

Supporting information

Ozonolysis of Alkynes – A Flexible Route to Alpha-Diketones. Synthesis of AI-2

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Table of contents

Equipment....p 2
Materials....p 2
Experimental section....p 2
Ozonolysis general procedure....p 2
Compounds 1-8....p 2-5
AI-2 synthesis....p 5-7
Instrumental spectra....p 7-25

Equipment:

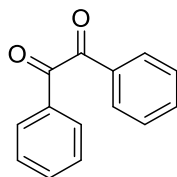
Purification by flash chromatography was performed with SiliaFlash Irregular Silica Gels F60, 40 - 63 μm , 60 Å (R10030B) purchased from Silicycle, Silica pads purifications were done with Silica gel 60 (0.015-0.040 mm) for column chromatography Millipore-Sigma. Ozone was generated by an Ozonology inc. device model no. L-50. NMR spectra were collected on Varian MR-400 and Avance NEO 400 MHz instruments. Mass spectra were collected on a Agilent QTOF 6540 instrument. Condensing of solutions was done on a R-100 BUCHI rotary evaporation. unless otherwise stated.

Materials:

All solvents were purchased from commercial sources and used without further purification: Acetone ACS reagent grade, dichloromethane Certified ACS Fisher Scientific. tert-butyldimethylsilyl chloride Oakwood, propyne TCI, imidazole SigmaAldrich, 1,4-butanediol SigmaAldrich, triphenylphosphine SigmaAldrich, n-butyllithium solution (2.5 M in hexanes) SigmaAldrich, benzene-1,2-diamine SigmaAldrich.

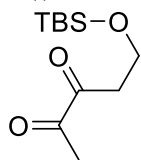
Experimental Section:**Ozonolysis general procedure:**

An oven dried scintillation vial was charged with alkyne (~0.5 mol), and homogenized into a 10 mL 1:1 mixture of acetone and dichloromethane. The ~0.05 M solution were cooled to -78°C under argon and then subjected to ozone for 5-15 minutes in the dark. Pure oxygen was then allow to flow through the blue solution for 30 seconds followed by argon for an additional 30 seconds. To the clear colorless solution ~1.1 equivalent of triphenylphosphine (PPh_3) was added as a concentrated solution in dichloromethane. The flask was wrapped with aluminum and allowed to warm to room temperature for 1 hour. The neon green solution was then reduce to a crude product with exclusion of light and product isolated by column chromatography or preparative TLC as stated.

Compounds 1-8:**Benzil: (1)**

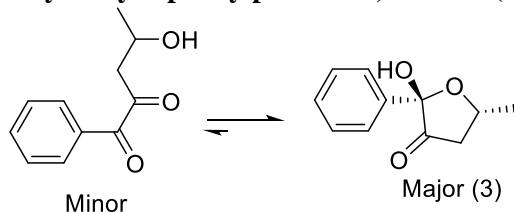
See general ozonolysis procedure. A vial was charged with the according alkyne (83 mg, 0.47 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~9 minutes. Ozonides were quenched with PPh_3 (144 mg, 1.2 eq). The condensed solution was subjected to column chromatography (hexanes: ethyl acetate, 19:1) mixture affording (1) 70 mg (70%) as a solid. Mp $93-95^{\circ}\text{C}$ (lit. $95-96^{\circ}\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 7.1$ Hz, 4H), 7.67 (t, $J = 7.4$ Hz, 2H), 7.52 (t, $J = 7.7$ Hz, 4H).

5-((tert-butyldimethylsilyl)oxy)pentane-2,3-dione: (2)



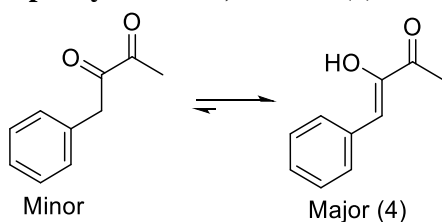
See general ozonolysis procedure. A vial was charged with the according alkyne (87 mg, 0.44 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~5 minutes. Ozonides were quenched with PPh₃ (138 mg, 1.2 eq). The condensed solution was subjected to column chromatography (hexanes: methanol, 20:1) mixture affording (2) 97 mg (~95%) as a green oil. ¹H NMR (400 MHz, CDCl₃) δ 3.91 (t, *J* = 6.2 Hz, 1H), 2.90 (t, *J* = 6.1 Hz, 1H), 2.29 (s, 3H), 0.83 (s, 9H), 0.02 (s, 6H).

4-hydroxy-1-phenylpentane-1,2-dione: (3)

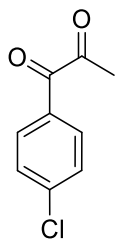


See general ozonolysis procedure. A vial was charged with the according alkyne (78 mg, 0.49 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~14 minutes. Ozonides were quenched with PPh₃ (153 mg, 1.2 eq). The condensed solution was subjected to column chromatography (hexanes: ethyl acetate, 1:1) mixture affording (3) 94 mg (80%) as a green oil. ¹H NMR (400 MHz, D₂O) δ 7.62 – 7.49 (m, 2H), 7.47 – 7.39 (m, 3H), 4.79 – 4.69 (m, 1H), 2.89 (dd, *J* = 18.9, 5.3 Hz, 1H), 2.52 (dd, *J* = 18.8, 9.6 Hz, 1H), 1.52 (d, *J* = 6.1 Hz, 3H). ¹³C NMR (100.5 MHz, D₂O) δ 213.8, 129.5, 128.7, 128.5, 126.1, 99.4, 71.0, 41.7, 19.7. HRMS (ESI) *m/z* [M – H][–] calcd for [C₁₁H₁₁O₃][–] 191.0714; found 191.0711.

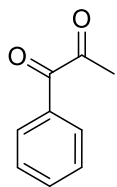
1-phenylbutane-2,3-dione: (4)



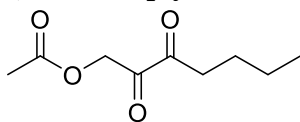
See general ozonolysis procedure. A vial was charged with the according alkyne (76 mg, 0.56 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~13- minutes. Ozonides were quenched with PPh₃ (153 mg, ~1 eq). The condensed solution was subjected to column chromatography (hexanes: methanol, 20:1) mixture affording (4) 86 mg (~95%) as a green solid. ¹H NMR (400 MHz; CDCl₃) 7.83 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.46 (s, 1H), 2.52 (s, 3H).

