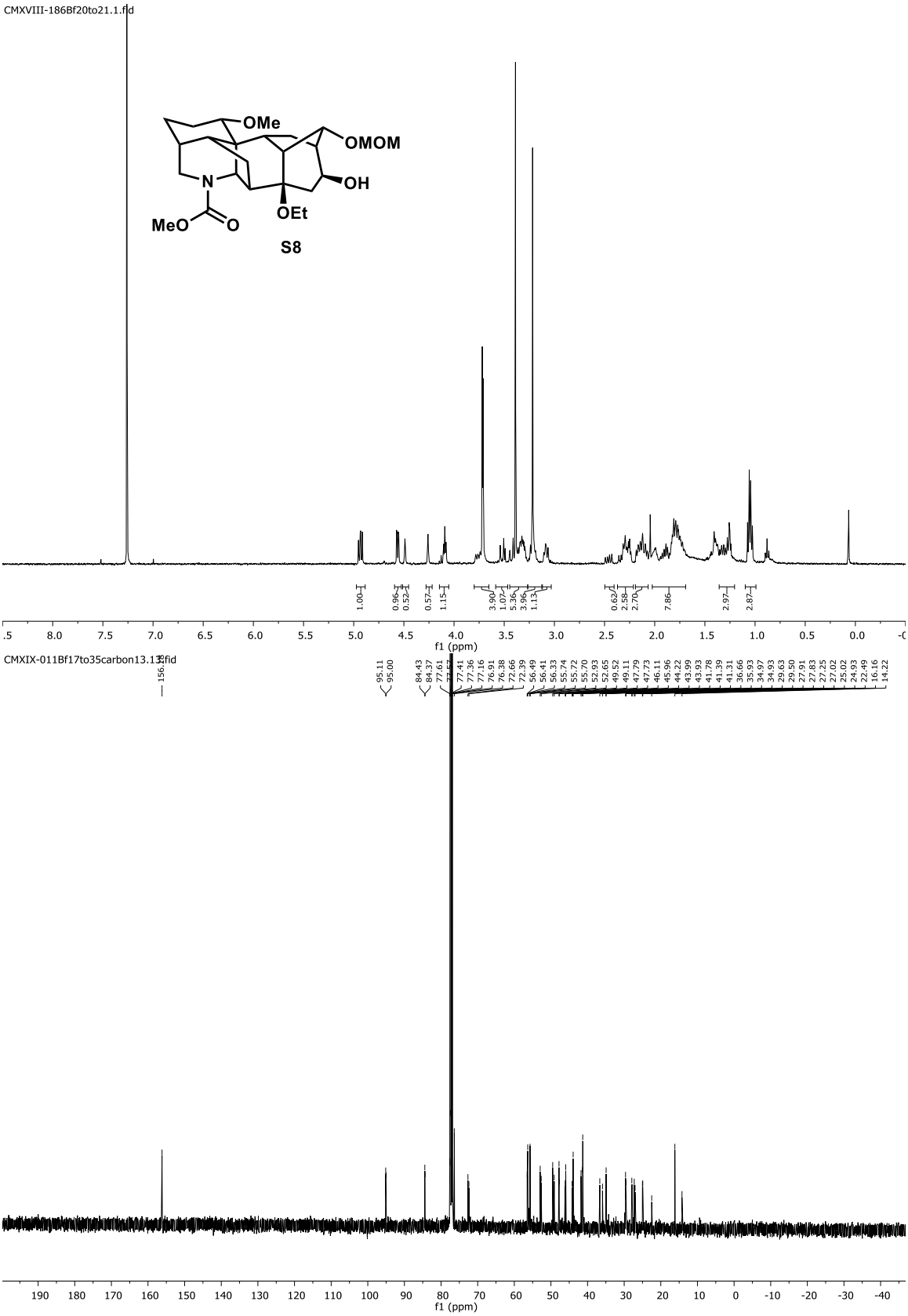
CMXIX-009A.1.fid

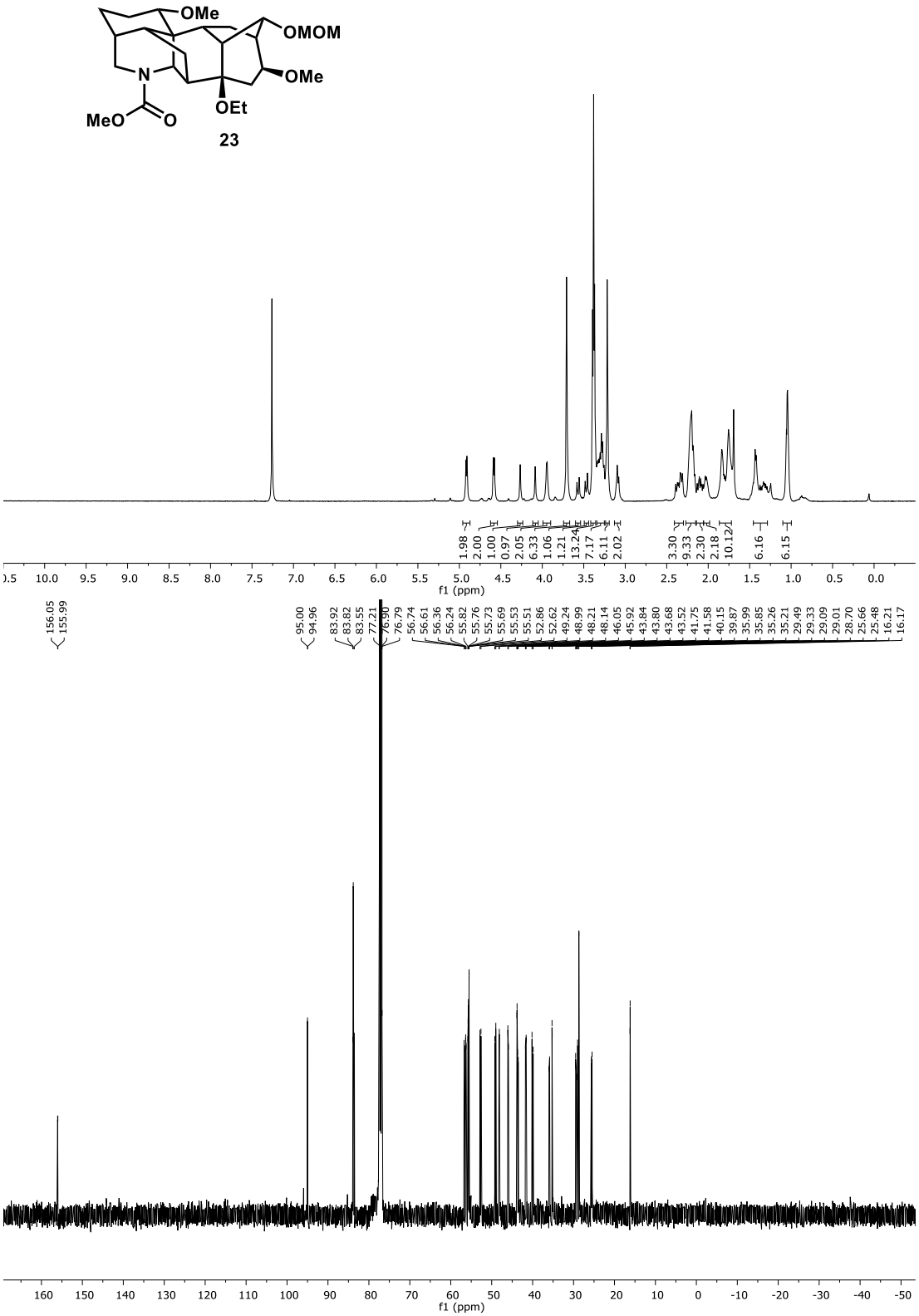


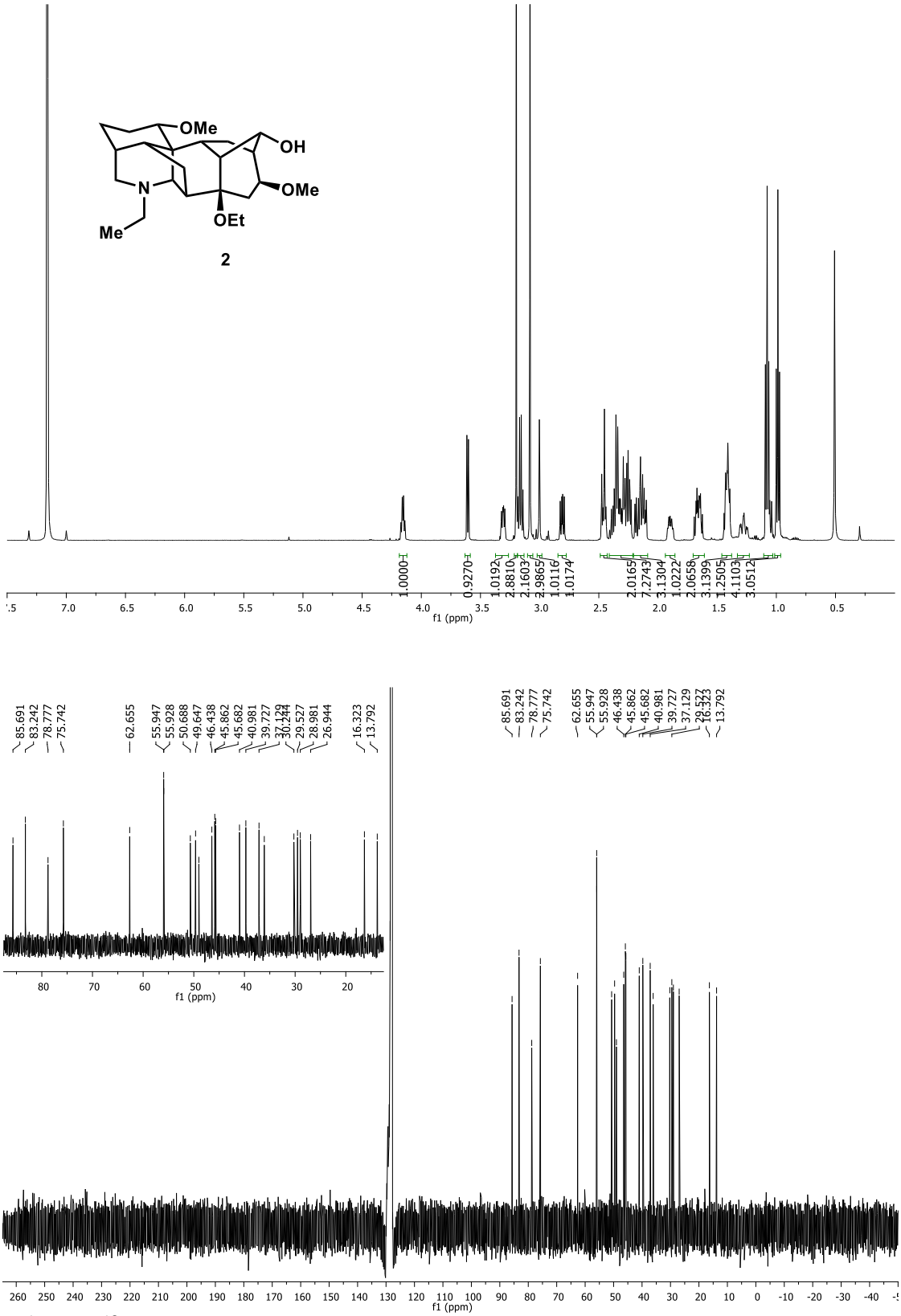
22

CMXVIII-204Bcarbon1.13.fid

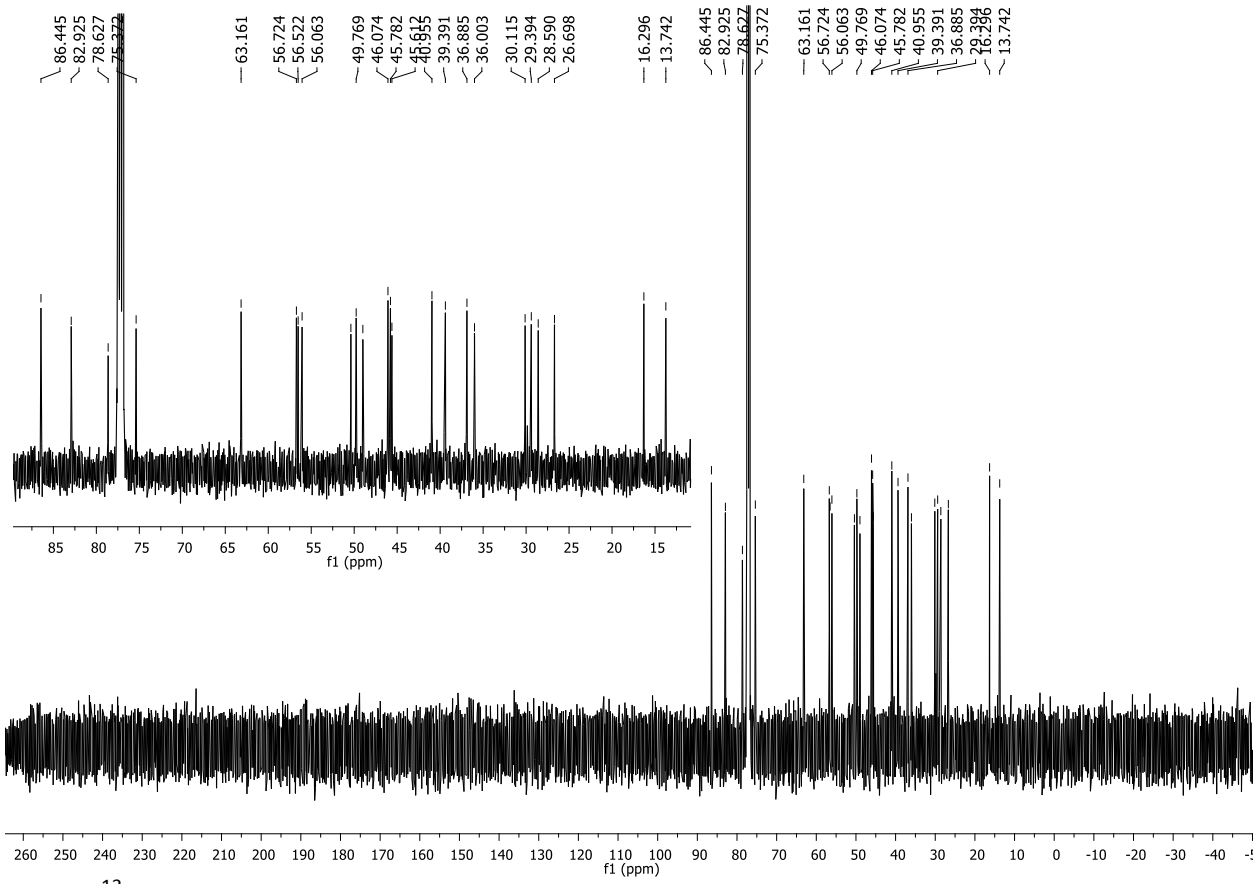



CMXVIII-186Bf20to21.1.fid
OMe
OMOM
OH
N
OEt
MeO
O
S8
f1 (ppm)
CMXIX-011Bf17to35carbon13.1.fid
f1 (ppm)


OMe
OMOM
N
OMe
OEt
MeO
O
23
1.98
2.00
1.00
0.97
2.05
6.33
1.06
1.21
13.24
7.17
6.11
2.02
3.30
9.33
2.30
2.18
10.12
6.16
6.15
f1 (ppm)
156.05
155.99
95.00
94.96
83.92
83.82
