Electronic Supplementary Material (ESI) for Chemical Science

Modular Synthesis of the Pentacyclic Core of Batrachotoxin and Select Batrachotoxin Analogue Designs

Supporting Information

(*44 pages*)

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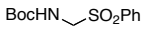
General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~20 Torr) by rotary evaporation. Dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), acetonitrile (MeCN), and toluene were passed through columns of activated alumina immediately prior to use. Methanol, dichloroethane (DCE), triethylamine, *N*,*N*-diisopropylamine and *N*,*N*,*N*-diisopropylethylamine were distilled from CaH_2 immediately prior to use. 2,6-Lutidine was dried over activated 3Å molecular sieves. Chromatographic purification of products was accomplished using forced flow chromatography on Silicycle silica gel 60 (40–63 μm). Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with aqueous potassium permanganate or aqueous ceric ammonium molybdate (CAM) solution.

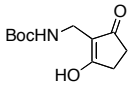
Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Inova spectrometer operating at 400, 500 or 600 and 100, 125 or 150 MHz for ^1H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded as either thin films using NaCl plates on a Thermo-Nicolet 300 FT-IR spectrometer and are reported in frequency of absorption. High resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

Experimental procedures and characterization for compounds appearing in Schemes 1–3:



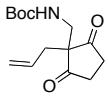
8

***tert*-Butyl ((phenylsulfonyl)methyl)carbamate.** Formic acid (8.0 mL, 212 mmol, 1.2 equiv) was added dropwise to a vigorously stirred solution of $PhSO_2Na$ (72.5 g, 442 mmol, 2.5 equiv), *t*-butylcarbamate (20.7 g, 177 mmol), and 37% w/w aqueous formaldehyde (28.7 g, 353 mmol, 2.0 equiv) in 410 mL of H_2O and 135 mL of CH_3OH. The solution was stirred for 10 days, during which time a white precipitate formed. The solid material was collected by vacuum filtration with a sintered glass funnel, and the flask and filter cake were washed with 5 x 20 mL portions of H_2O. The isolated product **8** was dried in vacuo (37.6 g, 78%). Additional purification of this material was deemed unnecessary based on the recorded NMR data. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, 2H, J = 7.7 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.55 (t, 2H, J = 7.8 Hz), 5.33 (br s, 1H), 4.53 (d, 2H, J = 7.0 Hz), 1.25 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.1, 137.0, 134.4, 129.4, 129.2, 81.3, 62.3, 28.2 ppm; IR (thin film) ν 3355, 1696, 1366, 1288, 1145, 1087, 1009 cm^{-1}; HRMS (ES^+) calcd $C_{12}H_{17}NO_4S$ 294.0776 found 294.0770 (MNa^+).



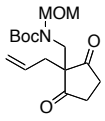
9

tert-Butyl ((2-hydroxy-5-oxocyclopent-1-en-1-yl)methyl)carbamate. To a solution of **8** (17.8 g, 65.5 mmol, 1.1 equiv) and 1,3-cyclopentanedione (5.8 g, 59.6 mmol) in 250 mL of THF was added dropwise over 7 min 1,8-diazabicyclo[5.4.0]undec-7-ene (8.9 mL, 59.5 mmol, 1.0 equiv). After stirring this mixture for 10 min, a second portion of 1,8-diazabicyclo[5.4.0]undec-7-ene was added (9.8 mL, 65.5 mmol, 1.1 equiv) dropwise. The reaction was stirred for 21 h then concentrated under reduced pressure to one-third its original volume. The contents were transferred to a separatory funnel with 100 mL of $CHCl_3$ and the organic layer was washed with 400 mL of a pH 4 aqueous NaH_2PO_4/Na_2HPO_4 buffer. The aqueous fraction was collected and extracted with 5 x 160 mL of $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to an orange oil. Purification of this material by chromatography on silica gel (gradient elution: 3.5→4% $MeOH/CH_2Cl_2$) afforded vinylogous acid **9** as a white solid (11.6 g, 86%). TLC R_f = 0.56 (10% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.34 (br s, 1H), 3.77 (d, 2H, J = 6.4 Hz), 2.56-2.53 (m, 2H), 2.46-2.43 (m, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 116.2, 81.7, 31.5, 28.45, 28.50 ppm; **note:** ^{13}C NMR signal for C17 could not be detected; IR (thin film) ν 3315, 2978, 2929, 1643, 1523, 1383, 1169 cm^{-1}; HRMS (ES^+) calcd $C_{11}H_{17}NO_4$ 250.1056 found 250.1051(MNa^+).



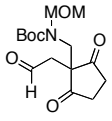
10

To a suspension of **9** (5.1 g, 22.3 mmol) and K_2CO_3 (6.2 g, 44.7 mmol, 2.0 equiv) in 90 mL of acetone was added allyl bromide (7.8 mL, 89.4 mmol, 4.0 equiv). The reaction was stirred at 60 °C for 6 h, cooled to room temperature, and filtered through a large pad of Celite. The flask and filter cake were rinsed with ~80 mL of CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure to a dark yellow oil. This material was transferred to a separatory funnel with 100 mL of CH_2Cl_2 and 40 mL of a pH 4 aqueous NaH_2PO_4/Na_2HPO_4 buffer. The organic layer was collected and the aqueous fraction was extracted with 4 x 50 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil. The product was determined to be a ~2:1 mixture of C– to O– allylated products by ^{1}H NMR, and was deemed pure for immediate use in the subsequent reaction. The allylated material was dissolved in 200 mL of toluene and stirred at reflux for 48 h. Following this time, the reaction was cooled to room temperature and concentrated under reduced pressure. Purification of the isolated material by chromatography on silica gel (40% EtOAc/hexanes) furnished the diketone **10** as a yellow oil (5.8 g, 98% yield). TLC R_f = 0.67 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60-5.52 (m, 1H), 5.09-5.07 (m, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 3.32 (d, 2H, *J* = 6.4 Hz), 2.79-2.72 (m, 2H), 2.67-2.58 (m, 2H), 2.36 (d, 2H, *J* = 7.5 Hz), 1.39 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.1, 156.0, 131.2, 120.5, 80.3, 61.2, 43.9, 37.5, 36.4, 28.4 ppm; IR (thin film) ν 3373, 2979, 2931, 1719, 1520, 1251, 1170 cm^{-1}; HRMS (ES$^+$) calcd $C_{14}H_{21}NO_4$ 290.1369 found 290.1363 (MNa$^+$).



11

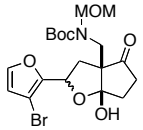
A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with diketone **10** (7.7 g, 28.8 mmol), paraformaldehyde (1.3 g, 43.2 mmol, 1.5 equiv), and 95 mL of CH_2Cl_2. The flask was placed in an ice bath and freshly distilled chlorotrimethylsilane (9.4 g, 86.4 mmol, 3.0 equiv) was added dropwise over a 3 min period. The mixture was stirred at 0 °C for 4 h and then a solution of Et_3N (1.9 mL, 13.6 mmol, 0.5 equiv) in 17 mL of MeOH was added. White smoke emanated from the reaction mixture upon addition of this methanolic solution. The contents were stirred for 30 min at 0 °C. Following this time, the reaction mixture was slowly poured into a separatory funnel containing 300 mL of saturated aqueous $NaHCO_3$ (**note:** vigorous gas evolution is observed in this quench). The organic layer was collected, and the aqueous layer was extracted with 4 x 100 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (gradient elution: 14:4:1→ 7:2:1 hexanes/CH_2Cl_2/acetone) afforded the carbamate **11** as a light yellow oil (7.2 g, 80%). TLC R_f = 0.41 (7:2:1 hexanes/CH_2Cl_2/acetone); ^{1}H NMR ($CDCl_3$, 400 MHz, 45 °C) δ 5.57-5.47 (m, 1H), 5.05-4.99 (m, 2H), 4.44 (s, 2H), 3.53 (s, 2H), 3.11 (s, 3H), 2.65-2.56 (m, 2H), 2.52-2.46 (m, 2H), 2.23 (d, 2H, *J* = 7.1 Hz), 1.40 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, 45 °C) δ 213.8, 155.3, 130.8, 120.4, 81.2, 80.2, 60.7, 55.2, 48.9, 40.0, 35.9, 28.2 ppm; IR (thin film) ν 2979, 2933, 1726, 1705, 1419, 1367, 1299, 1159 cm^{-1}; HRMS (ES$^+$) calcd $C_{16}H_{25}NO_5$ 334.1631 found 334.1626 (MNa$^+$).



12

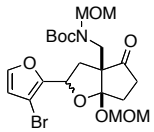
A stream of O_3 was bubbled for 45 min through a –78 °C solution of alkene **11** (9.30 g, 29.9 mmol) in 150 mL of CH_2Cl_2 containing approximately 3 mg of Sudan III dye. At the end of this period, the solution changed from red to pale blue-gray in color. Thin layer chromatography indicated complete consumption of starting material. The

solution was then sparged with a stream of N_2 gas for 45 min while warming to room temperature. Dimethyl sulfide (11.0 mL, 149 mmol, 5.0 equiv) was added and the mixture was stirred for 8 h. All volatiles were then removed under reduced pressure to afford an off-white foam. Purification of this material by chromatography on silica gel (gradient elution: 40→50% EtOAc/hexanes then 1:1:1 EtOAc/hexanes/CH_2Cl_2) afforded aldehyde **12** as a white solid (7.8 g, 83%). TLC R_f = 0.40 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 4.51 (s, 2H), 3.38 (s, 2H), 3.21 (s, 5H), 2.87 (d, 4H, *J* = 0.2 Hz), 1.40 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.3, 199.0, 155.5, 81.7, 80.4, 56.4, 55.8, 50.3, 49.5, 36.1, 28.2 ppm; IR (thin film) ν 2930, 2854, 1723, 1718, 1418, 1369, 1297, 1158, 1086 cm^{-1}; HRMS (ES$^+$) calcd $C_{15}H_{23}NO_6$ 336.1423 found 336.1419 (MNa$^+$).



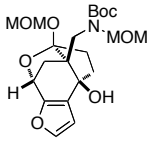
18

To an ice-cold solution of diisopropylamine (4.62 mL, 32.7 mmol, 1.25 equiv) in 100 mL of THF was added *n*-BuLi (21.8 mL of a 1.5 M solution in hexanes, 32.7 mmol, 1.25 equiv). The mixture was stirred at 0 °C for 20 min and then cooled to –78 °C before 3-bromofuran (2.94 mL, 32.7 mmol, 1.25 equiv) was added dropwise via cannula. After stirring this mixture at –78 °C for 3 h, a solution of lithium bromide (2.84 g, 32.7 mmol, 1.25 equiv) in 20 mL of THF was added. After 45 min, aldehyde **12** (8.20 g, 26.2 mmol, azeotropically dried with toluene) was added as a solution in 75 mL THF. Transfer of this material was made quantitative with an additional 25 mL of THF. Following an additional 30 min at –78 °C, the reaction was quenched by the addition of 300 mL of saturated aqueous NH_4Cl. The contents were transferred to a separatory funnel with 200 mL of EtOAc and the organic phase was collected. The aqueous fraction was extracted with 2 x 300 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow foam. Purification of this material by chromatography on silica gel (35% EtOAc/hexanes) afforded a 3:2 diastereomeric mixture of hemi-ketals **18** (10.7 g, 89%) as a white foam. TLC R_f = 0.52 (50% EtOAc/hexanes); HRMS (ES$^+$) calcd $C_{19}H_{26}BrNO_7$ 482.0791 found 482.0788 (MNa$^+$).



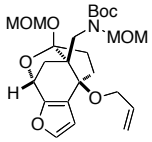
19

Chloromethyl methyl ether (6.7 mL, 88.6 mmol, 4.0 equiv) and diisopropylethylamine (19.3 mL, 111.0 mmol, 5.0 equiv) were added sequentially to a solution of hemi-ketals **18** (10.2 g, 22.2 mmol) in 110 mL of CH_2Cl_2. The solution was stirred at reflux for 15 h, then cooled to room temperature and diluted with 150 mL of a pH 4 aqueous NaH_2PO_4/Na_2HPO_4 buffer. After 30 min of vigorous stirring, the mixture was transferred with 100 mL of CH_2Cl_2 to a separatory funnel containing 120 mL of a pH 4 aqueous NaH_2PO_4/Na_2HPO_4 buffer. The organic layer was collected, and the aqueous fraction was extracted with 3 x 100 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow foam. Purification of this material by chromatography on silica gel (35% EtOAc/hexanes) afforded a 2:1 diastereomeric mixture of ketones **19** (9.0 g, 80%) as a light yellow foam. TLC R_f = 0.56 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of diasteromers) δ 7.32-7.28 (m, 2H), 6.35-6.31 (m, 2H), 5.27-5.23 (m, 2H), 5.11-5.10 (m, 2H), 5.03-4.96 (m, 2H), 4.72-4.68 (m, 4H), 4.62-4.50 (m, 2H), 4.09-4.01 (m, 2H), 3.44 (s, 6H), 3.37 (s, 2H), 3.27 (s, 6H), 2.68-2.64 (m, 2H), 2.52-2.49 (m, 4H), 2.44-2.38 (m, 4H), 1.42 (s, 18H) ppm; HRMS (ES$^+$) calcd $C_{21}H_{30}BrNO_8$ 526.1053 found 526.1049 (MNa$^+$). The relative stereochemistry of the major and minor diastereomeric products was not assigned.



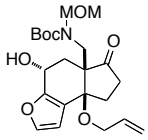
20

To a –78 °C solution of ketones **19** (1.59 g, 3.14 mmol) in 31 mL of THF was added *n*-BuLi (1.4 mL of a 2.5 M solution in hexanes, 3.5 mmol, 1.1 equiv) dropwise over 30 sec. After stirring the mixture at –78 °C for 45 min, the reaction was quenched with 45 mL of saturated aqueous NH_4Cl. The mixture was warmed to room temperature, diluted with 25 mL of EtOAc and 15 mL of H_2O, and stirred vigorously until the both phases had clearly separated. The material was transferred to a separatory funnel, the organic layer was collected, and the aqueous fraction was extracted with 2 x 75 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (40% EtOAc/hexanes) afforded tertiary alcohol **20** (793 mg, 59%) as a clear oil and the debrominated **19-exo** product (401 mg, 30%) as a clear oil. Tertiary alcohol **20**: TLC R_f = 0.37 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, 1H, *J* = 1.8 Hz), 6.46 (s, 1H), 5.28 (s, 1H), 4.99 (d, 1H, *J* = 6.4 Hz), 4.96 (d, 1H, *J* = 5.3 Hz), 4.91 (d, 1H, *J* = 9.6 Hz), 4.73 (d, 1H, *J* = 5.9 Hz), 4.60 (d, 1H, *J* = 10.2 Hz), 4.07 (d, 1H, *J* = 16.1 Hz), 3.78 (dd, 1H, *J* = 15.5, 0.4 Hz), 3.41 (s, 3H), 3.30 (s, 3H), 2.21-1.91 (m, 5H), 1.61-1.56 (m, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.7, 155.2, 142.1, 122.7, 114.8, 108.5, 92.1, 81.7, 80.4, 77.6, 70.6, 61.3, 56.4, 56.0, 44.2, 37.0, 35.6, 34.5, 28.6 ppm; IR (thin film) ν 3417, 2976, 1699, 1674, 1307, 1148, 1030 cm^{-1}; HRMS (ES$^+$) calcd $C_{21}H_{31}NO_8$ 448.1948 found 448.1942 (MNa^+).



21

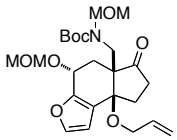
Allyl bromide (1.1 mL, 12.6 mmol, 8.0 equiv) was added dropwise to a vigorously stirred solution of alcohol **20** (670 mg, 1.57 mmol) and tetrabutylammonium iodide (582 mg, 1.57 mmol, 1.0 equiv) in 11 mL of CH_2Cl_2 and 21 mL of 50% w/w aqueous NaOH (**note:** a rapid stir rate, a large stir bar, and a large flask size to solution volume ratio should be used to obtain an optimal product yield). The biphasic solution was stirred for 12 h, then cooled to 0 °C and diluted with 50 mL of EtOAc and 50 mL of H_2O. The mixture was transferred to a separatory funnel, the organic fraction was collected, and the aqueous layer was extracted with 3 x 50 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (20% EtOAc/hexanes) afforded allyl ether **21** (652 mg, 89%) as a white solid. TLC R_f = 0.58 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, 1H, *J* = 1.2 Hz), 6.33 (dd, 1H, *J* = 1.9, 0.8 Hz), 6.00-5.90 (m, 1H), 5.33 (d, 1H, *J* = 17.5 Hz), 5.14 (d, 1H, *J* = 10.2 Hz), 4.96 (t, 3H, *J* = 9.3 Hz), 4.85 (d, 1H, *J* = 10.2 Hz), 4.67 (d, 1H, *J* = 6.5 Hz), 4.51 (dd, 1H, *J* = 11.4, 5.4 Hz), 4.18-4.15 (m, 1H), 3.82 (dd, 1H, *J* = 11.5, 4.6 Hz), 3.47 (d, 1H, *J* = 15.4 Hz), 3.40 (s, 3H), 3.27 (s, 3H), 2.27-2.13 (m, 4H), 1.88 (q, 1H, *J* = 9.6 Hz), 1.54-1.45 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 156.6, 142.4, 135.6, 119.3, 116.8, 115.6, 108.1, 92.1, 82.4, 80.0, 79.7, 70.4, 65.9, 59.9, 56.5, 55.5, 42.4, 36.5, 35.3, 33.7, 28.5 ppm; IR (thin film) ν 2978, 2930, 1700, 1295, 1146, 1034 cm^{-1}; HRMS (ES$^+$) calcd $C_{24}H_{35}NO_8$ 488.2261 found 488.2249 (MNa^+).



21A

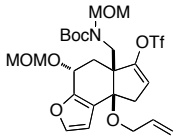
Acetyl chloride (0.56 mL, 7.8 mmol, 3.0 equiv) was added to 18 mL of MeOH. The mixture was stirred at 0 °C for 30 min and then added dropwise over 2 min via cannula to an ice-cold solution of bis-acetal **21** (1.22 g, 2.62 mmol) in 9 mL of MeOH and 6 mL of THF. After 15 min, the reaction was quenched by slow addition of 60 mL of

saturated aqueous $NaHCO_3$. The reaction was diluted with 60 mL of EtOAc and warmed to room temperature. The contents were transferred to a separatory funnel with 40 mL of EtOAc and 30 mL of H_2O. The organic layer was collected and the aqueous fraction was extracted with 2 x 80 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a white foam. Purification of this material by chromatography on silica gel (gradient elution: 40→50% EtOAc/hexanes) afforded keto-alcohol **21A** (1.0 g, 92%) as a white solid. TLC R_f = 0.27 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H *J* = 1.5 Hz), 6.37 (d, 1H, *J* = 2.0 Hz), 5.80 (ddt, 1H, *J* = 16.8, 10.8, 5.6 Hz), 5.20 (dd, 1H, *J* = 17.2, 1.4 Hz), 5.08 (d, 1H, *J* = 10.2 Hz), 4.68 (dt, 3H, *J* = 29.6, 7.9 Hz), 4.17 (d, 1H, *J* = 15.1 Hz), 3.85 (d, 2H, *J* = 5.1 Hz), 3.25 (d, 4H, *J* = 16.9 Hz), 2.89 (d, 1H, *J* = 9.2 Hz), 2.80 (dd, 1H, *J* = 19.3, 9.9 Hz), 2.71 (d, 1H, *J* = 15.2 Hz), 2.58 (q, 1H, *J* = 11.4 Hz), 2.42 (dd, 1H, *J* = 12.0, 9.2 Hz), 2.20 (dd, 1H, *J* = 15.2, 6.3 Hz), 1.88 (dd, 1H, *J* = 19.6, 9.7 Hz), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.2, 156.1, 154.5, 144.2, 134.9, 119.4, 116.4, 108.4, 81.2, 80.6, 80.2, 65.5, 60.5, 58.2, 55.8, 48.3, 35.6, 34.4, 30.6, 28.4 ppm; IR (thin film) ν 3502, 2976, 2928, 1729, 1701, 1417, 1296, 1141, 1087 cm^{-1}; HRMS (ES$^+$) calcd $C_{22}H_{31}NO_7$ 444.1999 found 444.1995 (MNa^+).



22

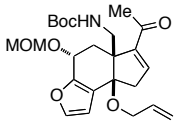
To a solution of keto-alcohol **21A** (447 mg, 1.06 mmol) in 13 mL of CH_2Cl_2 were added chloromethyl methyl ether (0.56 mL, 7.4 mmol, 7.0 equiv) and diisopropylethylamine (2.77 mL, 15.9 mmol, 15.0 equiv). White smoke emanated from the reaction mixture upon addition of diisopropylethylamine. The solution was heated to reflux for 12 h, cooled to room temperature, and diluted with 45 mL a pH 4 aqueous NaH_2PO_4/Na_2HPO_4 buffer. After 30 min of vigorous stirring, the contents were transferred to a separatory funnel with 50 mL of CH_2Cl_2. The organic layer was collected, and the aqueous fraction was extracted was extracted with 3 x 50 mL of CH_2Cl_2. The combined organic extracts were washed with 1 x 50 mL of saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (40% EtOAc/hexanes) afforded ketone **22** (457 mg, 92%) as a clear oil. TLC R*f* = 0.51 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1H), 6.44 (d, 1H, *J* = 2.0 Hz), 5.82 (ddt, 1H, *J* = 16.8, 10.8, 5.6 Hz), 5.23 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.10 (d, 1H, *J* = 10.2 Hz), 4.79-4.65 (m, 4H), 4.58 (d, 1H, *J* = 6.7 Hz), 4.15-3.97 (m, 1H), 3.84-3.74 (m, 2H), 3.41 (s, 3H), 3.31 (s, 3H), 3.24-3.20 (m, 1H), 2.89 (d, 1H, *J* = 14.8 Hz), 2.64-2.35 (m, 3H), 1.93 (ddt, 2H, *J* = 14.5, 7.2, 5.7 Hz), 1.45 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.4, 156.0, 152.4, 144.1, 134.8, 121.1, 116.4, 108.3, 94.0, 81.3, 80.8, 80.5, 65.7, 62.9, 55.8, 55.6, 55.0, 48.5, 36.2, 33.3, 32.3, 28.4 ppm; IR (thin film) ν 2976, 2933, 1745, 1700, 1417, 1367, 1298, 1146, 1087, 1034 cm^{-1}; HRMS (ES$^+$) calcd $C_{24}H_{35}NO_8$ 488.2261 found 488.2255 (MNa^+).



