Supporting Information

Enantioselective Synthesis of a Cyclopropane Derivative of Spliceostatin A and Evaluation of Bioactivity

Arun K. Ghosh*,† Guddeti Chandrashekar Reddy,† Satish Kovela,† Nicola Relitti,† Veronica K. Urabe,‡ Beth E. Prichard,‡ and Melissa S. Jurica‡

†Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907; ‡Department of Molecular Cell and Developmental Biology and Center for Molecular Biology of RNA, University of California, Santa Cruz, California 95064

E-mail: akghosh@purdue.edu

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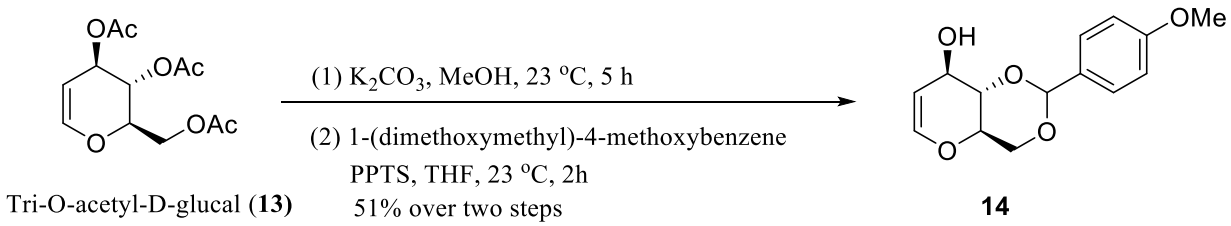
General Information:

All chemicals and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: Dichloromethane, 1,2-dichloroethane and toluene from calcium hydride, diethyl ether and tetrahydrofuran from Na/Benzophenone. All reactions were carried out under an argon atmosphere. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 A, 250 μm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AV-III-400-HD with 5mm BBFO Z-gradient SmartProbe and Bruker DRX-500 with 5mm TXI Z-gradient cryoprobe. Chemical shifts (δ values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet). Optical rotations were recorded on a Perkin Elmer 341 polarimeter. LRMS spectra were recorded on Agilent 6120

Quadrupole LC-MS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

Experimental Details:

(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-ol (14):



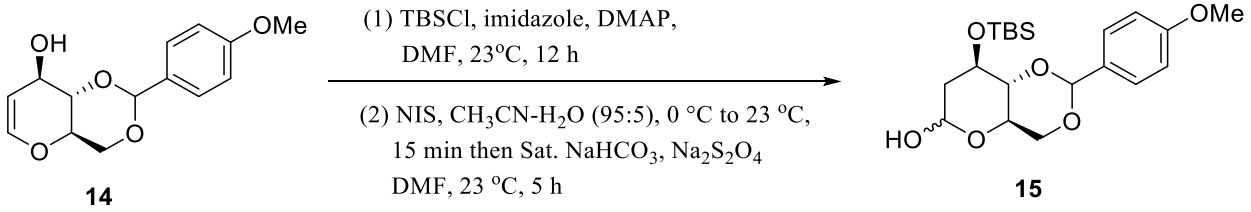
Tri-O-acetyl-D-glucal (**13**) **14**

To a tri-*O*-acetyl-D-glucal **13** (10 g, 36.73 mmol) in MeOH (50 mL) was added K_2CO_3 (101 mg, 0.73 mmol) at 23 °C, reaction mixture was stirred for 5 h and then the solvent was evaporated under reduced pressure and then directly chromatographed (5% MeOH/ EtOAc) to afford D-glucal (5 g, 93%) as a white powder.

To a stirred solution of D-glucal (5 g, 34.20 mmol) in THF (50 mL) was added 1-(dimethoxymethyl)-4-methoxybenzene (8.15 mL, 47.90 mmol) and PPTS (1.72 g, 6.80 mmol) at 23 °C, the reaction mixture was stirred for 2 h, and then the reaction mixture was diluted with EtOAc, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford **14** (5 g, 55 %) as a white amorphous powder. $[\alpha]_D^{20}$ = □21.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 6.93 – 6.87 (m, 2H), 6.33 (ddd, *J* = 6.1, 1.8, 0.6 Hz, 1H), 5.56 (s, 1H), 4.77 (dd, *J* = 6.1, 2.0 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.35 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.94 – 3.86 (m, 1H), 3.83 – 3.75 (m, 5H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 144.1, 129.4, 127.5, 113.6, 103.4, 101.7, 80.6, 68.3, 68.2, 66.5, 55.2; LRMS-ESI (*m/z*): 265.0 $[M+H]^+$.

Reference for allyl alcohol **14**: (1) Roën, A.; Padrón, J. I.; Mayato, C.; Vázquez, J. T. *J. Org. Chem*. **2008**, *73*, 3351–3363

(4a*R*,8*R*,8a*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)hexahydropyrano[3,2-d][1,3]dioxin-6-ol (15):



14 **15**

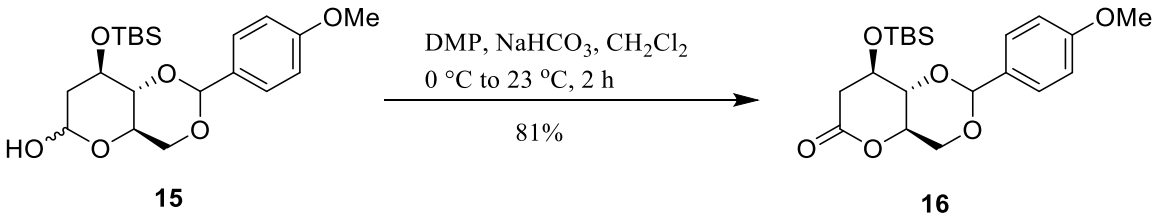
To a solution of allylic alcohol **14** (4.9 g, 18.56 mmol) in DMF (36 mL) were added imidazole (3.02 g, 44.40 mmol), DMAP (0.23 g, 1.85 mmol) and TBSCl (3.34 g, 22.27 mmol) at 23 °C, the reaction mixture was stirred for 12 h, and then the reaction mixture was diluted with EtOAc, quenched with saturated $NaHCO_3$, extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by silica gel chromatography (5% EtOAc/hexanes) to afford silyl ether (6.38 g, 91 %) as a colorless oil. $[\alpha]_D^{20}$ = □71.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 6.93 – 6.86 (m, 2H), 6.29 (ddd, *J* = 6.1, 1.7, 0.6 Hz, 1H), 5.55 (s, 1H), 4.66 (dd, *J* = 6.2, 2.0 Hz, 1H), 4.50 (dt, *J* = 7.3, 1.8 Hz, 1H), 4.33 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.90 – 3.83 (m, 1H), 3.83 – 3.74 (m, 5H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 143.2, 129.8, 127.2, 113.4, 105.3, 101.2, 80.5, 68.7, 68.2, 67.2, 55.2, 25.7, 18.1, -4.5, -4.9; LRMS-ESI (*m/z*): 379.1 $[M+H]^+$.

To a stirred solution of above silyl ether (3 g, 7.93 mmol) in CH_3CN-H_2O (95:5, 64 mL) was added NIS (1.96 g, 8.72 mmol) at 0 °C and the reaction mixture was allowed to 23 °C and stirred at the same temperature for 15 min, CH_3CN was removed under reduced pressure, then the residue was dissolved in DMF (80 mL), to that solution were added saturated $NaHCO_3$ (80 mL) and $Na_2S_2O_4$ (5.52 g, 31.70 mmol) at 23 °C, and then the reaction mixture was stirred for 5 h, diluted with EtOAc (800 mL), washed with water (100 mL) followed by brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford hemiacetal **15** (2.8 g, 89 %, diastereomeric ratio: 1:0.55) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 6.90 – 6.85 (m, 2H), 5.52 (s, 0.65H), 5.50 (s, 0.35H), 5.34 (t, *J* = 4.0 Hz, 0.65H), 4.90 (m, 0.35H), 4.30 – 4.16 (m, 1.7H), 4.01 (td, *J* = 9.9, 4.8 Hz, 0.65H), 3.90 (ddd, *J* = 8.4, 5.2, 2.5 Hz, 0.35H), 3.80 (s, 3H), 3.79 – 3.67 (m, 1H), 3.47– 3.32 (m, 1.4H),

3.25 (d, J = 6.8 Hz, 0.35H), 2.68 (t, J = 2.5 Hz, 0.65H), 2.27 (ddd, J = 13.0, 5.2, 2.2 Hz, 0.35H), 2.14 (ddd, J = 13.4, 5.2, 1.0 Hz, 0.65H), 1.82 – 1.73 (m, 0.65H), 1.70 – 1.60 (m, 0.35H), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 130.0, 129.9, 127.3, 127.2, 113.3, 101.5, 101.4, 94.4, 92.9, 68.9, 68.8, 66.8, 66.2, 63.2, 55.1, 42.2, 39.3, 25.7, 25.6, 18.1, 18.1, -4.5, -5.0.

Reference for silyl ether: (2) Boulineau, F. P.; Wei, A. *Carbohydr. Res.* **2001**, *334*, 271-279.

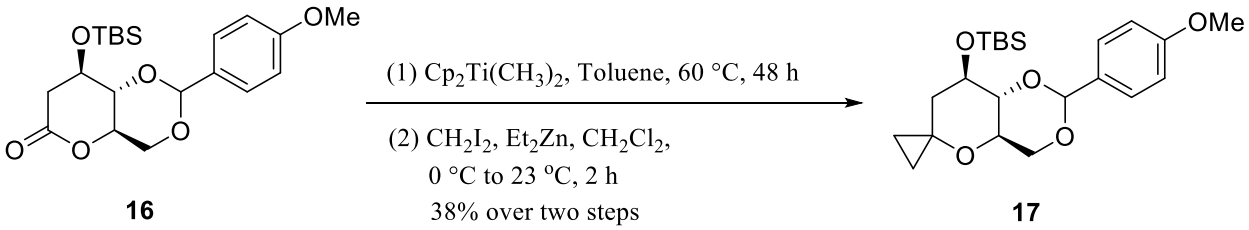
(4a*R*,8*R*,8a*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)tetrahydropyrano[3,2-d][1,3]dioxin-6(4*H*)-one (16):



15 **16**

To a stirred solution of hemiacetal **15** (2 g, 5.05 mmol) in CH_2Cl_2 (20 mL) were added Dess□martin periodinane (3.21 g, 7.57 mmol) and $NaHCO_3$ (1.7 g, 20.2 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 23 °C. After completion of starting material, the reaction mixture was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ in the ration of 1:1 and stirred vigorously for 10 min, then it was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford **16** (1.6 g, 81 %) as a white amorphous powder. $[\alpha]_D^{20}$ = □23.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 6.92 – 6.87 (m, 2H), 5.54 (s, 1H), 4.43 (dd, J = 10.6, 5.2 Hz, 1H), 4.23 (td, J = 7.8, 5.4 Hz, 1H), 4.07 (td, J = 10.0, 5.2 Hz, 1H), 3.84 – 3.78 (s, 3H, overlapped with 1H, m), 3.71 (dd, J = 9.8, 7.7 Hz, 1H), 3.12 (dd, J = 17.8, 8.0 Hz, 1H), 2.64 (dd, J = 17.8, 5.4 Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.1, 129.1, 127.2, 113.5, 101.5, 81.2, 68.0, 67.9, 67.5, 55.2, 39.2, 25.5, 17.9, -4.6, -5.1; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{31}O_6Si$, 395.1884; found 395.1887.

***tert*-Butyl(((4a'*R*,8'*R*,8a'*R*)-2'-(4-methoxyphenyl)tetrahydro-4'*H*-spiro[cyclopropane-1,6'-pyrano[3,2-d][1,3]dioxin]-8'-yl)oxy)dimethylsilane (17):**



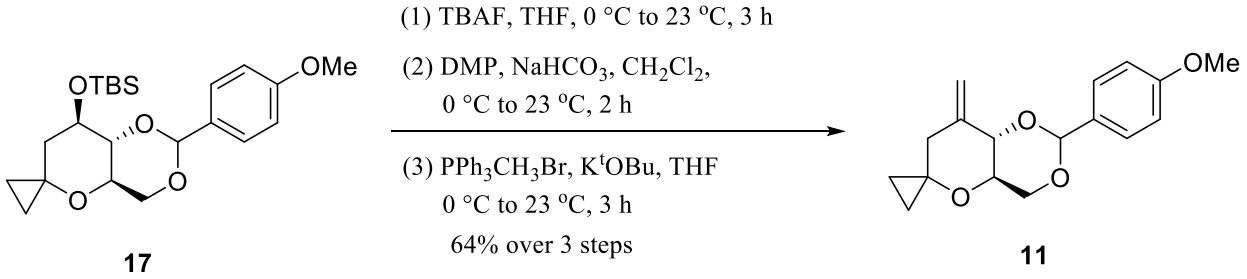
16 **17**

To a stirred solution of cyclic ester **16** (1.5 g, 3.79 mmol) in toluene (15 mL) Petasis reagent (0.22 M in THF-toluene, 35 mL) was added at 23 °C and the reaction mixture was heated at 60 °C for 2 days in dark (covered with aluminum foil). The reaction mixture diluted with CH_2Cl_2, quenched with water and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford the enol-ether (1.35 g, 90 %) as a yellow amorphous powder. $[\alpha]_D^{20}$ = +17.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 6.91 – 6.85 (m, 2H), 5.52 (s, 1H), 4.49 (d, *J* = 1.9 Hz, 1H), 4.33 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.24 (d, *J* = 1.2 Hz, 1H), 3.95 – 3.87 (m, 1H), 3.81 (s, 3H), 3.75 (t, *J* = 10.2 Hz, 1H), 3.55 (dd, *J* = 9.4, 8.4 Hz, 1H), 3.51 – 3.41 (m, 1H), 2.63 (dd, *J* = 14.2, 5.7 Hz, 1H), 2.42 – 2.31 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 156.2, 129.8, 127.3, 113.4, 101.4, 94.6, 82.7, 70.5, 69.6, 68.7, 55.2, 38.3, 25.6, 18.1, -4.5, -5.0; LRMS-ESI (*m/z*): 393.1 $[M+H]^+$.

To a solution of CH_2I_2 (1.32 mL, 16.50 mmol) in CH_2Cl_2 (60 mL) was added Et_2Zn (1M in hexanes, 6.6 mL, 6.60 mmol) at 0 °C and the mixture was stirred for 30 min. To this mixture, a solution of above enol-ether (1.3 g, 3.28 mmol) in CH_2Cl_2 (40 mL) was added at 0 °C, and then the reaction mixture was warmed to 23 °C and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (5% EtOAc/hexanes) to afford **17** (0.65 g, 42 %) as a white amorphous powder. $[\alpha]_D^{20}$ = □7.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 6.92 – 6.85 (m, 2H), 5.52 (s, 1H), 4.19 – 4.13 (m, 1H), 4.04 – 3.97 (m, 1H), 3.81 (s, 3H), 3.71 – 3.64 (m, 1H), 3.54 – 3.47 (m, 2H),

2.35 – 2.25 (m, 1H), 1.42 – 1.33 (m, 1H), 0.92 – 0.84 (m, 10H), 0.74 – 0.65 (m, 1H), 0.58 – 0.50 (m, 1H), 0.50 – 0.42 (m, 1H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 130.1, 127.3, 113.3, 101.4, 83.8, 70.0, 69.9, 68.8, 58.6, 55.2, 40.9, 25.7, 18.1, 12.2, 11.1, -4.5, -5.0; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{35}O_5Si$, 407.2248; found 407.2246.

(4a'*R*,8a'*S*)-2'-(4-Methoxyphenyl)-8'-methylenetetrahydro-4'*H*-spiro[cyclopropane-1,6'-pyrano[3,2-d][1,3]dioxine] (11):



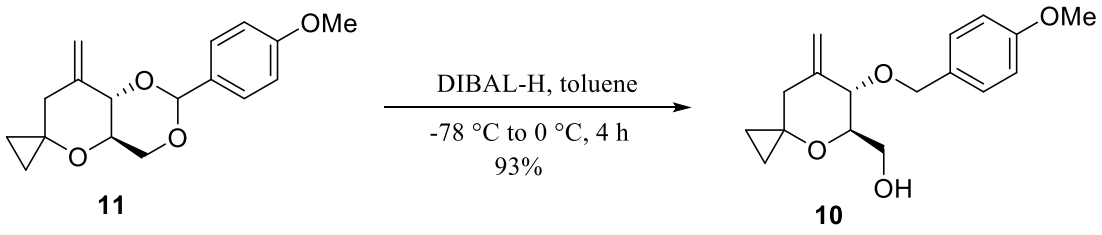
To a stirred solution of **17** (0.64 g, 1.57 mmol) in THF (12 mL) was TBAF (1 M in THF, 2.36 mL, 2.36 mmol) at 0 °C and the reaction mixture was stirred at 23 °C for 3 h. After completion of starting material, the reaction mixture was quenched with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford corresponding alcohol (0.43 g, 94 %) as a white amorphous powder. $[\alpha]_D^{20}$ = +25.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 6.93 – 6.88 (m, 2H), 5.53 (s, 1H), 4.21 – 4.16 (m, 1H), 4.03 (s, 1H), 3.81 (s, 3H), 3.71 – 3.65 (m, 1H), 3.55 – 3.49 (m, 2H), 2.58 – 2.45 (m, 1H), 2.34 – 2.23 (m, 1H), 1.56 – 1.43 (m, 1H), 0.98 – 0.88 (m, 1H), 0.76 – 0.66 (m, 1H), 0.64 – 0.54 (m, 1H), 0.54 – 0.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 129.7, 127.5, 113.6, 101.9, 83.9, 69.4, 69.1, 68.7, 58.6, 55.2, 38.6, 12.2, 11.2; LRMS-ESI (*m/z*): 293.0 $[M+H]^+$.