83.55
77.21
76.90
76.79
56.74
56.61
56.36
56.24
55.82
55.76
55.73
55.69
55.53
55.51
52.86
52.62
49.24
48.99
48.21
48.14
46.05
45.92
43.84
43.80
43.68
43.52
41.75
41.58
40.15
39.87
35.99
35.85
35.26
35.21
29.49
29.33
29.09
29.01
28.70
25.66
25.48
16.21
16.17
f1 (ppm)

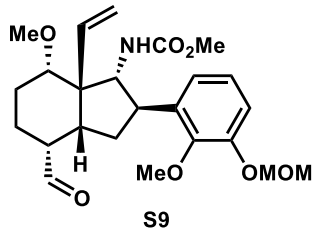


^{1}H and ^{13}C NMR spectra for synthetic weisaconitine D (**2**) in C_6D_6



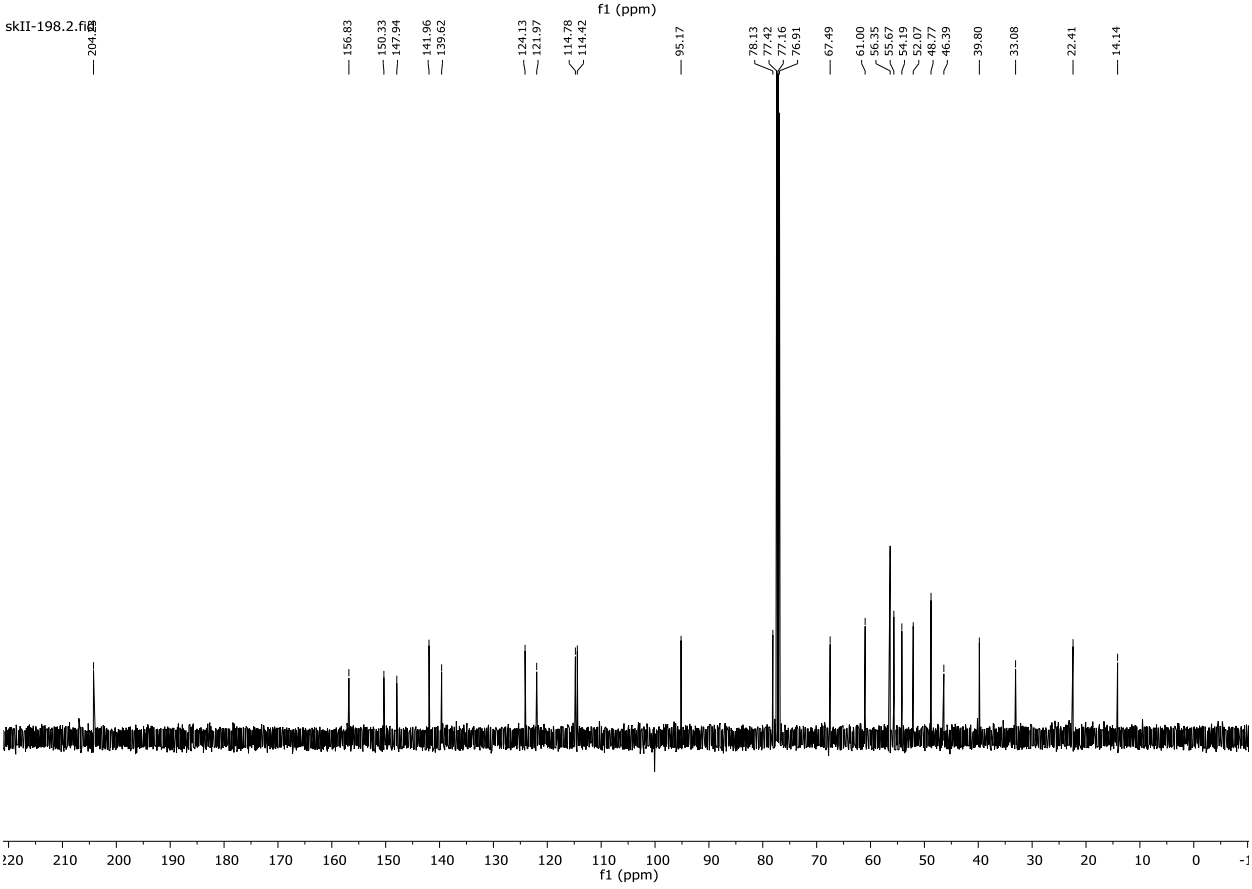
^{13}C NMR spectra for synthetic weisaconitine D (**2**) in $CDCl_3$