1-(4-chlorophenyl)propane-1,2-dione: (5)

See general ozonolysis procedure. A vial was charged with the according alkyne (73 mg, 0.48 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~15 minutes. Ozonides were quenched with PPh₃ (139 mg, 1.1 eq). The condensed solution was subjected to column chromatography (hexanes: ethyl acetate, 9:1) mixture affording **(5)** 70 mg (80%). ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 2.52 (s, 3H).

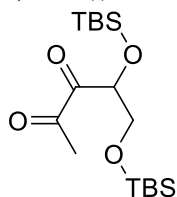
1-phenylpropane-1,2-dione: (6)

See general ozonolysis procedure. A vial was charged with the according alkyne (60 mg, 0.52 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~8 minutes. Ozonides were quenched with PPh₃ (150 mg, 1.1 eq). The condensed solution was subjected to column chromatography (hexanes: methanol, 20:1) mixture affording **(6)** 62 mg (81%). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 1H).

2,3-dioxoheptyl acetate: (7)

See general ozonolysis procedure. A vial was charged with the according alkyne (64 mg, 0.42 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~6. minutes. Ozonides were quenched with PPh₃ (109 mg, 1.0 eq). The condensed solution was subjected to column chromatography (hexanes: methanol, 20:1) mixture affording **(7)** 63 mg (80%) as a green oil. ¹H NMR (400 MHz, CDCl₃) δ 5.10 (s, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.17 (s, 3H), 1.62 – 1.27 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100.5 MHz, CDCl₃) δ 198.7, 190.9, 170.3, 65.5, 35.9, 24.8, 22.2, 20.3, 13.8. HRMS (ESI) *m/z* [M – H][–] calcd for [C₉H₁₁O₄][–] 185.0819; found 185.0818.

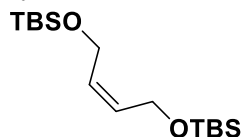
4,5-bis((tert-butyldimethylsilyl)oxy)pentane-2,3-dione: (8)



See general ozonolysis procedure. A vial was charged with the according alkyne (182 mg, 0.55 mmol) and an acetone/ dichloromethane solution. The reaction with ozone was allowed for ~10 minutes. Ozonides were quenched with PPh_3 (145 mg, 1.0 eq). The condensed solution was subjected to column chromatography (hexanes: methanol, 20:1) mixture affording (**8**) 193 mg (~95%) ^1H NMR (400 MHz; CDCl_3) 4.97 (t, $J = 4.8$ Hz, 1H), 4.00 (dd, $J = 10.3, 4.9$ Hz, 1H), 3.77 (dd, $J = 10.3, 4.7$ Hz, 1H), 2.32 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.08-0.03 (m, 12H). ^{13}C NMR (100.5 MHz, CDCl_3): δ 200.1, 199.8, 77.5, 74.8, 66.2, 25.9, 25.8, 24.7, 18.4, 18.4, -4.8, -5.0, -5.4, -5.5. HRMS (ESI) m/z $[\text{M} - \text{H}]^-$ calcd for $[\text{C}_{17}\text{H}_{35}\text{O}_4\text{Si}_2]^-$ 359.2079; found 359.2074.

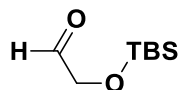
AI-2 synthesis:

Synthesis of 2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene: (Bis-OTBS-alkene)



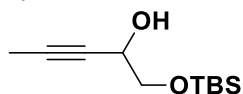
To an oven dried glass flask with stir bar was added TBSCl (10.22 g, 67.8 mmol), followed by DCM 100 mL and imidazole (4.64 g, 1.01 eq.). The solution was stir with an argon atmosphere in an ice bath for 10 minutes, then 1,4-butanediol (2.74 mL, 0.49 eq.) was added and mixed for overnight. After filtering through a pad of fine silica with additional DCM the material was then condensed, affording a clear colorless oil 10.19 g (97%) of the title compound. This material was used without further purification. ^1H NMR (400 MHz; CDCl_3) 5.55 (t, $J = 3.36$ Hz, 2H), 4.23 (d, $J = 0.16$ Hz, 4H), 0.90 (s, 18H), 0.06 (s, 12H).

Synthesis of 2-((tert-butyldimethylsilyl)oxy)acetaldehyde: (10)



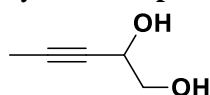
To a round bottom charged with stir bar was added Bis-OTBS-alkene (8.00 g, 25.3 mmol) followed by 100 mL of DCM. The solution was cooled to -78 and then ozone was bubbled through the solution until the solution turned blue after 30 minutes. Oxygen was then passed through until the solution became clear, and then triphenylphosphine (4.78 g, 1.1 equivalents) was added and the solution was warmed to R.T. overnight with an argon balloon. The solution was condensed to a slurry, and passed through a pad of fine silica with additional DCM flushing and then condensed to afford 4.41 g (>98%) of **10** as a clear colorless oil. This material was used without further purification. ^1H NMR (400 MHz; CDCl_3) 9.70 (s, 1H), 4.21 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

Synthesis of 1-((tert-butyldimethylsilyl)oxy)pent-3-yn-2-ol: OTBS-alkyne



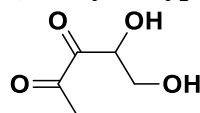
To an oven dried round-bottom with stir bar was added propyne (5.25 mL, 1M) in THF, the solution was cooled to -78 while under an argon flow. Then n-BuLi (3 mL, 2.5M) was added and the solution was mixed for 1 hour. After which (10) (0.57 mL, 2.9 mmol) in THF 3 mL was added under argon. The reaction mixture was allowed to come to room temperature overnight. Saturated NH₄Cl solution was added and 3x ethyl acetate extraction was done followed by a brine washing. The organics were dried over sodium sulfate and then partially condensed affording 0.451 g (73%) of a yellow oil of the title compound. This material was used without further purification. ¹H NMR (400 MHz; CDCl₃) 4.35 (m, 1H), 3.73 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.59 (dd, 10.1, 7.6 Hz, 1H), 2.56 (d, *J* = 4.1 Hz, 1H (OH)), 1.84 (d, *J* = 2.16 Hz, 2H), 0.91 (s, 9H), 0.09 (d, *J* = 2.0 Hz, 6H).