22A

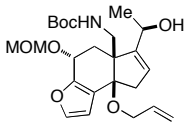
A solution of ketone **22** (203 mg, 0.44 mmol) in 1.0 mL of THF was added via cannula to a –78 °C solution of $KN(SiMe_3)_2$ (130 mg, 0.65 mmol, 1.5 equiv) in 1.0 mL of THF. Transfer of the ketone was made quantitative with an additional 2 x 0.5 mL of THF. The resulting yellow mixture was stirred at –78 °C for 40 min. A solution of *N*-(5-chloro-2-pyridyl)triflimide (234 mg, 0.60 mmol, 1.4 equiv), in 1.0 mL of THF was then added dropwise via cannula. Transfer of the triflimide was made quantitative with an additional 2 x 0.5 mL of THF. The deep orange solution was stirred at –78 °C for 3 h before the reaction was quenched by the addition of 12 mL of saturated aqueous NH_4Cl. The mixture was warmed to room temperature and transferred to a separatory funnel with 10 mL of EtOAc and 8 mL of H_2O. The organic layer was collected and the aqueous fraction was extracted with 2 x 30 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow, amorphous solid. Purification of the isolated material by chromatography on silica gel (gradient elution:

20→30% EtOAc/hexanes) furnished vinyl triflate **22A** as a clear oil (247 mg, 95%). TLC R_f = 0.63 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotameric isomers) δ ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 (s, 1H), 6.38 (s, 1H), 5.81 (ddt, 1H, *J* = 17.2, 10.5, 5.3 Hz), 5.31 (s, 1H), 5.22 (d, 1H, *J* = 17.2 Hz), 5.11 (d, 1H, *J* = 10.1 Hz), 5.02-4.40 (m, 1H), 4.91 (d, 1H, *J* = 10.5 Hz), 4.81-4.78 (m, 2H), 4.60-4.56 (m, 1H), 4.00-3.52 (m, 1H), 3.81-3.66 (m, 3H), 3.38 (s, 3H), 3.27 (s, 3H), 2.93 (d, 1H, *J* = 15.2 Hz), 2.69-2.59 (m, 2H), 2.02 (dd, 1H, *J* = 15.5, 4.4 Hz), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of rotameric isomers) δ 156.6, 151.8, 149.9, 143.7, 134.4, 121.3, 120.1, 116.8, 109.3, 108.6, 94.2, 82.1, 80.9, 80.3, 66.5, 62.0, 55.7, 55.5, 53.2, 48.5, 41.2, 33.7, 28.4 ppm; IR (thin film) ν 2933, 1707, 1423, 1211, 1146, 1032 cm^{-1}; HRMS (ES$^+$) calcd $C_{25}H_{34}F_3NO_{10}S$ 620.1754 found 620.1751 (MNa^+).



23

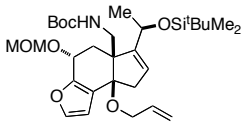
In an inert atmosphere N_2 glove box, $Pd(PPh_3)_4$ (192 mg, 166 μmol, 0.1 equiv), LiCl (423 mg, 10.0 mmol, 6.0 equiv), and CuCl (823 mg, 8.3 mmol, 5.0 equiv) were weighed into an oven-dried Schlenk flask containing vinyl triflate **22A** (993 mg, 1.7 mmol). The flask was stoppered with a polyethylene cap and the side-arm fitted with a rubber septum. The vessel was removed from the glove box and charged with tributyl-1-ethoxyvinyltin (618 μL, 1.8 mmol, 1.1 equiv) and 33 mL of DMSO. The suspension was degassed through two freeze-pump-thaw cycles and then restored to a nitrogen atmosphere. The sealed vessel was placed in a 60 °C oil bath and the contents stirred at this temperature for 13 h. Following this time, the mixture was cooled to room temperature and transferred with 120 mL of Et_2O to a separatory funnel containing 200 mL of saturated aqueous NaCl and 60 mL of 5% aq NH_4OH. The organic layer was collected, and the aqueous fraction was extracted with 2 x 80 mL of Et_2O. The combined organic extracts were washed with 40 mL of saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to a brown oil. The isolated material was dissolved in 55 mL of EtOAc and cooled to 0 °C. To this solution was added 5.4 mL of 4.0 N aqueous HCl dropwise. The reaction mixture was stirred for 5.5 h at 0 °C then quenched by slow addition of 100 mL of saturated aqueous $NaHCO_3$. The solution was warmed to room temperature and transferred to a separatory funnel with 120 mL of EtOAc and 40 mL of saturated aqueous $NaHCO_3$. The organic layer was collected and the aqueous fraction was extracted of 2 x 75 mL of EtOAc. The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (gradient elution: 30→60% EtOAc/hexanes) furnished methyl ketone **23** as an off-white foam (633 mg, 85% over 2 steps). TLC R_f = 0.57 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, *J* = 1.8 Hz), 6.46 (d, 1H, *J* = 16.8 Hz), 6.40 (d, 1H, *J* = 1.3 Hz), 5.87 (ddt, 1H, *J* = 16.8, 10.9, 5.6 Hz), 5.60 (dd, 1H, *J* = 8.1, 3.8 Hz), 5.25 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.14 (dd, 1H, *J* = 10.4, 1.3 Hz), 4.78 (s, 1H), 4.64 (d, 1H, *J* = 6.9 Hz), 4.41 (d, 1H, *J* = 7.0 Hz), 3.95-3.81 (m, 2H), 3.75 (dd, 1H, *J* = 14.0, 7.9 Hz), 3.37 (s, 3H), 3.25 (dd, 1H, *J* = 13.9, 4.1 Hz), 3.12-3.00 (m, 2H), 2.80 (dd, 1H, *J* = 17.9, 3.2 Hz), 2.19 (s, 3H), 1.71 (dd, 1H, *J* = 15.0, 3.9 Hz), 1.42 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.7, 156.4, 151.8, 147.2, 143.5, 139.6, 134.8, 122.0, 116.9, 109.1, 93.9, 84.0, 78.8, 66.9, 62.9, 55.5, 54.1, 45.7, 45.6, 30.1, 28.6, 27.5 ppm; IR (thin film) ν 3454, 2980, 2932, 1711, 1676, 1504, 1167, 1028 cm^{-1}; HRMS (ES$^+$) calcd $C_{24}H_{33}NO_7$ 470.2155 found 470.2150 (MNa^+).



24

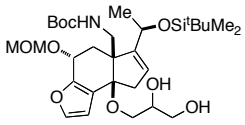
To a –78 °C solution of ketone **23** (191 mg, 0.43 mmol) in 8.5 mL of toluene was added dropwise diisobutylaluminum hydride (0.70 mL of a 1.0 M solution in toluene, 0.70 mmol, 1.64 equiv). The reaction was stirred at –78 °C for 50 min and then quenched with 5 mL of 1.0 M aqueous potassium sodium tartrate. The ice bath was removed and the mixture was stirred vigorously at room temperature for 5 h. The contents were then transferred to a separatory funnel with 10 mL of EtOAc and the organic phase was collected. The aqueous layer was extracted with 2 x 20 mL of EtOAc. The combined organic extracts were washed with 15 mL of saturated aqeous NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by

chromatography on silica gel (gradient elution: 50→75% EtOAc/hexanes) afforded secondary alcohol **24** as a clear oil (145 mg, 76%, single diastereomer). TLC R_f = 0.36 (1:1:1 EtOAc/hexanes/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, 1H, *J* = 1.9 Hz), 6.35 (d, 1H, *J* = 1.9 Hz), 5.82 (ddt, 1H, *J* = 16.8, 10.9, 5.6 Hz), 5.71 (s, 1H), 5.21-5.16 (m, 2H), 5.09 (d, 1H, *J* = 10.4 Hz), 4.85 (d, 1H, *J* = 6.9 Hz), 4.82 (d, 1H, *J* = 4.7 Hz), 4.62 (d, 1H, *J* = 6.9 Hz), 4.26 (q, 1H, *J* = 6.3 Hz), 4.15 (s, 1H), 3.84 (d, 2H, *J* = 5.4 Hz), 3.35 (s, 3H), 3.30 (dd, 1H, *J* = 14.2, 6.7 Hz), 3.10 (dd, 1H, *J* = 14.2, 6.3 Hz), 2.75-2.61 (m, 2H), 2.29 (d, 1H, *J* = 15.7 Hz), 2.13 (dd, 1H, *J* = 15.8, 5.3 Hz), 1.36 (s, 9H), 1.28 (d, 3H, *J* = 6.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 150.2, 149.8, 143.4, 134.8, 125.0, 122.7, 116.9, 109.6, 95.1, 84.4, 79.0, 66.9, 63.7, 61.7, 56.1, 55.6, 45.5, 44.4, 32.5, 28.6, 23.0 ppm; IR (thin film) ν 3448, 2926, 2853, 1701, 1149, 1083 cm^{-1}; HRMS (ES$^+$) calcd $C_{24}H_{35}NO_7$ 472.2312 found 472.2308 (MNa^+). The stereochemistry at C20 was assigned based on 1D NOE correlations (see attached spectra).



24A

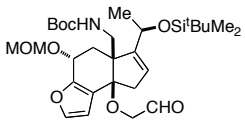
To a –78 °C solution of alcohol **24** (80 mg, 0.18 mmol) in 1.8 mL of CH_2Cl_2 was added 2,6-lutidine (83 μL, 0.72 mmol, 4.0 equiv) and ^{t}BuMe$_2$SiOTf (82 μL, 0.36 mmol, 2.0 equiv). The reaction was stirred at –78 °C for 2 h then quenched by the addition of 5 mL of saturated aqueous NH_4Cl. The mixture was transferred to a separatory funnel with 5 mL of CH_2Cl_2. The organic phase was collected and the aqueous layer was extracted with 4 x 10 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a clear oil. Purification of this material by chromatography on silica gel (10% EtOAc/hexanes) yielded the desired product as a clear oil, which solidified upon standing (100 mg, 99%). TLC R_f = 0.70 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 1H, *J* = 1.9 Hz), 6.37 (d, 1H, *J* = 1.9 Hz), 5.93-5.83 (m, 1H), 5.63 (t, 1H, *J* = 1.5 Hz), 5.49 (dd, 1H, *J* = 9.0, 3.3 Hz), 5.24 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.13 (dd, 1H, *J* = 10.5, 1.4 Hz), 4.90 (d, 1H, *J* = 6.8 Hz), 4.84-4.80 (m, 2H), 4.71 (d, 1H, *J* = 6.8 Hz), 3.93 (d, 2H, *J* = 5.3 Hz), 3.62 (dd, 1H, *J* = 14.2, 9.1 Hz), 3.43 (s, 3H), 3.18 (dd, 1H, *J* = 14.3, 3.6 Hz), 2.74 (dt, 1H, *J* = 15.7, 2.2 Hz), 2.63 (dt, 1H, *J* = 15.7, 2.2 Hz), 2.39 (dd, 1H, *J* = 15.5, 6.0 Hz), 2.01 (dd, 1H, *J* = 15.5, 2.0 Hz), 1.45 (br d, 9H),1.36 (d, 3H, *J* = 6.5 Hz), 0.84 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 150.9, 150.7, 142.6, 135.1, 122.7, 121.9, 116.5, 109.5, 95.5, 85.7, 78.8, 67.2, 66.5, 64.6, 55.6, 54.6, 43.3, 40.3, 31.4, 25.9, 24.5, 18.4, -3.3, -5.0, -5.3 ppm; IR (thin film) ν 3456, 2930, 2856, 1715, 1498, 1172, 1084, 1042 cm^{-1}; HRMS (ES$^+$) calcd $C_{30}H_{49}NO_7Si$ 586.3176 found 586.3172 (MNa^+).



24B

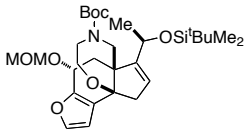
To a solution of **24A** (208 mg, 0.37 mmol) in 1.5 mL of THF were added sequentially *N*-methylmorpholine *N*-oxide (60 mg, 0.52 mmol, 1.4 equiv) and OsO_4 (330 μL of a 4 wt% solution in H_2O, 52 μmol, 0.14 equiv). The light yellow mixture was stirred for 4 h and the reaction was then quenched by the addition of 5 mL of saturated aqueous $Na_2S_2O_3$. The contents were transferred to a separatory funnel with 5 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of EtOAc. The combined organic extracts were washed with 10 mL of saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure to an off-white foam. This material (~1:1 mixture of diastereomers) was deemed pure by ^{1}H NMR and used immediately in the subsequent reaction. TLC R_f = 0.30 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of diol diastereomers) δ 7.32-7.30 (m, 2H), 6.32-6.31 (m, 2H), 5.73 (s, 2H), 5.15-5.08 (m, 2H), 4.88-4.86 (m, 2H), 4.81-4.78 (m, 2H), 4.73-4.68 (m, 3H), 4.64-4.62 (m, 2H), 4.28 (m, 1H), 3.92-3.81 (m, 2H), 3.73-3.67 (m, 2H), 3.56-3.51 (m, 3H), 3.44-3.39 (m, 2H), 3.39-3.37 (m, 6H), 3.32-3.31 (m, 1H), 3.28-3.27 (m, 2H), 2.89-2.82 (m, 2H), 2.79-2.74 (m, 2H), 2.61-2.52 (m, 4H), 2.07-1.93 (m, 4H), 1.40-1.39 (m, 18H), 1.26-1.25 (m, 6H), 0.81 (m, 18H), -0.09--0.10 (m, 6H), -0.15--0.16 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of diol diastereomers) δ 156.44, 156.38, 150.78, 150.60, 148.96, 148.91, 143.1, 142.9, 124.41, 124.39, 122.5, 109.51, 109.32, 95.50, 95.44, 83.9, 83.6, 79.87, 79.84, 71.4, 71.1, 68.0, 67.4, 66.95, 66.88, 64.05, 63.90, 63.73, 55.7, 54.02, 53.96, 43.75, 43.72, 43.0, 41.8, 33.7,

33.3, 28.75, 28.72, 26.0, 23.95, 23.90, 18.47, 18.45, -4.89, -4.92, -5.27, -5.34 ppm; IR (thin film) ν 3418, 2931, 2858, 1760, 1698, 1367, 1253, 1170, 1094, 1038 cm^{-1}; HRMS (ES^+) calcd $C_{30}H_{51}NO_9Si$ 620.3231 found 620.3228 (MNa^+).



25

To a solution of diol **24B** (28 mg, 47 μmol) in 1.0 mL of CH_2Cl_2 was added solid $Pb(OAc)_4$ (21 mg, 47 μmol, 1.0 equiv) in a single portion. The solution changed from clear to light peach in color and became opaque within 10 seconds following this addition. The mixture was stirred for 30 min and the reaction was then quenched by the addition of 3 mL of saturated aqueous $Na_2S_2O_3$. The contents were transferred to a separatory funnel with 5 mL of CH_2Cl_2. The organic phase was collected and the aqueous layer was extracted with 3 x 5 mL of CH_2Cl_2. The combined organic extracts were washed with 5 mL of saturated aqueous NaCl, dried over Na_2SO_4, filtered through Celite and concentrated under reduced pressure to an off-white foam. Purification of this material by chromatography on silica gel (60% EtOAc/hexanes) afforded aldehyde **25** as a white foam (25 mg, 91% over 2 steps). TLC R_f = 0.56 (60% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.62 (s, 1H), 7.35 (d, 1H, *J* = 1.9 Hz), 6.32 (d, 1H, *J* = 1.9 Hz), 5.84 (dd, 1H, *J* = 9.4, 2.9 Hz), 5.63 (br s, 1H), 4.87 (d, 2H, *J* = 6.9 Hz), 4.83-4.78 (m, 3H), 4.69 (d, 2H, *J* = 6.9 Hz), 4.19-4.11 (m, 2H), 3.69 (dd, 1H, *J* = 14.4, 9.5 Hz), 3.41 (s, 3H), 3.13 (dd, 1H, *J* = 14.4, 3.2 Hz), 2.71-2.59 (m, 2H), 2.38 (dd, 1H, *J* = 15.6, 6.0 Hz), 2.02 (dd, 1H, *J* = 15.5, 2.1 Hz), 1.43 (s, 9H), 1.36 (d, 3H, *J* = 6.6 Hz), 0.82 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 156.8, 151.24, 151.06, 143.0, 122.5, 120.8, 109.1, 95.5, 86.0, 79.0, 71.6, 67.2, 64.4, 55.7, 54.7, 43.4, 39.7, 31.0, 28.7, 26.0, 24.5, 18.4, -4.9, -5.3 ppm; IR (thin film) ν 3404, 2930, 2856, 1708, 1508, 1251, 1094, 1030 cm^{-1}; HRMS (ES^+) calcd $C_{29}H_{47}NO_8Si$ 588.2969 found 588.2969 (MNa^+).



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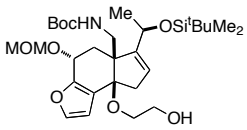
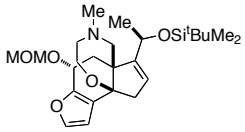


26A

To a solution of aldehyde **25** (216 mg, 0.38 mmol) in 4.4 mL of CH_2Cl_2 was added 0.2 mL of AcOH (3.4 mmol, 9 equiv) and $MgSO_4$ (210 mg, 1.74 mmol, 4.6 equiv). The suspension was stirred for 2.5 h and then solid $NaBH_3CN$ (48 mg, 0.76 mmol, 2 equiv) was added in a single portion. The contents were stirred for 1 h, after which time additional $NaBH_3CN$ (36 mg, 0.57 mmol, 1.5 equiv) and $MgSO_4$ (40 mg, 0.33 mmol, 0.9 equiv) was added. Following an additional 12 h of stirring, the reaction was quenched by the addition of 10 mL of saturated aqueous $NaHCO_3$. Upon cessation of gas evolution, the mixture was transferred to separatory funnel with 10 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 3 x 8 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a white foam. Purification of this material by chromatography on silica gel (gradient elution: 20→ 50% EtOAc/hexanes) afforded tertiary carbamate **26** (155 mg) as a white foam and alcohol **26A** (34 mg) as a clear oil (90% combined yield). Tertiary carbamate **26**: TLC R_f = 0.64 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (s, 1H), 6.38 (d, 1H, *J* = 1.7 Hz), 5.62 (s, 1H), 4.84 (s, 2H), 4.78 (d, 1H, *J* = 0.6 Hz), 4.62 (d, 1H, *J* = 6.8 Hz), 4.23-4.08 (m, 2H), 3.92-3.88 (m, 1H), 3.46 (d, 1H, *J* = 13.3 Hz), 3.39 (s, 3H), 3.31-3.13 (m, 3H), 3.05 (t, 1H, *J* = 12.4 Hz), 2.89 (d, 1H, *J* = 16.8 Hz), 2.61 (d, 1H, *J* = 16.8 Hz), 2.20 (q, 2H, *J* = 9.7 Hz), 1.50-1.39 (m, 12H), 0.87 (s, 9H), 0.02 (s, 3H), -0.05 (d, 3H, *J* = 5.4 Hz) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of rotameric isomers) δ 155.95, 155.82, 151.4, 151.0, 149.7, 149.0, 143.58, 143.45, 123.86, 123.71, 122.7, 122.1, 108.64, 108.59, 95.1, 94.9, 86.92, 86.85, 80.6, 79.9, 66.83, 66.69, 64.32, 64.20, 63.9, 57.7, 57.3, 55.54, 55.43, 49.3, 48.60, 48.54, 48.0, 45.2, 31.65, 31.63, 31.3, 28.9, 28.6, 26.1, 25.0, 24.5, 18.3, -4.63, -4.65, -4.69, -4.77 ppm; IR (thin film) ν 2929, 2855, 1693, 1421, 1251, 1139 1097, 1051 cm^{-1}; HRMS (ES^+) calcd $C_{29}H_{47}NO_7Si$ 572.3020 found 572.3016 (MNa^+). Primary alcohol **26A**: TLC R_f = 0.27 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.35 (d, 1H, *J* = 1.4 Hz), 6.37 (s, 1H), 5.79 (s, 1H), 5.05 (d, 1H, *J* = 10.3 Hz), 4.91 (d, 1H, *J* = 6.8 Hz), 4.85-4.84 (m, 1H), 4.76 (d, 1H, *J* = 5.4 Hz), 4.67 (d, 1H, *J* = 6.8 Hz), 4.19 (s, 1H), 4.00 (dd, 1H, *J* = 13.7, 10.8 Hz), 3.64 (s, 2H), 3.42 (s, 3H), 3.38 (s, 2H), 2.78 (d, 1H, *J* = 13.8 Hz),

2.60 (s, 2H), 2.09 (dd, 1H, J = 15.5, 5.8 Hz), 2.02 (t, 1H, J = 13.7 Hz), 1.44 (s, 9H), 1.29 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), -0.05 (s, 3H), -0.12 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.4, 150.6, 148.9, 142.8, 124.5, 122.7, 109.6, 95.5, 83.3, 79.8, 68.1, 66.9, 64.0, 62.4, 55.7, 54.0, 43.8, 42.4, 33.5, 28.7, 26.0, 23.9, 18.5, -4.9, -5.3 ppm; IR (thin film) ν 3435, 2929, 2856, 1707, 1510, 1250, 1172, 1094, 1048, 1032 cm^{-1}; HRMS (ES$^+$) calcd $C_{29}H_{49}NO_8Si$ 590.3125 found 590.3124 (MNa^+).