skII-198.1.fid

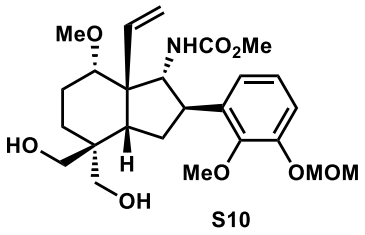


S9

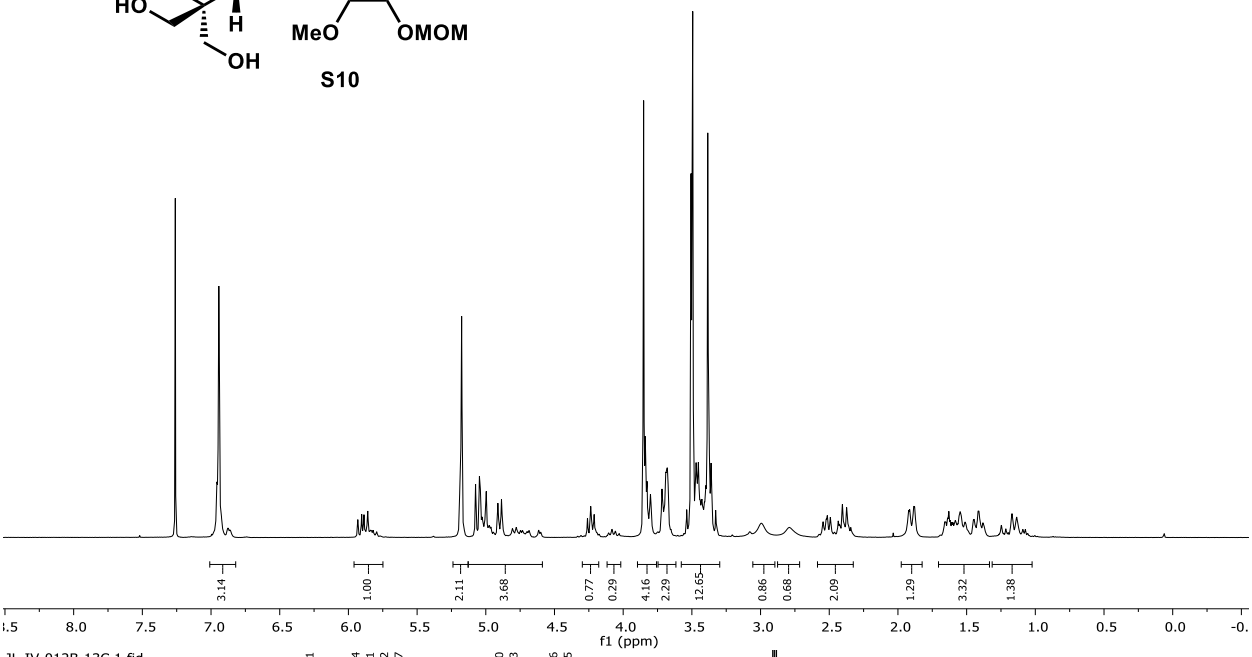
skII-198.2.fid



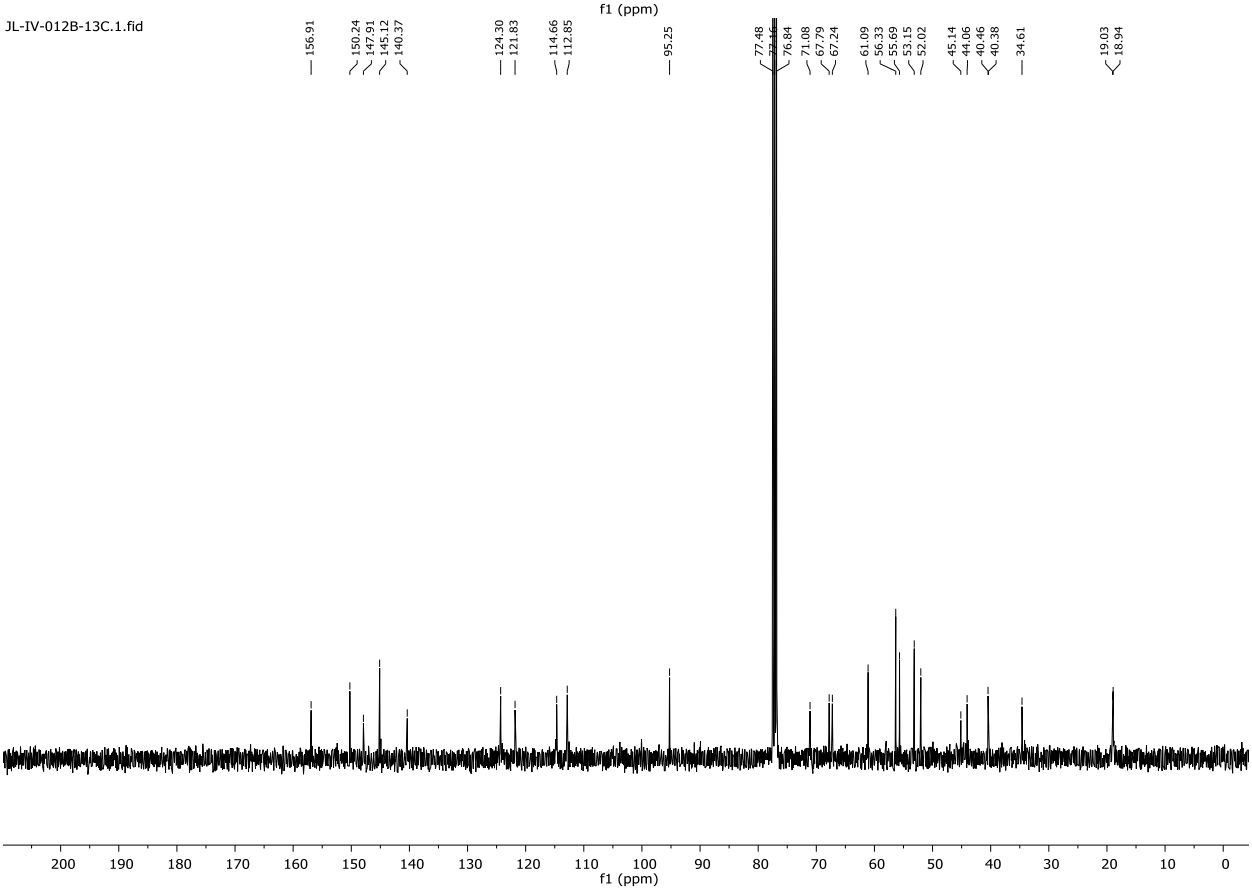
JL-IV-012B-1H.1.fid

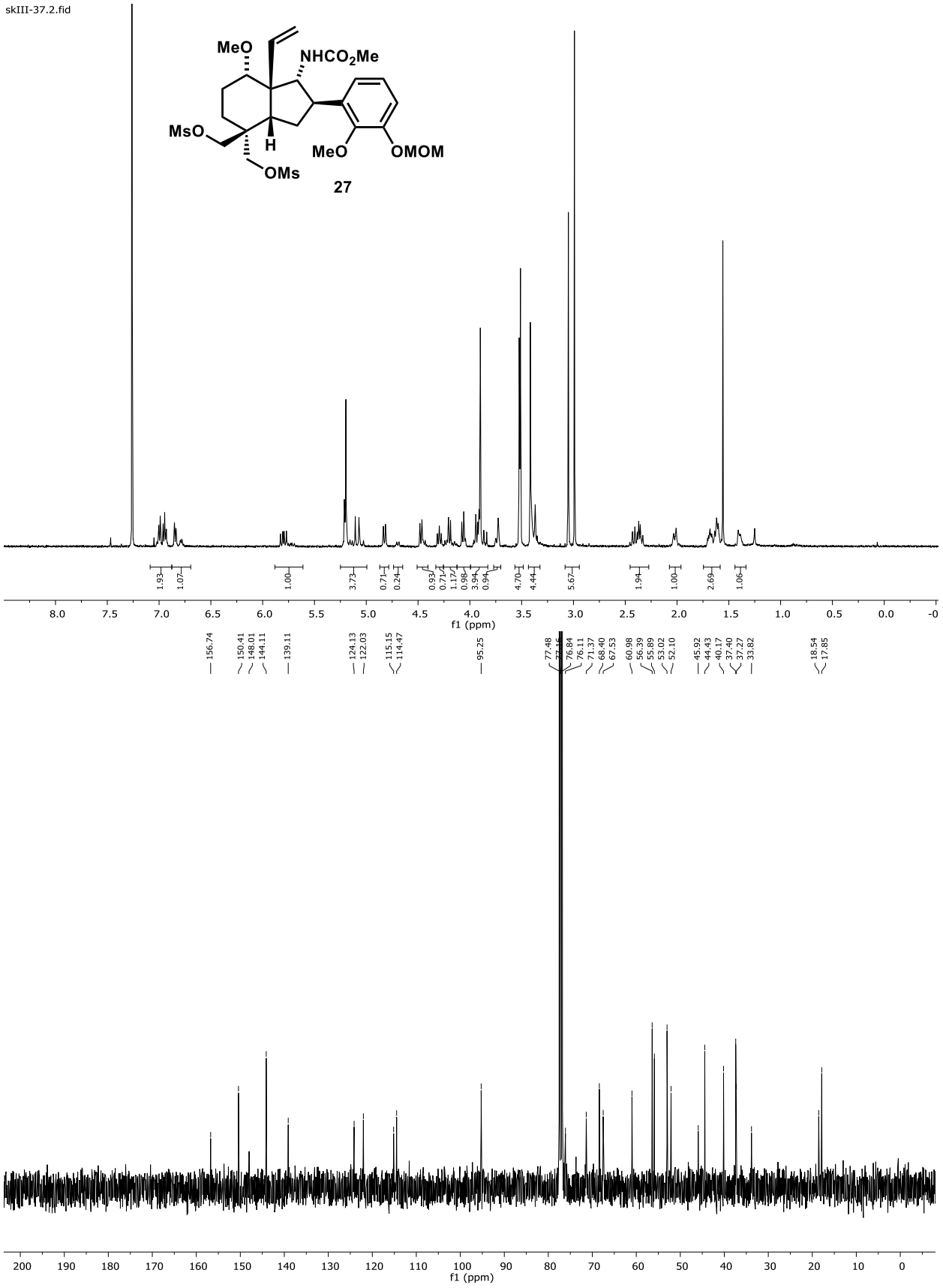


S10

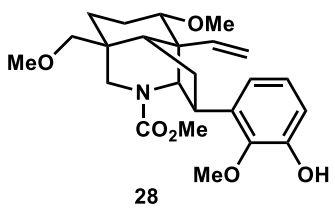


JL-IV-012B-13C.1.fid



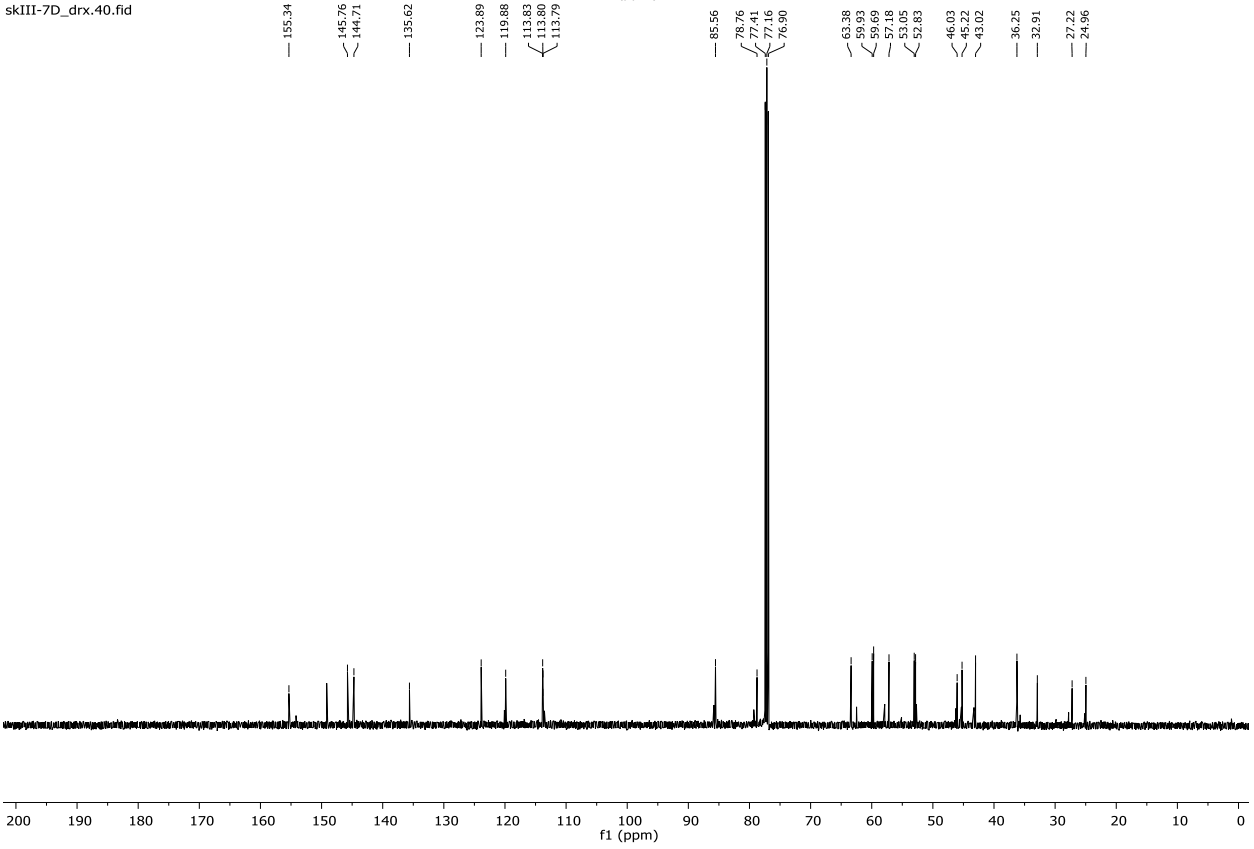

skIII-37.2.fid
MeO
NHCO2Me
MsO
H
MeO
OMOM
OMs
27
f1 (ppm)
f1 (ppm)