To a solution of above alcohol (0.43 g, 1.47 mmol) in CH_2Cl_2 (8 mL) were added DMP (1.24 g, 2.95 mmol) and $NaHCO_3$ (0.74 g, 8.84 mmol) at 0 °C. The reaction mixture temperature was allowed to 23 °C and stirred for 2 h. After completion of starting material the reaction mixture was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ in the ration of 1:1 and stirred vigorously for 10 min, then it was extracted with CH_2Cl_2 (2 x 30 mL). The combined

organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford corresponding ketone (270 mg, 63%, 72% brsm) as a white amorphous powder and recovered starting material (5 mg). $[\alpha]_D^{20}$ = +56.4 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 6.90 – 6.85 (m, 2H), 5.54 (s, 1H), 4.39 – 4.34 (m, 1H), 4.33 – 4.27 (m, 1H), 3.90 – 3.80 (m, 2H), 3.79 (s, 3H), 3.28 (d, *J* = 14.5 Hz, 1H), 1.99 (d, *J* = 14.6 Hz, 1H), 1.13 – 1.06 (m, 1H), 0.80 – 0.74 (m, 1H), 0.67 – 0.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 160.2, 129.0, 127.7, 113.6, 102.0, 83.1, 72.0, 69.2, 61.4, 55.2, 47.3, 12.4, 11.2; LRMS-ESI (*m/z*): 291.0 $[M+H]^+$.

To a suspension of PPh_3CH_3Br (1.28 g, 3.59 mmol) in THF (8 mL) was added solution of potassium *tert*-butoxide (1 M in THF, 2.7 mL, 2.7 mmol) at 0 °C and stirred for 30 min at same temperature, to that suspension was added a solution above obtained ketone (260 mg, 0.89 mmol) in THF (8 mL) at the same temperature, and then the reaction mixture temperature was allowed to warm up to 23 ^{o}C, it mixture was stirred for 3 h. The reaction mixture was quenched with water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5 % EtOAc/hexanes) to afford **11** (245 mg, 95 %) as a white amorphous powder. $[\alpha]_D^{20}$ = +52.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 6.94 – 6.85 (m, 2H), 5.62 (s, 1H), 5.12 (q, *J* = 1.8 Hz, 1H), 4.86 (q, *J* = 1.9 Hz, 1H), 4.18 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.81 (s, 3H), 3.73 (t, *J* = 10.3 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.04 (d, *J* = 13.9 Hz, 1H), 1.78 (d, *J* = 14.0 Hz, 1H), 1.02 – 0.88 (m, 1H), 0.71 – 0.55 (m, 2H), 0.52 – 0.42 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 141.5, 130.1, 127.5, 113.5, 105.9, 101.4, 80.0, 73.0, 69.3, 61.2, 55.2, 40.3, 12.1, 11.7; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{21}O_4$, 289.1434; found 289.1437.

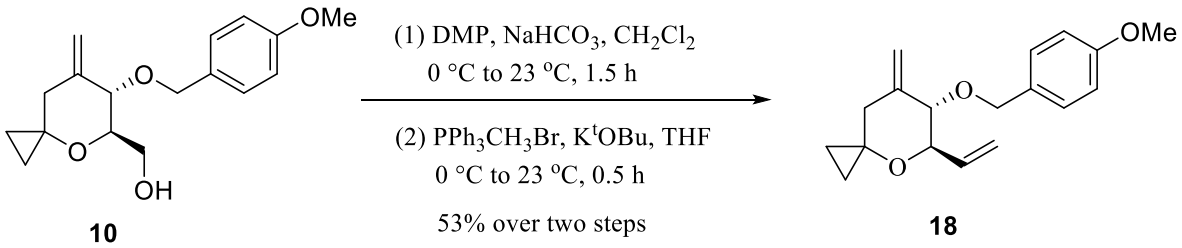
((5*R*,6*S*)-6-((4-Methoxybenzyl)oxy)-7-methylene-4-oxaspiro[2.5]octan-5-yl)methanol (10):



11 **10**

To a solution of **11** (240 mg, 0.83 mmol) in toluene (7 mL) was added DIBAL-H (1 M in hexane, 2.5 mL, 2.5 mmol) at -78 °C and stirred at the same temperature for 1 h, the mixture was warmed to 0 °C and stirred for 3 h. The reaction mixture was quenched with saturated sodium potassium tartrate at 0 °C and then warmed to 23 ^{o}C, stirred vigorously for 1 h, filtered through the pad of celite and washed with EtOAc. It was diluted with water and extracted with EtOAc (3 x 40 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford **10** (220 mg, 93 %) as a colorless oil. $[\alpha]_D^{20}$ = +120.6 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.92 – 6.86 (m, 2H), 5.15 (q, *J* = 1.7 Hz, 1H), 4.90 – 4.86 (m, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.94 – 3.89 (m, 1H), 3.81 (s, 3H), 3.76 – 3.64 (m, 2H), 3.39 – 3.33 (m, 1H), 2.85 (d, *J* = 13.4 Hz, 1H), 1.83 – 1.77 (m, 2H), 0.95 – 0.87 (m, 1H), 0.62 – 0.54 (m, 2H), 0.43 – 0.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 143.6, 129.9, 129.6, 113.8, 106.7, 80.4, 76.7, 72.6, 62.6, 60.7, 55.2, 40.5, 12.0, 11.4; LRMS-ESI (*m/z*): 291.1 $[M+H]^+$. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{23}O_4$, 291.1591; found 291.1594.

(5*R*,6*S*)-6-((4-Methoxybenzyl)oxy)-7-methylene-5-vinyl-4-oxaspiro[2.5]octane (18):



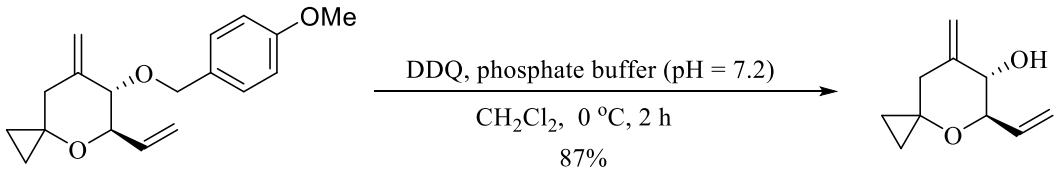
10 **18**

To a solution of **10** (220 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) were added DMP (640 mg, 1.51 mmol) and $NaHCO_3$ (382 mg, 4.55 mmol) at 0 °C. The reaction mixture temperature was allowed to 23 ^{o}C and stirred for 1.5 h. After completion of starting material, the reaction mixture was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ in the ration of 1:1 and stirred vigorously for 10 min, then it was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to

afford aldehyde (140 mg, 65%) as a colorless oil. $[\alpha]_D^{20}$ = +131.4 (*c* 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 0.8 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.90 – 6.85 (m, 2H), 5.19 (d, *J* = 1.3 Hz, 1H), 4.97 (t, *J* = 1.3 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.08 (dt, *J* = 7.6, 1.4 Hz, 1H), 3.98 (dd, *J* = 7.6, 0.8 Hz, 1H), 3.80 (s, 3H), 2.51 (dd, *J* = 13.5, 1.3 Hz, 1H), 2.18 (d, *J* = 13.6 Hz, 1H), 1.01 – 0.92 (m, 1H), 0.75 – 0.67 (m, 1H), 0.61 – 0.52 (m, 1H), 0.49 – 0.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 159.4, 141.3, 129.7, 129.4, 113.8, 109.9, 83.9, 75.9, 71.8, 60.9, 55.2, 39.1, 12.6, 11.2; LRMS-ESI (*m/z*): 289.1 $[M+H]^+$.

To a suspension of PPh_3CH_3Br (0.69 g, 1.94 mmol) in THF (4 mL) was added solution of potassium *tert*-butoxide (1 M in THF, 1.46 mL, 1.46 mmol) at 0 °C and stirred for 30 min at same temperature, to that suspension was added a solution above aldehyde (140 mg, 0.49 mmol) in THF (4 mL) and stirred at same temperature for 0.5 h. The reaction mixture was quenched with water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography over silica gel (5% EtOAc/hexanes) to afford **18** (113 mg, 81%) as a white amorphous powder. $[\alpha]_D^{20}$ = +93.5 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.91 – 6.84 (m, 2H), 6.00 – 5.89 (m, 1H), 5.33 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.22 (dt, *J* = 10.6, 1.3 Hz, 1H), 5.16 (d, *J* = 1.7 Hz, 1H), 4.87 (d, *J* = 1.9 Hz, 1H), 4.62 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 3.85 – 3.76 (m, 4H), 3.68 (d, *J* = 8.7 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 1H), 1.86 (d, *J* = 13.5 Hz, 1H), 1.00 – 0.90 (m, 1H), 0.66 – 0.52 (m, 2H), 0.42 – 0.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 143.4, 136.0, 130.1, 129.5, 117.6, 113.7, 107.2, 81.3, 80.3, 72.7, 60.2, 55.2, 40.5, 12.3, 11.3; LRMS-ESI (*m/z*): 287.1 $[M+H]^+$.

(5*R*,6*S*)-7-Methylene-5-vinyl-4-oxaspiro[2.5]octan-6-ol (19):

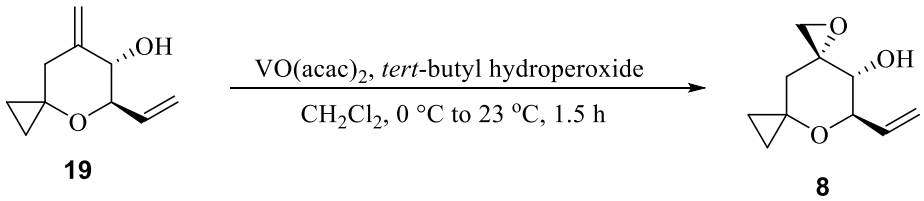


18 **19**

To a solution of **18** (110 mg, 0.38 mmol) in CH_2Cl_2 (4 mL) and phosphate buffer (0.4 mL, pH = 7.2) at 0 °C was added DDQ (113 mg, 0.5 mmol) in one portion, stirred at the same temperature for 1 h, after that another portion of DDQ (113 mg, 0.5 mmol) was added at 0 °C and stirred for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$, extracted with

CH_2Cl_2 (3 x 30 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 % EtOAc/hexanes) to afford **19** (55 mg, 87 %) as a colorless oil. $[\alpha]_D^{20}$ = +81.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.86 (m, 1H), 5.38 (dt, *J* = 17.3, 1.3 Hz, 1H), 5.32 (ddd, *J* = 10.4, 1.7, 0.8 Hz, 1H), 5.14 (q, *J* = 1.7 Hz, 1H), 4.87 (q, *J* = 1.9 Hz, 1H), 3.95 – 3.89 (m, 1H), 3.66 – 3.58 (m, 1H), 2.96 (dt, *J* = 13.7, 1.5 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.78 (d, *J* = 13.8 Hz, 1H), 1.01 – 0.94 (m, 1H), 0.66 – 0.55 (m, 2H), 0.44 – 0.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 135.9, 119.2, 106.3, 83.2, 72.2, 60.3, 40.4, 12.0, 11.5; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{15}O_2$, 167.1067; found 167.1064.

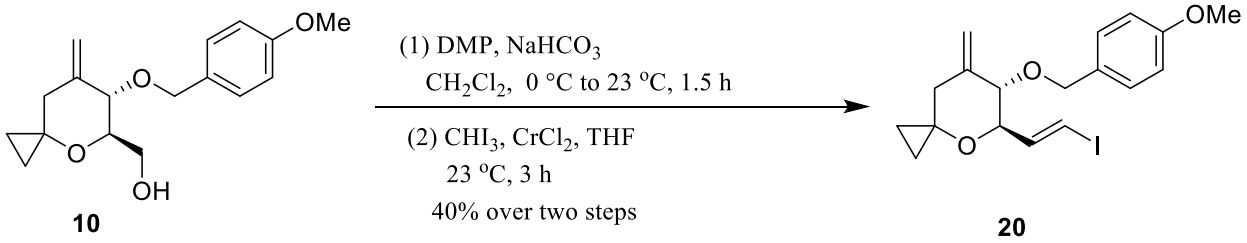
(3*R*,9*R*,10*R*)-9-Vinyl-1,8-dioxadispiro[2.1.25.33]decan-10-ol (8):



19 **8**

To a solution of **19** (45 mg, 0.27 mmol) in CH_2Cl_2 (2.5 mL) was added $VO(acac)_2$ (14 mg, 0.05 mmol) at 23 °C and it was cooled to 0 °C, *tert*-butyl hydroperoxide solution (5.5 M in decane, 0.1 mL, 0.57 mmol) was dilute with CH_2Cl_2 (0.9 mL) and it was added to the above mixture by dropwise, then the reaction mixture was warmed to 23 °C and stirred for 1.5 h. The reaction mixture was filtered through a small silica plug and rinsed with EtOAc (30 mL), concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 % EtOAc/hexanes) to afford **8** (28 mg, 57 %, 73 % brsm) as a white amorphous powder and recovered starting material (0.01 g). $[\alpha]_D^{20}$ = +98.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.92 (m, 1H), 5.35 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.29 – 5.23 (m, 1H), 3.90 – 3.83 (m, 1H), 3.67 (dd, *J* = 10.7, 9.7 Hz, 1H), 3.11 (d, *J* = 4.5 Hz, 1H), 2.89 (dd, *J* = 14.3, 1.7 Hz, 1H), 2.58 (d, *J* = 4.5 Hz, 1H), 1.74 (dd, *J* = 10.7, 1.1 Hz, 1H), 0.99 – 0.92 (m, 2H), 0.83 – 0.75 (m, 1H), 0.65 – 0.58 (m, 1H), 0.54 – 0.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 117.8, 79.7, 68.1, 58.4, 57.6, 48.4, 38.0, 11.9, 10.8; LRMS-ESI (*m/z*): 183.1 $[M+H]^+$. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{14}O_3Na$, 205.0835; found 205.0833.

(5*R*,6*S*)-5-((*E*)-2-Iodovinyl)-6-((4-methoxybenzyl)oxy)-7-methylene-4-oxaspiro[2.5]octane (20):

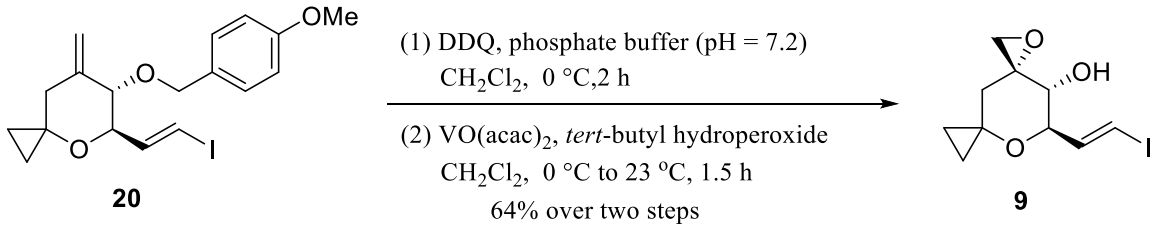


10 **20**

To a solution of alcohol **10** (80 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) were added DMP (233 mg, 0.55 mmol) and $NaHCO_3$ (139 mg, 1.65 mmol) at 0 °C, the reaction mixture temperature was allowed to warm up to 23 °C, it mixture was stirred for 1.5 h, the reaction mixture was quenched with saturated $Na_2S_2O_3$ followed by saturated $NaHCO_3$ in the ratio of 1:1 and stirred vigorously for 10 min, then it was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford an aldehyde (37 mg, 47%) as a colorless oil.

To a suspension of $CrCl_2$ (122 mg, 0.99 mmol) in THF (2 mL) was added a solution of above aldehyde (37 mg, 0.13 mmol) and CHI_3 (151 mg, 0.38 mmol) in THF (2 mL) at 23 °C and stirred for 3 h. The reaction was quenched with water, extracted with EtOAc (2 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford vinyl iodide **20** (45 mg, 85 %) as a colorless oil. $[\alpha]_D^{20}$ = +99.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.94 – 6.87 (m, 2H), 6.60 (dd, *J* = 14.6, 6.2 Hz, 1H), 6.38 (dd, *J* = 14.6, 1.2 Hz, 1H), 5.16 (q, *J* = 1.6 Hz, 1H), 4.89 (q, *J* = 1.8 Hz, 1H), 4.66 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 3.82 (s, 3H), 3.77 – 3.68 (m, 1H), 3.65 (dt, *J* = 9.0, 1.8 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 1.83 (d, *J* = 13.5 Hz, 1H), 0.98 – 0.86 (m, 1H), 0.64 – 0.52 (m, 2H), 0.43 – 0.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 143.5, 142.8, 129.8, 113.8, 107.6, 82.2, 79.7, 79.4, 72.7, 60.4, 55.2, 40.3, 12.2, 11.3. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{22}IO_3$, 413.0608; found 413.0612.