Synthesis of pent-3-yne-1,2-diol: (11)



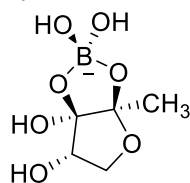
To a glass flask with stir bar was added OTBS-alkyne (2.02 g, 9.43 mmol) followed by THF (22.0 mL) and TBAF (11.5 mL, 1M) which was then stirred for 1 hour. Water was added and the solution went turbid. And 3x EtOAc washing was done and organics were dried on sodium sulfate and then condensed to an orange oil. The crude oil was dissolved minimal amount of acetone and transferred to a hexane soaked silica pad to which hexane was washed through followed by acetone. Which after condensing afforded 0.811 g (86%) as an orange solid which was used without further purification. ¹H NMR (400 MHz; CDCl₃) 4.41 (m, 1H), 3.70 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.63 (dd, *J* = 11.3, 6.7 Hz, 1H), 1.84 (d, *J* = 2.2 Hz, 3H). ¹³C NMR (400 MHz; D₂O) 4.40 (m, 1H), 3.64 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.58 (dd, *J* = 11.5, 6.4 Hz, 1H), 2.27 (br s, 1H), 2.14 (br s, 1H) 1.83 (d, *J* = 2.2 Hz, 3H).

4,5-dihydroxypentane-2,3-dione (DPD): (12)



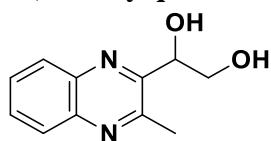
See general ozonolysis procedure. A vial was charged with (11) (47 mg, 0.47 mmol) and an acetone/dichloromethane solution. The reaction with ozone was allowed for ~5 minutes. Ozonides were quenched with PPh₃ (130 mg, 1.1 eq). The condensed material was triturated in D₂O and subjected to a pad of silica (D₂O washed). The ¹H NMR spectrum match the reported data in the literature. The condensed solution afforded an oil 39 mg (62%) which could be kept in a frozen matrix of D₂O or H₂O for a few weeks.

Synthesis of **AI-2: (13)**



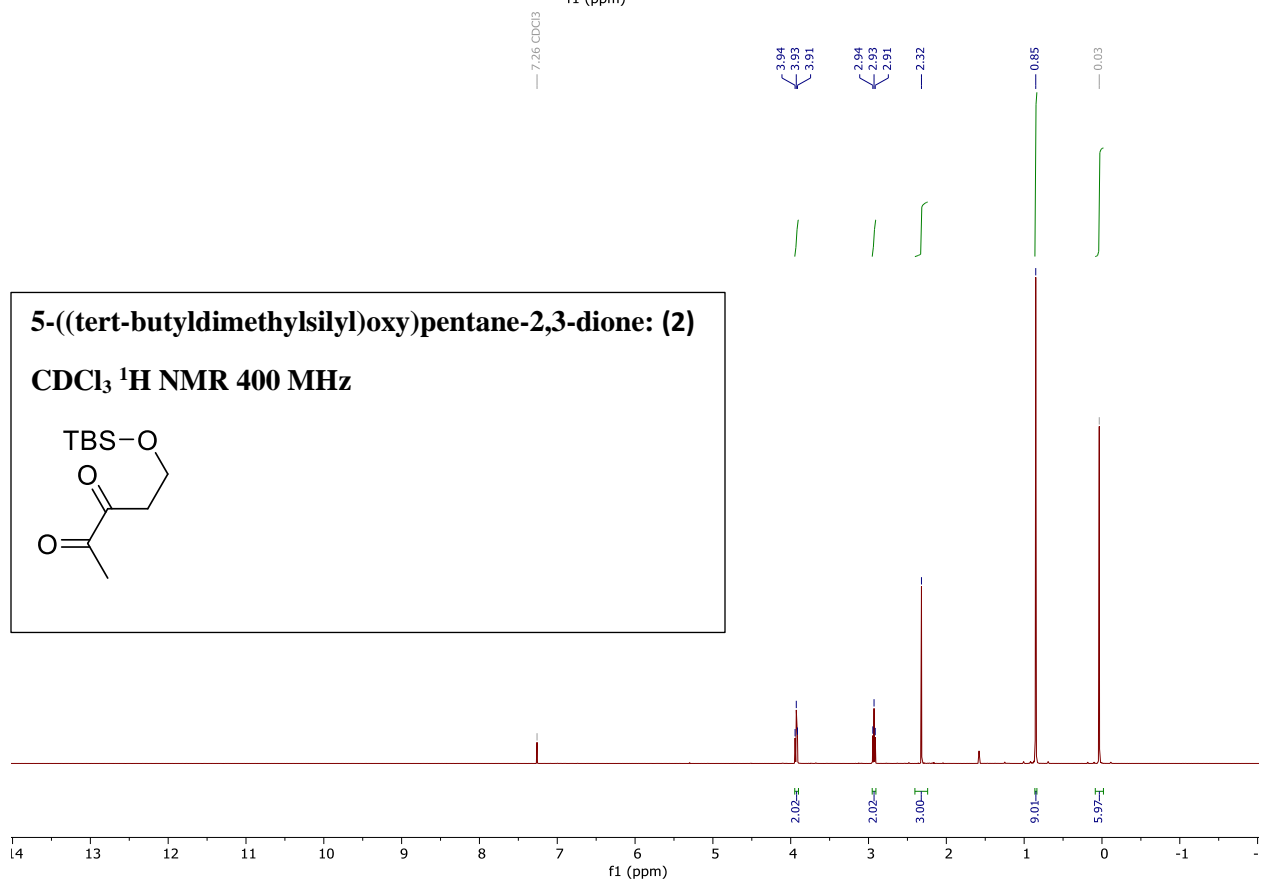
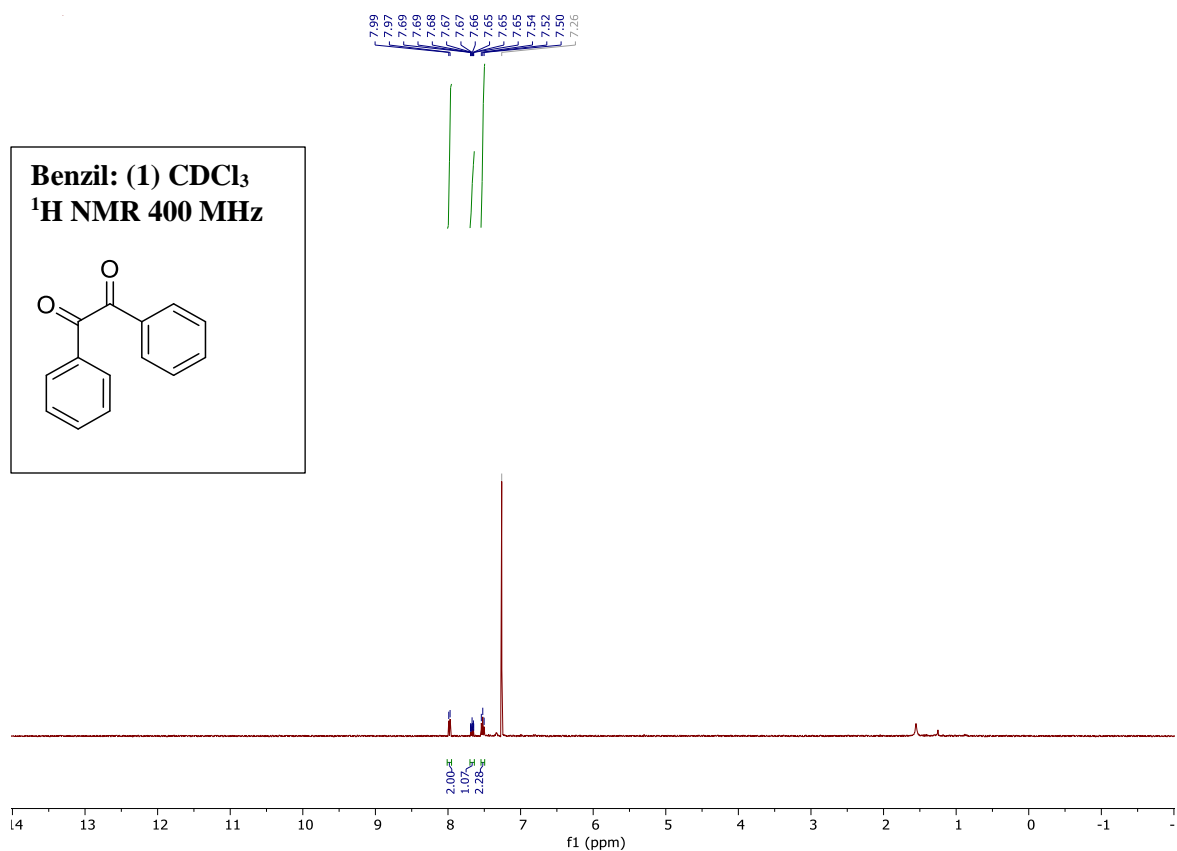
To freshly prepared and condensed (**12**) (133 mg, 1.01 mmol) was added boric acid in D₂O (1.5 mL, 0.515 M), to which the solution was filtered through a pad of fine silica to remove excess PPh₃ and OPPh₃ from the solution which could be kept in a frozen matrix of D₂O or H₂O for a few weeks.