skIII-7D_drx.2.fid

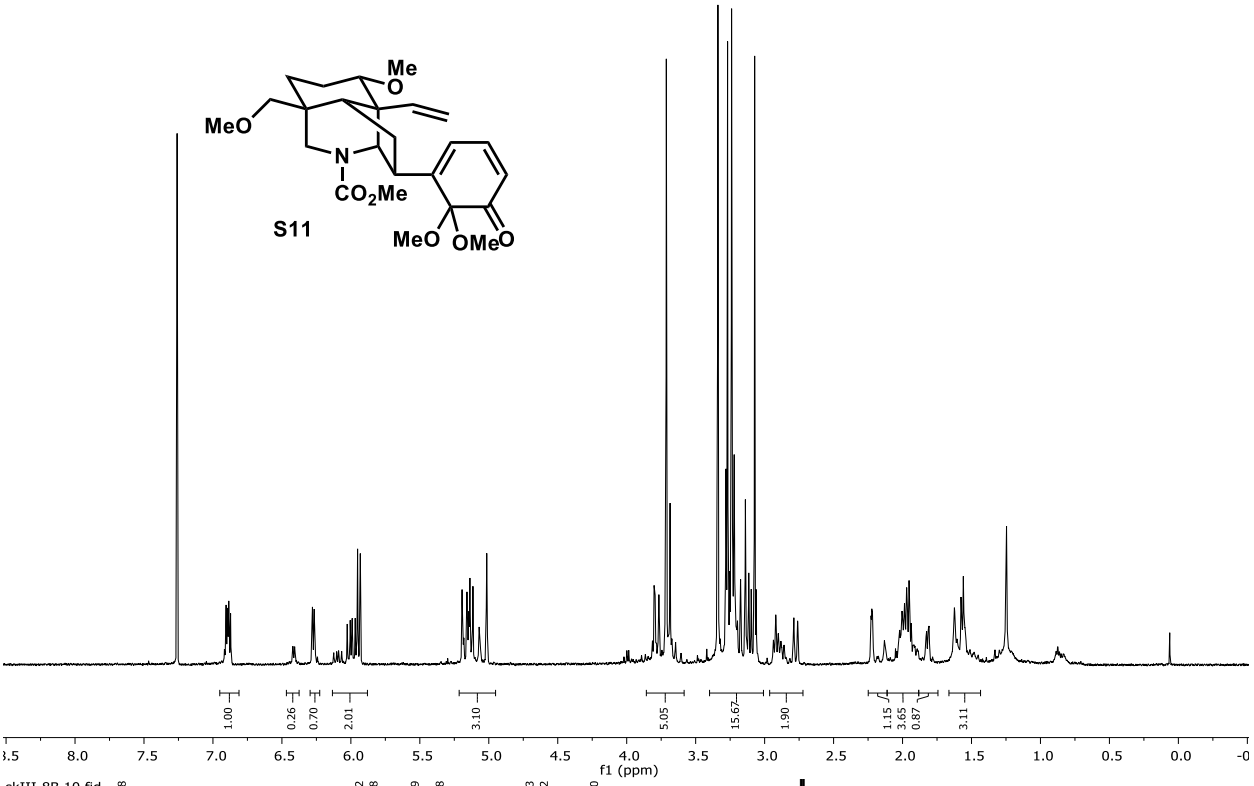


28

skIII-7D_drx.40.fid

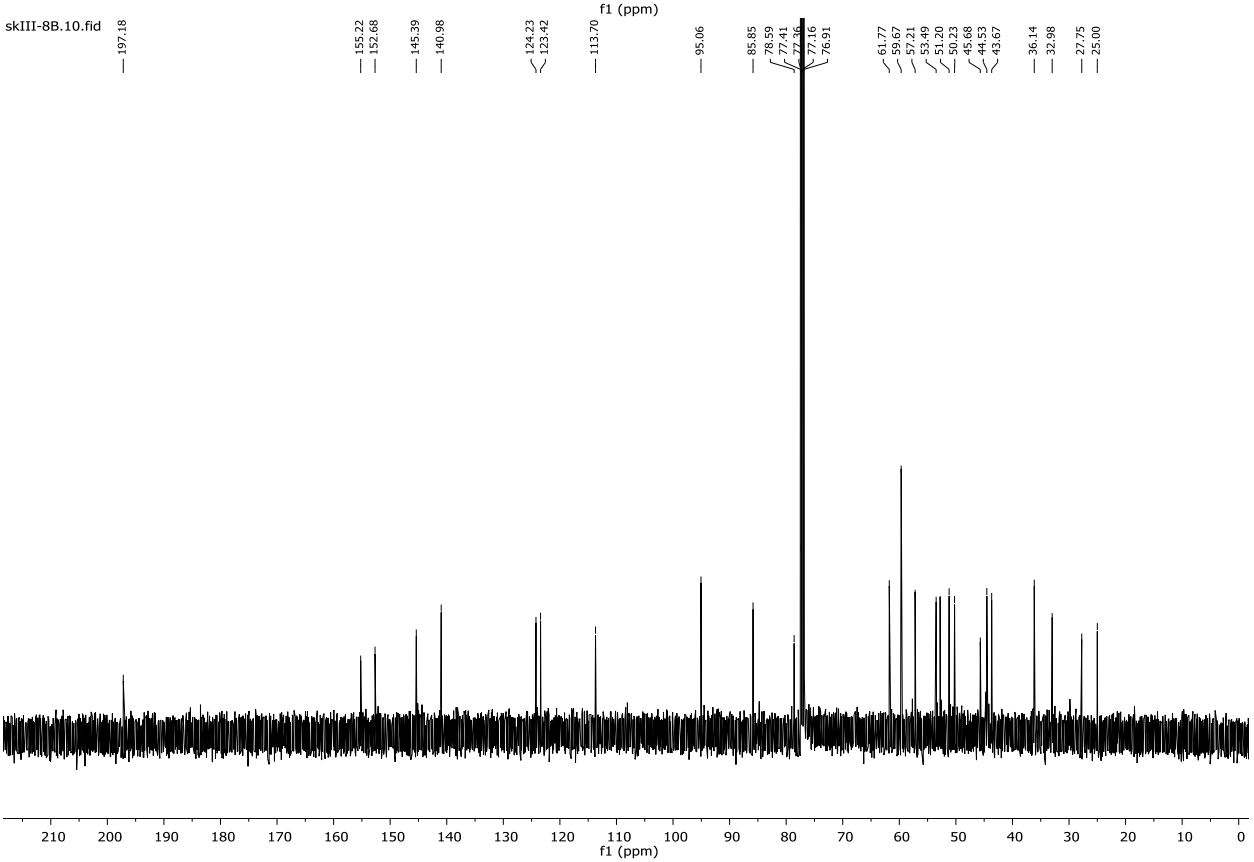


skIII-8B.1.fid

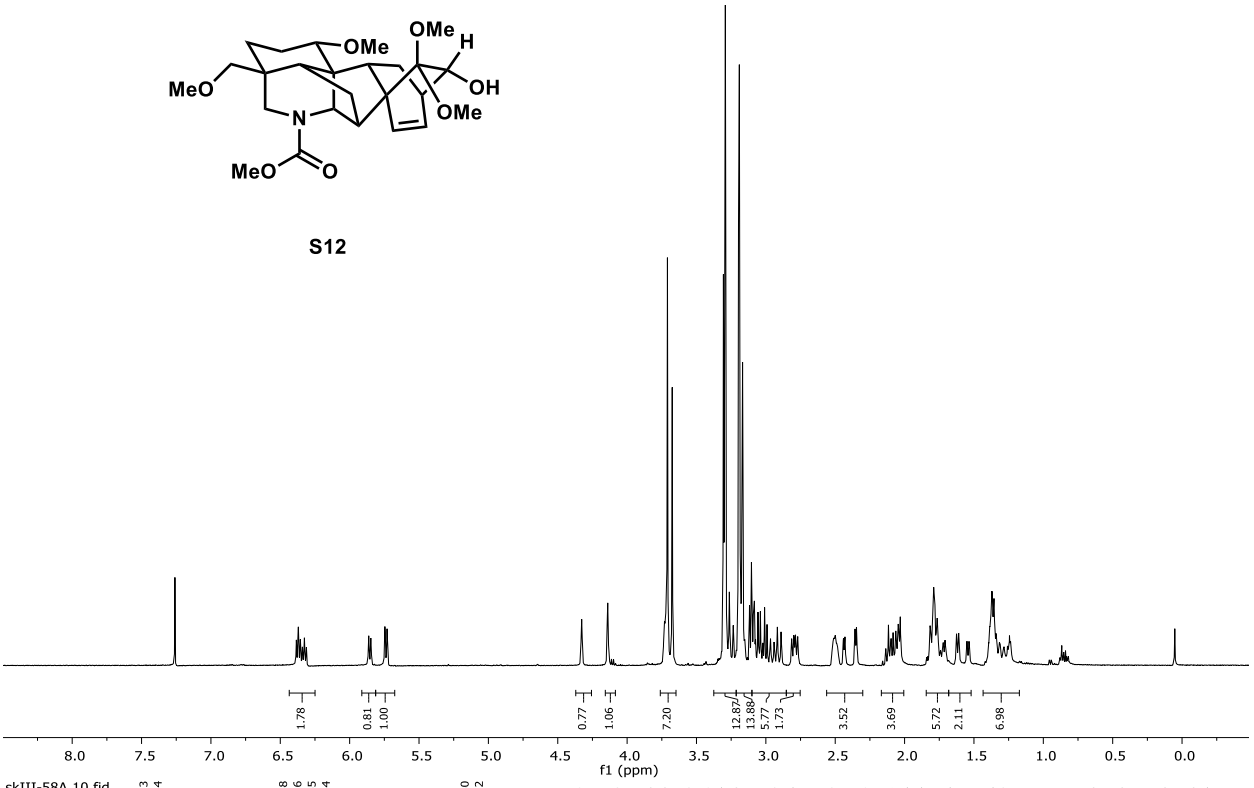


S11

skIII-8B.10.fid

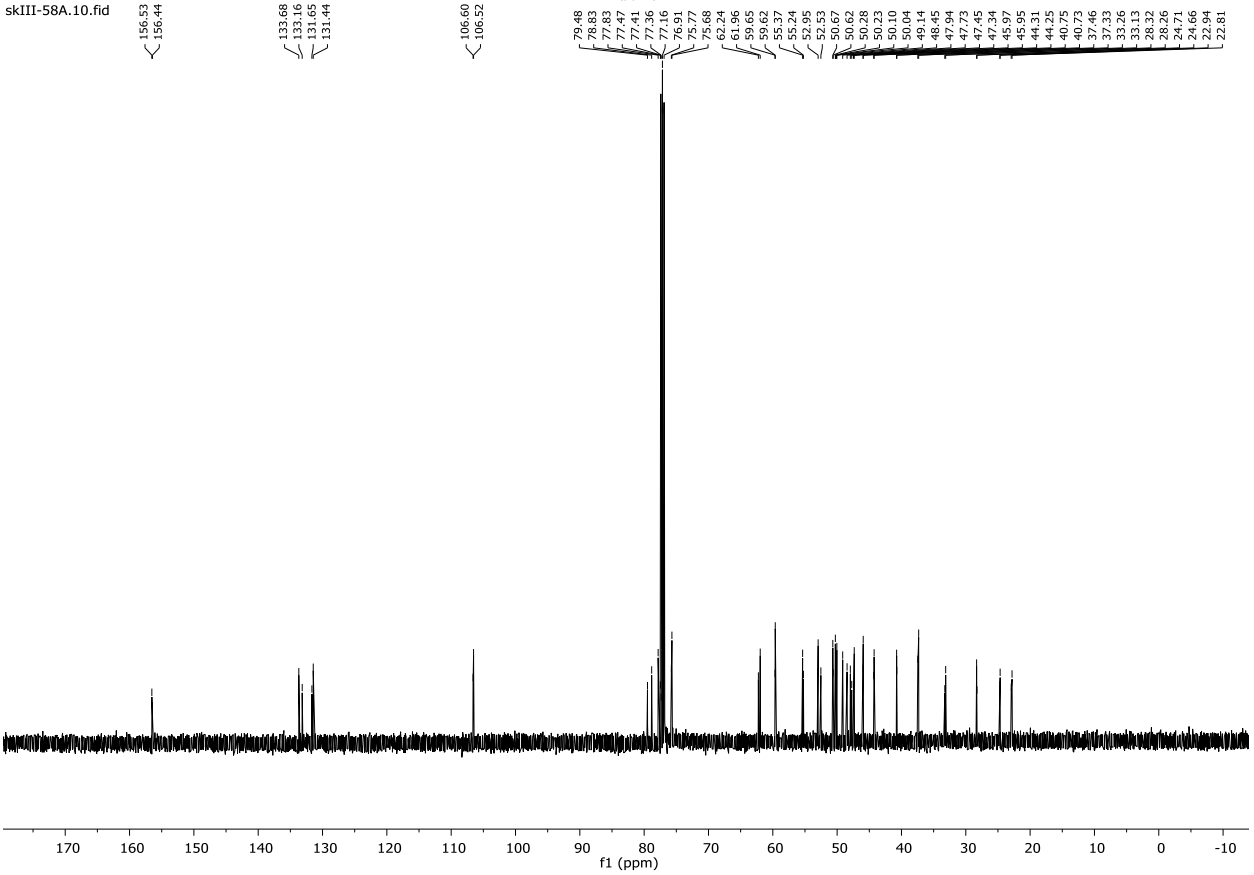


skIII-58A.1.fid

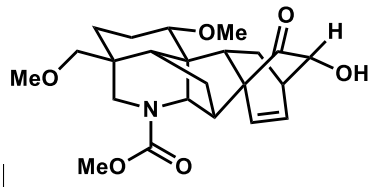


S12

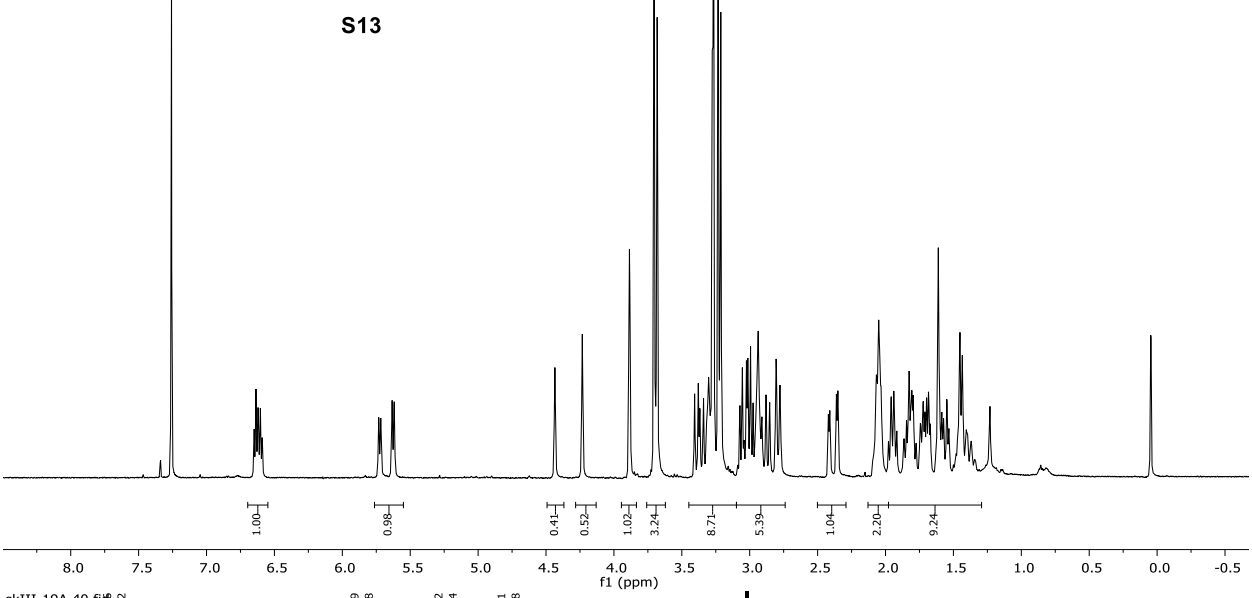
skIII-58A.10.fid