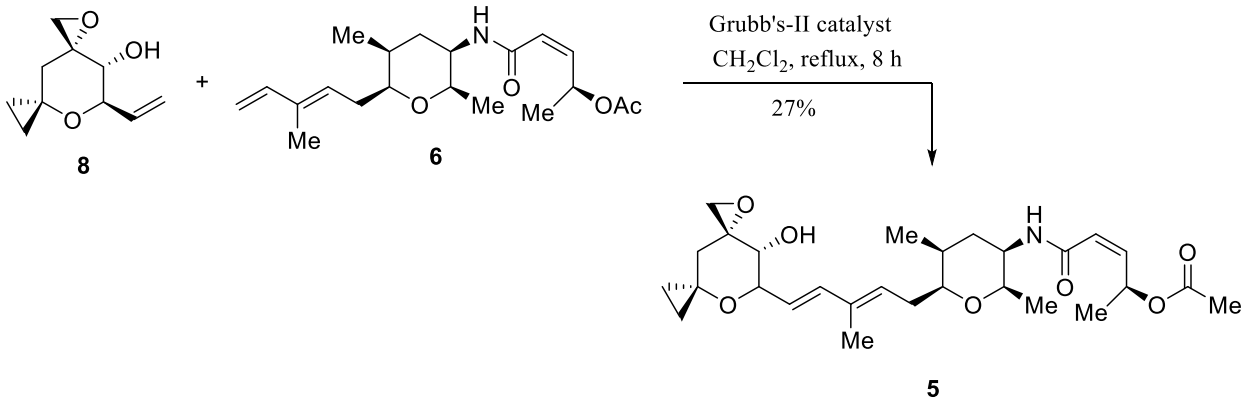
(3*R*,9*R*,10*R*)-9-((*E*)-2-Iodovinyl)-1,8-dioxadispiro[2.1.25.33]decan-10-ol (9):



To a solution of vinyl iodide **20** (40 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) and phosphate buffer (0.2 mL, pH = 7.2) at 0 °C was added DDQ (28 mg, 0.13 mmol) in one portion, stirred for 1 h, after that another portion of DDQ (28 mg, 0.13 mmol) was added at 0 °C and stirred for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (2 x 10 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 % EtOAc/hexanes) to afford corresponding allylic alcohol (24 mg, 85 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, J = 14.7, 6.3 Hz, 1H), 6.48 (d, J = 14.5 Hz, 1H), 5.13 (s, 1H), 4.88 (s, 1H), 3.95-3.91 (m, 1H), 3.64-3.60 (m, 1H), 2.93 (d, J = 13.7 Hz, 1H), 1.83-1.76 (m, 2H), 0.98-0.95 (m, 1H), 0.63-0.57 (m, 2H), 0.41-0.37 (m, 1H).

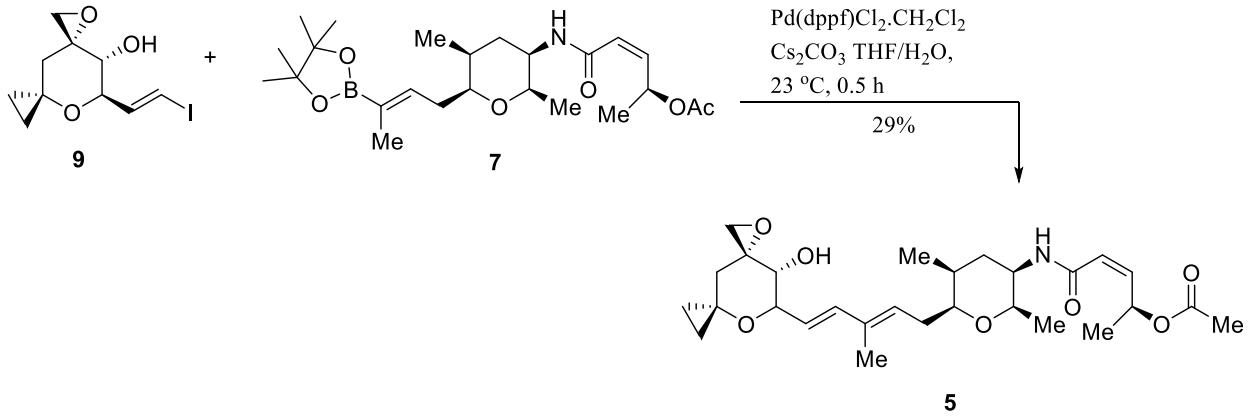
To a solution of above allyl alcohol (19 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) was added $VO(acac)_2$ (3.4 mg, 0.01 mmol) at 23 °C and it was cooled to 0 °C. To the mixture was added *tert*-butyl hydroperoxide solution (5.5 M in decane, 23 μL, 0.13 mmol), then the reaction mixture was warmed to 23 °C and stirred for 1.5 h, the reaction mixture was filtered through a small silica plug and rinsed with EtOAc (20 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford **9** (15 mg, 75 %) as a white amorphous powder. $[\alpha]_D^{20}$ = +54.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 14.6, 5.1 Hz, 1H), 6.42 (dd, J = 14.6, 1.5 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.65 (t, J = 10.4 Hz, 1H), 3.08 (d, J = 4.4 Hz, 1H), 2.86 (dd, J = 14.5, 1.7 Hz, 1H), 2.58 (d, J = 4.4 Hz, 1H), 1.82 (d, J = 11.2 Hz, 1H), 0.99 – 0.90 (m, 2H), 0.79 – 0.70 (m, 1H), 0.65 – 0.56 (m, 1H), 0.55 – 0.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 80.7, 79.1, 67.8, 58.3, 57.8, 48.4, 37.8, 11.8, 10.8. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{14}IO_3$, 308.9982; found 308.9980.

(2*S*,*Z*)-5-(((2*R*,3*R*,5*S*,6*S*)-6-((2*E*,4*E*)-5-((3*R*,10*R*)-10-Hydroxy-1,8-dioxadispiro[2.1.25.33]decan-9-yl)-3-methylpenta-2,4-dien-1-yl)-2,5-dimethyltetrahydro-2*H*-pyran-3-yl)amino)-5-oxopent-3-en-2-yl acetate (5):

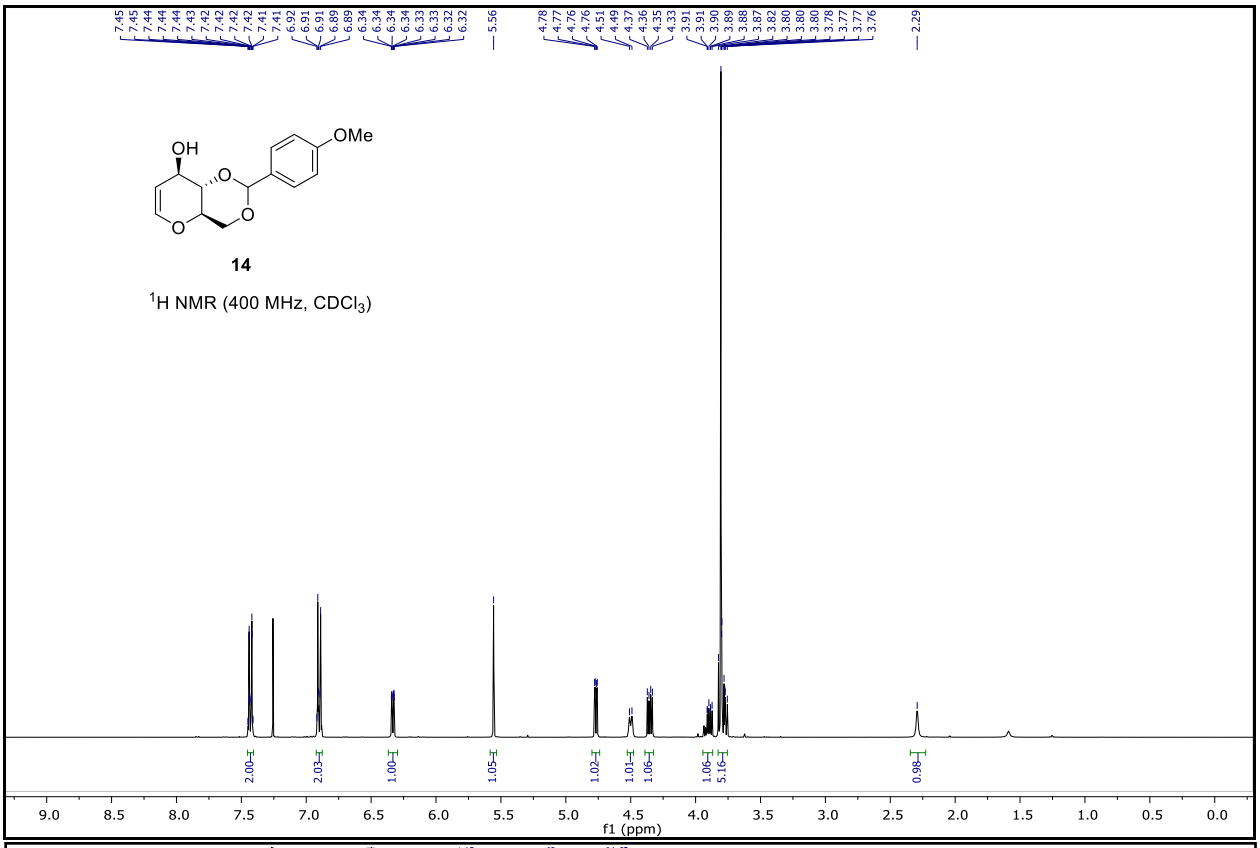


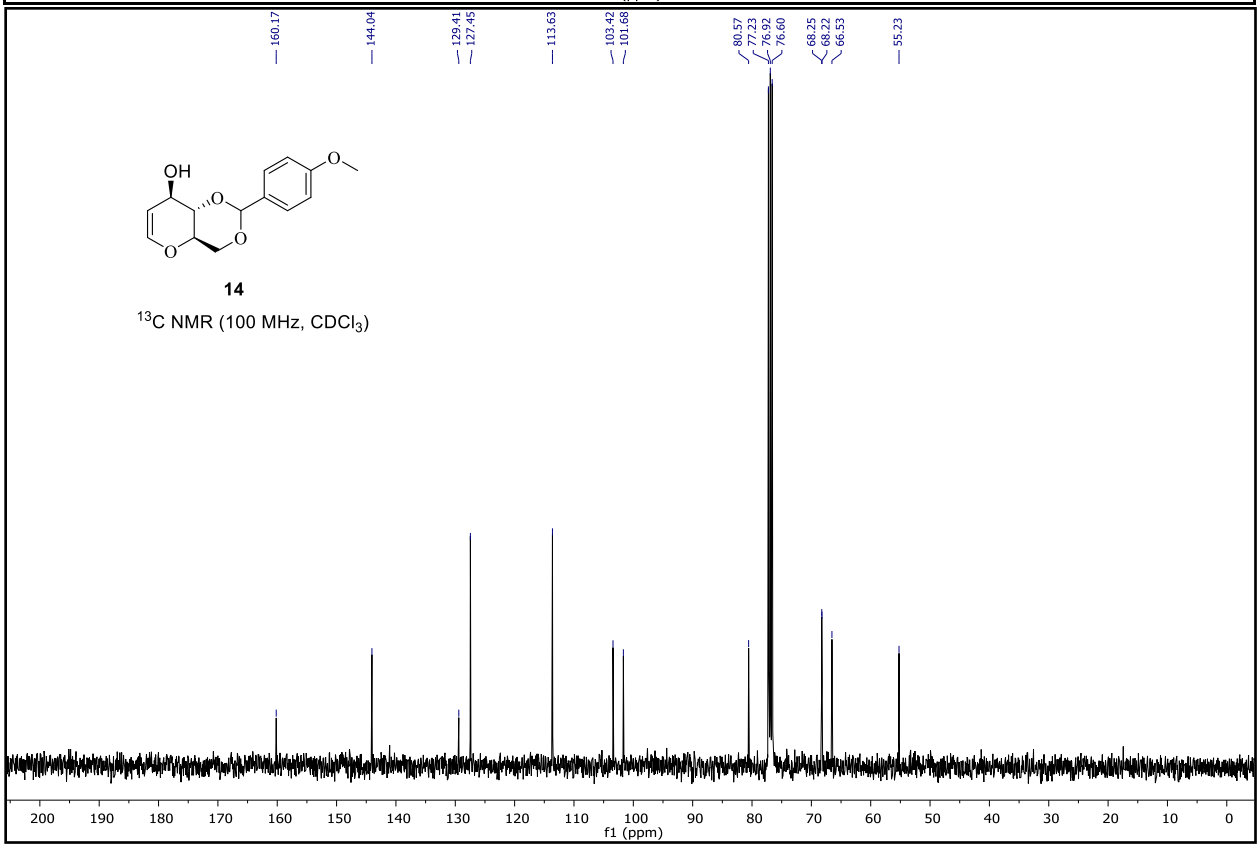
A solution of **8** (3.8 mg, 20.8 μmol) and Grubbs II catalyst (2.2 mg, 2.57 μmol) were prepared separately in CH_2Cl_2 (300 μL each) under argon atmosphere. To a stirred solution of **6** (6 mg, 17.1 μmol) in CH_2Cl_2 (100 μL), one portion of **8** (100 μL) and Ru-II (100 μL) were added under argon atmosphere. The mixture was then heated to reflux. After 1.5 h, one more portion of **8** (100 μL) and Ru-II (100 μL) were added, repeated the addition one more time after 1.5 h. After 8 total hours, the reaction mixture was cooled to 23 ^{o}C and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (50% EtOAc/hexanes) to afford **5** (2.3 mg, 27%) as a colorless oil. $[\alpha]_D^{20}$ = □18.8 (*c* 0.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 15.8 Hz, 1H), 6.30–6.22 (m, 1H), 5.98 (d, *J* = 9.1 Hz, 1H), 5.89 (dd, *J* = 11.6, 7.9 Hz, 1H), 5.73–5.62 (m, 2H), 5.48 (t, *J* = 7.2 Hz, 1H), 3.97–3.89 (m, 2H), 3.74–3.61 (m, 2H), 3.50 (td, *J* = 7.2, 2.7 Hz, 1H), 3.10 (d, *J* = 4.6 Hz, 1H), 2.90 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.58 (d, *J* = 4.5 Hz, 1H), 2.43–2.33 (m, 1H), 2.27–2.18 (m, 1H), 2.04 (s, 3H), 1.98–1.89 (m, 2H), 1.76 (s, 3H), 1.71 (d, *J* = 10.6 Hz, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.99–0.91 (m, 2H), 0.87–0.75 (m, 2H), 0.67–0.59 (m, 1H), 0.55–0.47 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.3, 164.8, 143.6, 138.0, 134.6, 129.1, 124.0, 122.5, 80.8, 79.9, 75.9, 68.9, 68.5, 58.6, 57.7, 56.0, 48.5, 47.1, 38.2, 35.8, 31.9, 28.9, 21.2, 19.9, 17.8, 15.1, 12.6, 12.1, 10.9.; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{42}NO_7$, 504.2956; found 504.2954.