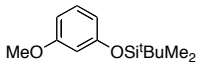
Alternative method for the preparation of **26**: To an ice-cold solution of alcohol **26A** (37 mg, 65 μmol) in 1.0 mL of CH_2Cl_2 was added Et_3N (45 μL, 0.32 mmol, 5 equiv) and methanesulfonyl chloride (15 μL, 0.19 mmol, 3 equiv). The reaction was stirred at 0 °C for 30 min and then quenched by the addition of 6 mL of saturated aqueous NH_4Cl. The solution was transferred to a separatory funnel with 6 mL of CH_2Cl_2 and 4 mL of H_2O. The organic phase was collected and the aqueous phase was extracted with 3 x 5 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (40% EtOAc/hexanes) afforded the methanesulfonate product as a clear oil (32 mg, 76%). TLC R_f = 0.51 (51% EtOAc/hexanes). The methanesulfonate product was immediately dissolved in 2.0 mL of THF and to this solution was added KO^{t}Bu (0.66 mL of a 0.3 M solution in THF, 0.20 mmol, 4.0 equiv). The resulting yellow mixture was stirred for 4 h and then diluted with 5 mL of saturated aqueous NH_4Cl. The contents were transferred to a separatory funnel with 5 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 3 x 5 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (20% EtOAc/hexanes) afforded tertiary carbamate **26** as a white foam (23 mg, 86%).



27

To a solution of tertiary carbamate **26** (32 mg, 0.59 mmol) in 1.0 mL of THF was added $LiAlH_4$ (0.24 mL of a 1.0 M solution in THF, 0.24 mmol, 4 equiv). The solution was stirred for 20 min and then heated to 65 °C and stirred for an additional 3.5 h. Following this time, the mixture was cooled to room temperature and H_2O (10 μL), 15% v/v aqueous NaOH (10 μL), and H_2O (30 μL) were added successively. The resulting white, opaque suspension was filtered through a small pad of Celite, rinsing the flask and filter cake with ~10 mL of Et_2O. The combined filtrates were concentrated under reduced pressure to a yellow solid. Purification of this material by chromatography on silica gel (30% EtOAc/hexanes) afforded tertiary amine **27** as a white crystalline solid (20 mg, 73%). TLC R_f = 0.60 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36 (s, 1H), 6.36 (s, 1H), 5.61 (s, 1H), 4.87 (d, 2H, J = 6.0 Hz), 4.68 (t, 2H, J = 7.8 Hz), 3.46-3.44 (m, 1H), 3.41 (s, 3H), 3.39-3.35 (m, 1H), 2.92 (dd, 1H, J = 14.8, 5.3 Hz), 2.83-2.79 (m, 2H), 2.70-2.63 (m, 1H), 2.55-2.47 (m, 2H), 2.32 (s, 3H), 1.90 (dd, 1H, J = 15.0, 4.9 Hz), 1.35 (d, 3H, J = 6.4 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.3, 143.3, 123.9, 122.6, 108.8, 95.3, 86.7, 66.7, 65.1, 63.9, 61.2, 60.8, 58.3, 55.6, 48.3, 45.4, 37.3, 29.9, 26.2, 24.7, 18.4, -4.17, -4.35 ppm; IR (thin film) ν 2930, 2855, 1462, 1253, 1150, 1095, 1052, 1019 cm^{-1}; HRMS (ES$^+$) calcd $C_{25}H_{41}NO_5Si$ 486.2652 found 486.2644 (MNa^+).

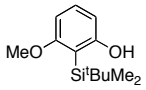
Experimental procedures and characterization data for select dienophile precursors:



S1

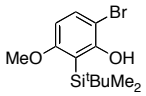
To a solution of 3-methoxyphenol (1.7 g, 13.8 mmol) and ^{t}BuMe$_2$SiCl (2.7 g, 18.0 mmol, 1.3 equiv) in 12.6 mL of DMF was added solid imidazole (1.5 g, 22.0 mmol, 1.6 equiv) in a single portion. Following the addition, the solution was stirred for 45 min. The reaction was quenched by the addition of 70 mL of H_2O and diluted with 20 mL of Et_2O. The contents were transferred to a separatory funnel with 20 mL of Et_2O. The organic phase was collected and the aqueous layer was extracted with 3 x 75 mL of Et_2O. The combined organic extracts were washed with 1 x 25 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to furnish a

yellow oil. Purification of this material by chromatography on silica gel (gradient elution: 3→8% EtOAc/hexanes) afforded silyl ether **S1** as a clear oil (2.9 g, 88%). TLC R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (t, 1H, *J* = 8.2 Hz), 6.53 (dd, 1H, *J* = 8.3, 2.4 Hz), 6.46 (dd, 1H, *J* = 8.0, 2.2 Hz), 6.41 (t, 1H, *J* = 2.3 Hz), 3.78 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.9, 157.1, 129.9, 112.8, 107.0, 106.6, 55.5, 25.9, 18.5, -4.1 ppm; IR (thin film) ν 2956, 2932, 2859, 1600, 1491, 1290, 1270, 1202, 1152, 976, 841 cm^{-1}; HRMS (ES$^+$) calcd $C_{13}H_{22}O_2Si$ 239.1467 found 239.1459 (MH^+).



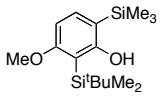
S2

To a –78 °C solution of diisopropylamine (5.2 mL, 36.9 mmol, 4.1 equiv) in 50 mL of THF was added ^{n}BuLi (14.4 mL of a 2.5M solution in hexanes, 36 mmol, 4.0 equiv). The mixture was stirred at – 78 °C for 30 min, warmed to 0 °C for 20 min, and then re-cooled to –78 °C before a solution of silyl ether **S1** (2.15 g, 9.00 mmol) in 20 mL of THF was added dropwise via cannula. Transfer of this material was made quantitative with 5 mL of THF. The solution was warmed to room temperature and then heated to 63 °C for 30 min. Following this time, the solution was cooled to room temperature and the reaction was quenched by addition of 75 mL of saturated aqueous NH_4Cl and 75 mL of Et_2O. The contents were transferred to a separatory funnel with 40 mL of Et_2O and the organic phase was collected. The aqueous layer was extracted with 3 x 80 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish a yellow oil. Purification of this material by chromatography on silica gel (5→8% EtOAc/hexanes) afforded phenol **S2** as a pale yellow solid (1.19 g, 56%). TLC R_f = 0.32 (8% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (t, 1H, *J* = 8.1 Hz), 6.43 (dd, 1H, *J* = 8.2, 0.4 Hz), 6.36 (dd, 1H, *J* = 8.0, 0.8 Hz), 5.01 (s, 1H), 3.73 (s, 3H), 0.92 (s, 9H), 0.37 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 162.2, 131.7, 110.0, 108.8, 102.7, 55.1, 27.1, 18.6, -1.7 ppm; IR (thin film) ν 3533, 2954, 2895, 2855, 1592, 1457, 1431, 1250, 1077, 826, 777 cm^{-1}.



S3

To a solution of phenol **S2** (674 mg, 2.83 mmol) in 31 mL of deoxygenated THF (sparged with N_2 gas for 1 h) at –40 °C was added N-bromosuccinimide (327 mg, 1.84 mmol, 0.65 equiv) in the dark. After stirring this mixture for 10 min, an additional portion of N-bromosuccinimide was added (327 mg, 1.84 mmol, 0.65 equiv). The resultant bright yellow solution was stirred in the dark at –40 °C for 50 min. The reaction was then quenched by addition of 20 mL of saturated aqueous $Na_2S_2O_3$ and warmed to room temperature. The contents were transferred to a separatory funnel with 20 mL of Et_2O and the organic phase was collected. The aqueous layer was extracted with 3 x 30 mL of Et_2O. The combined organic extracts were washed with 1 x 15 mL of saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (100% heptanes) yielded phenol **S3** a clear oil (362 mg, 40%). TLC R_f = 0.41 (100% heptanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, 1H, *J* = 8.7 Hz), 6.34 (d, 1H, *J* = 8.8 Hz), 5.68 (s, 1H), 3.72 (s, 3H), 0.91 (s, 9H), 0.34 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 157.3, 133.4, 112.2, 104.4, 102.8, 55.3, 27.1, 18.7, -1.6 ppm; IR (thin film) ν 3512, 2954, 2894, 2854, 1580, 1459, 1414, 1303, 1279, 1240, 1081, 827 cm^{-1}.

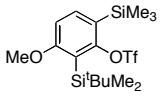


S4

To a solution of phenol **S3** (237 mg, 0.75 mmol) and Me_3SiCl (244 mg, 2.25 mmol, 3.0 equiv) in 7.5 mL of CH_2Cl_2 was added imidazole (3.0 mL of a 1.0 M solution in CH_2Cl_2, 3.0 mmol, 4.0 equiv). Following the addition, the solution was stirred for 1 h. The reaction was then quenched by the addition of 8 mL of H_2O and diluted with 10 mL of Et_2O. The contents were transferred to a separatory funnel with 10 mL of Et_2O. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of Et_2O. The combined organic extracts were washed with 1 x 15 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish

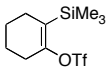
the trimethylsilyl ether as a white, crystalline solid. This material was deemed pure by ^{1}H NMR and used immediately in the subsequent reaction.

To a –78 °C solution of trimethylsilyl ether in 10 mL of Et_2O was added ^{t}BuLi dropwise over 1 min. The solution was warmed slowly to 0 °C over 2.5 h, following which time the reaction was quenched by addition of 20 mL of saturated aqueous NH_4Cl. The mixture was warmed to room temperature and the contents then transferred to a separatory funnel with 20 mL of Et_2O. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of Et_2O. The combined organic extracts were washed with 1 x 10 mL of saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to a white solid. Purification of this material by chromatography on silica gel (100% hexanes→1% Et_2O/hexanes) afforded phenol **S4** as a white, crystalline solid (164 mg, 71% over 2 steps). TLC R_f = 0.39 (100% hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, 1H, J = 8.1 Hz), 6.45 (d, 1H, J = 8.1 Hz), 5.47 (s, 1H), 3.73 (s, 3H), 0.93 (s, 9H), 0.42 (s, 6H), 0.28 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 167.2, 138.2, 117.6, 108.1, 102.4, 54.9, 27.1, 18.7, -0.5, -1.6 ppm; IR (thin film) ν 3594, 2956, 2856, 1579, 1559, 1460, 1368, 1243, 1197, 1173, 1114, 1080, 839 cm^{-1}.



S5

To an ice-cold suspension of NaH (15 mg, 0.63 mmol, 1.6 equiv) in 1 mL of DMF was added dropwise via cannula a solution of phenol **S4** (123 mg, 0.40 mmol) in 2 mL of DMF. Transfer of this material was made quantitative with 1 mL of DMF. After stirring this mixture for 50 min at 0 °C, $PhNTf_2$ was added (1.0 mL of a 0.44 M solution in DMF, 0.44 mmol, 1.1 equiv). The flask was removed from the ice bath and the reaction was warmed to room temperature. The reaction was stirred for 2 h at this temperature then quenched by addition of 10 mL of saturated aqueous NH_4Cl. The contents were transferred to a separatory funnel with 15 mL of Et_2O and 5 mL of H_2O. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of Et_2O. The combined organic extracts were washed with 1 x 10 mL of saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to an orange crystalline solid. Purification of this material by chromatography on silica gel (100% hexanes→4% EtOAc/hexanes) afforded aryl triflate **S5** as a light orange, crystalline solid (154 mg, 88%). TLC R_f = 0.51 (2% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, 1H, J = 8.2 Hz), 6.86 (d, 1H, J = 8.2 Hz), 3.81 (s, 3H), 0.91 (s, 9H), 0.33 (s, 6H), 0.32 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 155.9, 139.3, 126.5, 122.3, 118.7 (q, J_{CF} = 319 Hz), 109.6, 55.2, 28.6, 18.3, 0.7, -0.7 ppm; IR (thin film) ν 2931, 2855, 1581, 1392, 1251, 1211, 1137, 1039, 842 cm^{-1}.

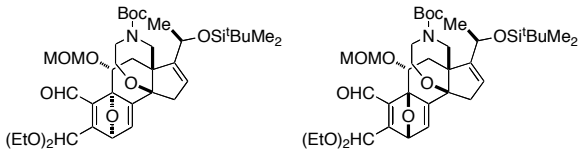


S6

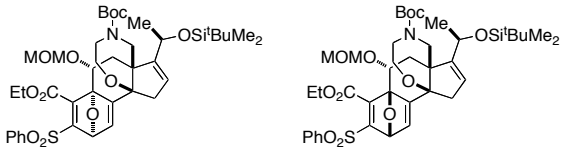
To a –78 °C solution of 2-(trimethylsilyl)cyclohex-2-enone[1] (190 mg, 1.13 mmol) in 4 mL of THF was added L-selectride (1.15 mL of a 1.0 M solution in THF, 1.15 mmol, 1.02 equiv). The reaction was stirred at –78 °C for 3.5 h. Following this time, a solution of $PhNTf_2$ (484 mg, 1.36 mmol, 1.2 equiv) in 1 mL of THF was added dropwise via syringe. The resulting clear solution was warmed to room temperature and stirred for an additional 13 h, during which time the mixture became light yellow. The reaction was quenched with 10 mL of saturated aqueous NH_4Cl and the contents were transferred to a separatory funnel with 20 mL of Et_2O and 10 mL of H_2O. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (2→4% Et_2O/hexanes) afforded vinyl triflate **S6**[2] as a clear oil (130 mg, 38%). TLC R_f = 0.68 (5% Et_2O/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (tt, 2H, J = 6.0, 2.8 Hz), 2.19 (tt, 2H, J = 5.7, 2.8 Hz), 1.78-1.72 (m, 2H), 1.60-1.54 (m, 2H), 0.18 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 128.1, 118.5 (q, J_{CF} = 318 Hz), 28.63, 28.47, 23.2, 22.0, -1.1 ppm; IR (thin film) ν 2949, 1652, 1411, 1248, 1209, 1145, 989, 895, 841 cm^{-1}; HRMS (ES$^+$) calcd $C_{10}H_{17}F_3O_3SSi$ 325.0518 found 325.0512 (MNa$^+$).

Experimental procedures and characterization data for Diels-Alder adducts (Table 1 and Figure 4):

General method for regio- and stereochemical assignment of Diels-Alder adducts. Regio- and stereochemical assignments were based on ^{1}H NOE analysis where indicated. In cycloaddition reactions with tetracycle **26**, characteristic H11 shifts ranging from 5.0–5.4 ppm were noted for the desired α-oxo-bridged products. By contrast, H11 chemical shifts of 4.3–4.5 ppm are measured for structurally equivalent β-oxo-bridged isomers. The characteristic resonance frequency of H11 was used in subsequent product analyses to tentatively assign α- vs. β-oxo bridge stereochemistry. In Diels-Alder reactions with intermediate **21**, NOE experiments from initial experiments confirmed that cycloaddition occurred exclusively from the β-face of the furan. For all other cycloaddition reactions with **21**, the oxo-bridged stereochemistry was assigned by analogy. **Note:** For many compounds, ^{1}H NMR spectra of Diels-Alder products displayed mixtures of rotameric isomers. In select instances, peak signals coalesced by performing ^{1}H NMR analysis at elevated temperature (as noted). For certain products, resolution of the ^{1}H NMR spectra was not possible even when recorded at high temperature. Data for these compounds are reported from analyses performed at ambient temperature.

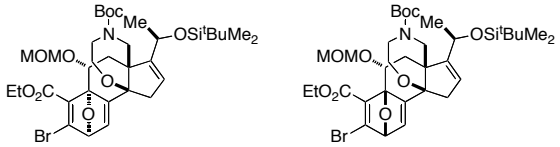


Entry 1, Table 1: A suspension of furan **26** (12.5 mg, 23 μmol), 4,4-diethoxybut-2-ynal (57 mg, 0.37 mmol, 16 equiv), di-*t*-butylhydroxytoluene (0.5 mg, 23 μmol, 0.1 equiv), and Na_2CO_3 (2.5 mg, 23 μmol, 1.0 equiv) was stirred in the dark at 90 °C for 21 h. Following this time, the orange-brown mixture was cooled to room temperature and filtered through Celite. The flask and filter cake were washed with ~10 mL of CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure to a brown oil. Purification of this material by chromatography on silica gel (15→30% EtOAc/hexanes) afforded cycloadduct **A** (3.5 mg) as a yellow oil and cycloadduct **B** (3.5 mg) as a yellow oil (42% combined yield). Isomer **A**: TLC R_f = 0.37 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz, 45 °C) δ 10.14 (s, 1H), 6.54 (s, 1H), 5.70 (s, 1H), 5.57 (s, 1H), 5.43 (s, 1H), 5.35-5.34 (m, 1H), 4.74-4.71 (m, 2H), 4.34 (s, 1H), 4.06-4.04 (m, 2H), 3.77-3.72 (m, 2H), 3.68-3.56 (m, 4H), 3.53-3.48 (m, 3H), 3.32 (s, 3H), 2.93 (d, 1H, *J* = 16.7 Hz), 2.22-2.13 (m, 2H), 1.83 (t, 1H, *J* = 12.4 Hz), 1.50 (s, 9H), 1.34-1.33 (m, 3H), 1.24-1.18 (m, 6H), 0.88 (s, 9H), 0.03-0.02 (m, 6H) ppm; IR (thin film) ν 2930, 1692, 1367, 1251, 1055 cm^{-1}. Isomer **B**: TLC R_f = 0.51 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.14 (s, 1H), 6.81 (d, 1H, *J* = 1.9 Hz), 5.72 (s, 1H), 5.63 (s, 1H), 5.48 (d, 1H, *J* = 1.8 Hz), 4.71 (d, 1H, *J* = 6.6 Hz), 4.60 (d, 1H, *J* = 6.6 Hz), 4.56 (d, 1H, *J* = 5.5 Hz), 4.51 (d, 1H, *J* = 15.4 Hz), 4.23 (dd, 1H, *J* = 13.5, 4.6 Hz), 3.83-3.78 (m, 1H), 3.60-3.53 (m, 5H), 3.50 (d, 1H, *J* = 15.5 Hz), 3.38-3.35 (m, 1H), 3.32 (s, 3H), 3.18 (d, 1H, *J* = 13.0 Hz), 2.50-2.48 (m, 1H), 2.37-2.33 (m, 2H), 2.12 (d, 1H, *J* = 17.2 Hz), 1.45 (s, 9H), 1.28-1.22 (m, 6H), 1.18 (t, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H) ppm; IR (thin film) ν 2929, 1692, 1367, 1251, 1053 cm^{-1}. Isomer **A**: the structure and the stereochemistry of the oxo bridge were assigned based on 1D NOE correlations (see attached spectra). Isomer **B**: The stereochemistry of the oxo bridge was assigned following the general procedure outlined above.



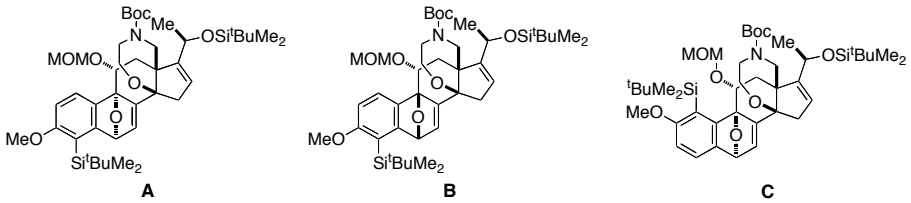
Entry 2, Table 1: A solution of furan **26** (37 mg, 67 μmol) and ethyl-3-(phenylthio)propiolate[3] (46 mg, 0.19 mmol, 2.9 equiv) in 0.6 mL of toluene was stirred at 63 °C for 5 h. Following this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (gradient elution: 4→11% acetone/$CHCl_3$) afforded cycloadduct **A** as a white amorphous solid and cycloadduct **B** as a white foam (47 mg, 90% combined yield). Major isomer **A**: TLC R_f = 0.37 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, 2H, *J* = 7.7 Hz), 7.64 (t, 1H, *J* = 7.4 Hz), 7.55 (t, 2H, *J* = 7.7 Hz), 6.74-6.69 (m, 1H), 5.71 (br s, 1H), 5.56-5.50 (m, 1H), 4.97 (d, 1H, *J* = 12.3 Hz), 4.67 (d, 1H, *J* = 6.9

Hz), 4.56 (d, 1H, *J* = 6.9 Hz), 4.33-4.24 (m, 3H), 4.14-3.94 (m, 2H), 3.80-3.44 (m, 4H), 3.17-3.08 (m, 3H), 2.97 (d, 1H, *J* = 17.0 Hz), 2.29-2.24 (m, 1H), 2.08 (dd, 1H, *J* = 13.2, 3.4 Hz), 1.76-1.70 (m, 1H), 1.48-1.46 (m, 9H), 1.39-1.28 (m, 6H), 0.88-0.84 (m, 9H), -0.01--0.02 (m, 6H) ppm; IR (thin film) ν 2931, 1723, 1691, 1410, 1367, 1322, 1251, 1154, 1106, 1048 cm^{-1}; HRMS (ES^+) calcd $C_{40}H_{57}NO_{11}SSi$ 810.3320 found 810.3328 (MNa^+). Minor isomer **B**: TLC R_f = 0.44 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, 2H, *J* = 7.6 Hz), 7.68 (t, 1H, *J* = 7.4 Hz), 7.58 (t, 2H, *J* = 7.8 Hz), 6.79 (s, 1H), 5.78 (s, 1H), 5.41 (d, 1H, *J* = 2.0 Hz), 4.65 (d, 1H, *J* = 6.7 Hz), 4.54-4.44 (m, 3H), 4.33-4.37 (m, 1H), 4.25-4.20 (m, 1H), 4.13 (dd, 1H, *J* = 13.6, 4.9 Hz), 3.70-3.65 (m, 1H), 3.56-3.54 (m, 2H), 3.36 (d, 1H, *J* = 15.0 Hz), 3.25 (s, 3H), 3.13 (d, 1H, *J* = 13.0 Hz), 2.97 (d, 1H, *J* = 17.2 Hz), 2.40-2.37 (m, 1H), 2.22 (dd, 1H, *J* = 17.3, 2.3 Hz), 2.00 (t, 1H, *J* = 14.2 Hz), 1.43 (s, 9H), 1.31 (t, 4H, *J* = 7.1 Hz), 1.27-1.25 (m, 6H), 0.87 (s, 9H), 0.19-0.12 (m, 6H) ppm; IR (thin film) ν 2931, 2857, 1727, 1692, 1448, 1411, 1367, 1320, 1257, 1161, 1132, 1083, 1049, 834, 776, 728, 598 cm^{-1}; HRMS (ES^+) calcd $C_{40}H_{57}NO_{11}SSi$ 810.3320 found 810.3316 (MNa^+). Isomers **A** and **B**: The stereochemistry of each oxo bridge was assigned following the general procedure outlined above. The structure of each isomer was assigned based on 1D NOE correlations (see attached spectra).