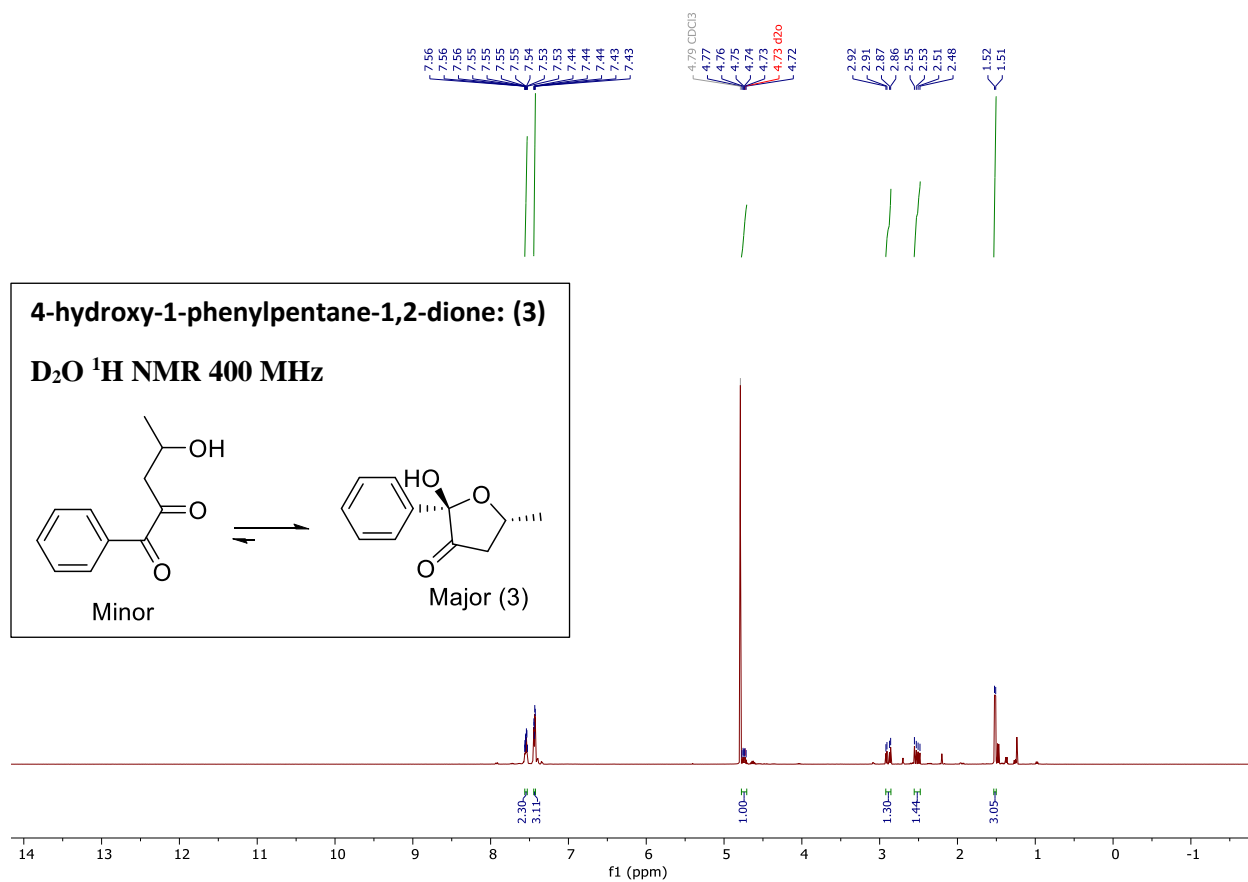
1-(3-methylquinoxalin-2-yl)ethane-1,2-diol: (**14**)