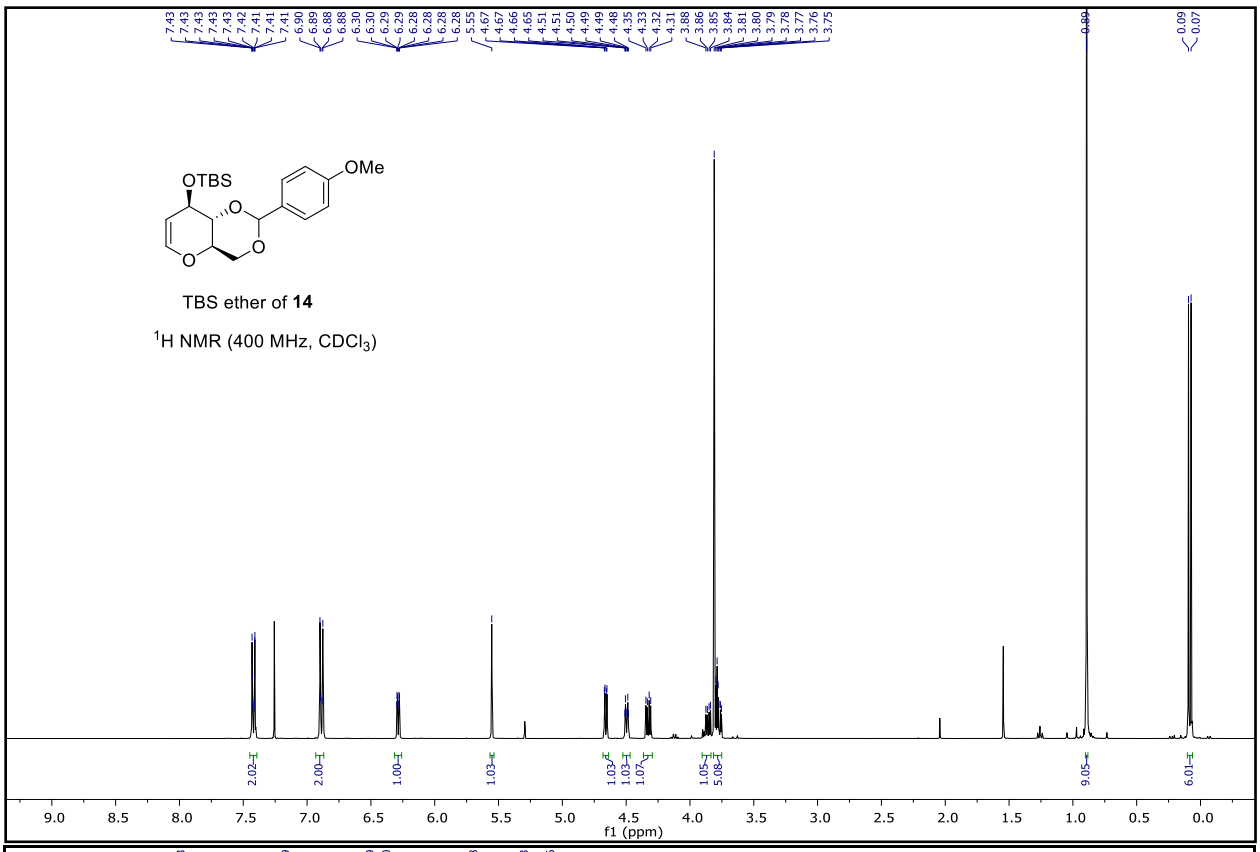
(2*S*,*Z*)-5-(((2*R*,3*R*,5*S*,6*S*)-6-((2*E*,4*E*)-5-((3*R*,10*R*)-10-Hydroxy-1,8-dioxadispiro[2.1.25.33]decan-9-yl)-3-methylpenta-2,4-dien-1-yl)-2,5-dimethyltetrahydro-2*H*-pyran-3-yl)amino)-5-oxopent-3-en-2-yl acetate (5):



Compound **9** (3 mg, 9.7 μmol) and **7** (4.3 mg, 9.7 μmol) were dissolved in 0.8 mL THF (degassed with an argon purge). To the obtained solution was added rigorously degassed (freeze-pump-thaw technique x 3-times) 0.2 mL of Cs_2CO_3 stock solution (stock solution: Cs_2CO_3 (0.16 g, 0.49 mmol) was dissolved in H_2O (2 mL)). To the above mixture was added $Pd(dppf)Cl_2.CH_2Cl_2$ (0.8 mg, 0.97 μmol) at 23 ^oC, stirred for 0.5 h, filtered through a layer of celite and rinsed with EtOAc. The organic layer was washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (50% EtOAc/hexanes) to provide **5** (1.4 mg, 29 %) as a colorless oil. $[\alpha]_D^{20}$ = □18.8 (*c* 0.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 15.8 Hz, 1H), 6.30–6.22 (m, 1H), 5.98 (d, *J* = 9.1 Hz, 1H), 5.89 (dd, *J* = 11.6, 7.9 Hz, 1H), 5.73–5.62 (m, 2H), 5.48 (t, *J* = 7.2 Hz, 1H), 3.97–3.89 (m, 2H), 3.74–3.61 (m, 2H), 3.50 (td, *J* = 7.2, 2.7 Hz, 1H), 3.10 (d, *J* = 4.6 Hz, 1H), 2.90 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.58 (d, *J* = 4.5 Hz, 1H), 2.43–2.33 (m, 1H), 2.27–2.18 (m, 1H), 2.04 (s, 3H), 1.98–1.89 (m, 2H), 1.76 (s, 3H), 1.71 (d, *J* = 10.6 Hz, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.99–0.91 (m, 2H), 0.87–0.75 (m, 2H), 0.67–0.59 (m, 1H), 0.55–0.47 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.3, 164.8, 143.6, 138.0, 134.6, 129.1, 124.0, 122.5, 80.8, 79.9, 75.9, 68.9, 68.5, 58.6, 57.7, 56.0, 48.5, 47.1, 38.2, 35.8, 31.9, 28.9, 21.2, 19.9, 17.8, 15.1, 12.6, 12.1, 10.9.; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{42}NO_7$, 504.2956; found 504.2954.

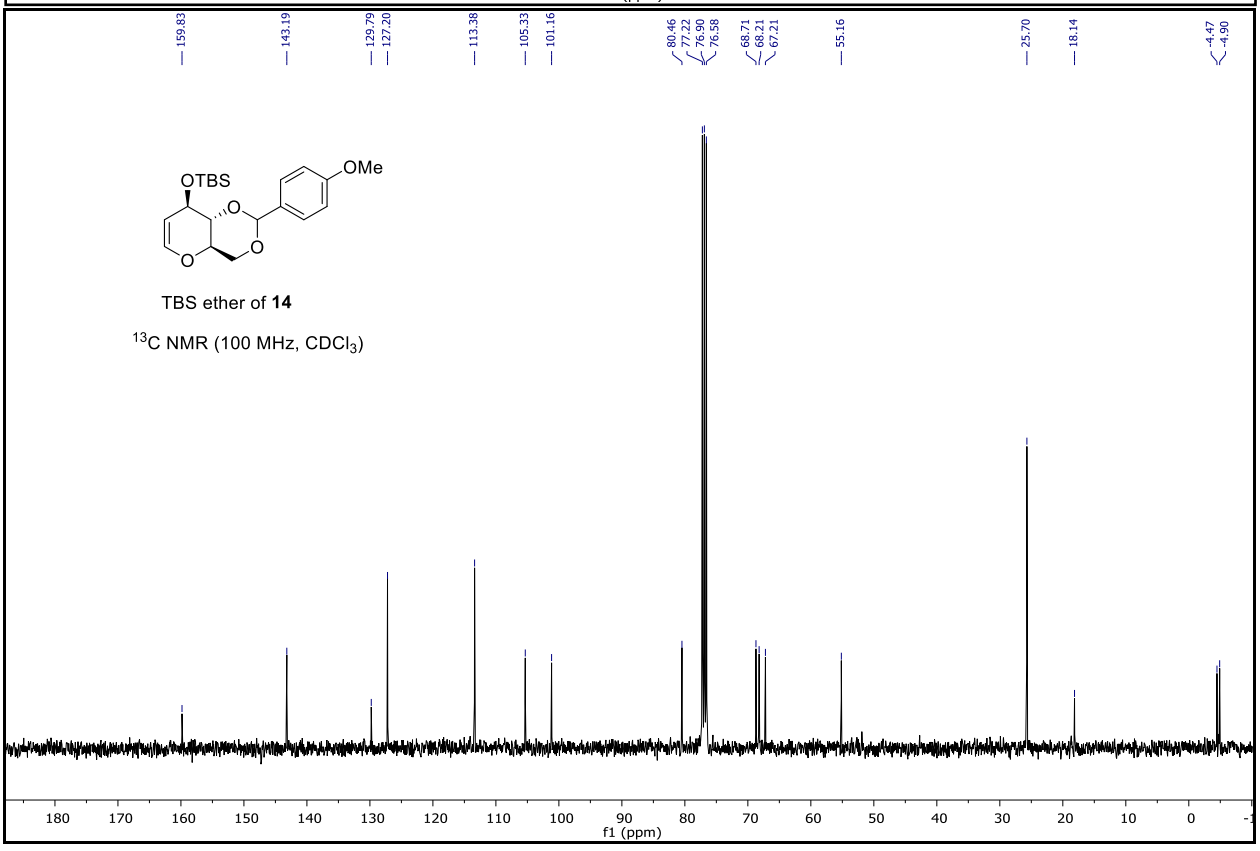

OH
OMe
O
O
O
14
1H NMR (400 MHz, CDCl3)
f1 (ppm)


OH
O
O
O
O
14
13C NMR (100 MHz, CDCl3)
f1 (ppm)



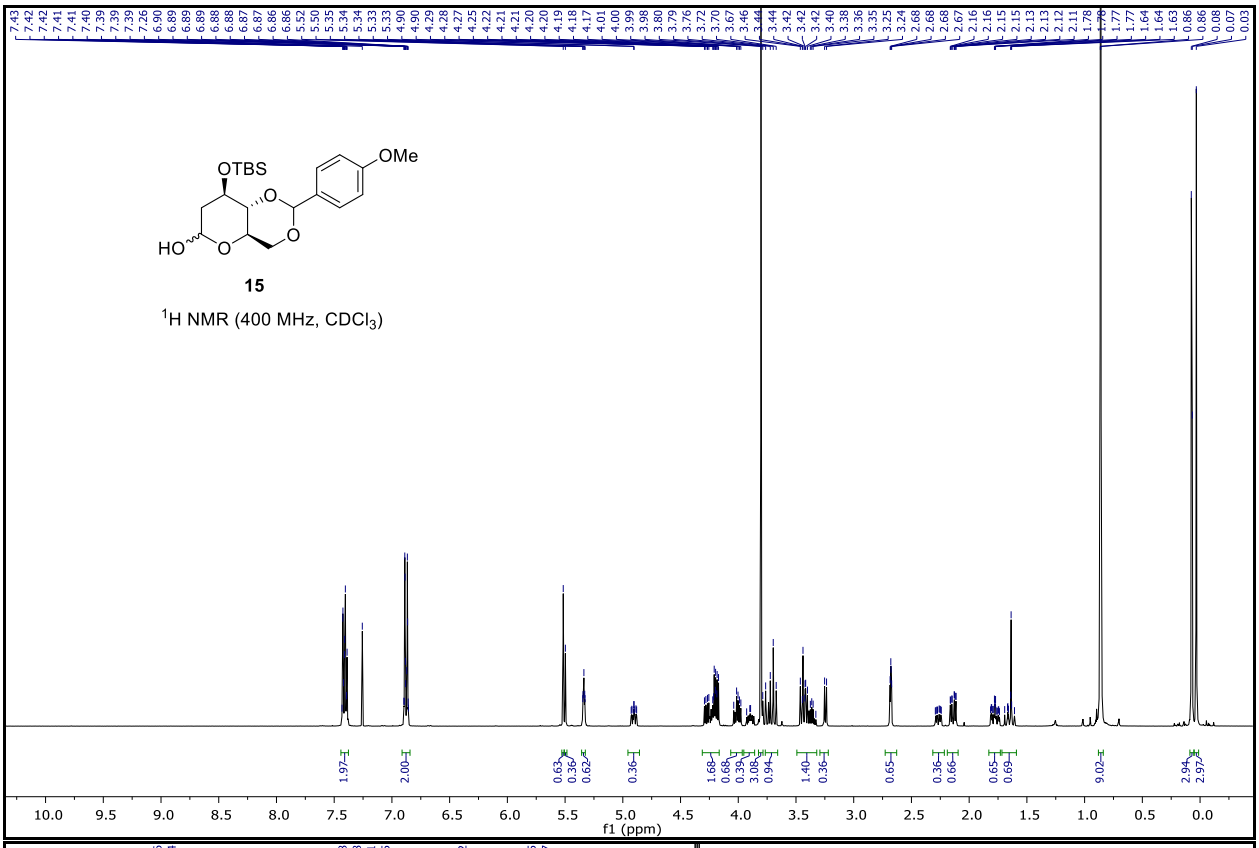
TBS ether of **14**

^{1}H NMR (400 MHz, $CDCl_3$)



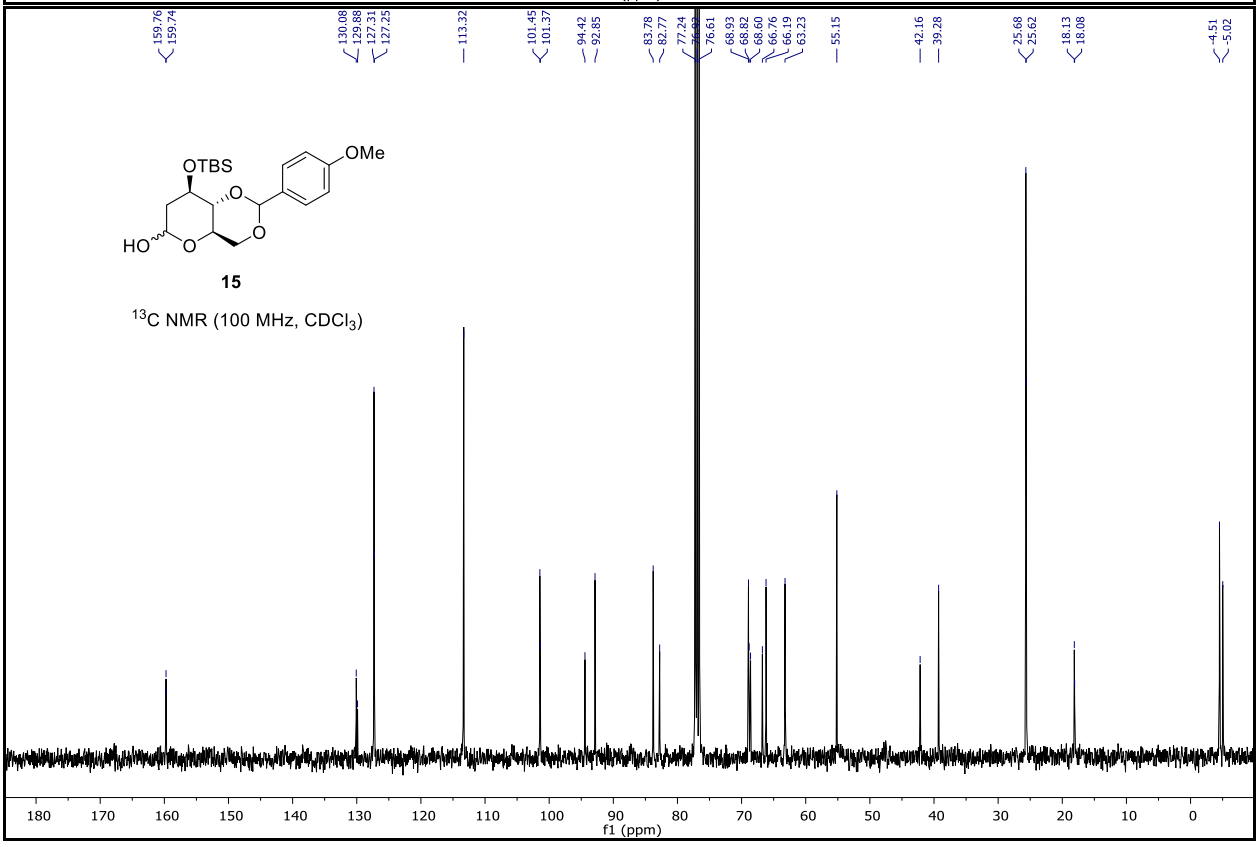
TBS ether of **14**

^{13}C NMR (100 MHz, $CDCl_3$)



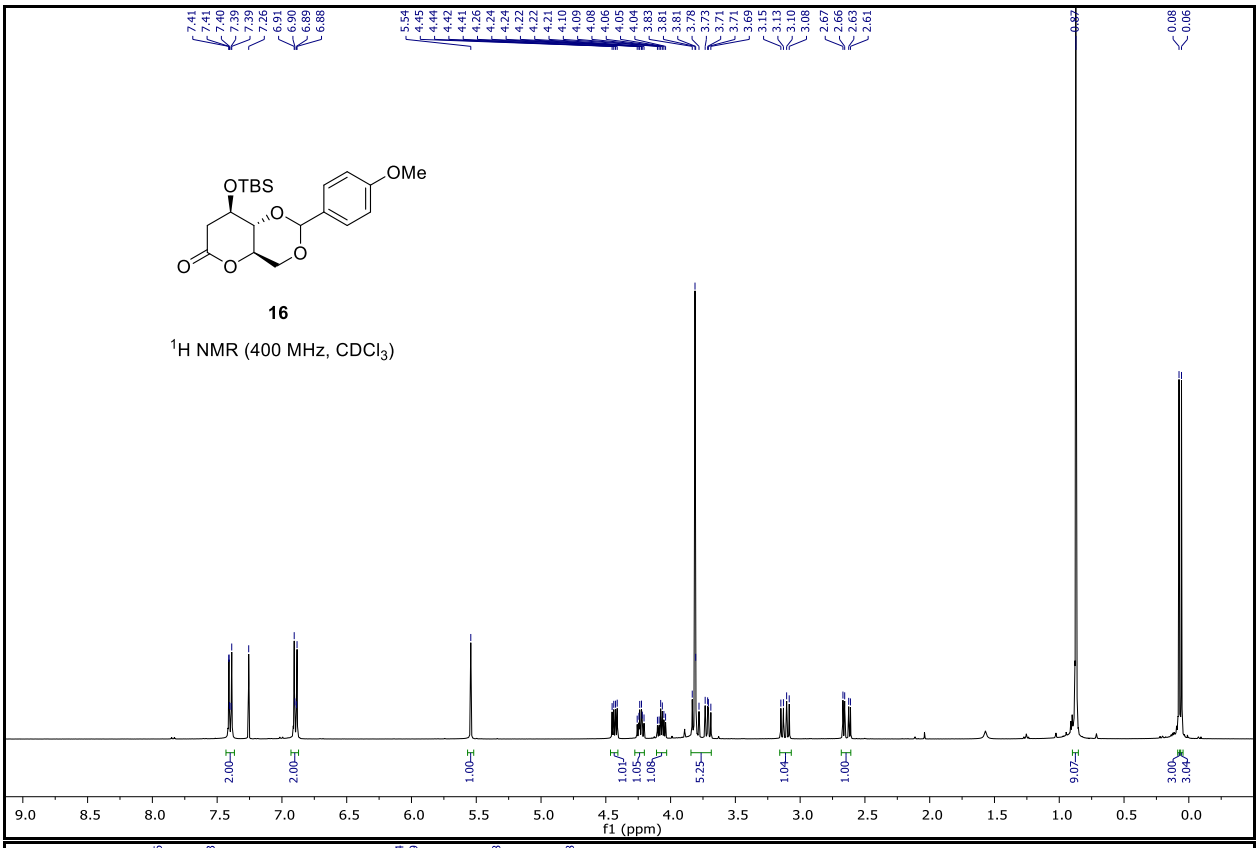
15

^{1}H NMR (400 MHz, $CDCl_3$)