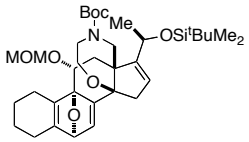
Entry 3, Table 1: A suspension of furan **26** (10.5 mg, 19 μmol), ethyl bromopropiolate (39.5 mg, 0.22 mmol, 12.0 equiv), and Na_2CO_3 (8 mg, 75 μmol, 4.0 equiv) in 0.5 mL of toluene was stirred at 105 °C for 44 h. Following this time, the opaque, brown mixture was cooled to room temperature and filtered through Celite. The flask and filter cake were washed with ~15 mL of Et_2O. The combined filtrates were concentrated under reduced pressure to a brown oil. Purification of this material by chromatography on silica gel (15→25% EtOAc/hexanes) afforded cycloadduct **A** (7.5 mg, 53%) as a yellow oil and cycloadduct **B** (4.5 mg, 32%) as a yellow oil. Major isomer **A**: TLC R_f = 0.19 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68-6.63 (m, 1H), 5.71 (br s, 1H), 5.34-5.31 (m, 1H), 5.20 (d, 1H, *J* = 1.9 Hz), 4.74 (d, 1H, *J* = 6.7 Hz), 4.70 (d, 1H, *J* = 6.7 Hz), 4.32-3.94 (m, 2H), 4.26 (q, 4H, *J* = 7.1 Hz), 4.15-4.04 (m, 1H), 3.76-3.66 (m, 2H), 3.52-3.49 (m, 2H), 3.32 (s, 3H), 2.96 (d, 1H, *J* = 16.9 Hz), 2.27-2.22 (m, 1H), 2.15-2.12 (m, 1H), 1.85-1.79 (m, 1H), 1.48 (s, 9H), 1.38-1.25 (m, 6H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; IR (thin film) ν 2931, 2857, 1732, 1463, 1410, 1368, 1250, 1151, 1099, 1023 cm^{-1}; HRMS (ES^+) calcd $C_{34}H_{52}BrNO_9Si$ 748.2493 found 750.2482 (MNa^+). Isomers **A** and **B**: The stereochemistry of each oxo bridge was assigned following the general procedure outlined above. The structure was determined through 1D NOE correlations (between H5 and H6) of the debrominated products.

General procedure for CsF-promoted Diels-Alder reactions. To a solution of furan diene and dienophile precursor (2.0–6.0 equiv) in MeCN was added solid CsF (3.0–10.0 equiv) in one portion. The suspension was stirred until thin layer chromatography indicated complete consumption of the starting furan (or the lack of additional conversion). The mixture was filtered through a small pad of dry Celite, and the flask and filter cake were rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure to a thin film, which was dissolved in 19:1 Et_2O:EtOAc and filtered a second time through dry Celite. The filter cake was washed with a solution of 19:1 Et_2O/EtOAc, and the combined filtrates were concentrated under reduced pressure. Purification of the isolated material was performed by chromatography on silica gel (conditions given below).

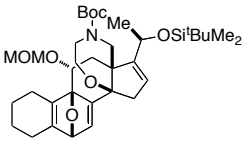


Entry 4, Table 1: Reaction performed with furan **26** (14 mg, 25 μmol), benzyne precursor **S5** (27 mg, 61 μmol, 2.4 equiv), CsF (20 mg, 0.131 mmol, 5.2 equiv) and 0.7 mL of MeCN. The reaction mixture was stirred for 21 h. Purification by chromatography on silica gel (15→20% EtOAc/hexanes) furnished cycloadduct **A** (6 mg) as a clear

oil and cycloadducts **B** and **C** as a 3:5 mixture of diastereomers (13 mg, 97% combined yield). Isomer **A**: TLC R_f = 0.28 (15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz, 45 °C) δ 7.25 (d, 1H, *J* = 8.0 Hz), 6.59 (s, 1H), 6.38 (d, 1H, *J* = 7.9 Hz), 5.74 (br s, 1H), 5.70 (br s, 1H), 5.01 (dd, 1H, *J* = 11.8, 3.5 Hz), 4.74-4.67 (m, 2H), 4.43-4.39 (m, 1H), 4.08 (d, 1H, *J* = 14.6 Hz), 3.94 (t, 1H, *J* = 12.2 Hz), 3.70 (s, 4H), 3.50-3.40 (m, 3H), 3.32 (s, 3H), 2.88 (d, 1H, *J* = 17.1 Hz), 2.36-2.31 (m, 1H), 2.21-2.19 (m, 1H), 2.03 (t, 1H, *J* = 12.8 Hz), 1.50 (s, 9H), 1.36 (d, 3H, *J* = 6.4 Hz), 0.92-0.90 (m, 18H), 0.30 (s, 3H), 0.26 (s, 3H), 0.06 (d, 6H, *J* = 2.1 Hz) ppm; IR (thin film) ν 2928, 2856, 1695, 1462, 1407, 1366, 1246, 1152, 1106 cm^{-1}; HRMS (ES$^+$) calcd $C_{42}H_{67}NO_8Si_2$ 792.4303 found 792.4318 (MNa^+). The relative stereochemistry of both the oxo bridge and the ^{t}BuMe$_2$Si-group were assigned based on 1D NOE correlations (see attached spectra). Isomers **B** and **C**: the stereochemistry of the oxo bridge for each product was assigned following the general procedure outlined above. The structure of each adduct was assigned based on 1D NOE correlations (see attached spectra).

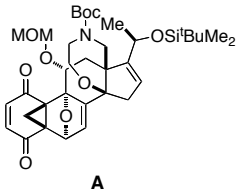


A



B

Entry 5, Table 1: Reaction performed with furan **26** (11 mg, 25 μmol), cyclohexyne precursor **S6** (21 mg, 69 μmol, 3.3 equiv), CsF (31 mg, 0.20 mmol, 9.9 equiv) and 0.5 mL of MeCN. The reaction mixture was stirred for 17 h. Purification by chromatography on silica gel (15→20% EtOAc/hexanes) afforded cycloadducts **A** (3 mg) as a clear oil and **B** (1 mg) as a clear oil (30% combined yield). Isomer **A**: TLC R_f = 0.24 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz, 45 °C) δ 6.58 (s, 1H), 5.70 (s, 1H), 5.05 (s, 1H), 4.72-4.61 (m, 3H), 4.37-4.36 (m, 1H), 4.07 (br s, 1H), 3.96 (d, 1H, *J* = 14.9 Hz), 3.69-3.60 (m, 2H), 3.50-3.48 (m, 2H), 3.38 (s, 3H), 2.93 (d, 1H, *J* = 17.0 Hz), 2.40-2.28 (m, 3H), 2.16 (s, 1H), 2.11-2.04 (m, 3H), 1.91-1.85 (m, 2H), 1.67 (br s, 2H), 1.49 (s, 9H), 1.33 (d, 3H, *J* = 6.2 Hz), 0.88 (s, 9H), 0.03 (d, 6H, *J* = 5.6 Hz) ppm; IR (thin film) ν 2929, 2856, 1695, 1366, 1251, 1152, 1100, 1044 cm^{-1}; HRMS (ES$^+$) calcd $C_{35}H_{55}NO_7Si$ 652.3646 found 652.3653 (MNa^+). Isomers **A** and **B**: the stereochemistry of each oxo bridge was assigned following the general procedure outlined above.



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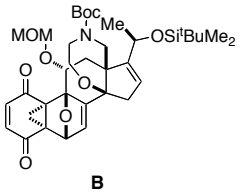

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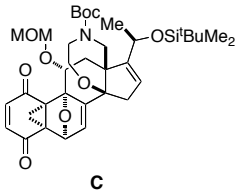
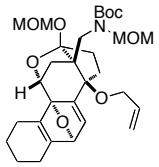


C

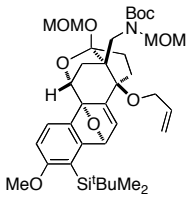
Entry 6, Table 1: Reaction performed with furan **26** (17.5 mg, 32 μmol), 1-bromo-6-(trimethylsilyl)-bicyclo[4.1.0]hept-3-ene-2,5-dione[4] (19.5 mg, 71 μmol, 2.2 equiv), CsF (19 mg, 0.13 mmol, 4.0 equiv), and 0.5 mL of MeCN. The reaction mixture was stirred for 2.5 h. Purification by chromatography on silica gel (30→50% EtOAc/hexanes) furnished cycloadducts **A**, **B**, and **C** as a 3:3:2 mixture of products as a yellow oil (21 mg, 99%). TLC R_f = 0.18 (30% EtOAc/hexanes), HRMS (ES$^+$) calcd $C_{36}H_{51}NO_9Si$ 692.3231 found 692.3238 (MNa^+). Isomers **A**, **B**, and **C**: the stereochemistry of each oxo bridge was assigned following the general procedure outlined above. In the endo product, H7 appears at 6.5 ppm and H6 at 5.0 ppm (Δ = 1.5 ppm), whereas in the exo products, H7 appears between 6.1–6.3 ppm and H7 at 5.5 (Δ ≤ 0.8 ppm). These chemical shift differences are consistent with the stereochemical assignment, as based on available literature precedent.[4]



29

Reaction performed with furan **21** (15 mg, 32 μmol), cyclohexyne precursor **S6 (**27 mg, 89 μmol, 2.8 equiv), CsF (30 mg, 0.20 mmol, 6.1 equiv) and 0.5 mL of MeCN. The reaction mixture was stirred for 23 h. Purification by

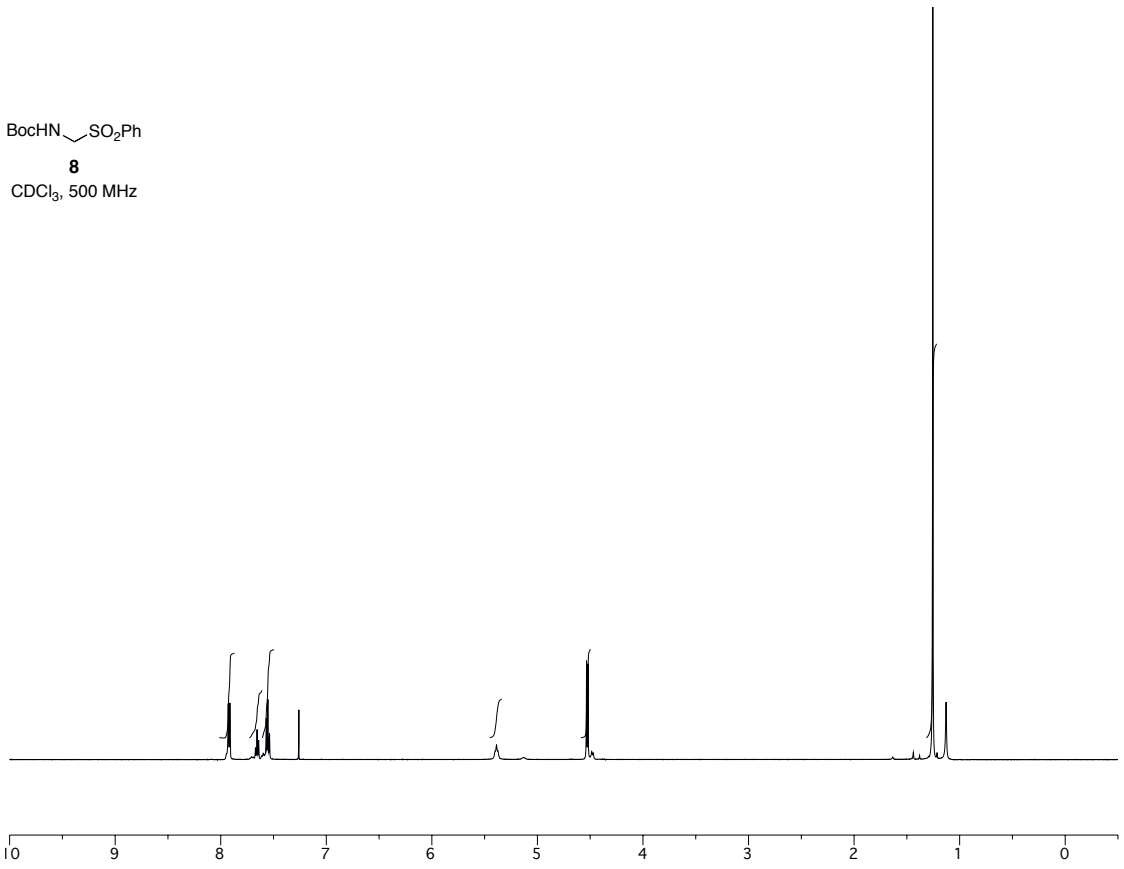
chromatography on silica gel (40→60% EtOAc/hexanes) furnished **29** as a clear oil. TLC R_f = 0.30 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.99-6.96 (m, 1H), 5.86-5.77 (m, 1H), 5.24-5.15 (m, 1H), 5.12 (s, 1H), 5.09 (d, 1H, *J* = 10.3 Hz), 5.04-5.00 (m, 1H), 4.92 (d, 1H, *J* = 10.2 Hz), 4.86 (d, 1H, *J* = 10.2 Hz), 4.66-4.62 (m, 2H), 4.32-3.48 (m, 4H), 3.38 (s, 3H), 3.27 (s, 3H), 2.40-2.33 (m, 2H), 2.28-2.09 (m, 7H), 2.04-1.96 (m, 3H), 1.77-1.77 (m, 1H), 1.69 (s, 1H), 1.48 (s, 9H) ppm; IR (thin film) ν 2932, 1699, 1293, 1146, 1080, 1033, 904 cm^{-1}; HRMS (ES$^+$) calcd $C_{30}H_{43}NO_8$ 568.2887 found 568.2887 (MNa^+). The stereochemistry of the oxo bridge was assigned following the general procedure outlined above.

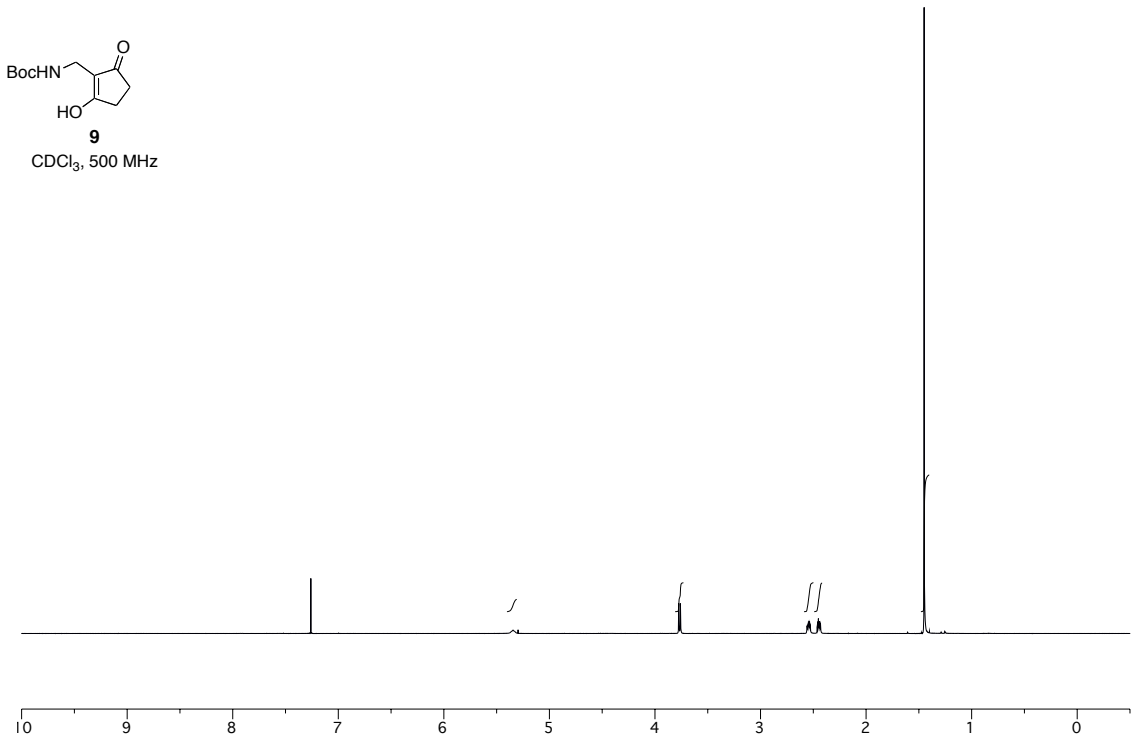


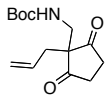
30

Reaction performed with furan **21** (13 mg, 28 μmol), benzyne precursor **S5** (25 mg, 57 μmol, 2.0 equiv), CsF (20 mg, 0.13 mmol, 4.7 equiv) and 0.7 mL of MeCN. The reaction mixture was stirred for 20 h. Purification by chromatography on silica gel (30% EtOAc/hexanes) furnished **30** as a clear oil (17 mg, 90%). TLC R_f = 0.30 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, 1H, *J* = 7.9 Hz), 6.95 (s, 1H), 6.32 (d, 1H, *J* = 7.9 Hz), 5.80 (d, 1H, *J* = 1.9 Hz), 5.67-5.52 (m, 1H), 5.07 (d, 1H, *J* = 6.3 Hz), 5.04-4.84 (m, 5H), 4.68 (d, 1H, *J* = 6.1 Hz), 4.12-3.27 (m, 3H), 3.70 (s, 3H), 3.40 (s, 3H), 3.27 (s, 3H), 2.92-2.87 (m, 1H), 2.58-2.49 (m, 2H), 2.30-2.13 (m, 3H), 2.08-2.03 (m, 1H), 1.51 (s, 9H), 0.87 (s, 9H), 0.34 (s, 3H), 0.28 (s, 3H) ppm; IR (thin film) ν 2928, 2855, 1700, 1453, 1420, 1366, 1292, 1246, 1147, 1034 cm^{-1}; HRMS (ES$^+$) calcd $C_{37}H_{55}NO_9Si$ 708.3544 found 708.3546 (MNa^+). The stereochemistry of the oxo bridge and the structure of the cycloadduct were assigned based on 1D NOE correlations (see attached spectra).

[1] C. Shih, E. L. Fritzen, J. S. Swenton, *J. Org. Chem*. **1980**, *45*, 4462-4471.
[2] N. Atanes, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Tetrahedron Lett*. **1998**, *39*, 3039-3040.
[3] M. Shen, A. G. Schultz, *Tetrahedron Lett*. **1981**, *22*, 3347-3350.
[4] G. E. Collis, D. Jayatilaka, D. Wege, *Austr. J. Chem*. **1997**, *50*, 505-513.