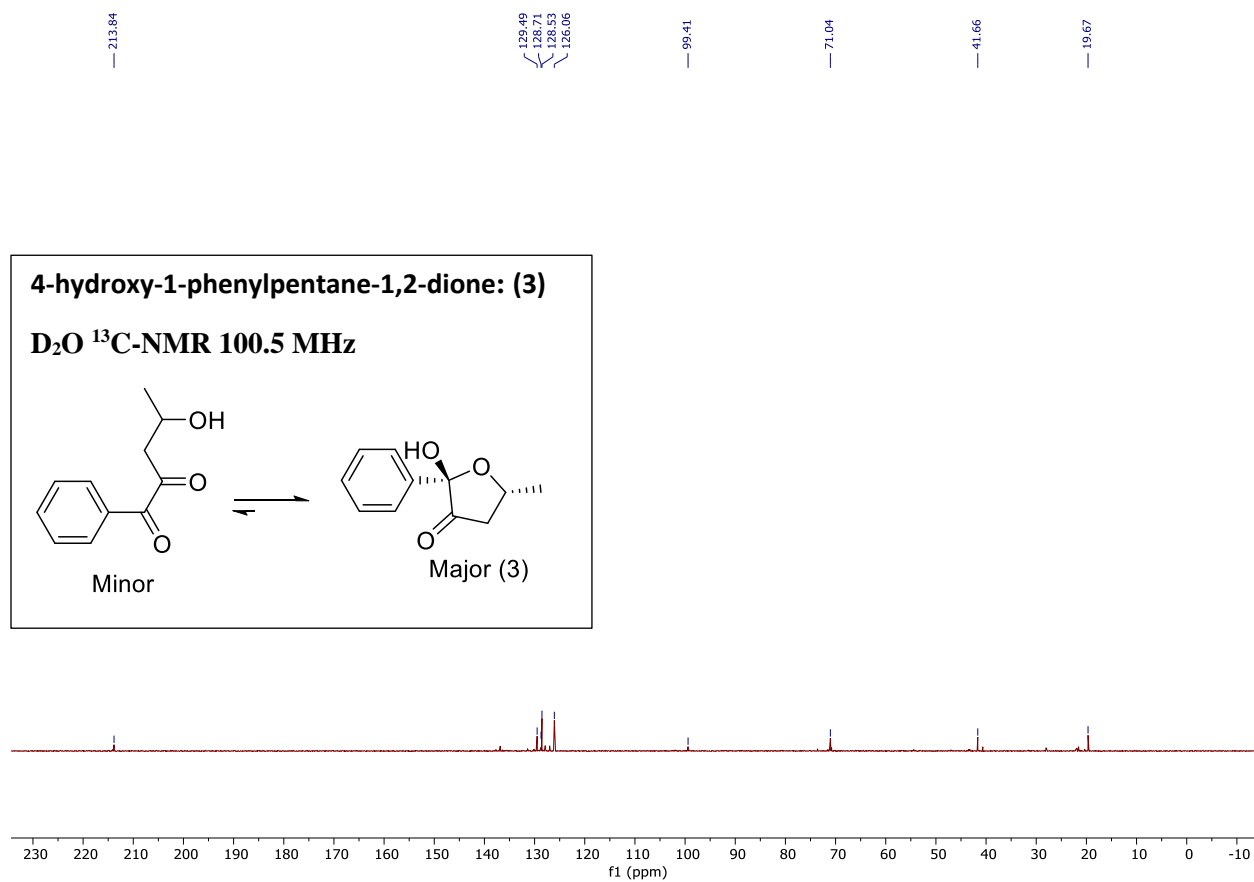


To freshly prepared crude (**12**) (60 mg, 0.45 mmol) in CDCl₃ was added benzene-1,2-diamine (74 mg, 0.68 mmol) in CDCl₃ (~2.5 mL) dropwise and the reaction was monitored via TLC over ~45 min in which the reaction was determined to be complete. The solution was condensed and separated by preparatory plate chromatography (hexanes: ethyl acetate, 6:4) affording (**14**) 76 mg (82%) as a white solid. The ¹H NMR matched an authentic sample previously synthesized. ¹H NMR (400 MHz, D₂O): δ 8.08 (m, 1H), 7.96 (m, 1H), 7.83 (m, 2H), 5.32 (dd, *J* = 6.7, 4.5 Hz, 1H), 4.01 (dd, *J* = 11.9, 4.5 Hz, 1H), 3.92 (dd, *J* = 11.9, 6.7 Hz, 1H), 2.79 (s, 3H).

Instrumental spectra:

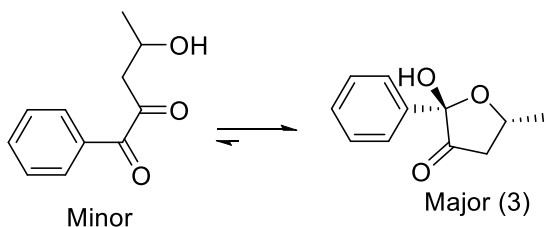




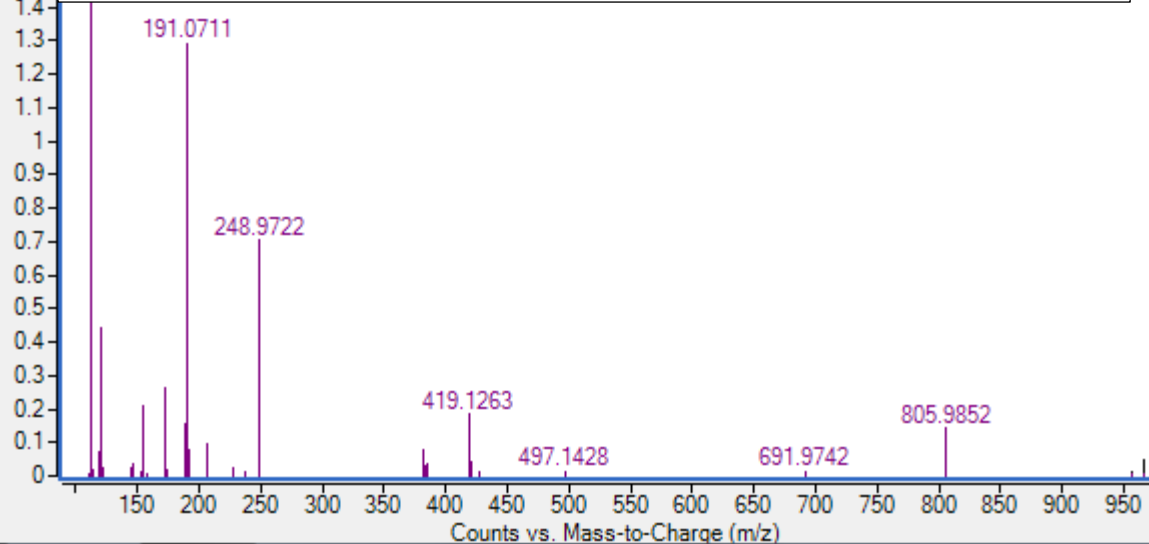


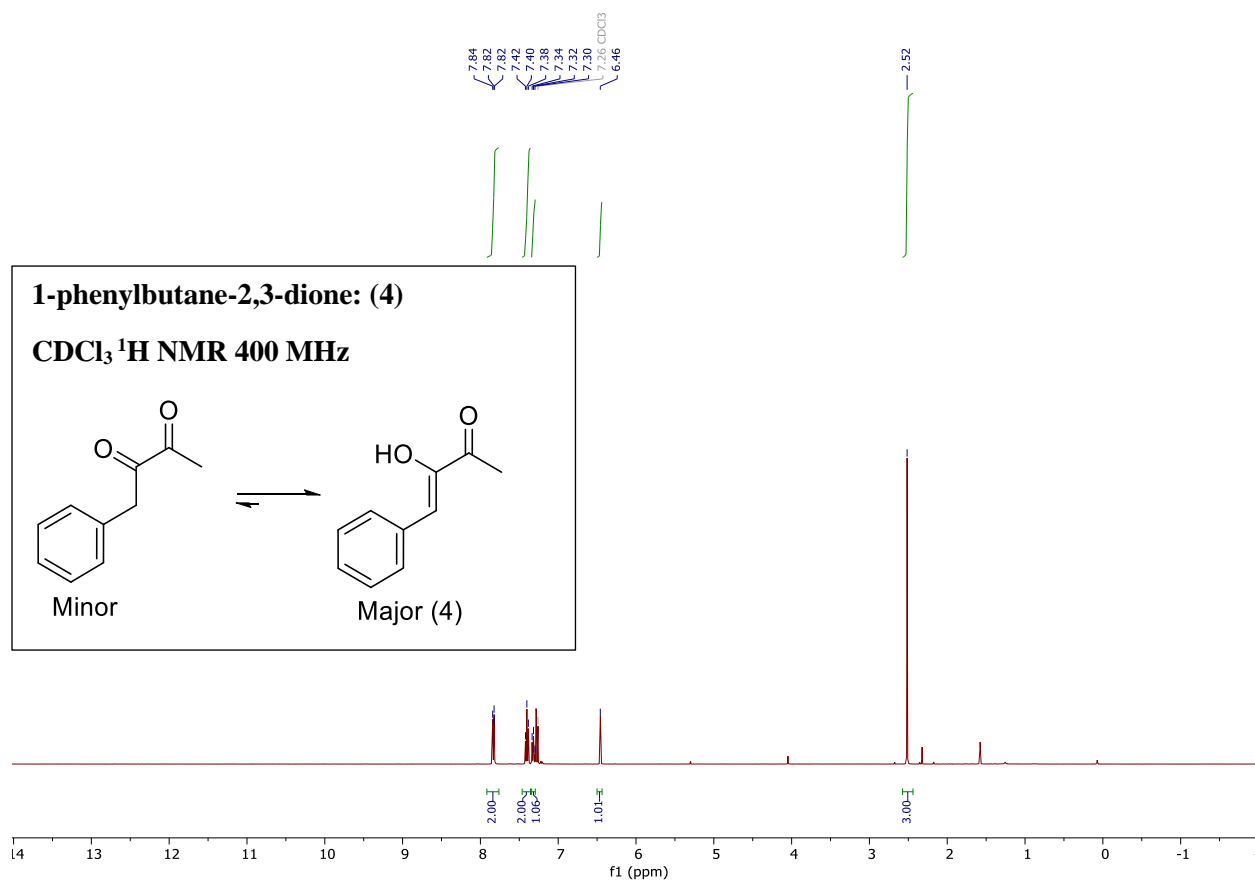
4-hydroxy-1-phenylpentane-1,2-dione: (3) Mass spectrum