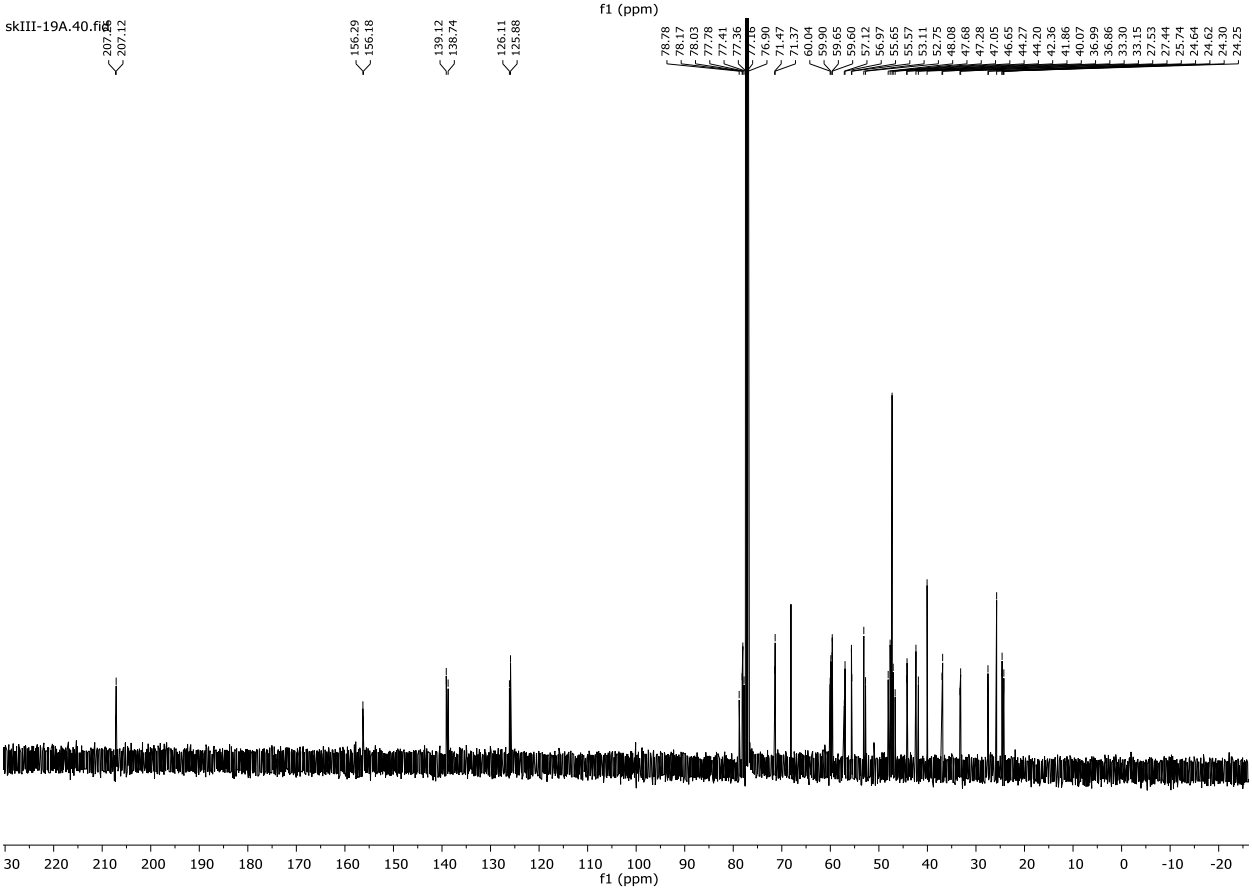
skIII-59.1.fid



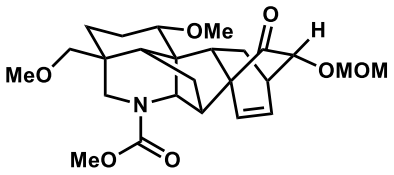
S13



skIII-19A.40.fid

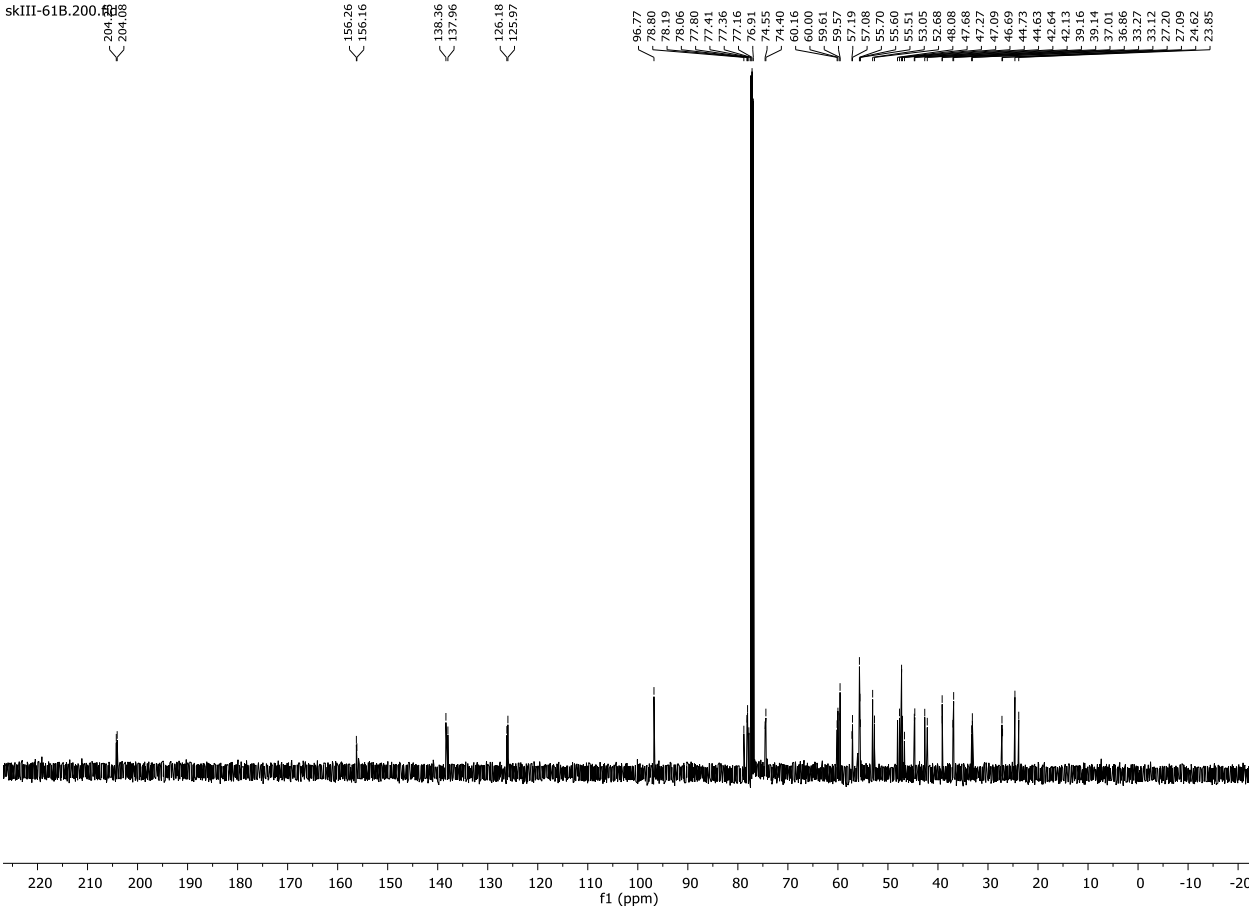


skIII-61B.2.fid

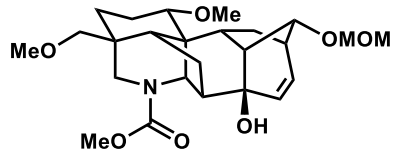


S14

skIII-61B.200.fid

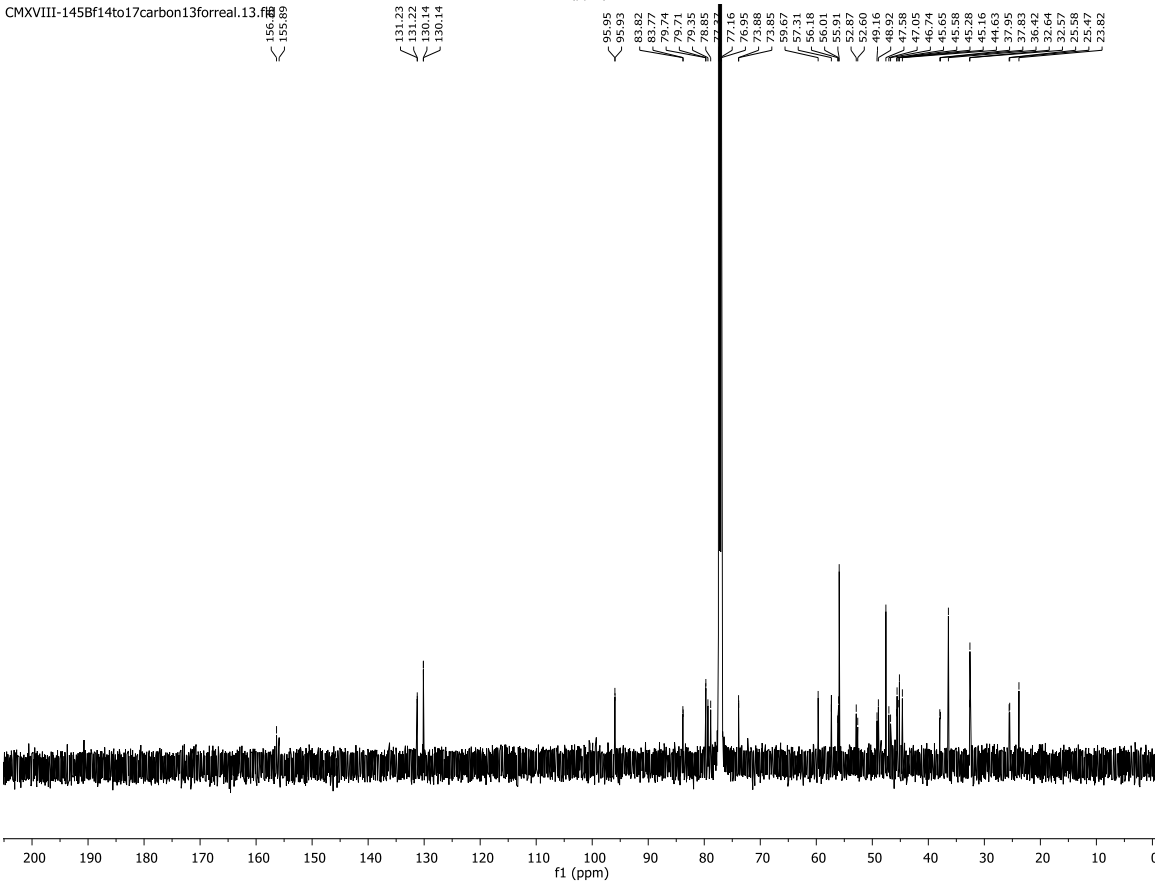


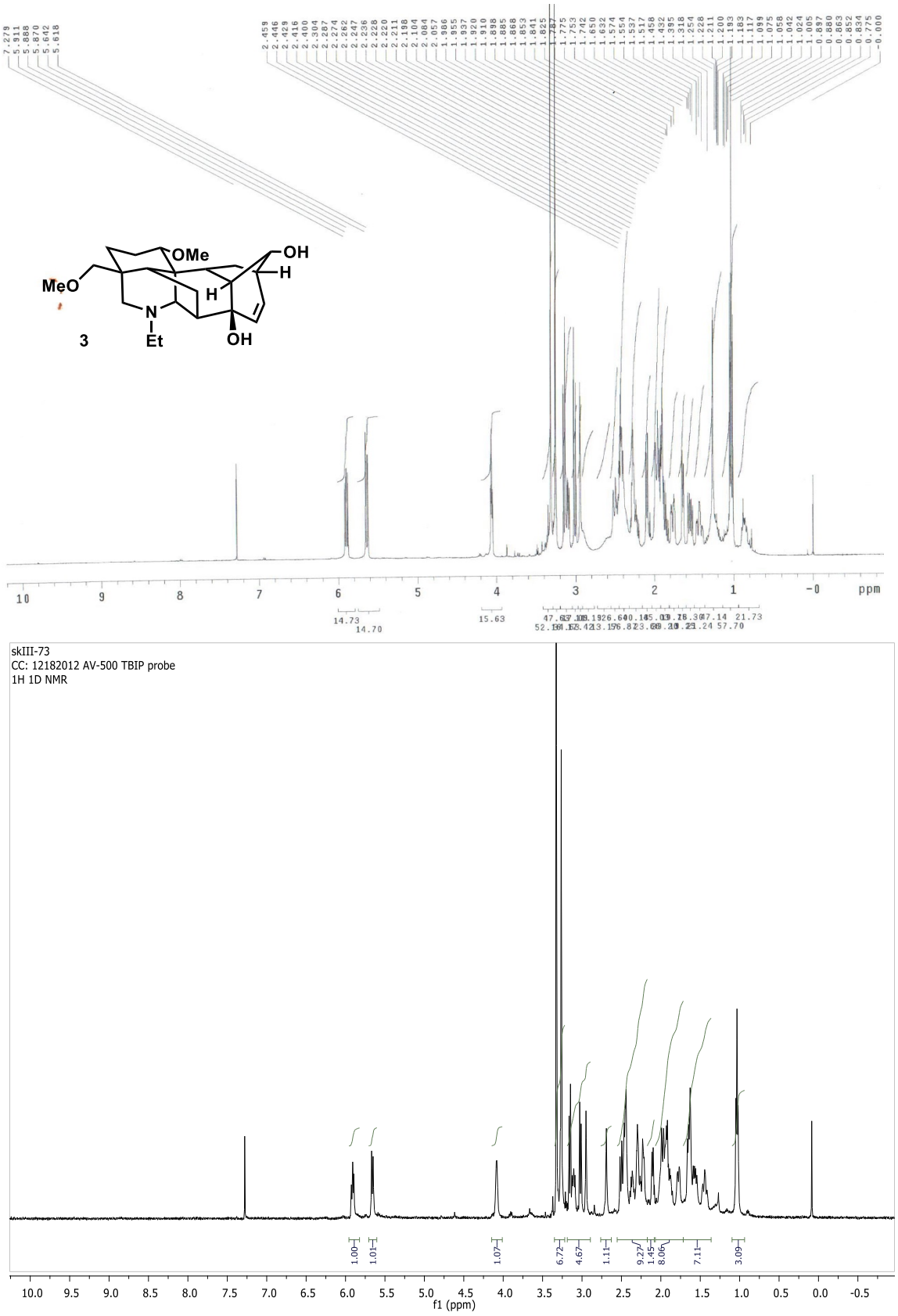
CMXVIII-145Bf19to21.1.fid