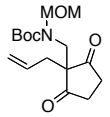






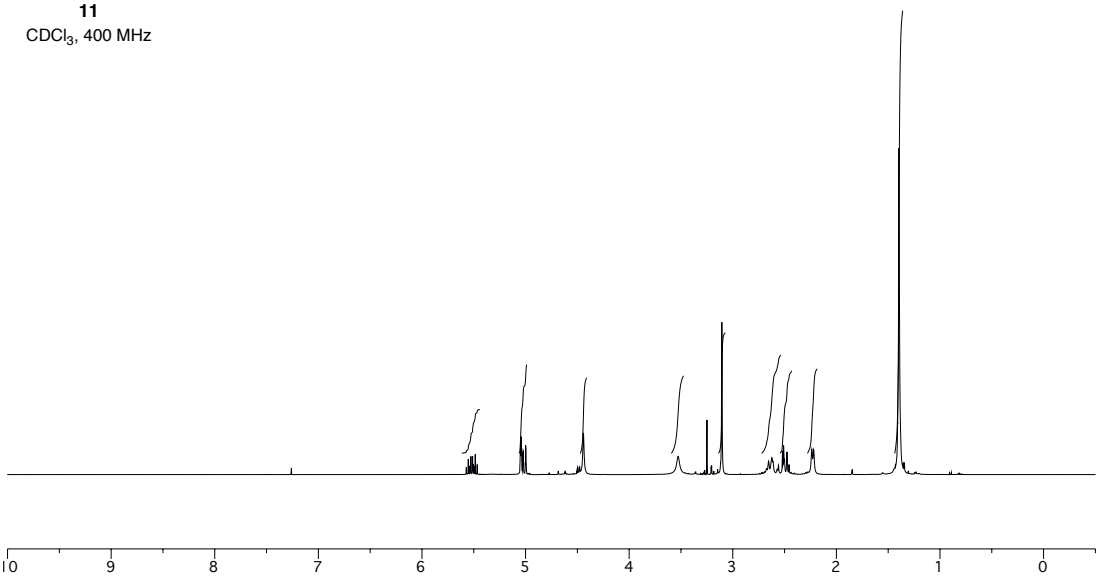
10

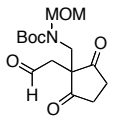
$CDCl_3$, 500 MHz



11

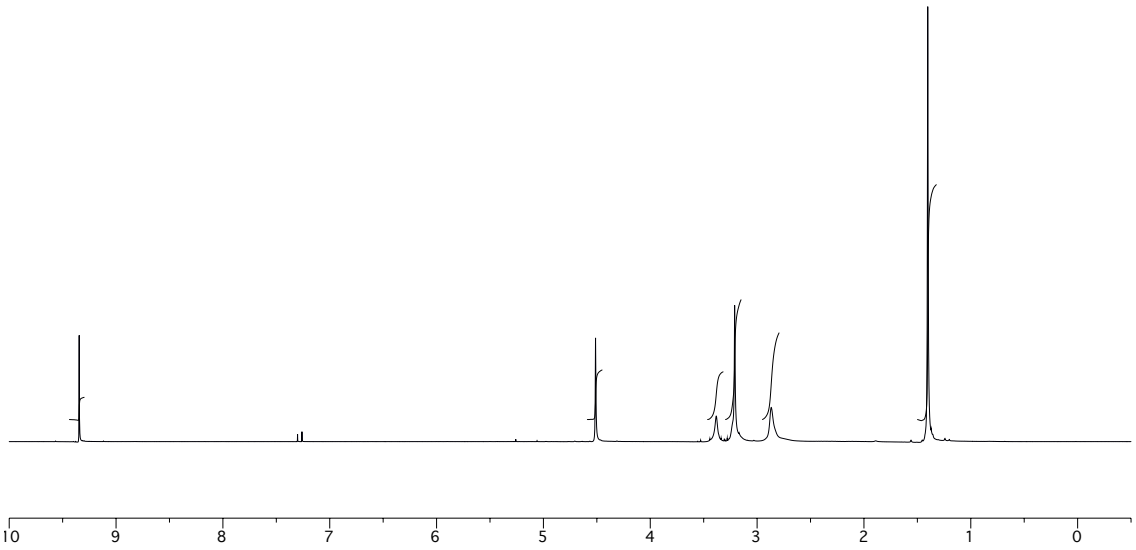
$CDCl_3$, 400 MHz

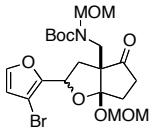




12

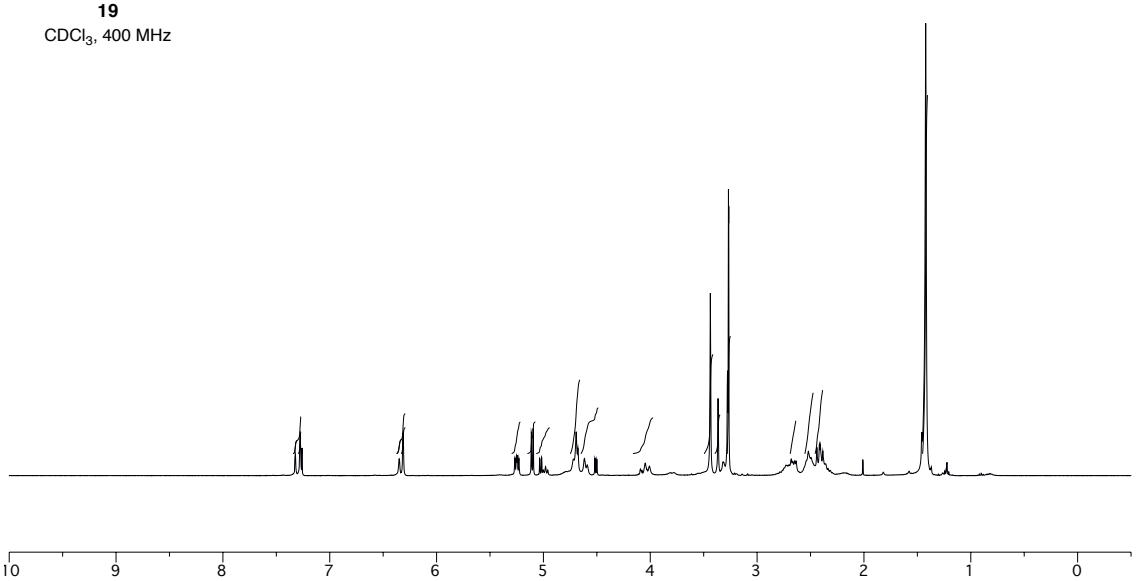
$CDCl_3$, 400 MHz

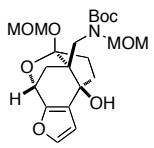




19

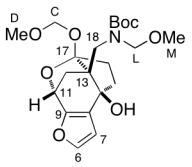
$CDCl_3$, 400 MHz





20

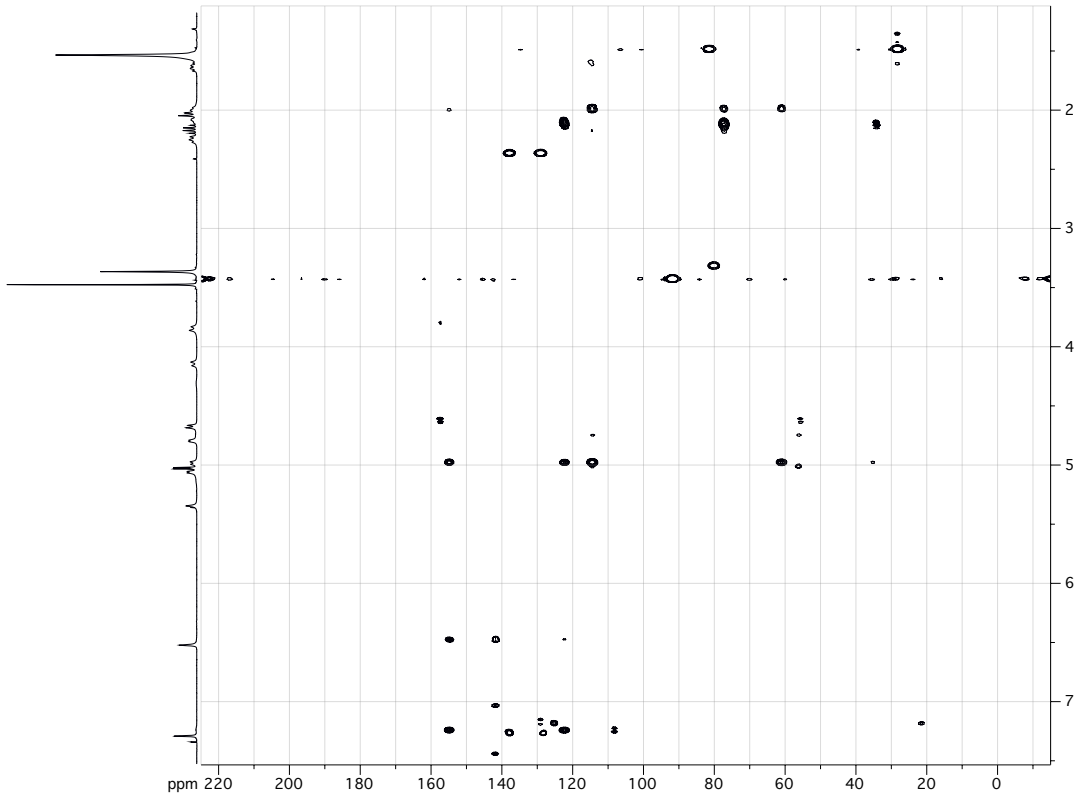
$CDCl_3$, 400 MHz

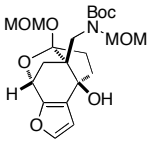


20

HMBC, $CDCl_3$, 500 MHz

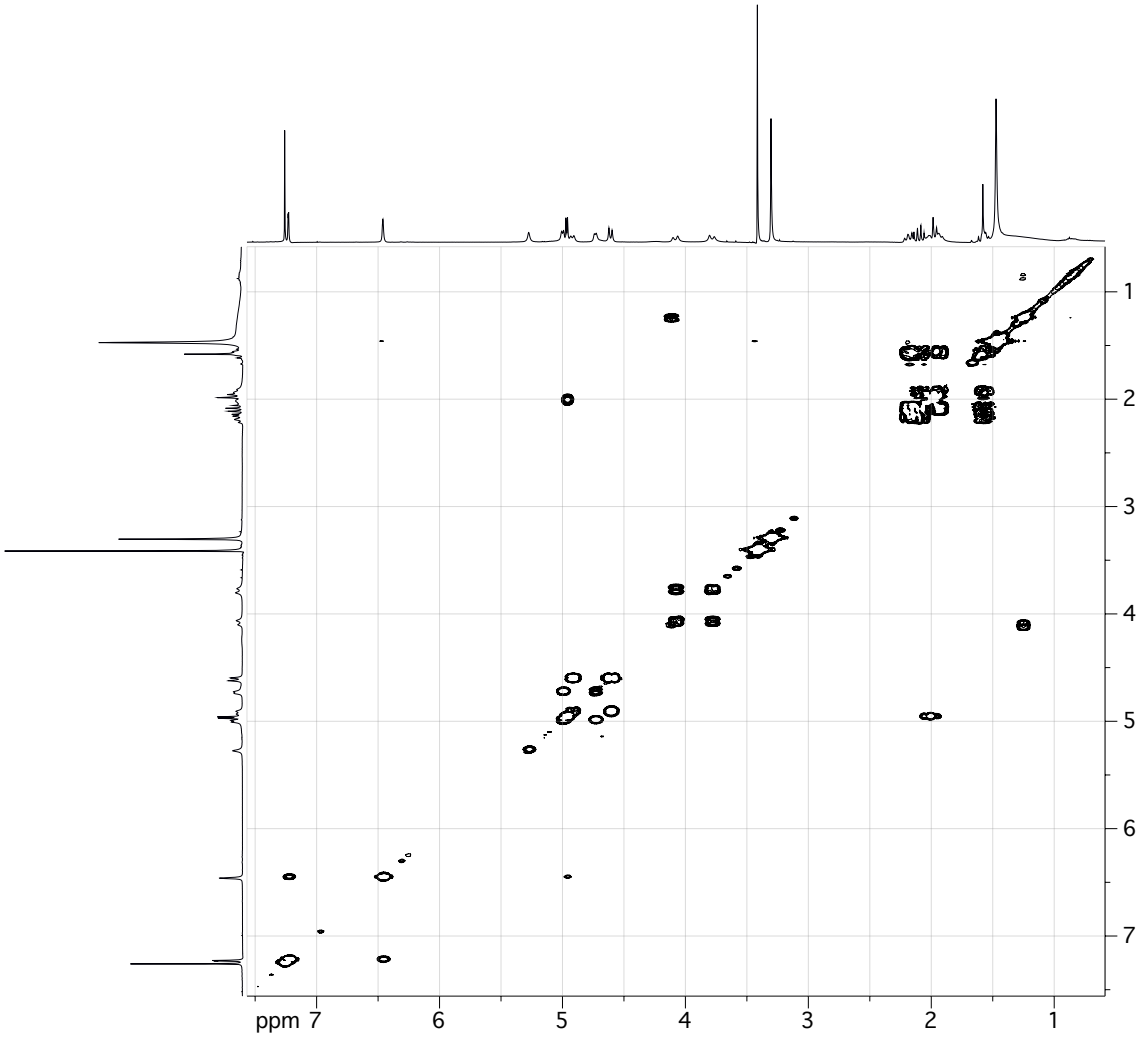
Position	^{1}H δ (ppm)	^{13}C δ (ppm)
H6	7.22	C9, 155; C8, 122; C7, 109
H7	6.46	C9, 155; C6, 142; C8, 122
HC_a	4.99	C17, 144; CD, 56.4
H11	4.96	C9, 155; C8, 122; C17, 114; C13, 61; C12, 36
HL_a	4.91	CJ, 158, CM, 56.0, C18, 44
HC_b	4.73	C17, 144; CD, 56.4
HL_b	4.60	CJ, 158, CM, 56.0, C18, 44
$H18_a$	4.07	CJ, 158; C14, 87; C13, 61
$H18_b$	3.78	CJ, 158; C17, 114; CL, 80; C15, 78; C13, 61
HD	3.41	CC, 92
HM	3.30	CL, 80