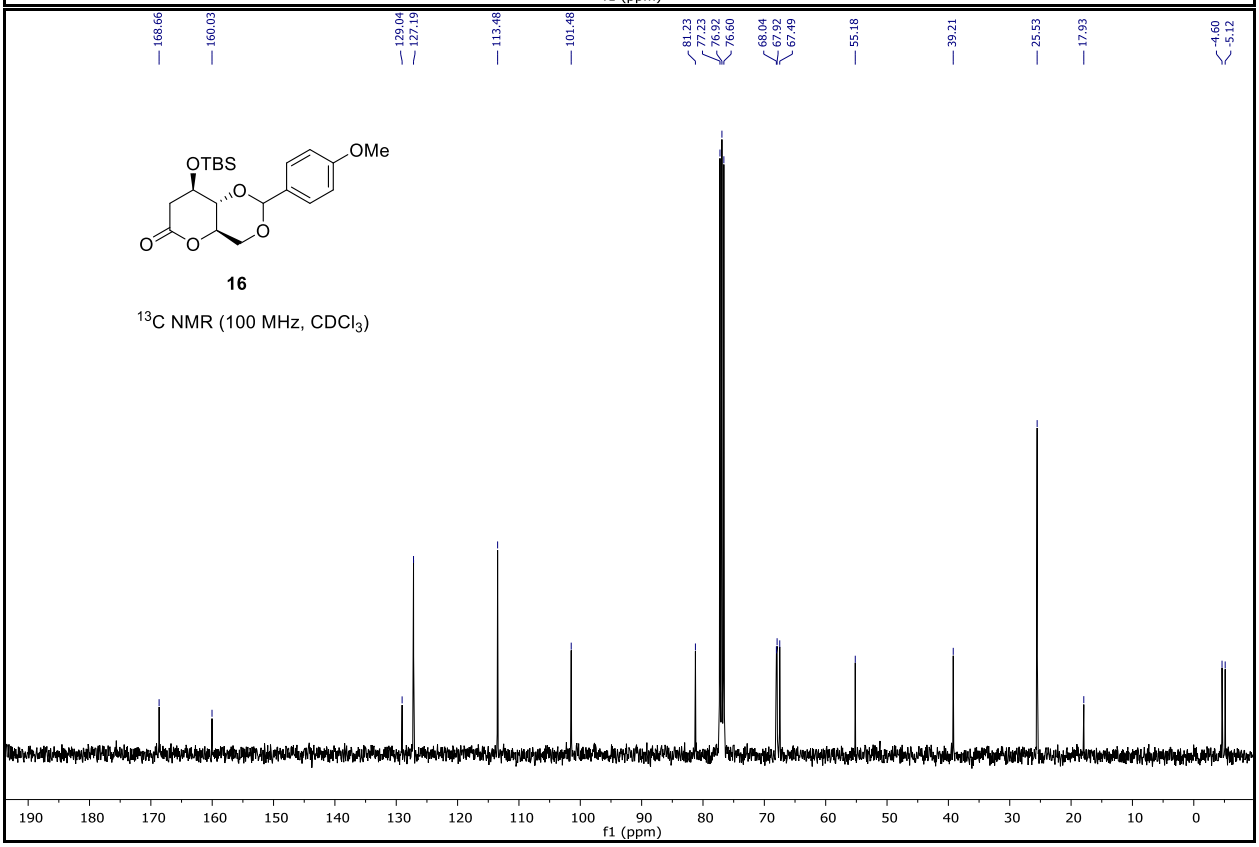
15

^{13}C NMR (100 MHz, $CDCl_3$)



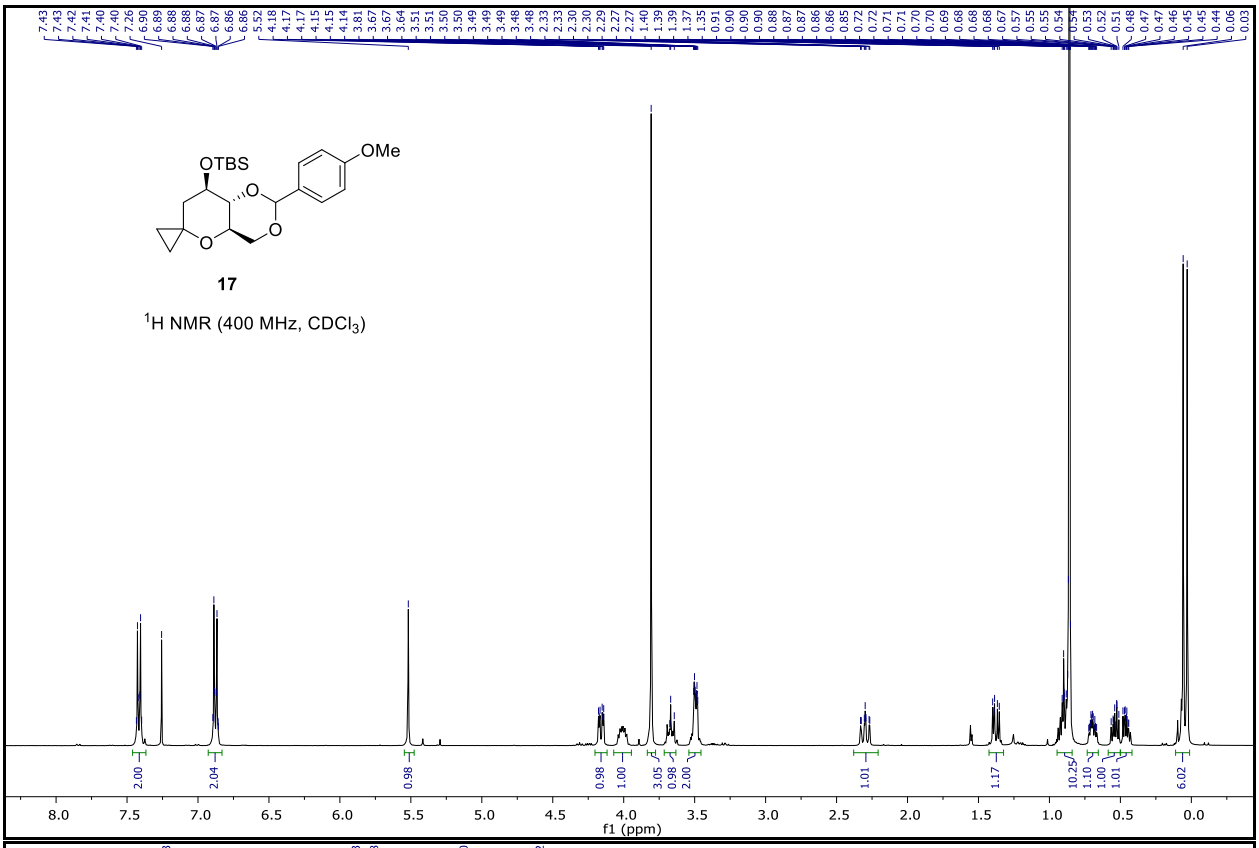
16

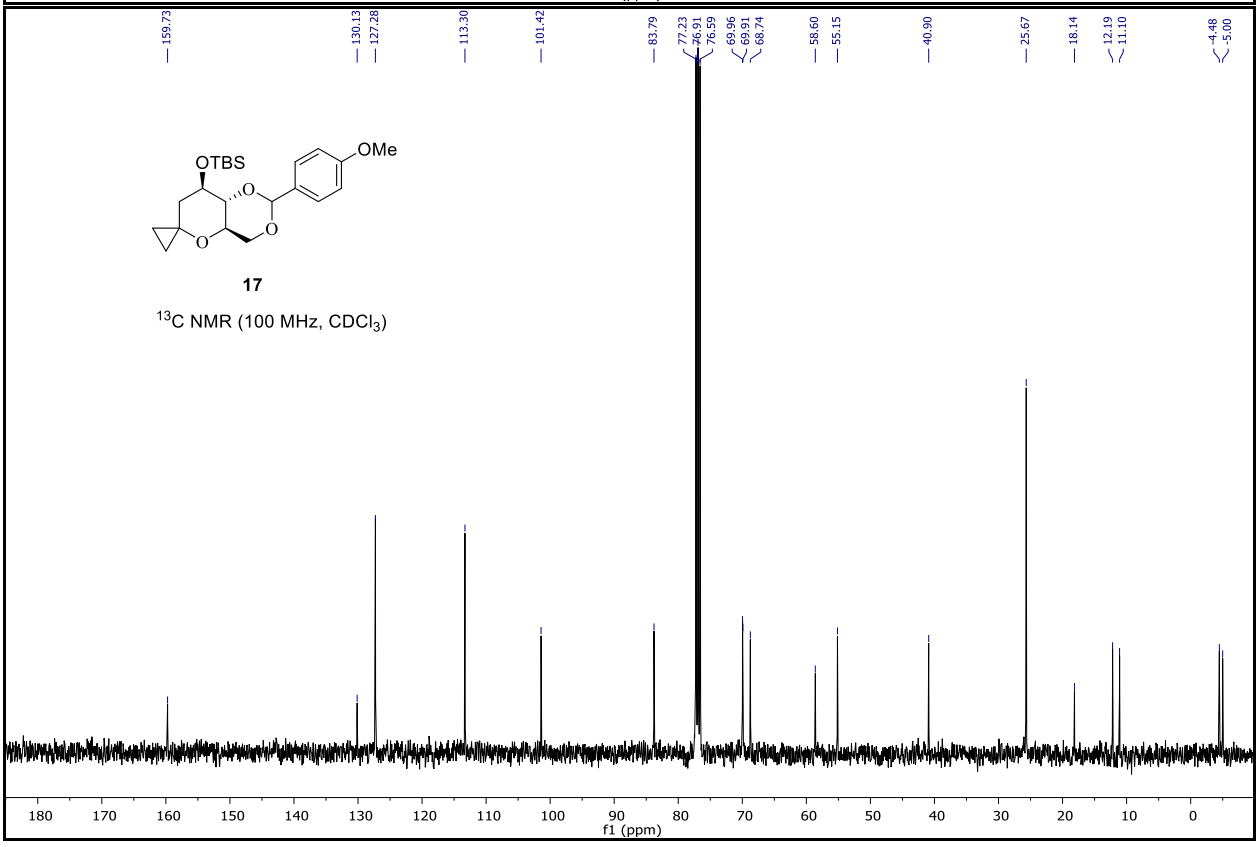
^{1}H NMR (400 MHz, $CDCl_3$)