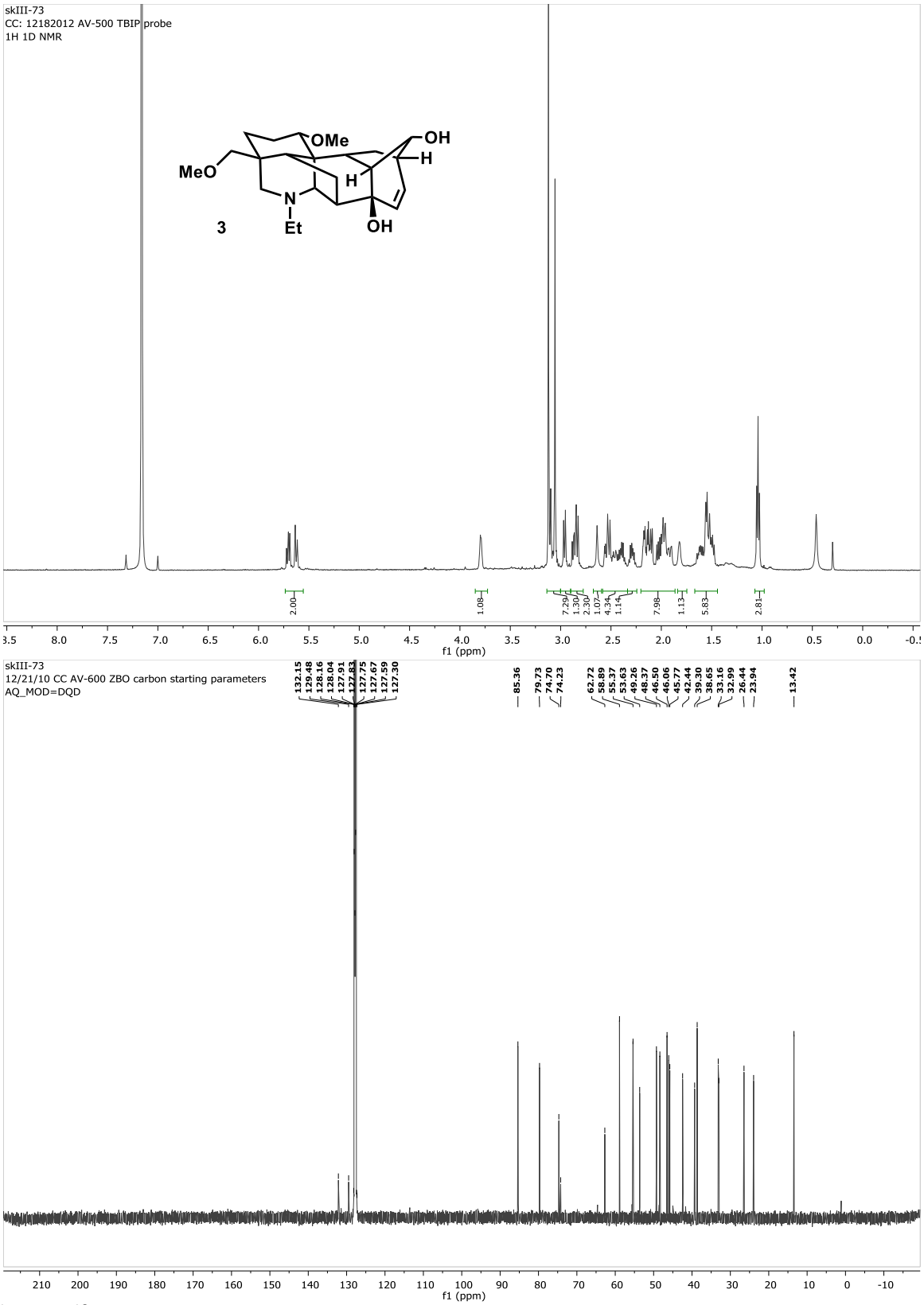
S15

CMXVIII-145Bf14to17carbon13forreal.13.fid

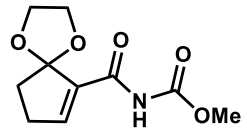




^{1}H NMR spectra for the Isolated (top) and synthetic liljestrandinine in $CDCl_3$

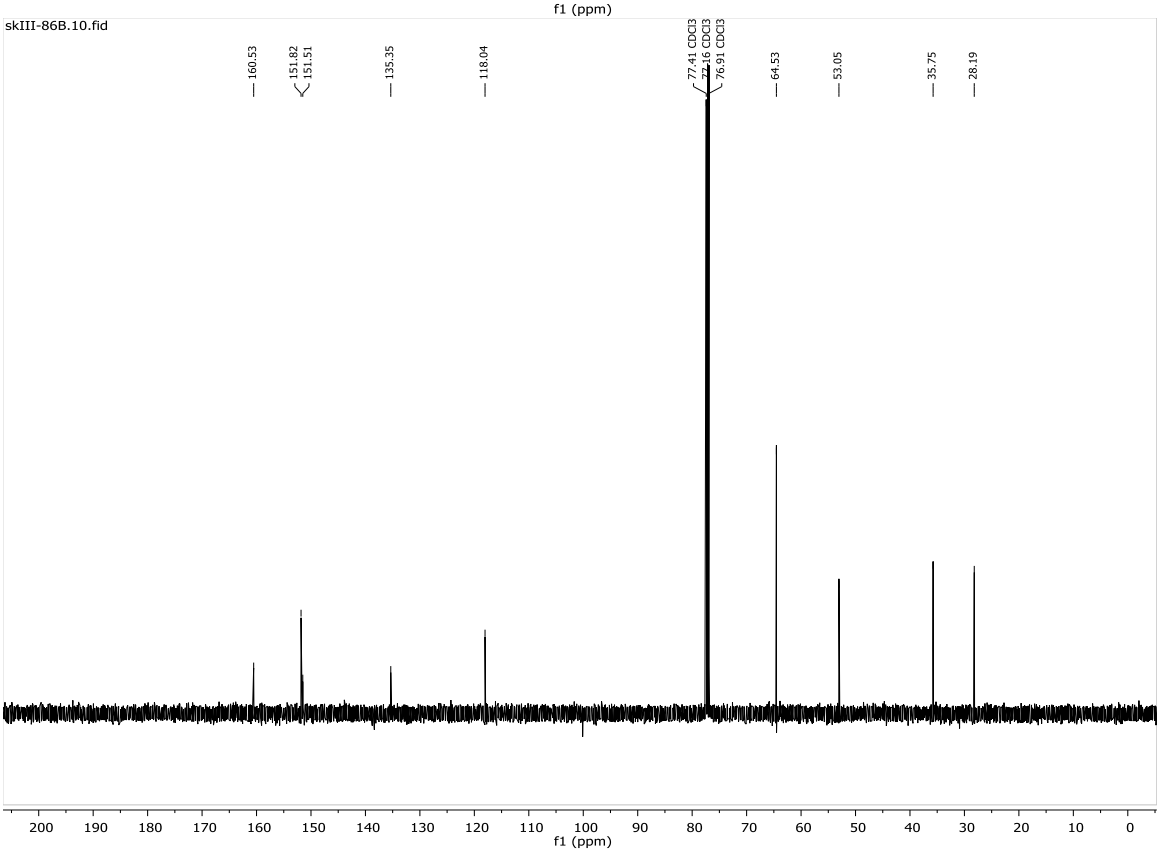


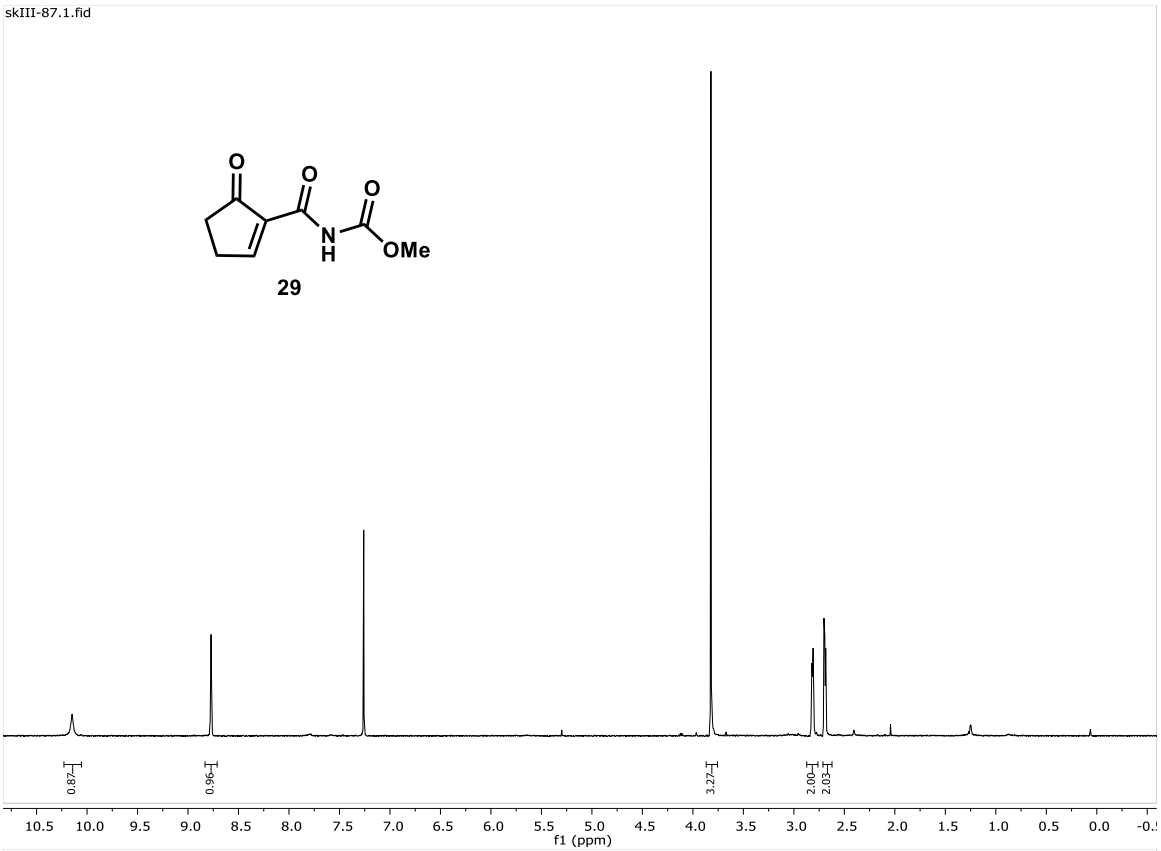
^{1}H and ^{13}C NMR spectra for the synthetic liljestrandinine in C_6D_6