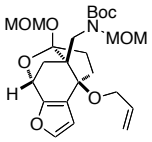




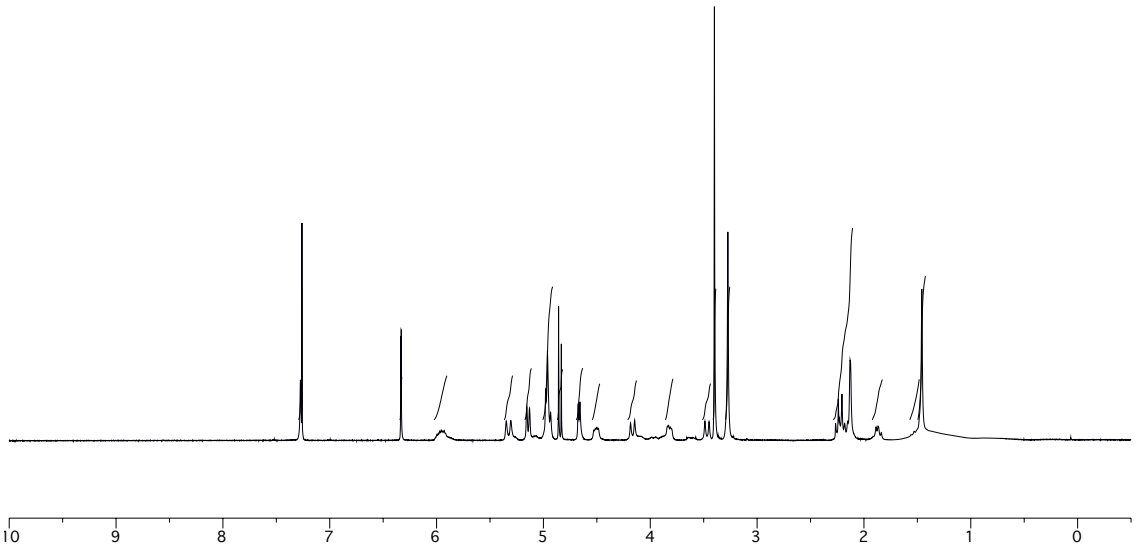
20

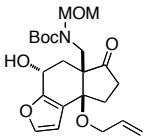
gCOSY, $CDCl_3$, 400 MHz



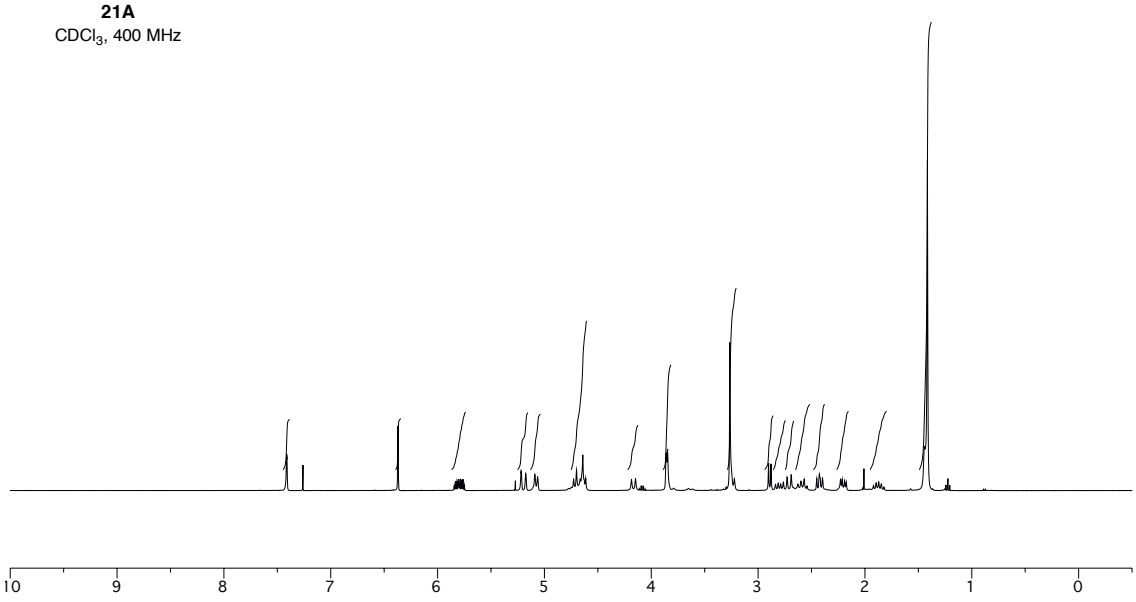


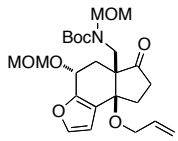
21
$CDCl_3$, 400 MHz



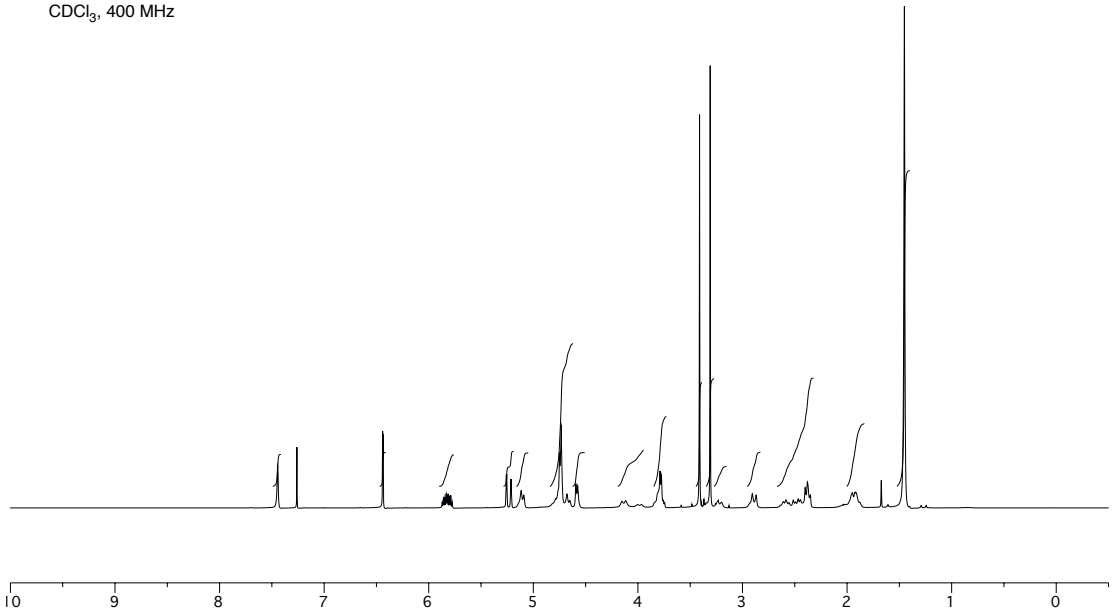


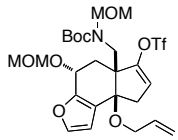
21A
$CDCl_3$, 400 MHz



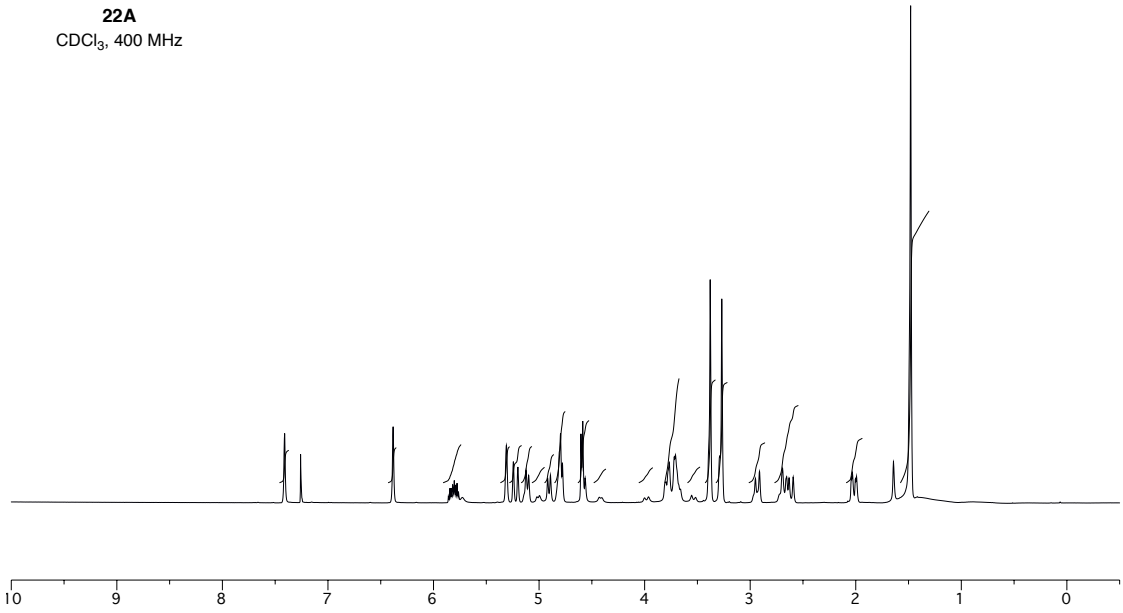


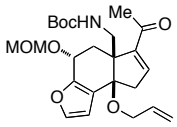
22
$CDCl_3$, 400 MHz



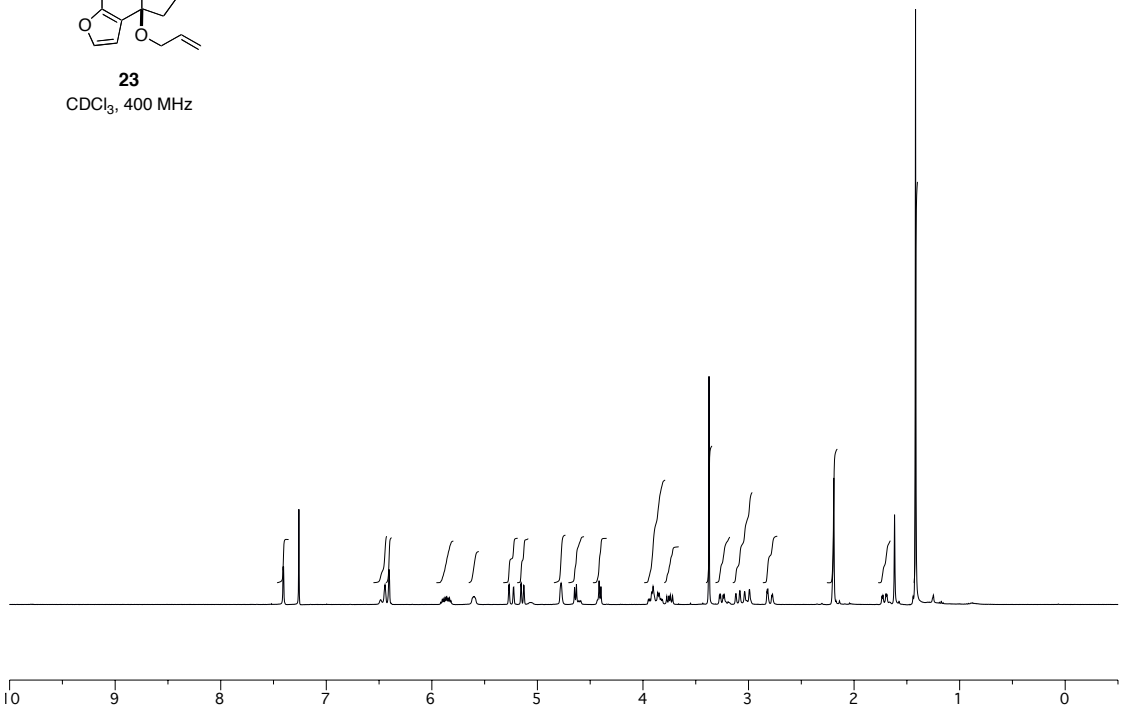


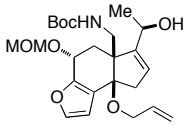
22A
$CDCl_3$, 400 MHz



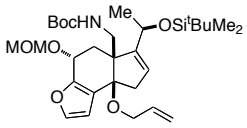


23
$CDCl_3$, 400 MHz

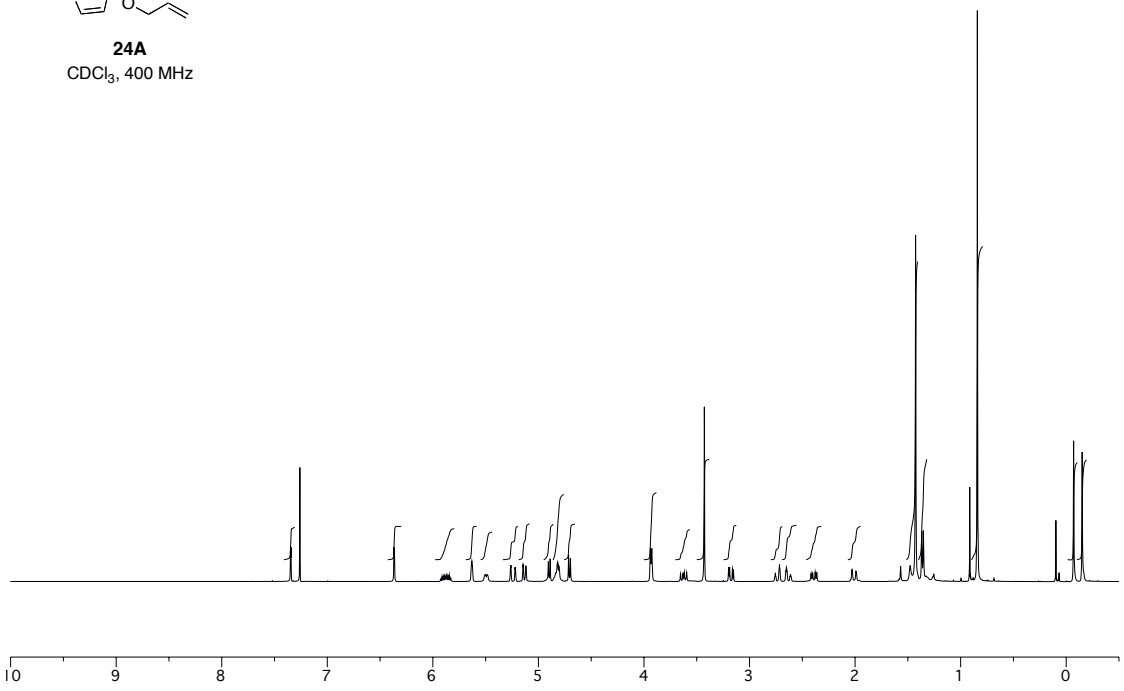


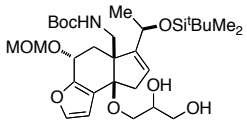


24
$CDCl_3$, 400 MHz

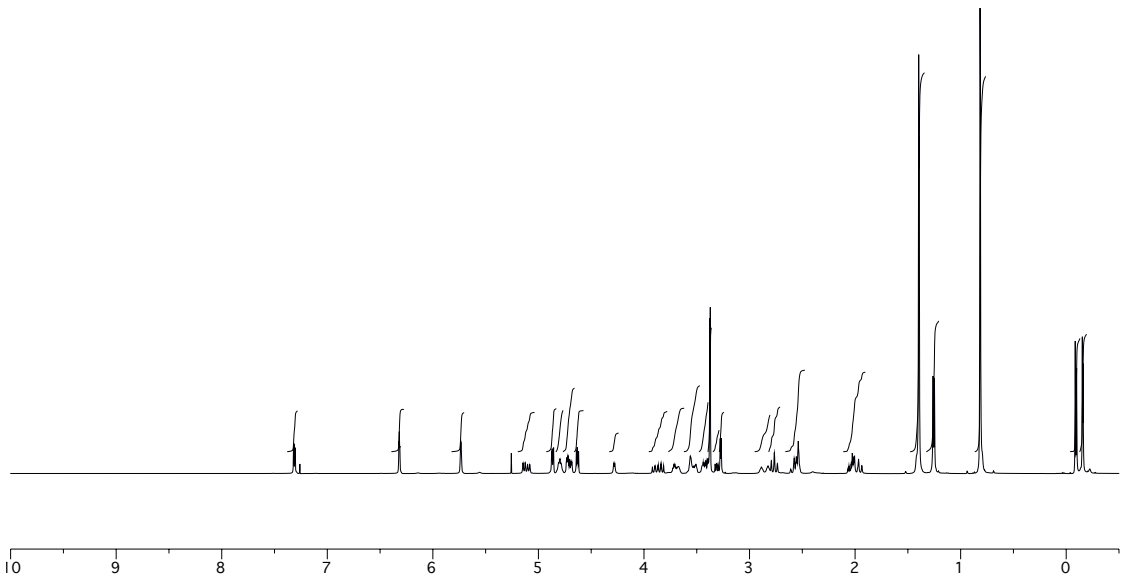


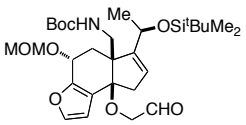
24A
$CDCl_3$, 400 MHz



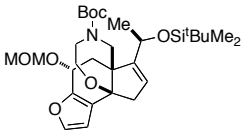


24B
$CDCl_3$, 500 MHz

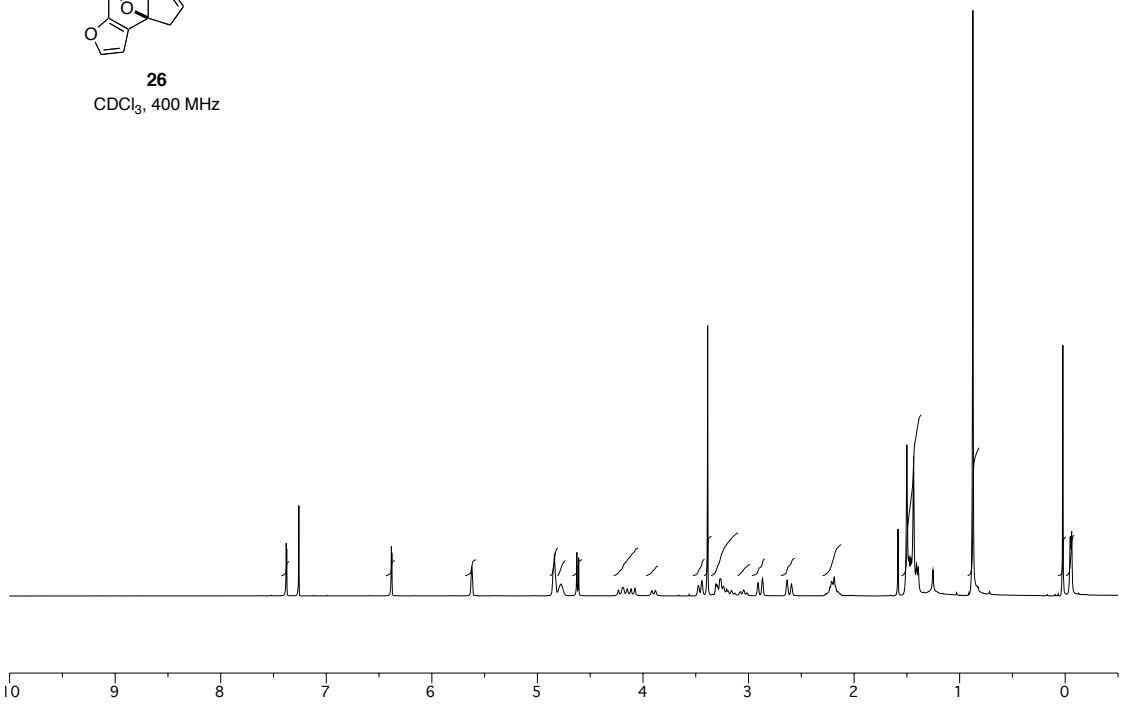


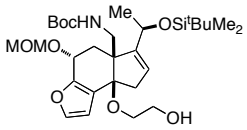


25
$CDCl_3$, 400 MHz



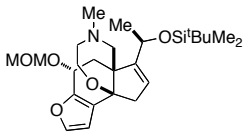
26
$CDCl_3$, 400 MHz





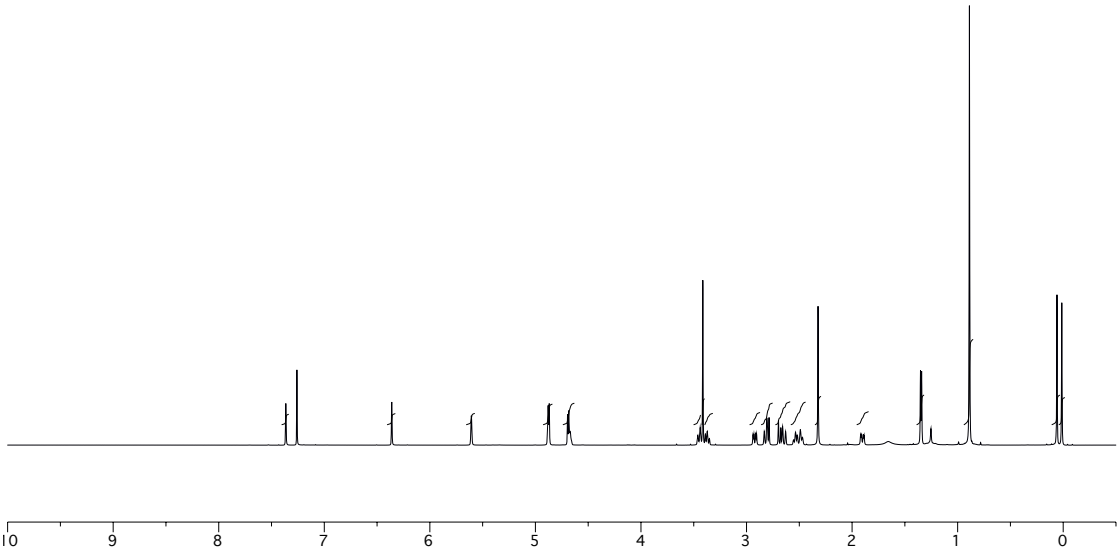
26A

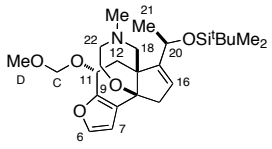
$CDCl_3$, 600 MHz



27

$CDCl_3$, 600 MHz

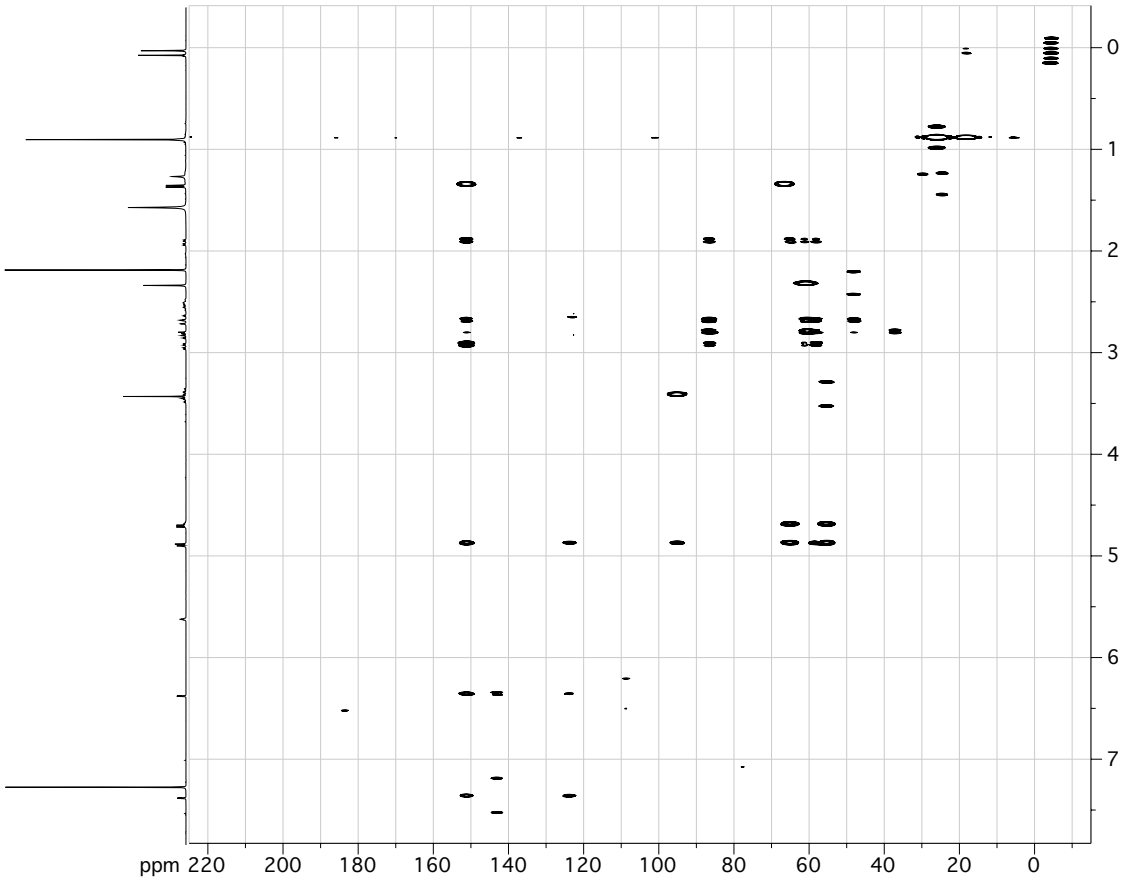


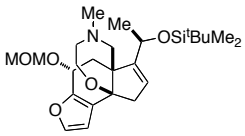


27

HMBC, $CDCl_3$, 500 MHz

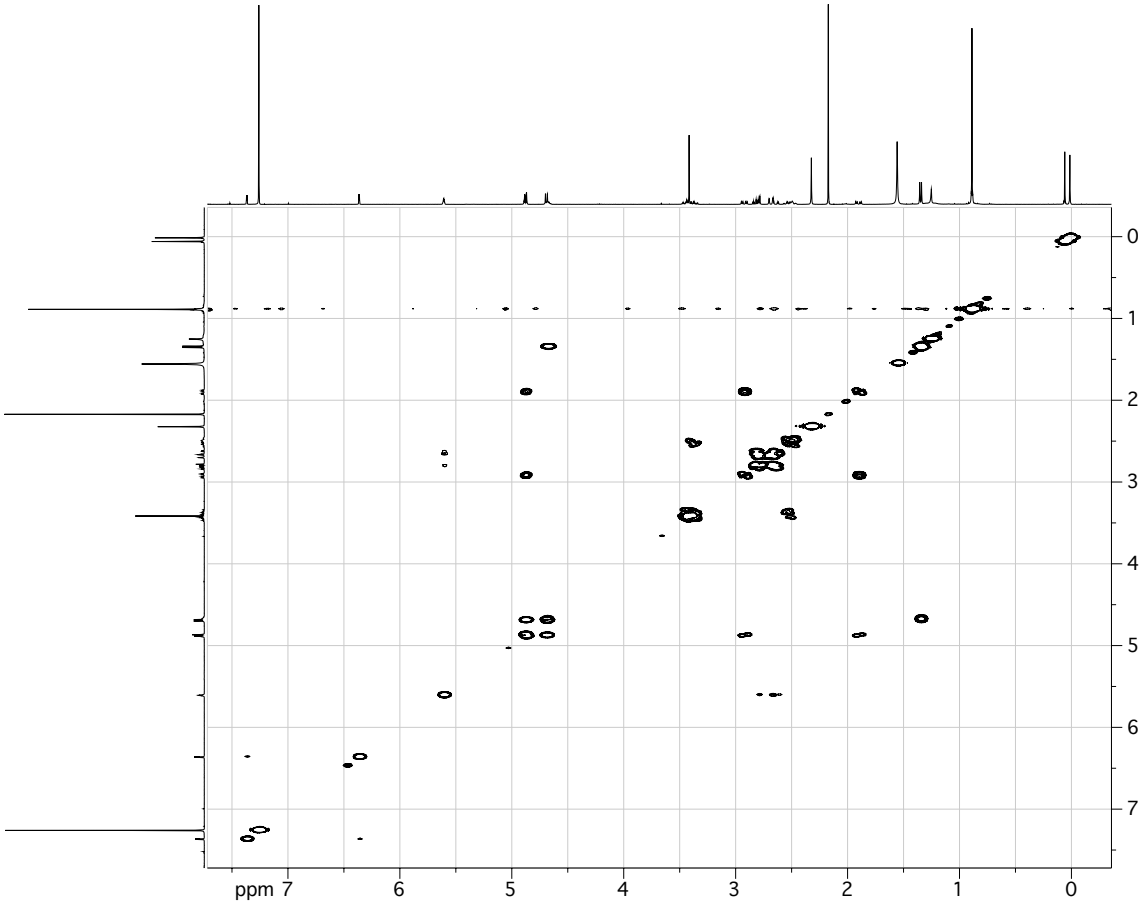
Position	^{1}H δ (ppm)	^{13}C δ (ppm)
H6	7.37	C9, 151; C8, 124
H7	6.36	C9, 151; C8, 124; C6, 144
H16	5.61	C14, 87; C13, 59
H11	4.87	C9, 151; C8, 124; CC, 96, C12, 38
H23$_a$	3.44	C14, 87
H23$_b$	3.37	C14, 87
HD	3.42	CC, 96
H12β	2.93	C9, 151; C14, 87; C13, 59
H15$_a$	2.81	C17, 151; C16, 123; C14, 87; C13, 59
H18$_a$	2.79	C17, 151; C14, 87; C22, 60.9; C13, 59; NMe, 49; C12, 37
H18$_b$	2.68	C17, 151; C14, 87; C22, 60.9; C13, 59; NMe, 49; C12, 37
H15$_b$	2.64	C17, 151; C16, 123; C14, 87; C13, 59
NMe	2.32	C18, 61.3; C22, 60.9
H12α	1.91	C9, 151; C14, 87; C11, 66; C13, 59
H21	1.35	C17, 151; C20, 67