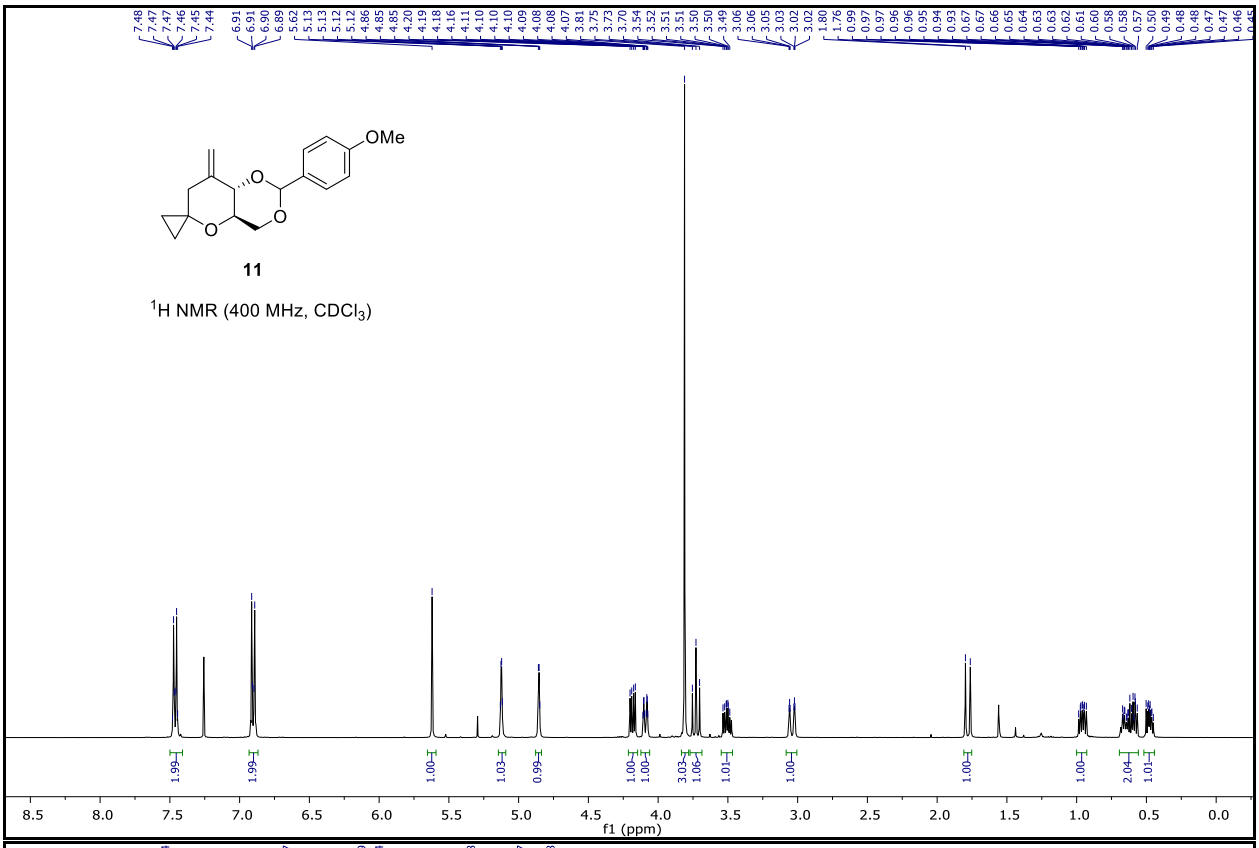


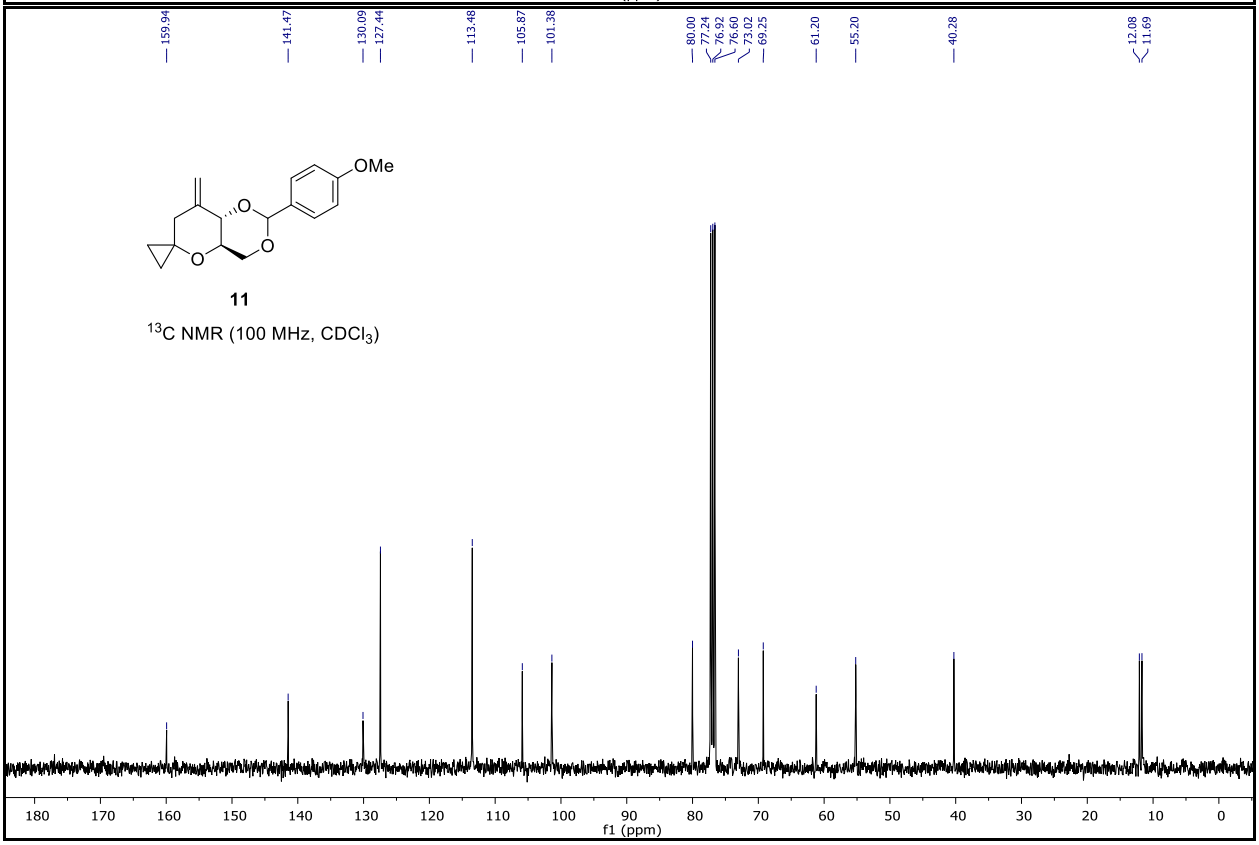
16

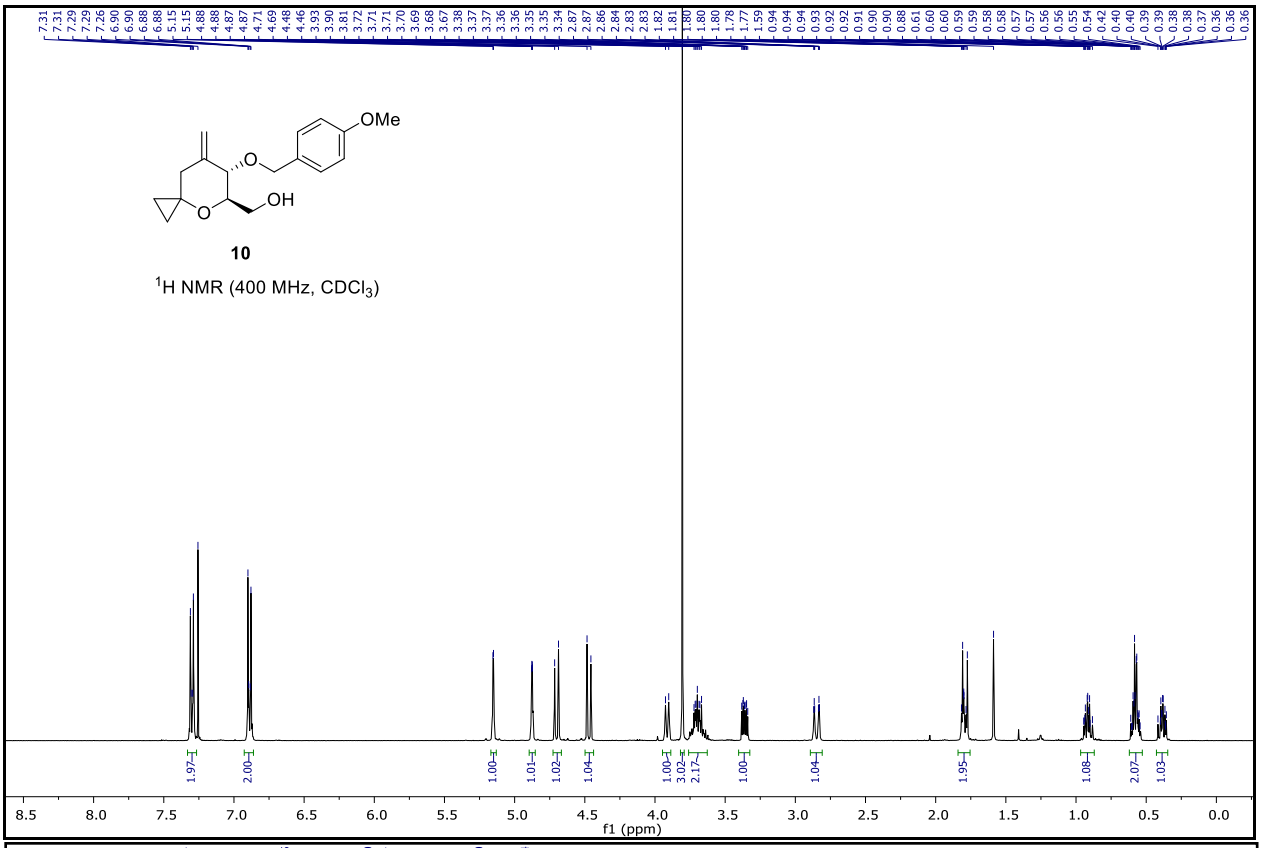
^{13}C NMR (100 MHz, $CDCl_3$)

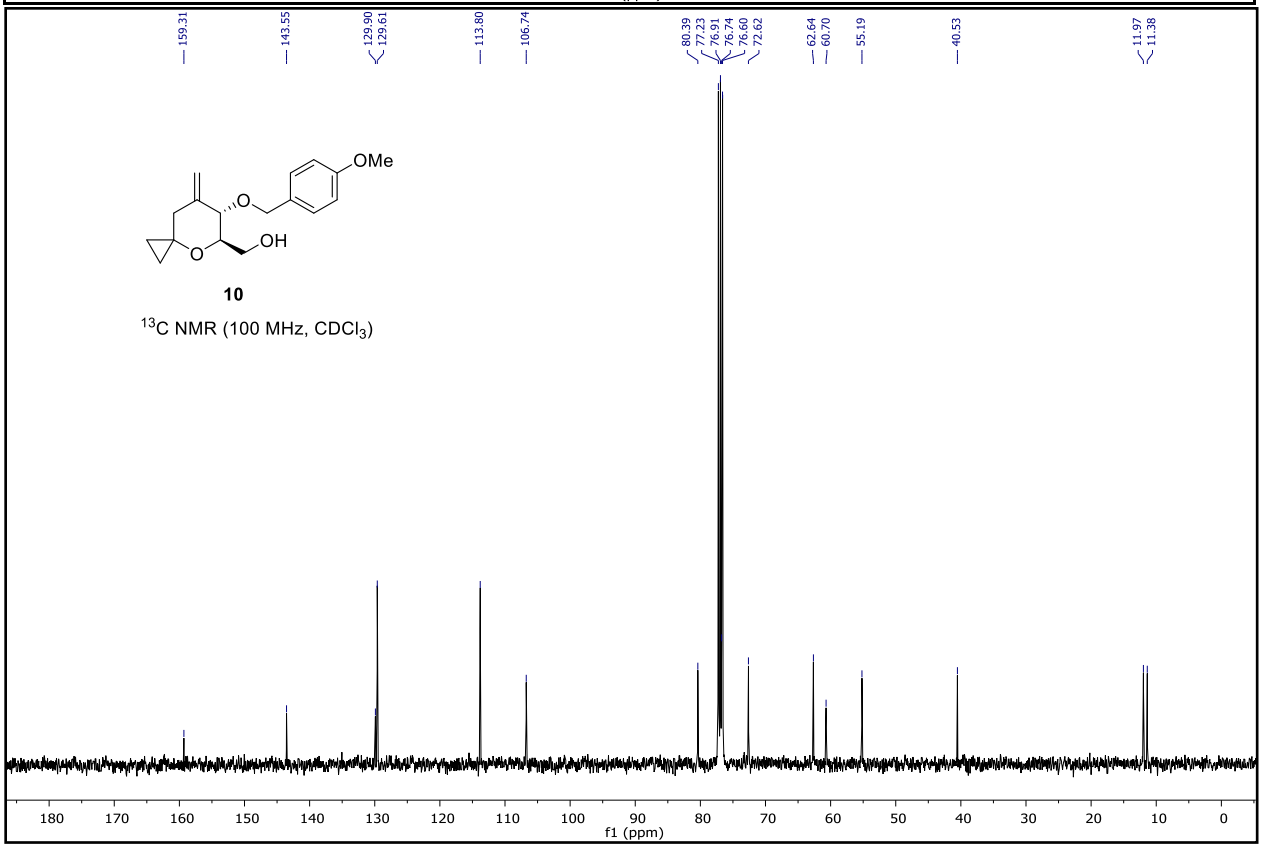

OTBS
OMe
O
O
O
17
1H NMR (400 MHz, CDCl3)
f1 (ppm)

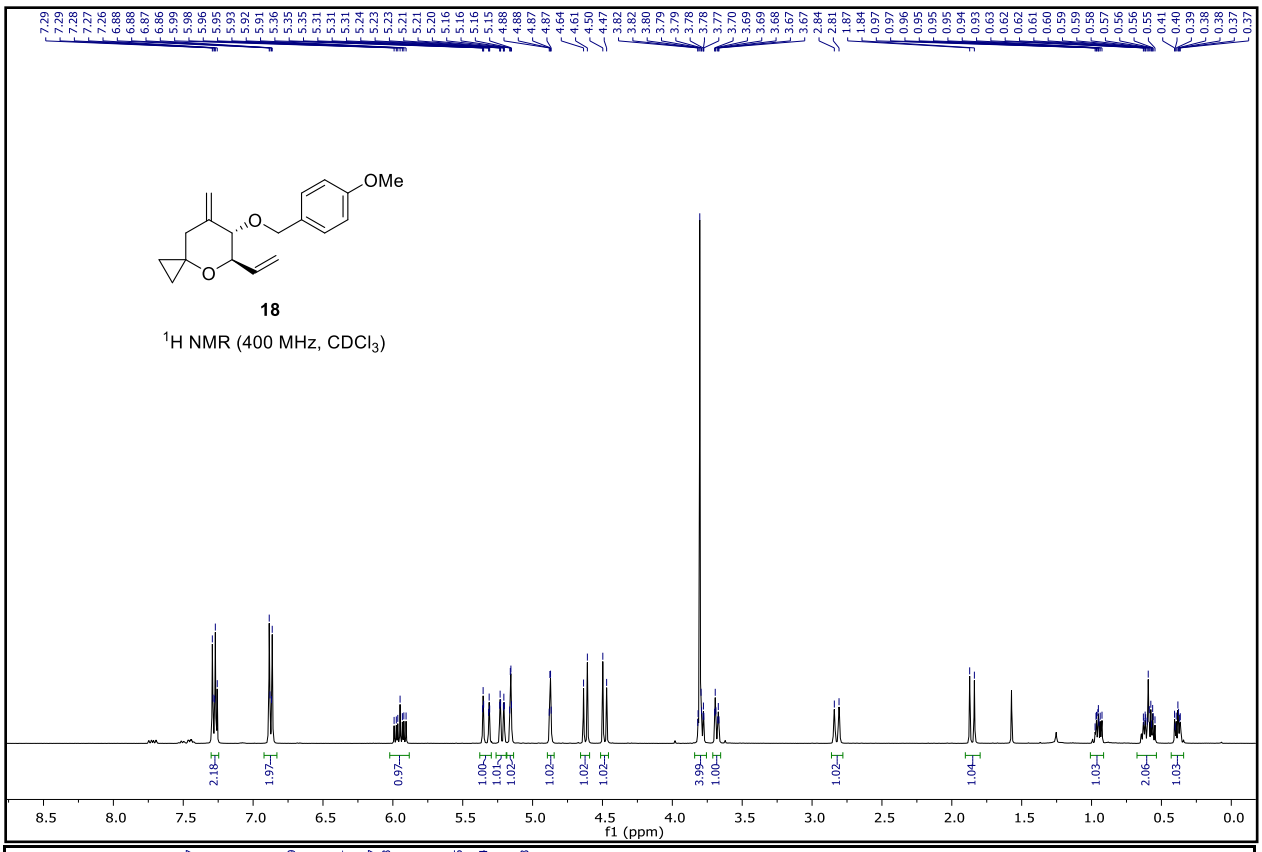

OTBS
OMe
O
O
O
17
13C NMR (100 MHz, CDCl3)
f1 (ppm)

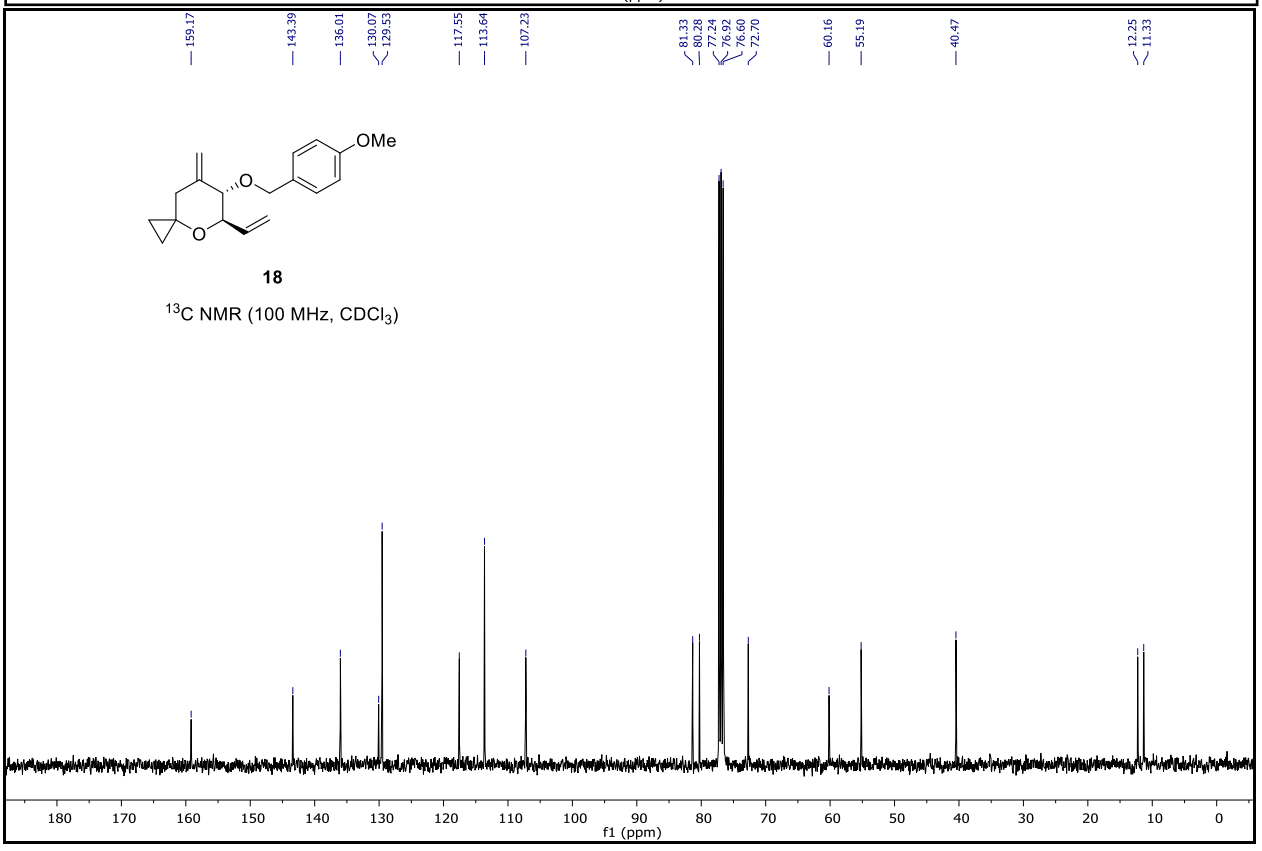

OMe
O
O
O
11
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)