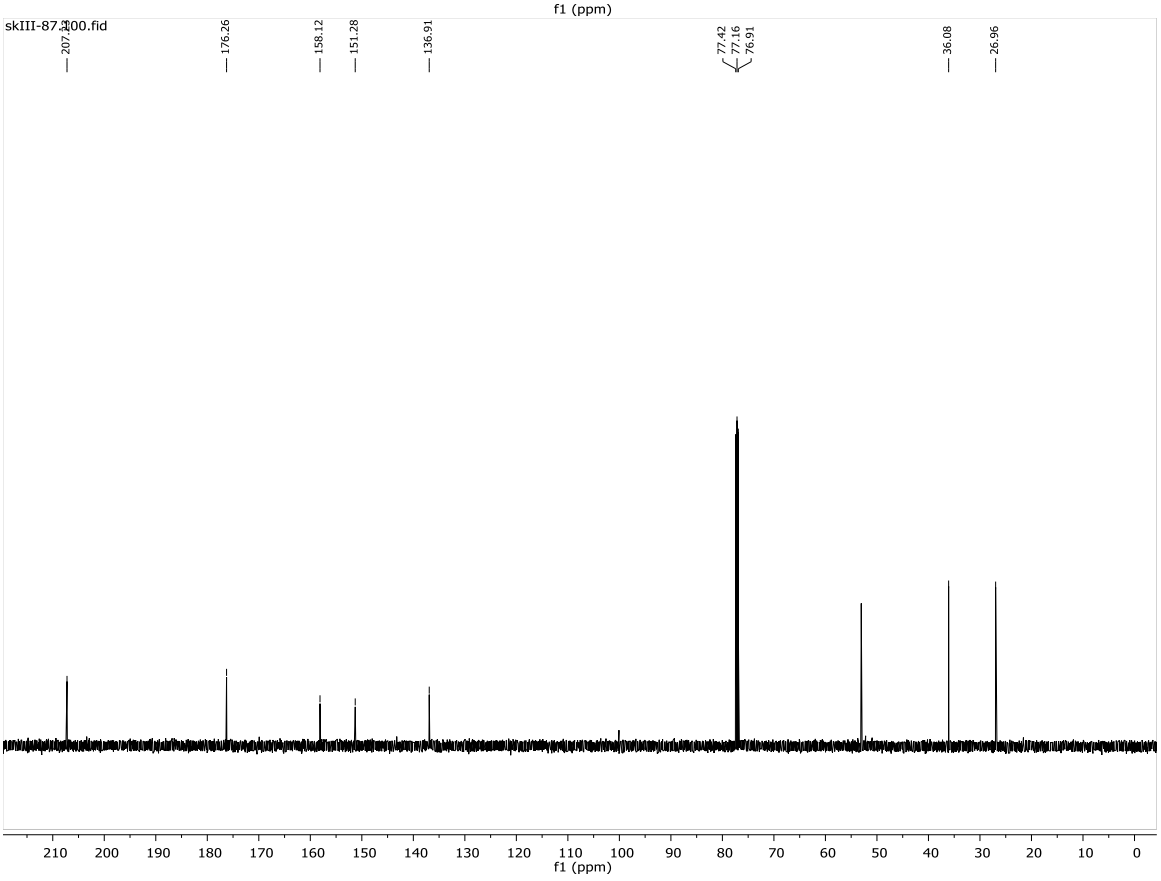

O
O
O
N
H
O
OMe

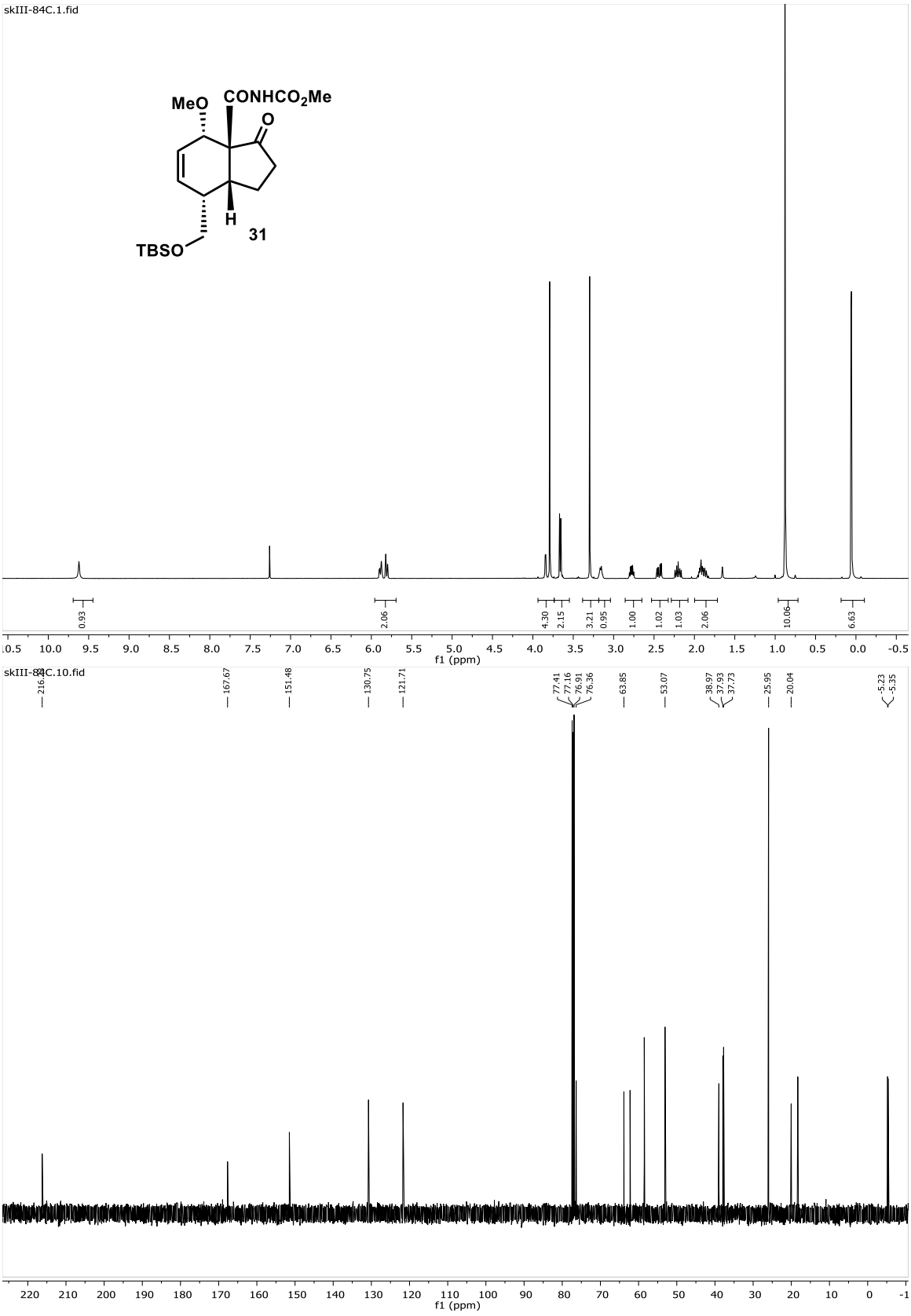
S17

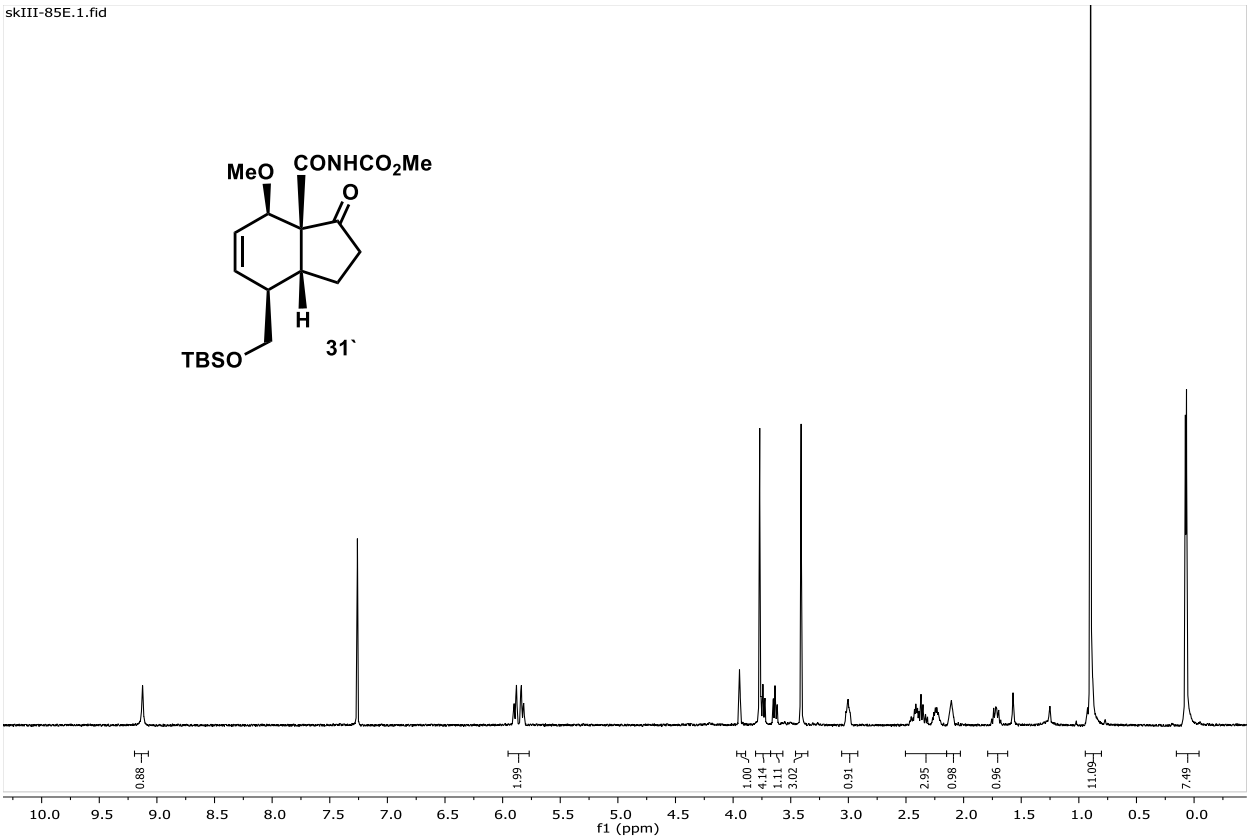
0.91
1.19
2.01
2.00
3.05
1.99
1.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

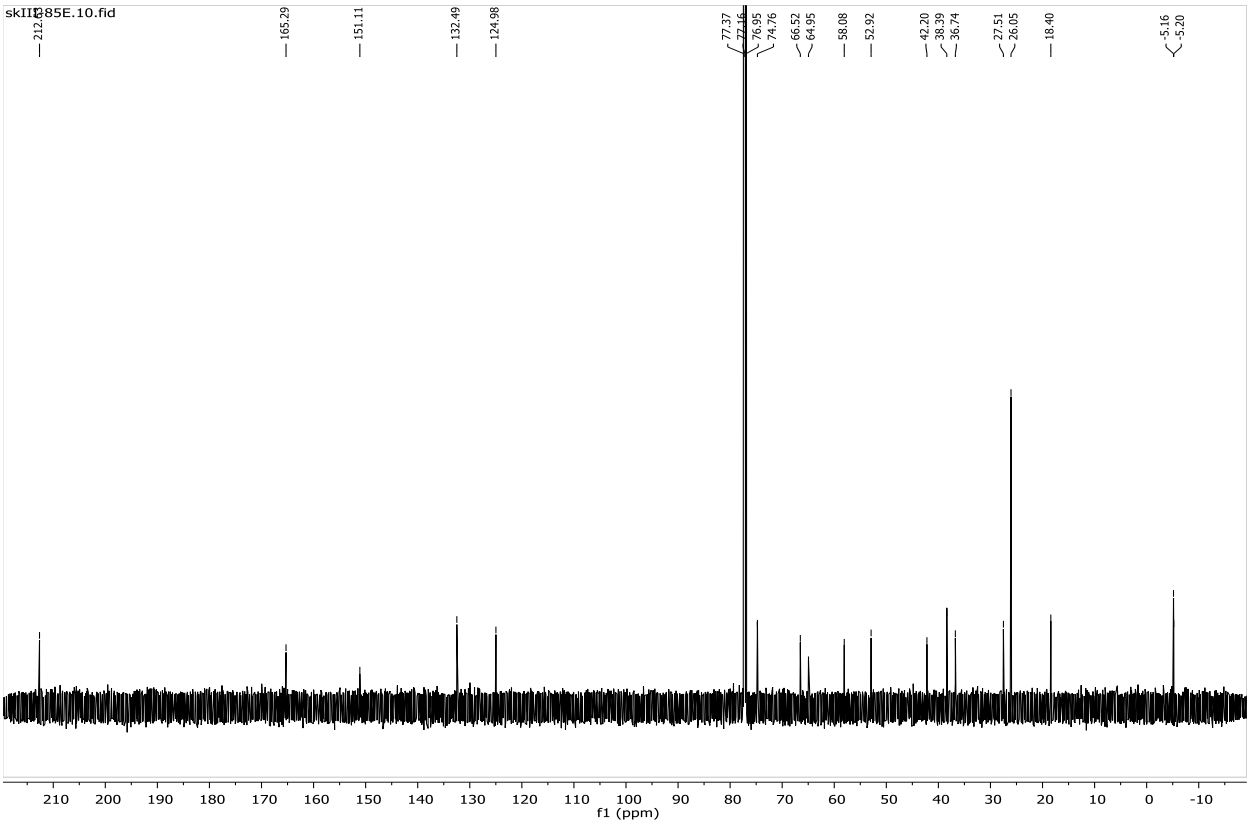

skIII-86B.10.fid
160.53
151.82
151.51
135.35
118.04
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
64.53
53.05
35.75
28.19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


skIII-87.1.fid
O
O
O
N
H
OMe
29
0.87
0.96
3.27
2.00
2.03
f1 (ppm)


skIII-87.100.fid
207.31
176.26
158.12
151.28
136.91
77.42
77.16
76.91
36.08
26.96
f1 (ppm)