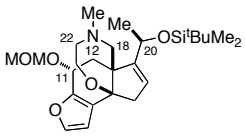




27

gCOSY, $CDCl_3$, 500 MHz

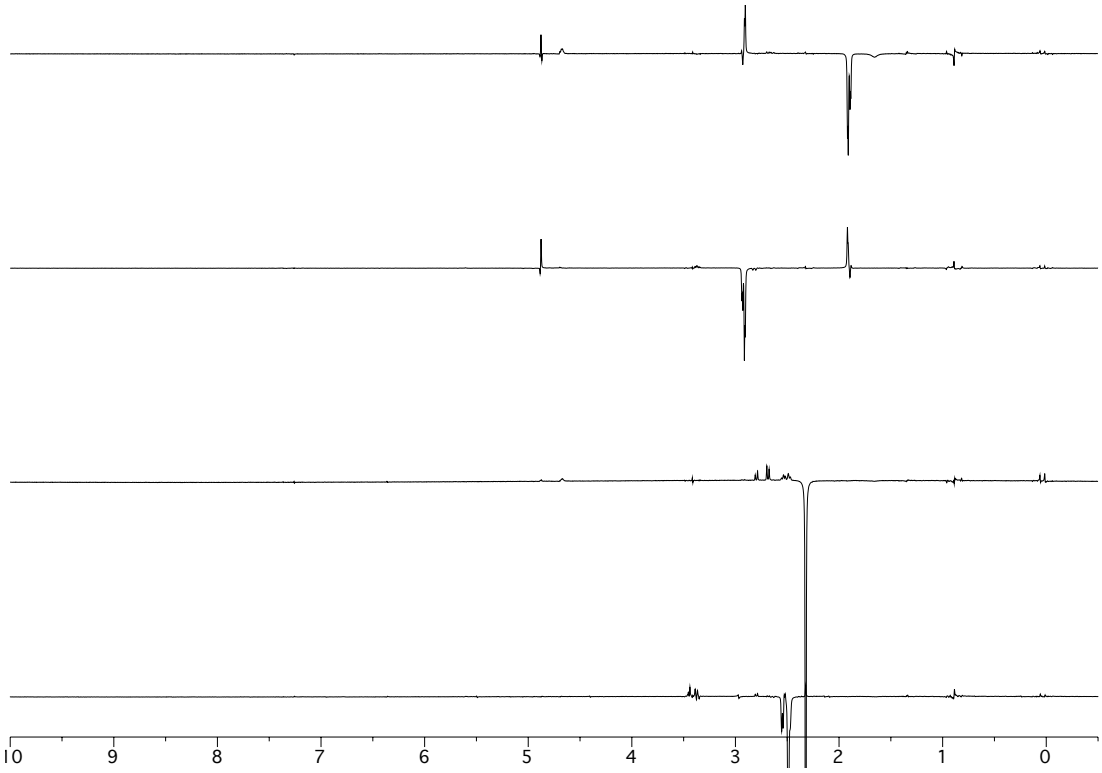


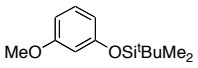


27

1D NOE, $CDCl_3$, 600 MHz

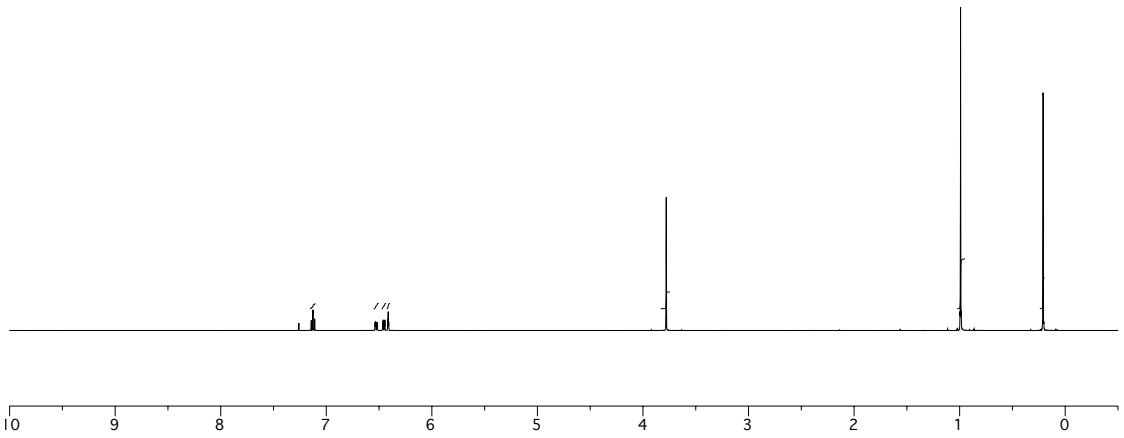
Position	^{1}H δ (ppm)	nOe							
H12β	2.93	H11, 4.87	$H23_b$, 3.37	H12α, 1.91					
$H22_{a,b}$	2.53, 2.49	$H23_a$, 3.44	$H23_b$, 3.37	$H18_a$, 2.79	NMe, 2.32	H21, 1.35			
NMe	2.32	H11, 4.87	H20, 4.67	H12β, 2.93	$H18_a$, 2.79	$H18_b$, 2.68	$H22_a$, 2.53	$H22_b$, 2.49	
H12α	1.91	H20, 4.67	H12β, 2.93	$H15_b$, 2.64					

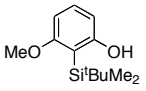




S1

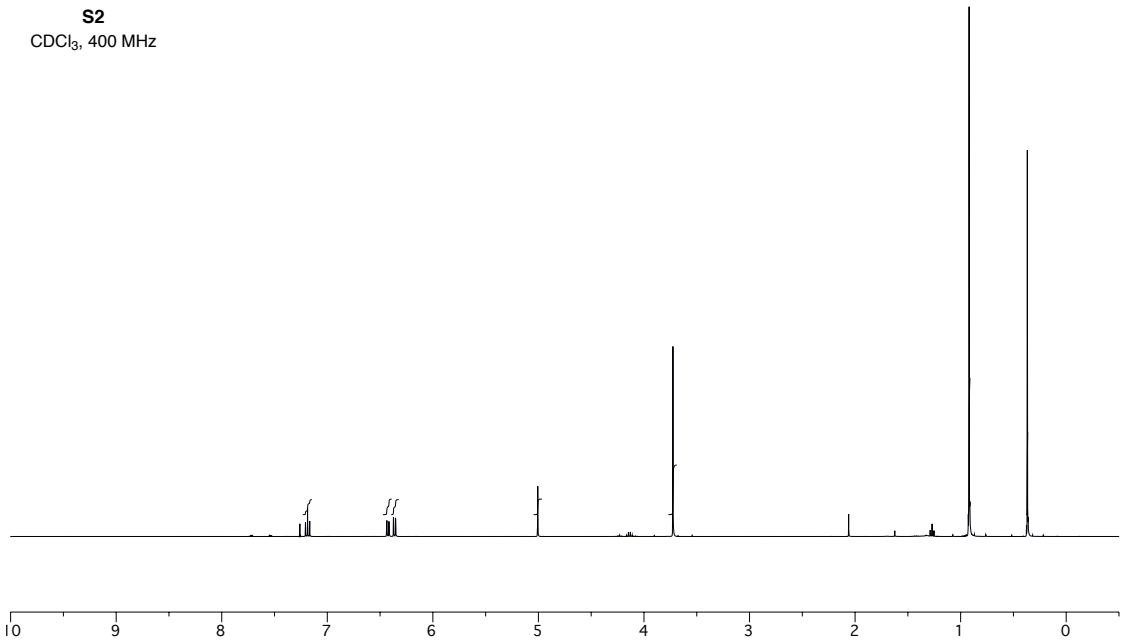
$CDCl_3$, 500 MHz

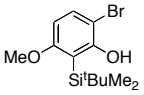




S2

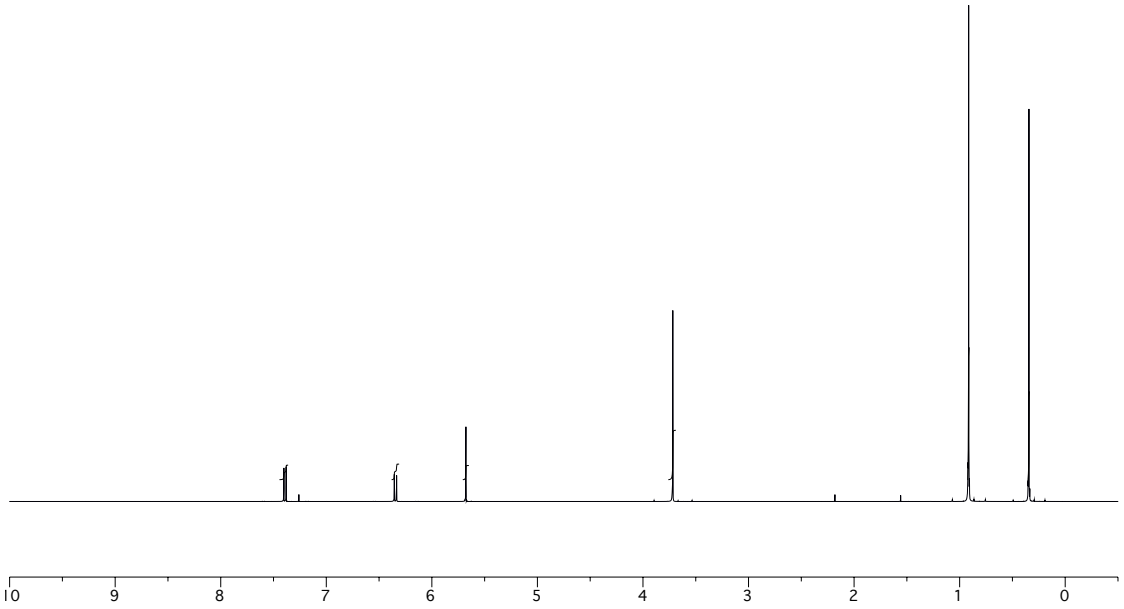
$CDCl_3$, 400 MHz

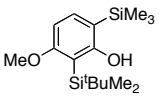




S3

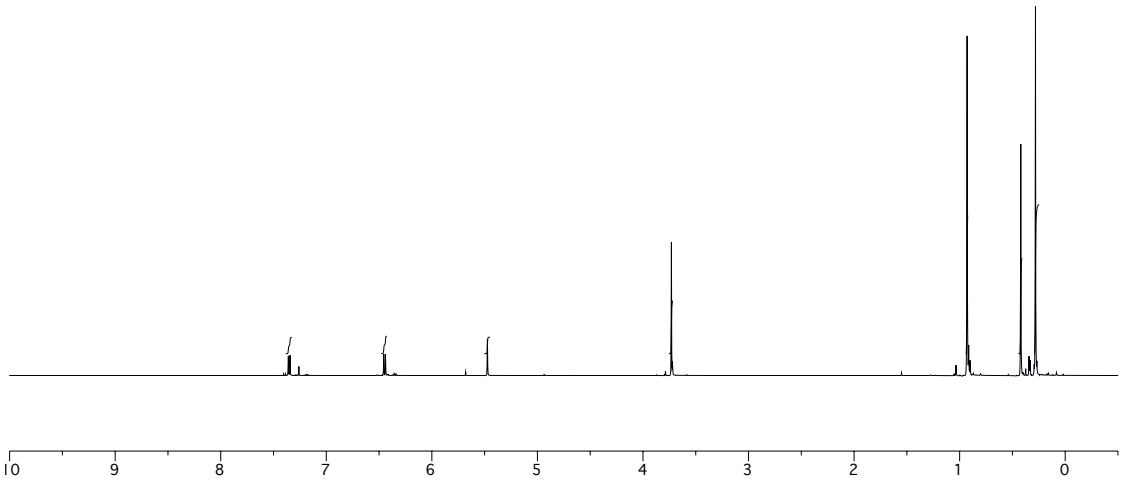
$CDCl_3$, 400 MHz

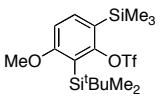




S4

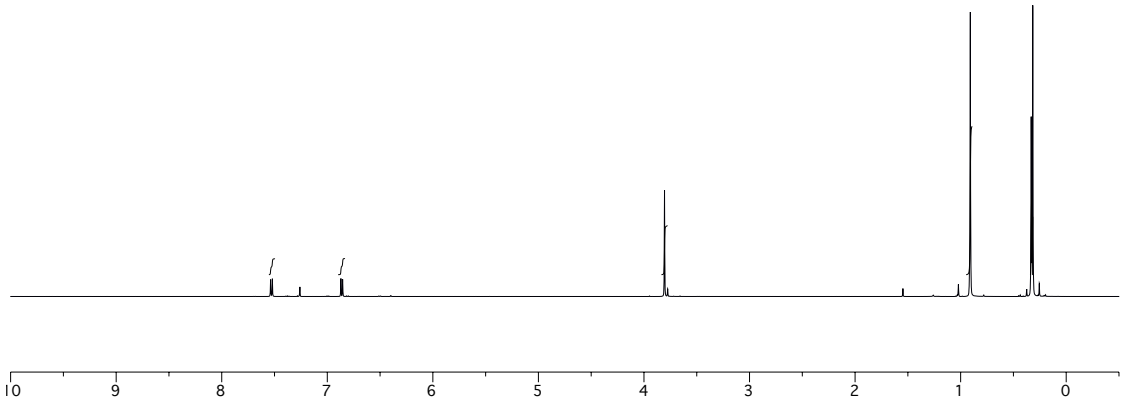
$CDCl_3$, 500 MHz

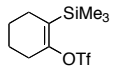




S5

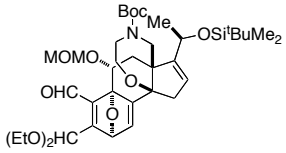
$CDCl_3$, 500 MHz





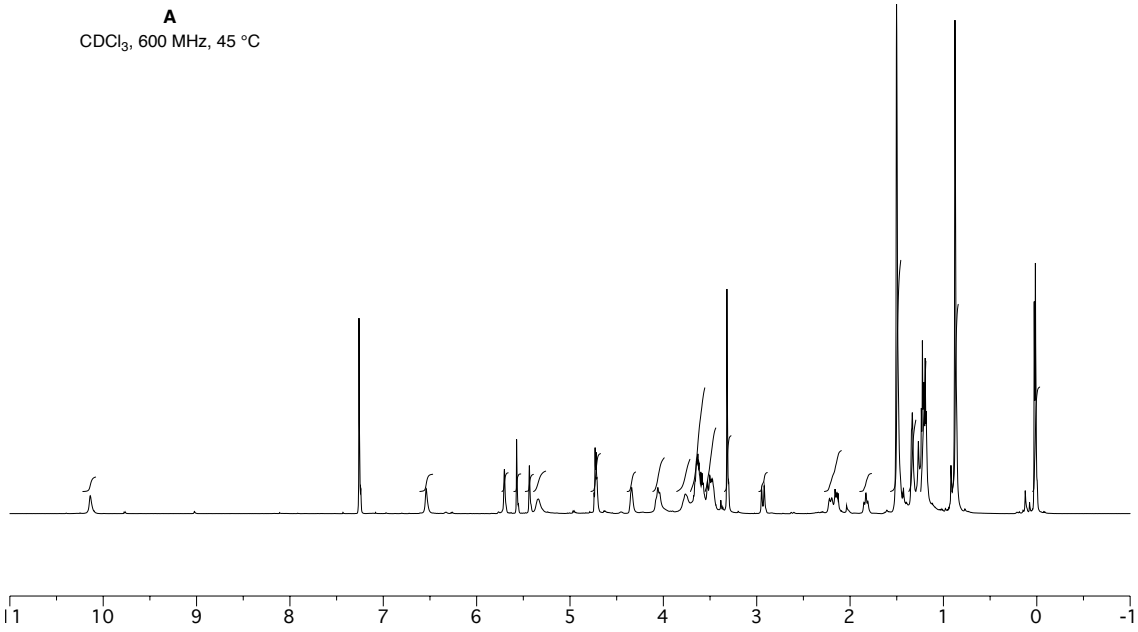
S6

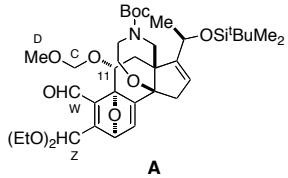
$CDCl_3$, 400 MHz



A

$CDCl_3$, 600 MHz, 45 °C

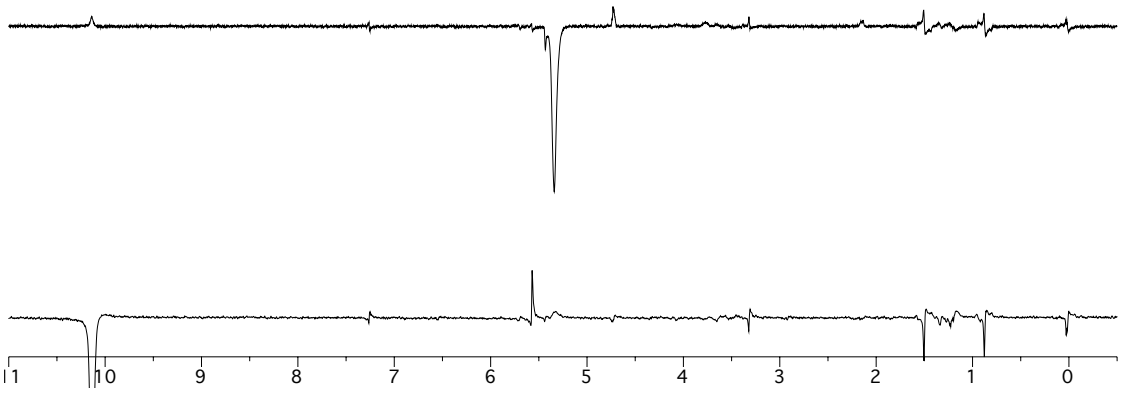


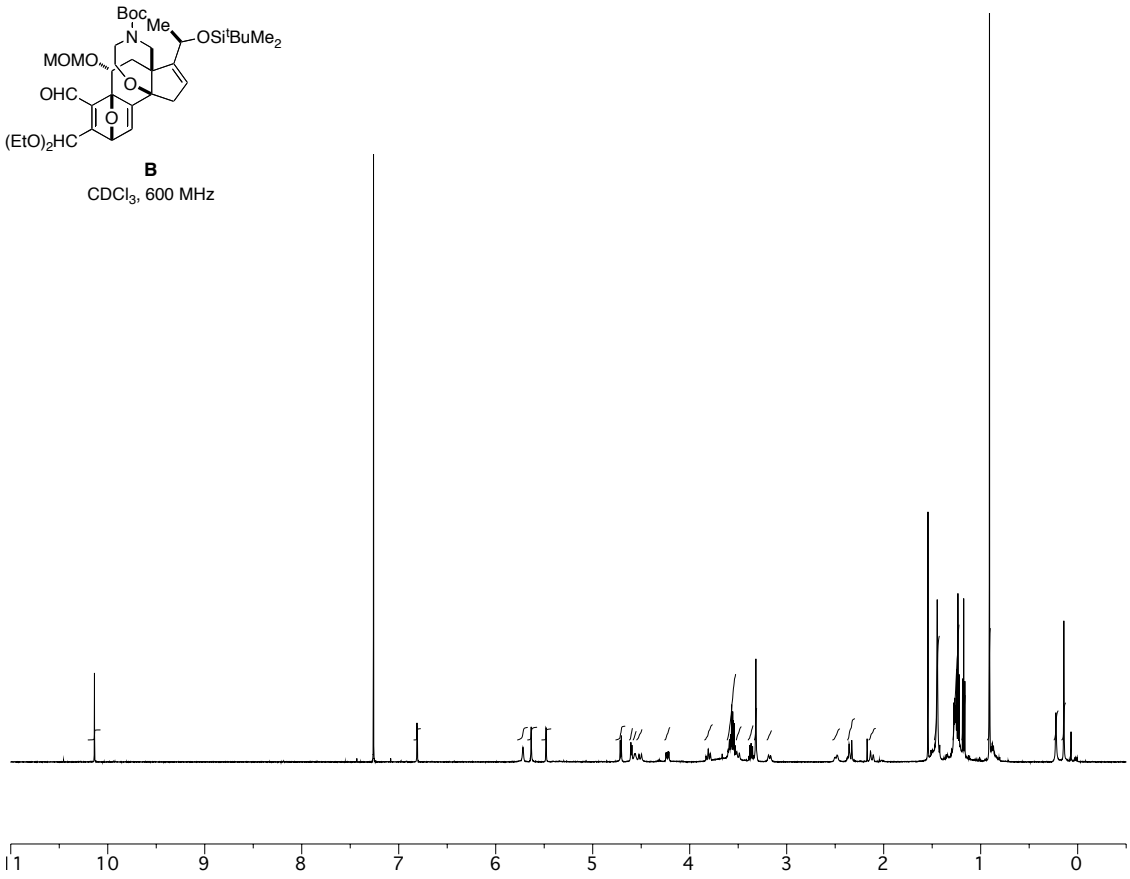


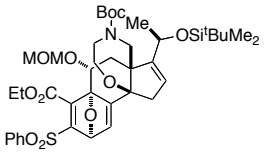
A

1D NOE, $CDCl_3$, 600 MHz, 45 °C

Position	^{1}H δ (ppm)	nOe			
HW	10.14	HZ, 5.57			
H11	5.34	HW, 10.14	HC, 4.73	HD, 3.32	H12, 2.12

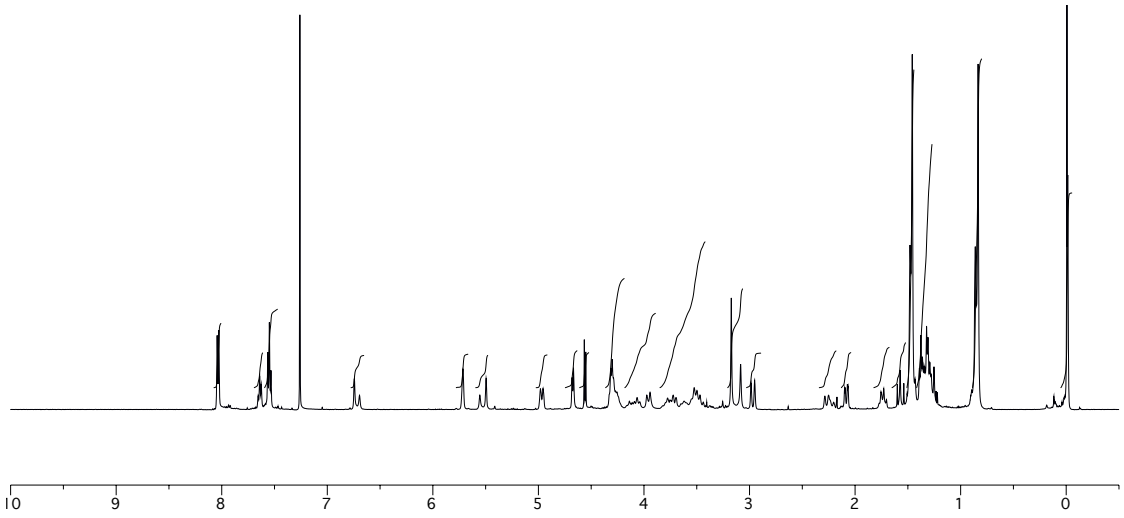


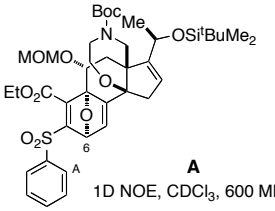

Boc
Me
N
OSi^{t}BuMe$_2$
MOMO
O
OHC
O
(EtO)$_2$HC
B
CDCl$_3$, 600 MHz
11
10
9
8
7
6
5
4
3
2
1
0