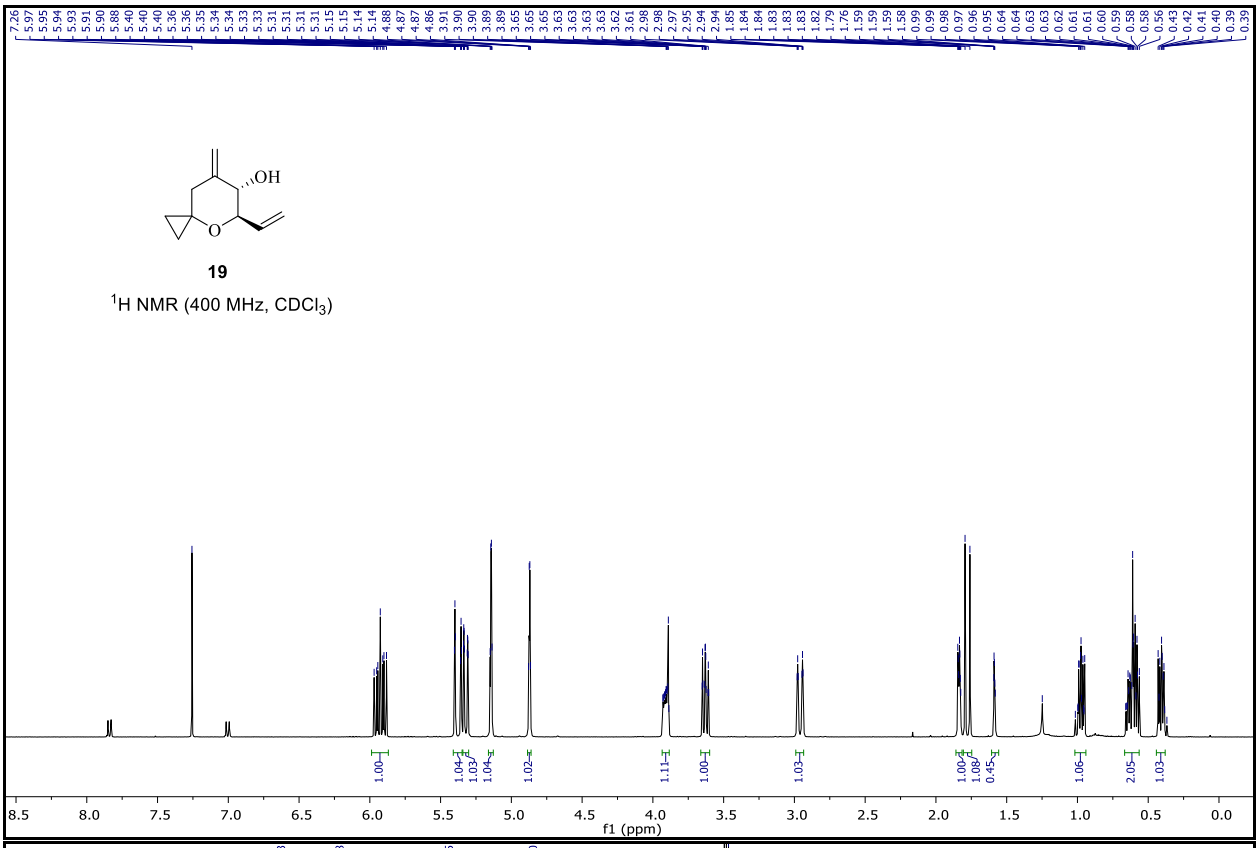

OMe
O
O
O
11
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

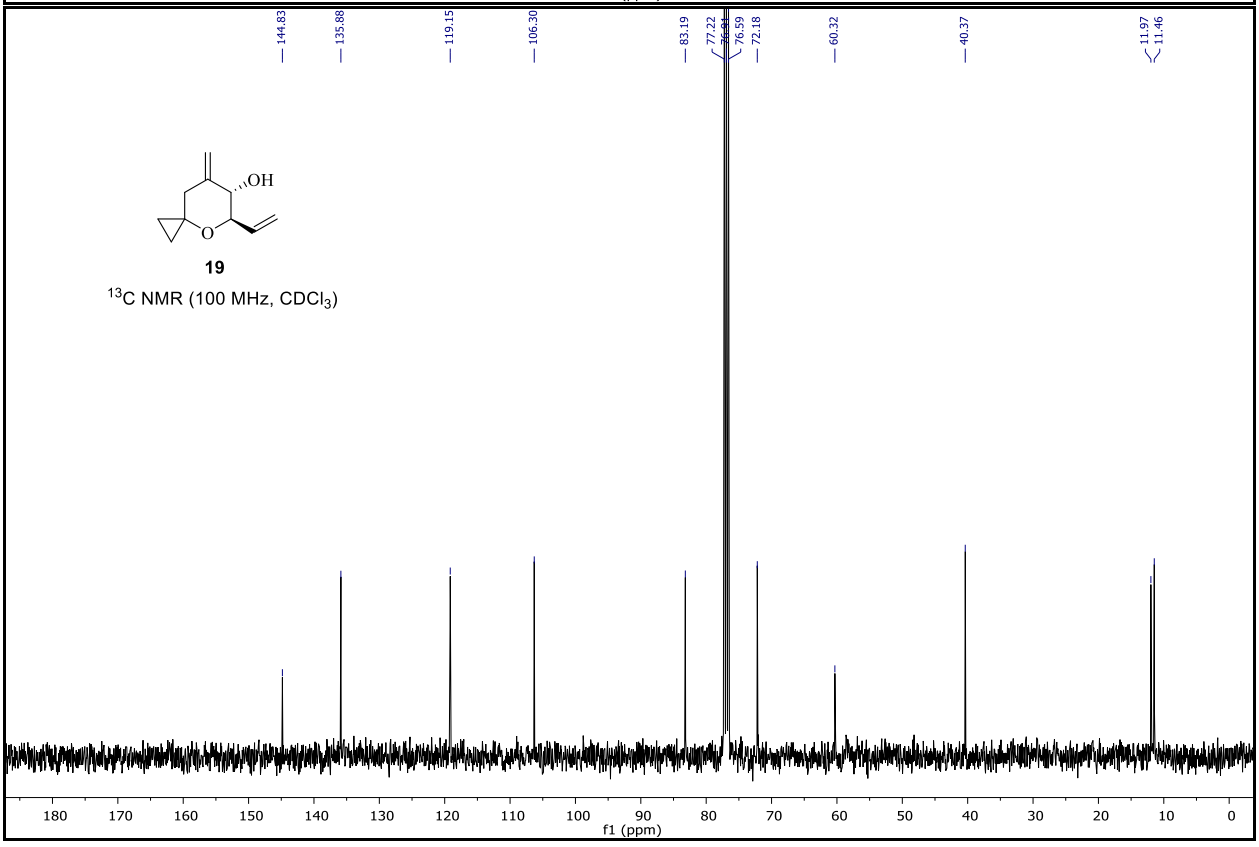

OMe
O
OH
O
10
1H NMR (400 MHz, CDCl3)
f1 (ppm)

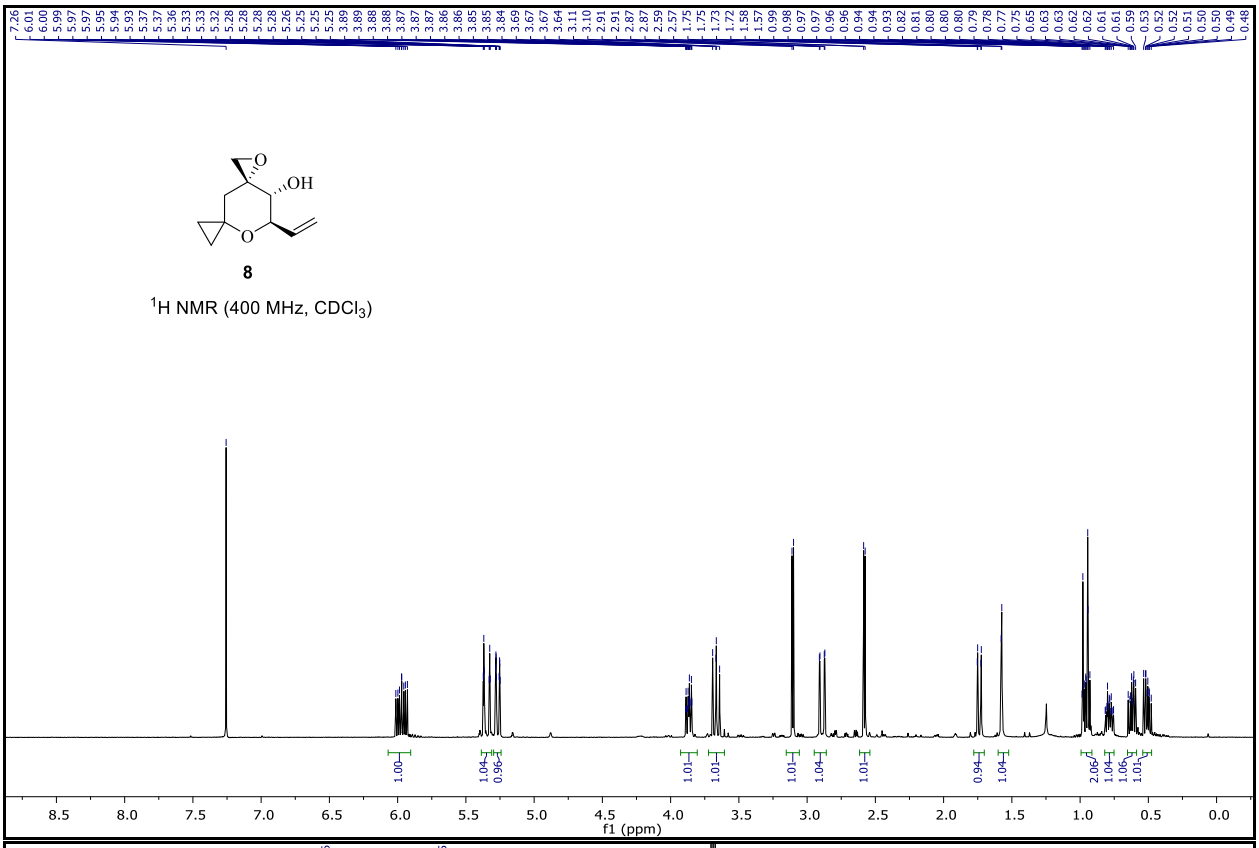

OMe
O
OH
O
10
13C NMR (100 MHz, CDCl3)
f1 (ppm)


OMe
O
O
18
1H NMR (400 MHz, CDCl3)
f1 (ppm)


OMe
O
O
18
13C NMR (100 MHz, CDCl3)
f1 (ppm)

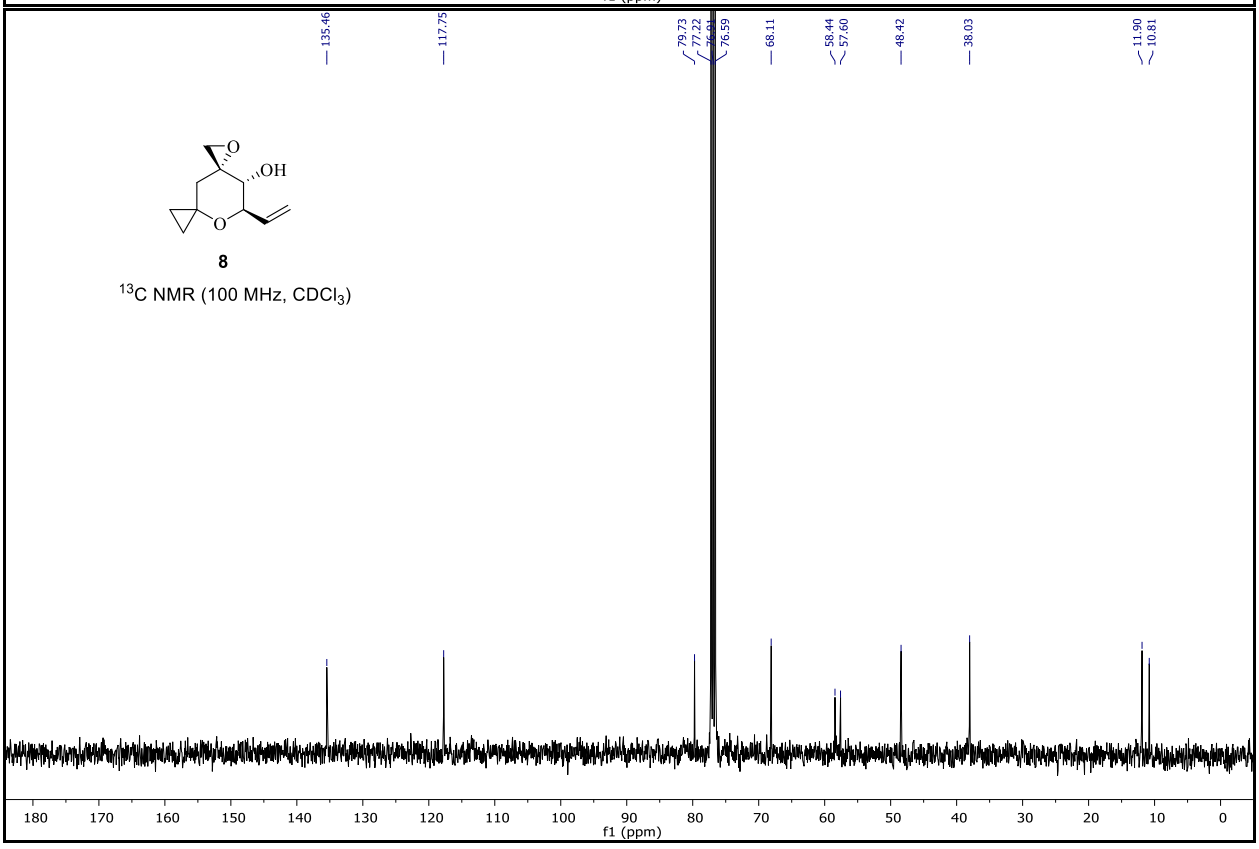

OH
O
19
1H NMR (400 MHz, CDCl3)
f1 (ppm)


144.83
135.88
119.15
106.30
83.19
77.22
76.81
76.59
72.18
60.32
40.37
11.97
11.46
OH
O
19
13C NMR (100 MHz, CDCl3)
f1 (ppm)



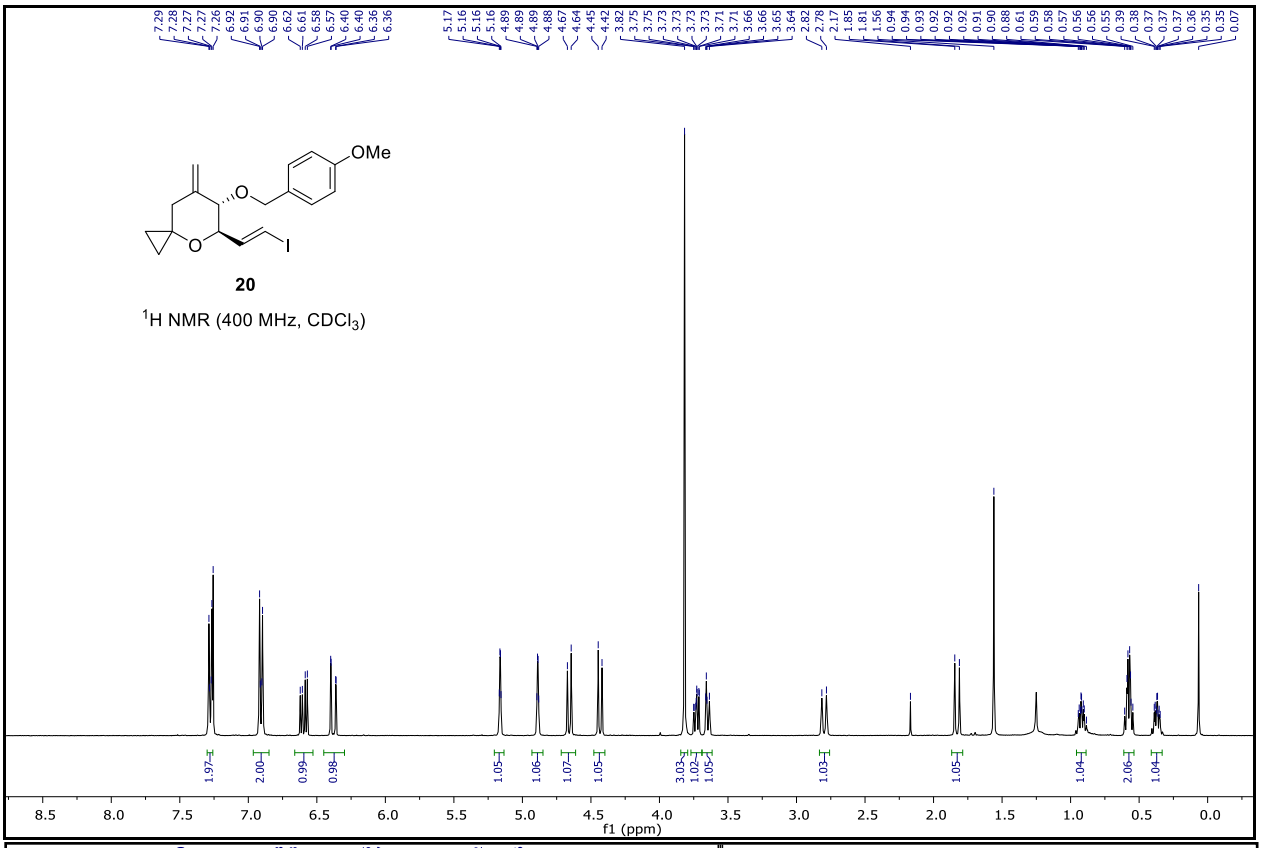
8

^{1}H NMR (400 MHz, $CDCl_3$)