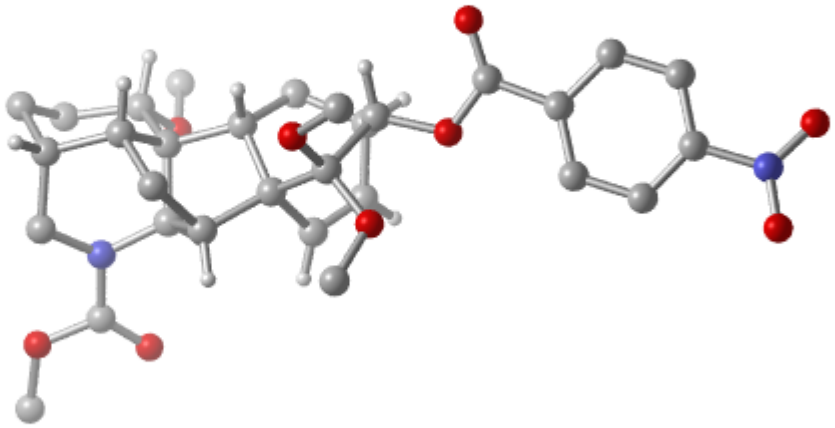

skIII-84C.1.fid
MeO
CONHCO2Me
O
H
TBSO
31
0.93
2.06
4.30
2.15
3.21
0.95
1.00
1.02
1.03
2.06
10.06
6.63
f1 (ppm)
skIII-84C.10.fid
216.24
167.67
151.48
130.75
121.71
77.41
77.16
76.91
76.36
63.85
53.07
38.97
37.93
37.73
25.95
20.04
-5.23
-5.35
f1 (ppm)


skIII-85E.1.fid
MeO
CONHCO2Me
O
H
TBSO
31`
0.88
1.99
1.00
4.14
1.11
3.02
0.91
2.95
0.98
0.96
11.09
7.49
f1 (ppm)


skIII-85E.10.fid
212.48
165.29
151.11
132.49
124.98
77.37
77.16
76.95
74.76
66.52
64.95
58.08
52.92
42.20
38.39
36.74
27.51
26.05
18.40
-5.16
-5.20
f1 (ppm)

7. X-ray data

Compound 24



CCDC 1403763

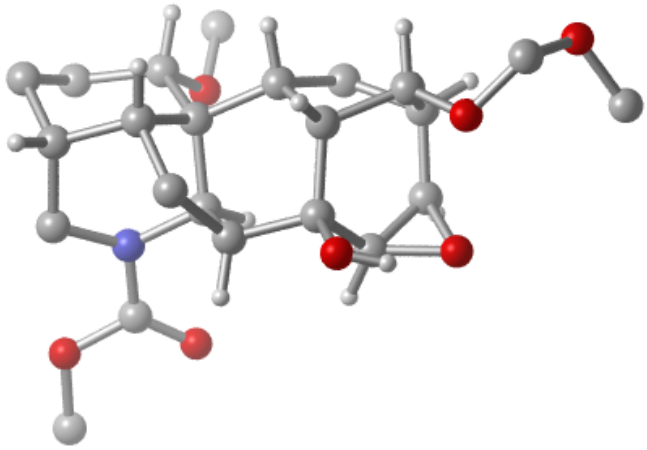
An X-ray quality crystal was obtained by slow diffusion of hexanes into a nearly sat. solution of **24** in EtOAc.

A colorless plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 20 seconds per frame using a scan width of 1.0°. Data collection was 93.1% complete to 67.000° in q. A total of 47090 reflections were collected covering the indices, -9<=*h*<=10, -62<=*k*<=62, -13<=*l*<=14. 47090 reflections were found to be symmetry independent, with an R_{int} of 0.0729. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 2(1)/a (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the TWINABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013.

Crystal data and structure refinement for **24**

X-ray ID	sarpong64	
Sample/notebook ID	JLII-050B	
Empirical formula	C30 H36 N2 O9	
Formula weight	568.61	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2(1)/a	
Unit cell dimensions	a = 9.0579(6) Å	a= 90°.
	b = 51.983(3) Å	b= 90.896(4)°.
	c = 11.7360(8) Å	g = 90°.
Volume	5525.3(6) $Å^3$	
Z	8	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.840 mm^{-1}	
F(000)	2416	
Crystal size	0.050 x 0.040 x 0.020 mm^3	
Crystal color/habit	colorless plate	
Theta range for data collection	3.401 to 68.876°.	
Index ranges	-9<=h<=10, -62<=k<=62, -13<=l<=14	
Reflections collected	47090	
Independent reflections	47090 [R(int) = 0.0729]	
Completeness to theta = 67.000°	93.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.815	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	47090 / 0 / 749	
Goodness-of-fit on F^2	1.423	
Final R indices [I>2sigma(I)]	R1 = 0.1549, wR2 = 0.4185	
R indices (all data)	R1 = 0.1825, wR2 = 0.4365	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.274 and -0.770 $e.Å^{-3}$	

Compound 25



CCDC 1402818

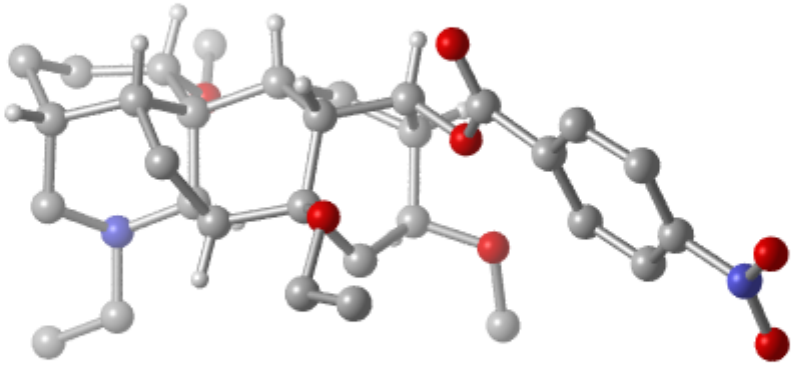
X-ray quality crystals were obtained upon slow vapor diffusion of α-hydroxy epoxide **25** in EtOAc by hexanes.

A colorless plate 0.060 x 0.050 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 99.0% complete to 67.000° in q. A total of 58954 reflections were collected covering the indices, -15<=*h*<=15, -15<=*k*<=15, -10<=*l*<=14. 3667 reflections were found to be symmetry independent, with an R_{int} of 0.0367. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Crystal data and structure refinement for **25**

X-ray ID	sarpong102	
Sample/notebook ID	CMXVIII-057	
Empirical formula	C23 H33 N O7	
Formula weight	435.50	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 12.9748(4) Å	a= 90°.
	b = 13.2435(4) Å	b= 109.5720(10)°.
	c = 12.4982(4) Å	g = 90°.
Volume	2023.50(11) $Å^3$	
Z	4	
Density (calculated)	1.430 Mg/m^3	
Absorption coefficient	0.868 mm^{-1}	
F(000)	936	
Crystal size	0.060 x 0.050 x 0.030 mm^3	
Theta range for data collection	3.615 to 68.343°.	
Index ranges	-15<=h<=15, -15<=k<=15, -10<=l<=14	
Reflections collected	58954	
Independent reflections	3667 [R(int) = 0.0367]	
Completeness to theta = 67.000°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.831	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3667 / 0 / 284	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0885	
R indices (all data)	R1 = 0.0377, wR2 = 0.0907	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.293 and -0.207 $e.Å^{-3}$	

Compound 26



CDC 1402820

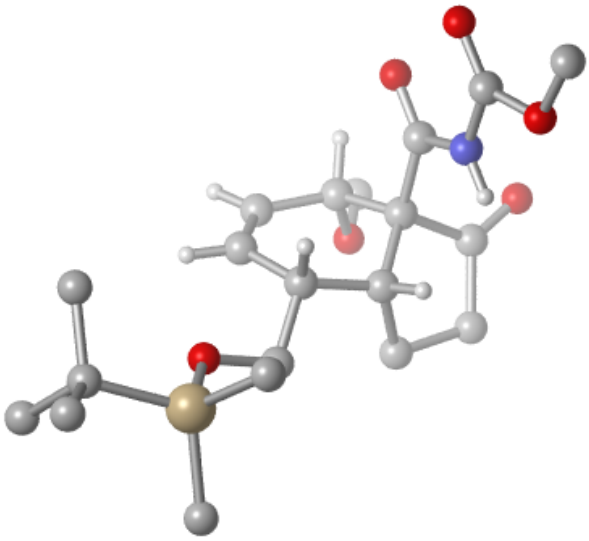
X-ray quality crystals were obtained upon slow vapor diffusion of *p*-nitrobenzoate **26** in EtOAc by hexanes.

A yellow prism 0.070 x 0.050 x 0.050 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 1 seconds per frame using a scan width of 2.0°. Data collection was 98.3% complete to 67.000° in q. A total of 61052 reflections were collected covering the indices, -14<=*h*<=14, -19<=*k*<=19, -19<=*l*<=18. 10230 reflections were found to be symmetry independent, with an R_{int} of 0.0475. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Crystal data and structure refinement for **26**

X-ray ID	sarpong112	
Sample/notebook ID	cm-43	
Empirical formula	C31 H42 N2 O7	
Formula weight	554.66	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 12.1886(4) Å	a= 70.955(2)°.
	b = 16.0833(6) Å	b= 82.179(2)°.
	c = 16.2622(6) Å	g = 70.930(2)°.
Volume	2846.50(18) $Å^3$	
Z	4	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	0.743 mm^{-1}	
F(000)	1192	
Crystal size	0.070 x 0.050 x 0.050 mm^3	
Theta range for data collection	2.876 to 68.371°.	
Index ranges	-14<=h<=14, -19<=k<=19, -19<=l<=18	
Reflections collected	61052	
Independent reflections	10230 [R(int) = 0.0475]	
Completeness to theta = 67.000°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.845	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10230 / 0 / 729	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.1072	
R indices (all data)	R1 = 0.0481, wR2 = 0.1121	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.320 and -0.263 $e.Å^{-3}$	

Compound (+)-31



CCDC 1402704

X-ray quality crystals were obtained by slow evaporation of a compound **31** solution (6 mg/0.5 mL) in hexanes. The absolute configuration was determined with Cu radiation.

A colorless blade 0.060 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 50 mm and exposure time was 45 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 25.000° in q. A total of 55002 reflections were collected covering the indices, -12<=*h*<=12, -16<=*k*<=15, -38<=*l*<=38. 8292 reflections were found to be symmetry independent, with an R_{int} of 0.1837. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Absolute stereochemistry was unambiguously determined to be *R* at C5, C6, C25 and C26, and *S* at C1, C2, C21 and C22, respectively.

Crystal data and structure refinement for **(+)-31**

X-ray ID	sarpong109	
Sample/notebook ID	skIII-119A	
Empirical formula	C20 H33 N O6 Si	
Formula weight	411.56	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.6244(18) Å	a= 90°.
	b = 13.337(2) Å	b= 90°.
	c = 31.677(5) Å	g = 90°.
Volume	4488.5(12) $Å^3$	
Z	8	
Density (calculated)	1.218 Mg/m^3	
Absorption coefficient	0.138 mm^{-1}	
F(000)	1776	
Crystal size	0.060 x 0.040 x 0.020 mm^3	
Theta range for data collection	1.286 to 25.520°.	
Index ranges	-12<=h<=12, -16<=k<=15, -38<=l<=38	
Reflections collected	55002	
Independent reflections	8292 [R(int) = 0.1837]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.928 and 0.550	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8292 / 0 / 519	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0670, wR2 = 0.1345	
R indices (all data)	R1 = 0.1209, wR2 = 0.1611	
Absolute structure parameter	-0.08(17)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.349 and -0.375 $e.Å^{-3}$	