A

$CDCl_3$, 500 MHz

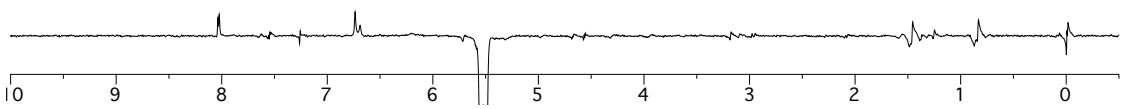


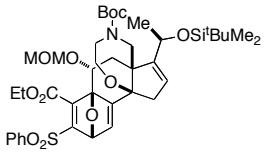


A

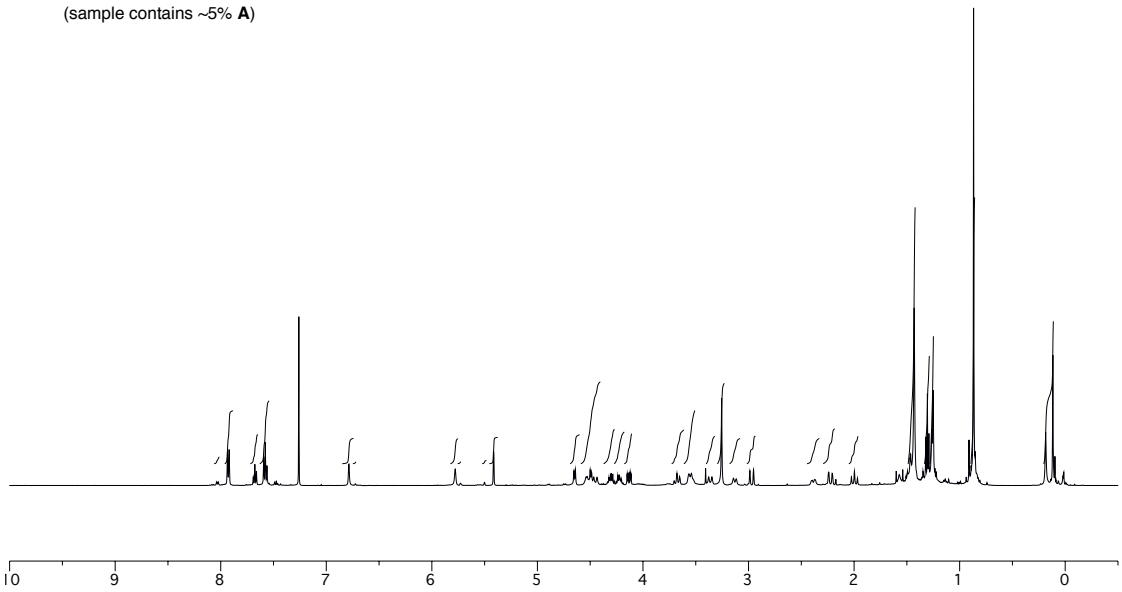
1D NOE, $CDCl_3$, 600 MHz

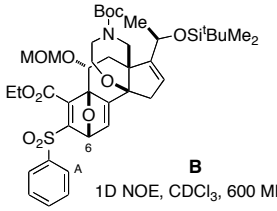
Position	**^{1}H δ (ppm)**	**nOe**	
H6	5.55	HA, 8.04	H7, 6.74





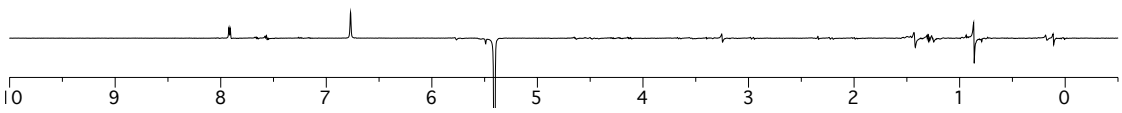
B
$CDCl_3$, 500 MHz
(sample contains ~5% **A**)

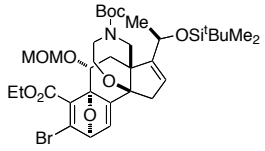




B
1D NOE, $CDCl_3$, 600 MHz

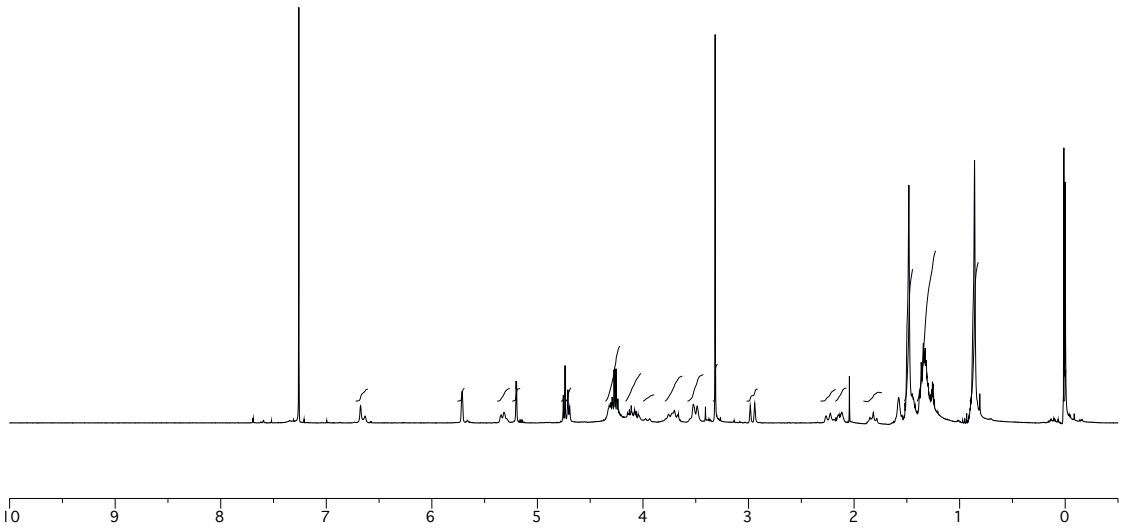
Position	**^{1}H δ (ppm)**	**nOe**	
H6	5.41	HA, 7.93	H7, 6.77

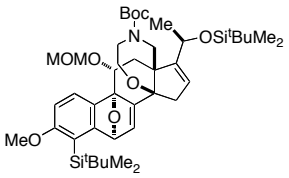




A

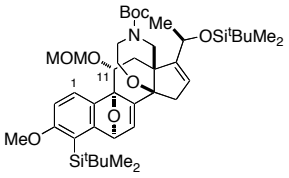
$CDCl_3$, 400 MHz





A

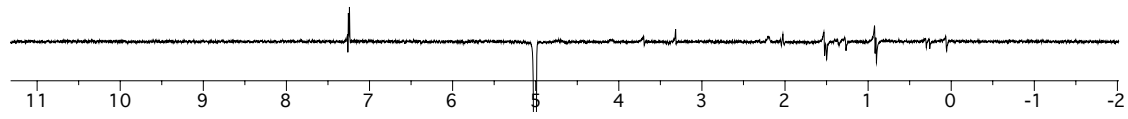
$CDCl_3$, 600 MHz, 45 °C

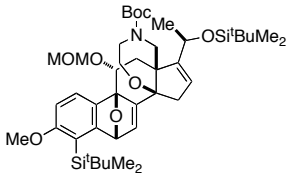


A

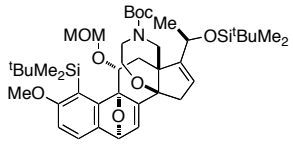
1D NOE, $CDCl_3$, 600 MHz, 45 °C

Position	**^{1}H δ (ppm)**	**nOe**
H11	5.01	H1, 7.25



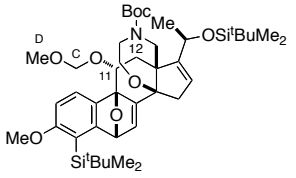


B

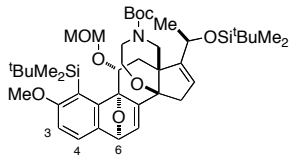


C

$CDCl_3$, 600 MHz



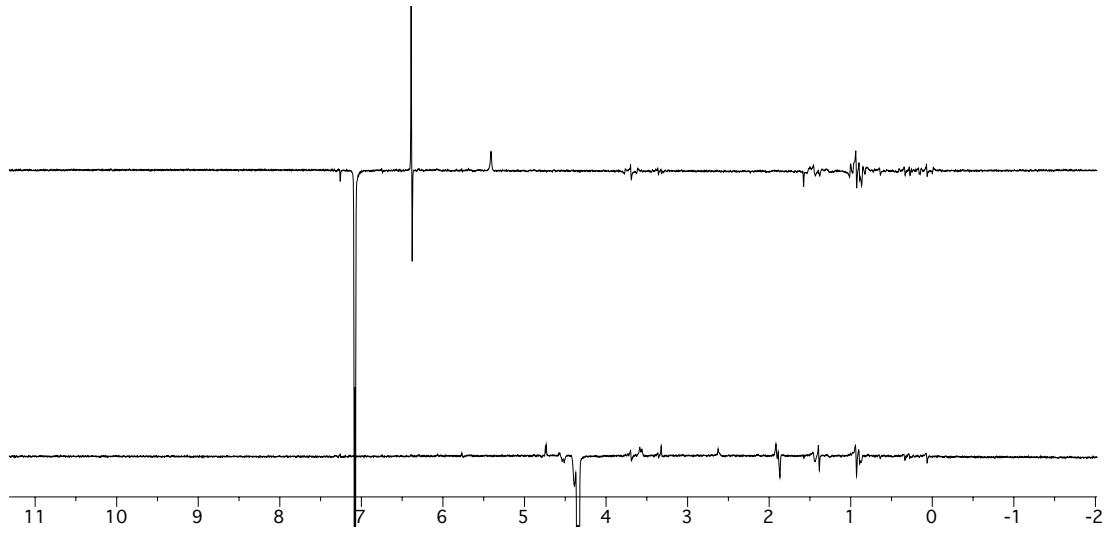
B

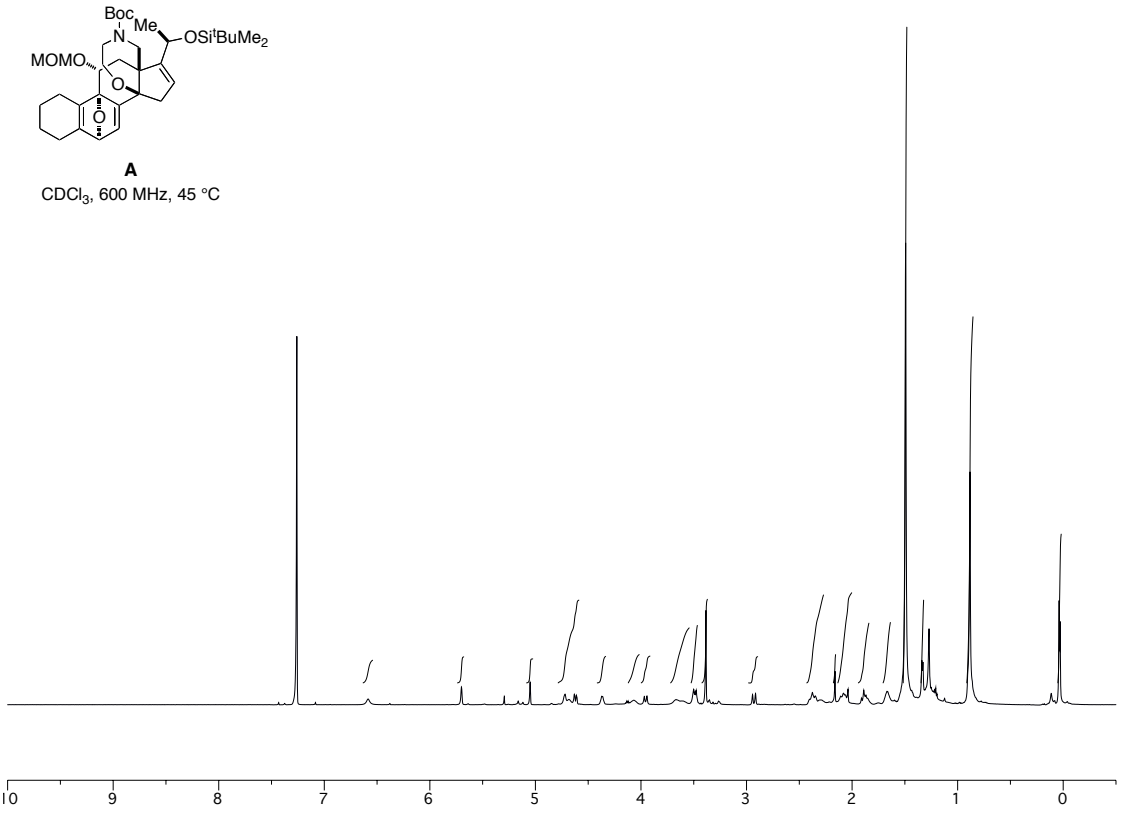


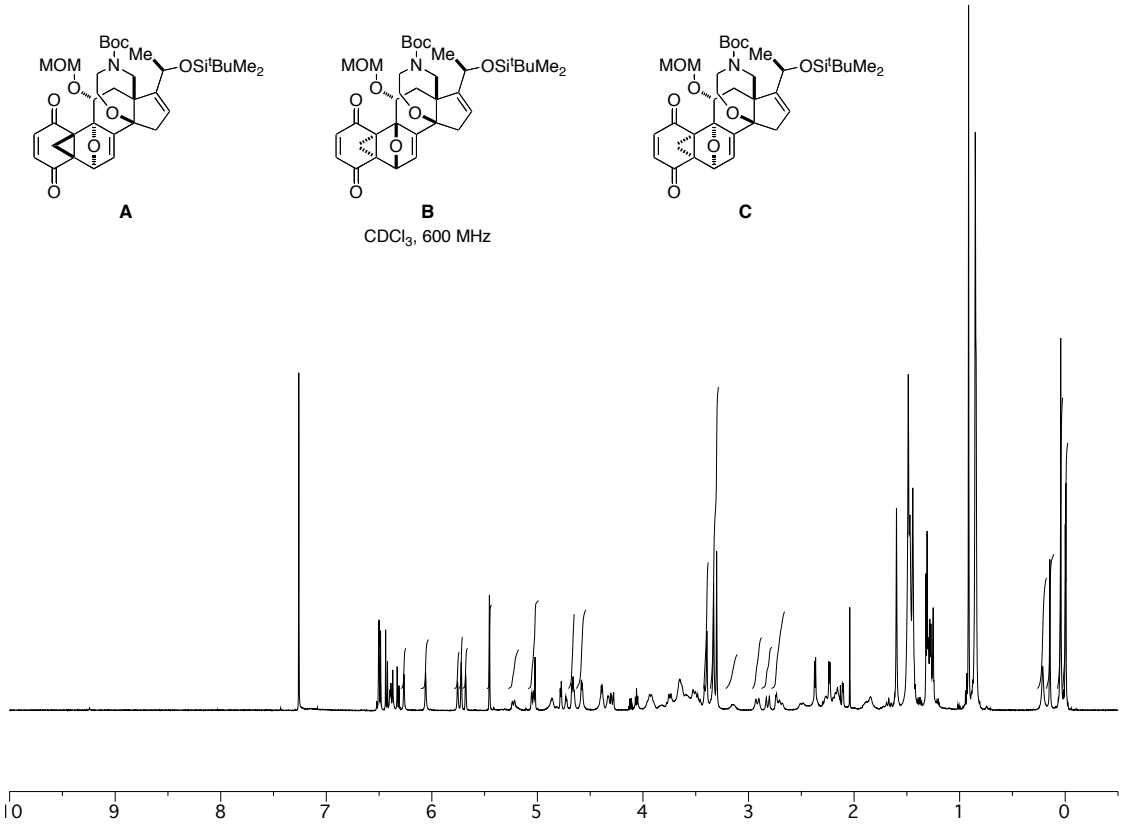
C

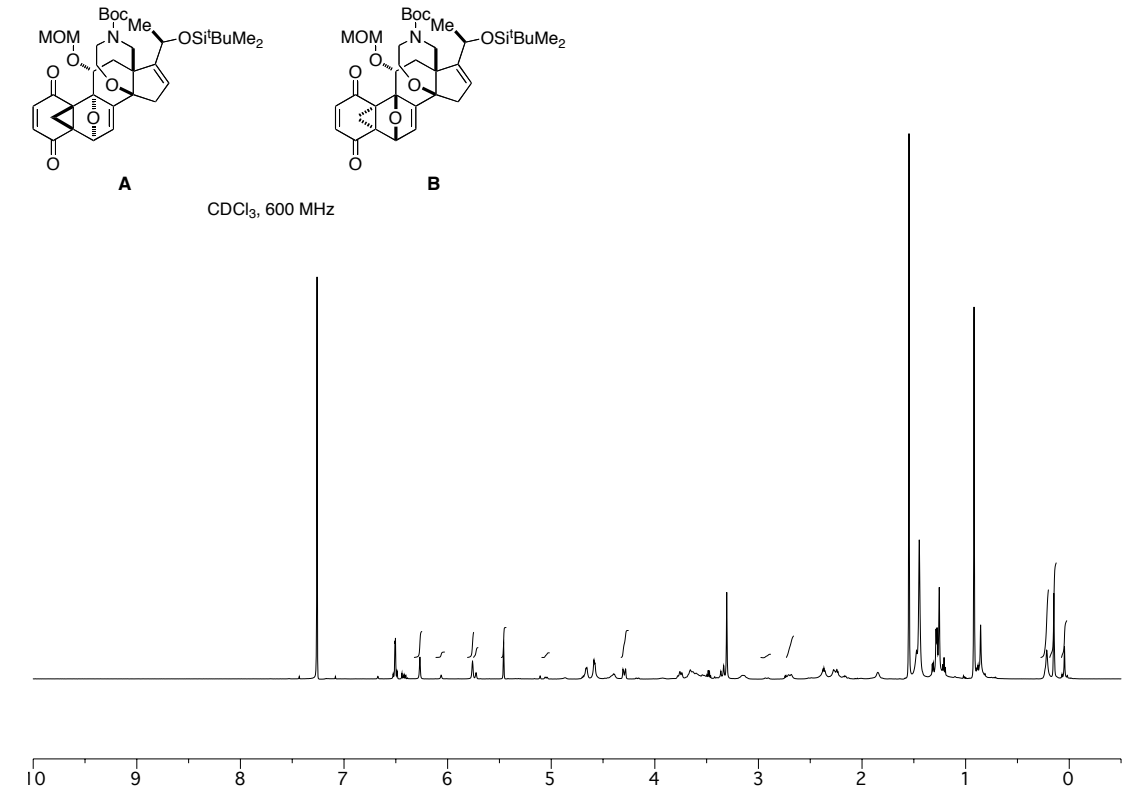
Position	^{1}H δ (ppm)	nOe		
B: H11	4.35	HC, 4.74	HD, 3.32	H12, 2.60
C: H4	7.07	H3, 6.38	H6, 5.41	

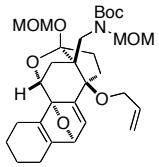
1D NOE, $CDCl_3$, 600 MHz




Boc
N
Me
OSi^{t}BuMe$_2$
MOMO
O
O
A
CDCl$_3$, 600 MHz, 45 °C
10
9
8
7
6
5
4
3
2
1
0

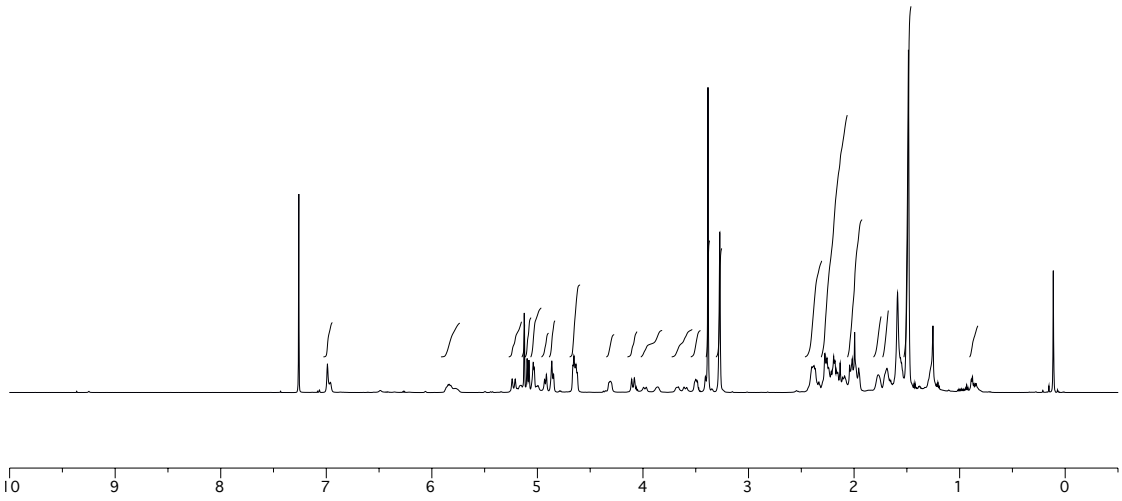

Boc
Me
N
MOM
O
OSi^{t}BuMe$_2$
A
B
C
CDCl$_3$, 600 MHz
10
9
8
7
6
5
4
3
2
1
0

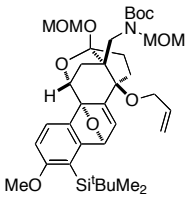

Boc
Me
N
MOM
O
OSi^{t}BuMe$_2$
A
B
CDCl$_3$, 600 MHz
10
9
8
7
6
5
4
3
2
1
0



29

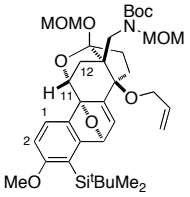
$CDCl_3$, 600 MHz





30

$CDCl_3$, 400 MHz



30

1D NOE, $CDCl_3$, 400 MHz

Position	**^{1}H δ (ppm)**	**nOe**		
H1	7.10	H2, 6.32	H11, 4.85	H12, 2.52