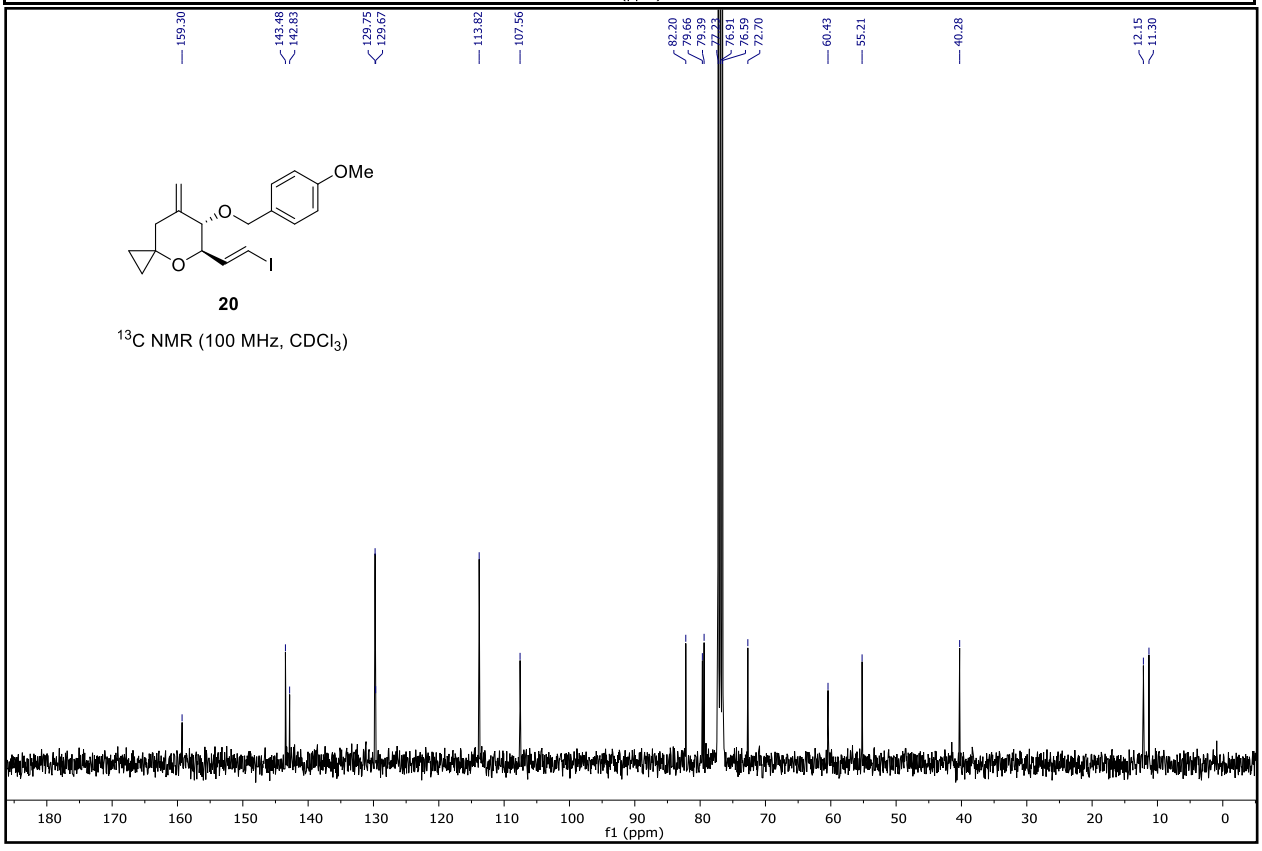
8

^{13}C NMR (100 MHz, $CDCl_3$)



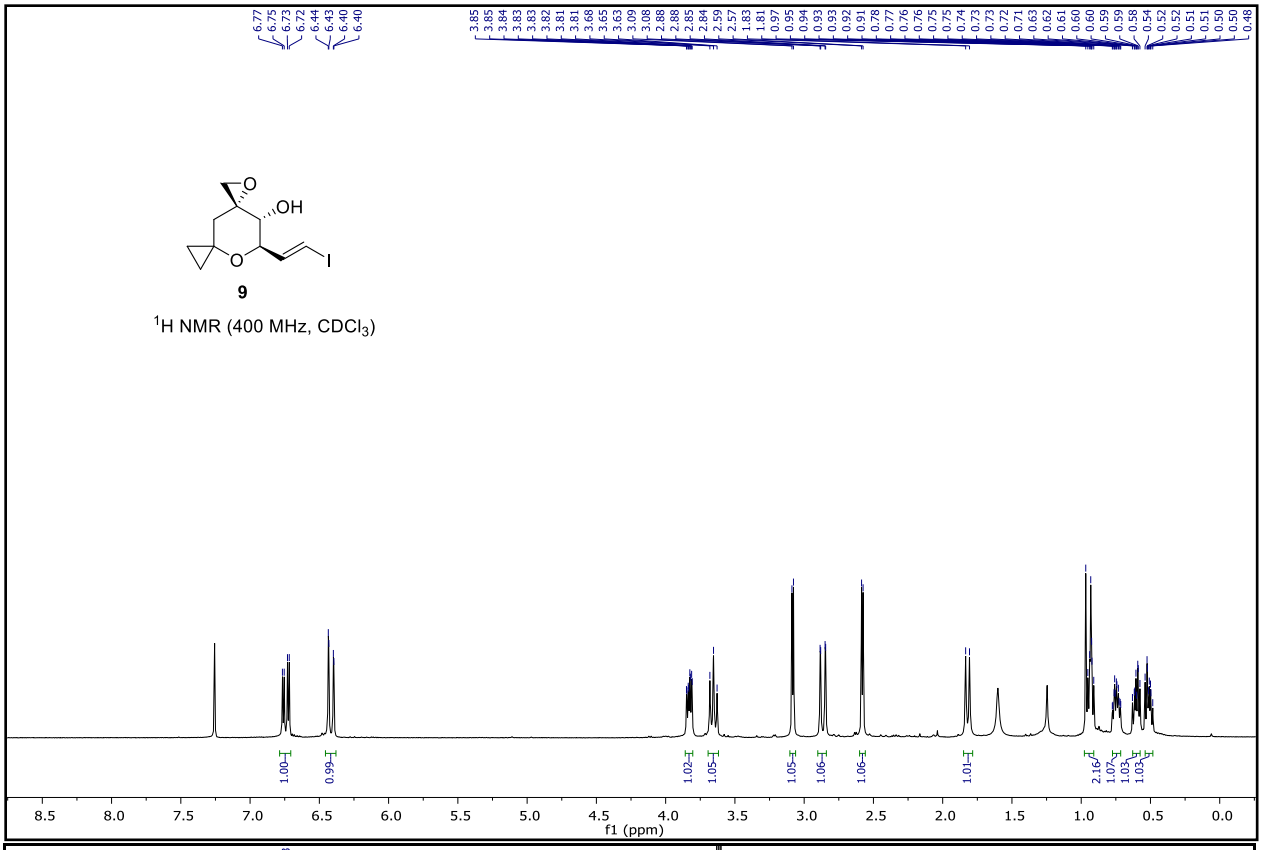
20

^{1}H NMR (400 MHz, $CDCl_3$)



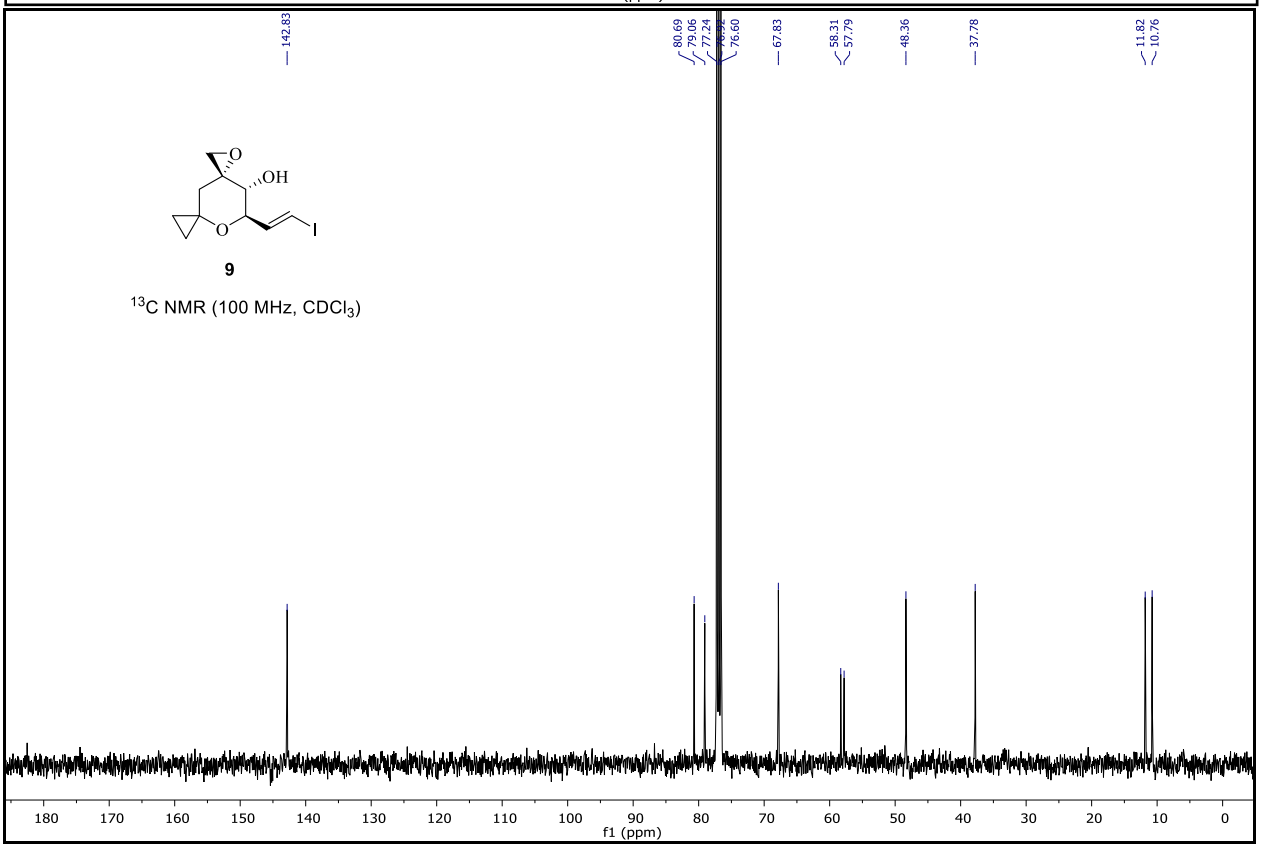
20

^{13}C NMR (100 MHz, $CDCl_3$)



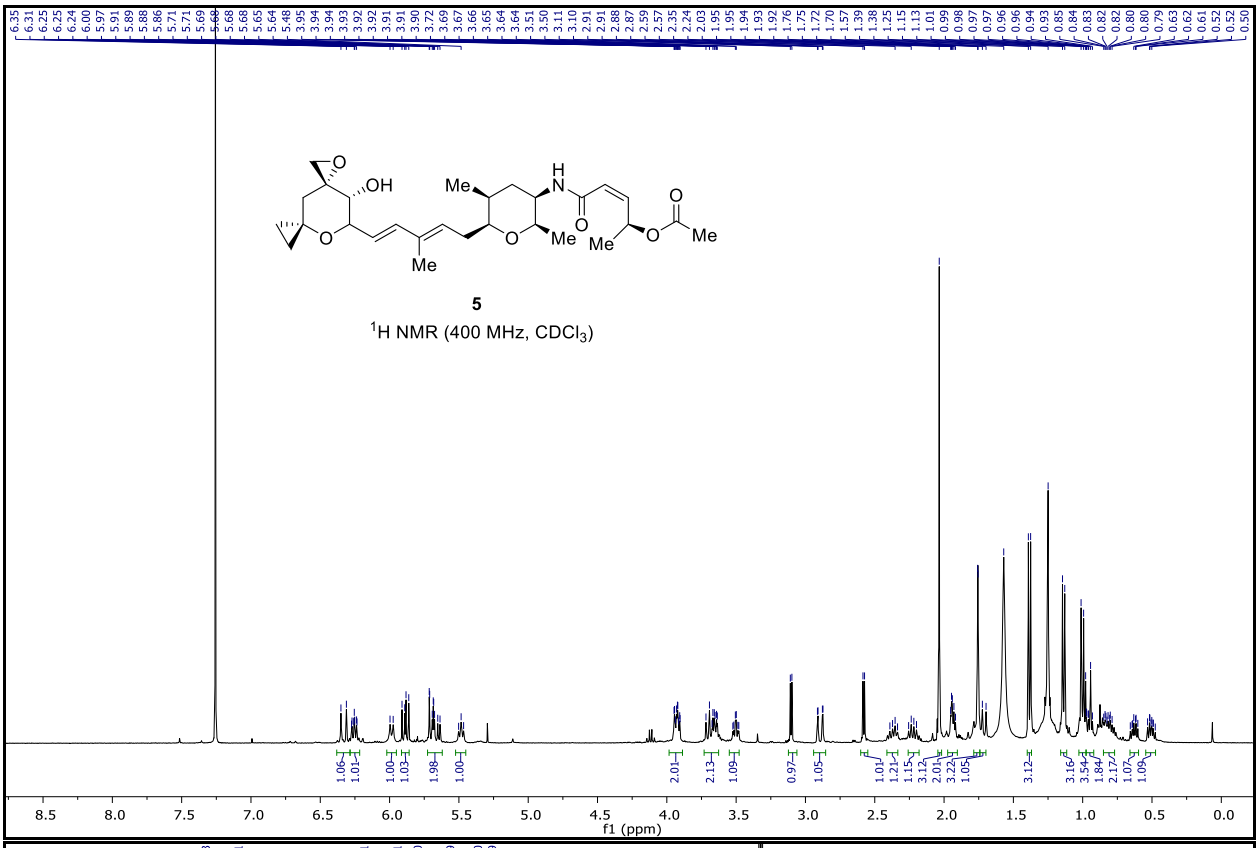
9

^{1}H NMR (400 MHz, $CDCl_3$)



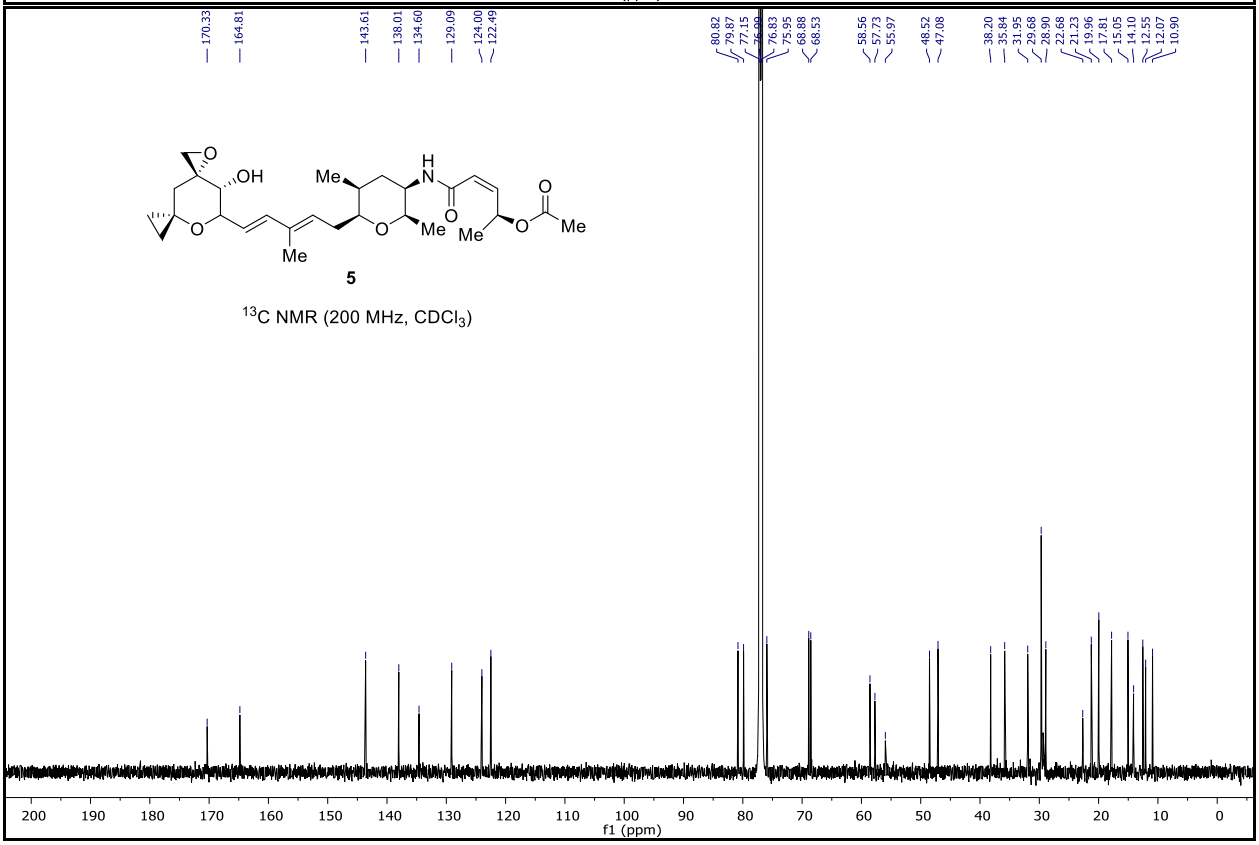
9

^{13}C NMR (100 MHz, $CDCl_3$)



5

^{1}H NMR (400 MHz, $CDCl_3$)



5

^{13}C NMR (200 MHz, $CDCl_3$)