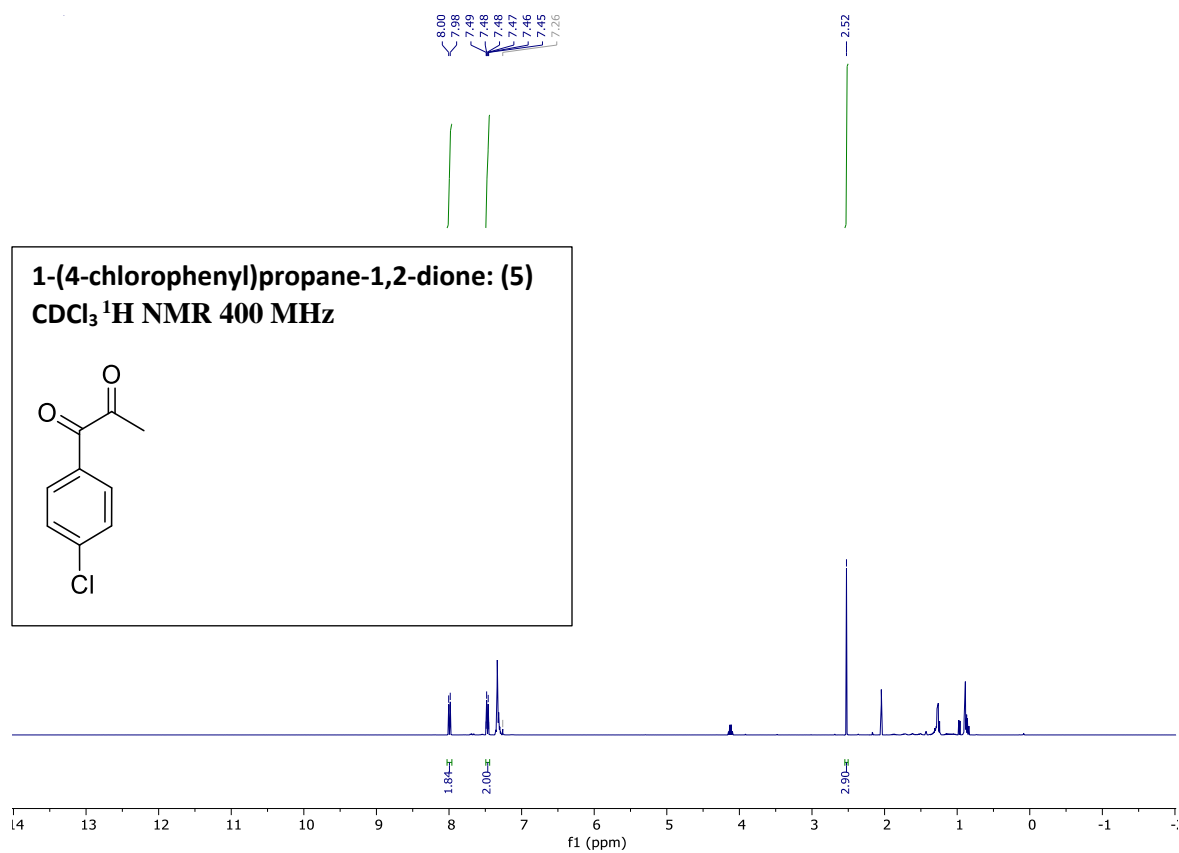
x10⁴

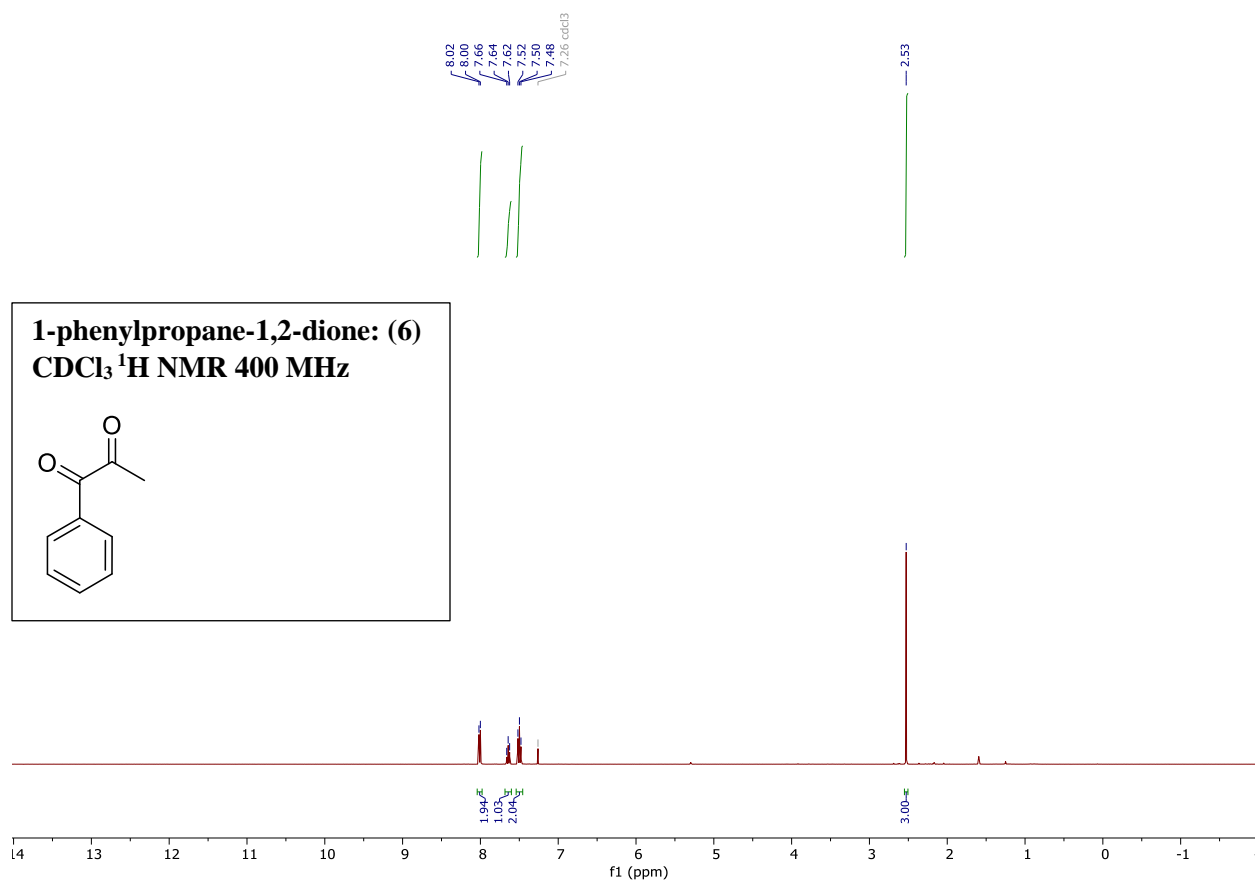


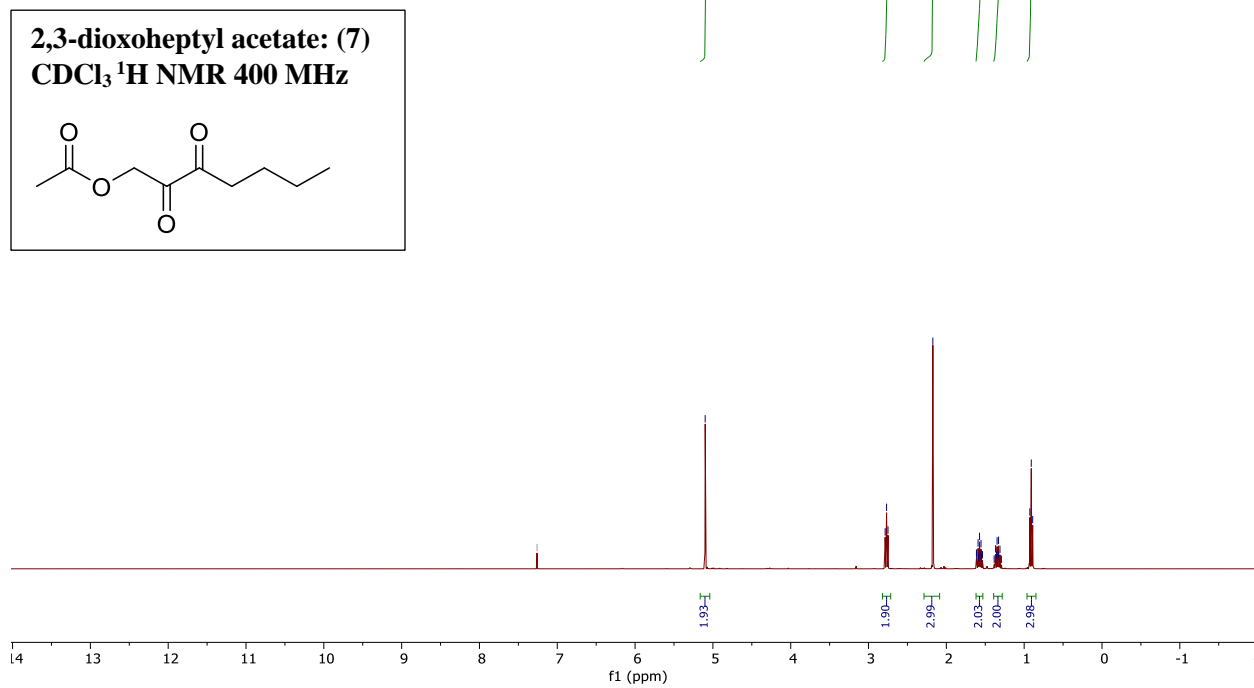
Formula (M)	Ion Formula	Mass (MFG)	m/z (Calc)	Diff (ppm)
C11 H12 O3	C11 H11 O3	192.0786	191.0714	1.39

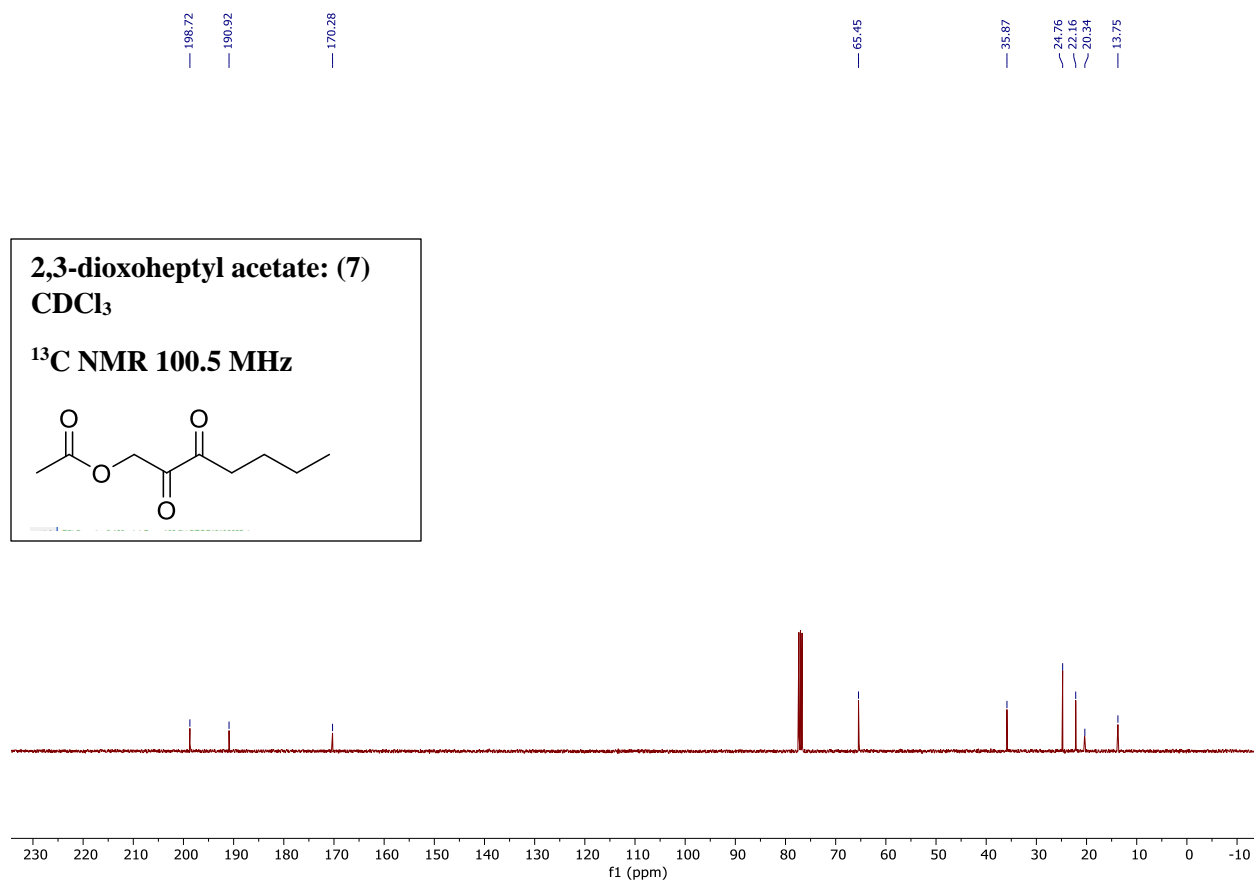


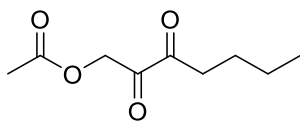




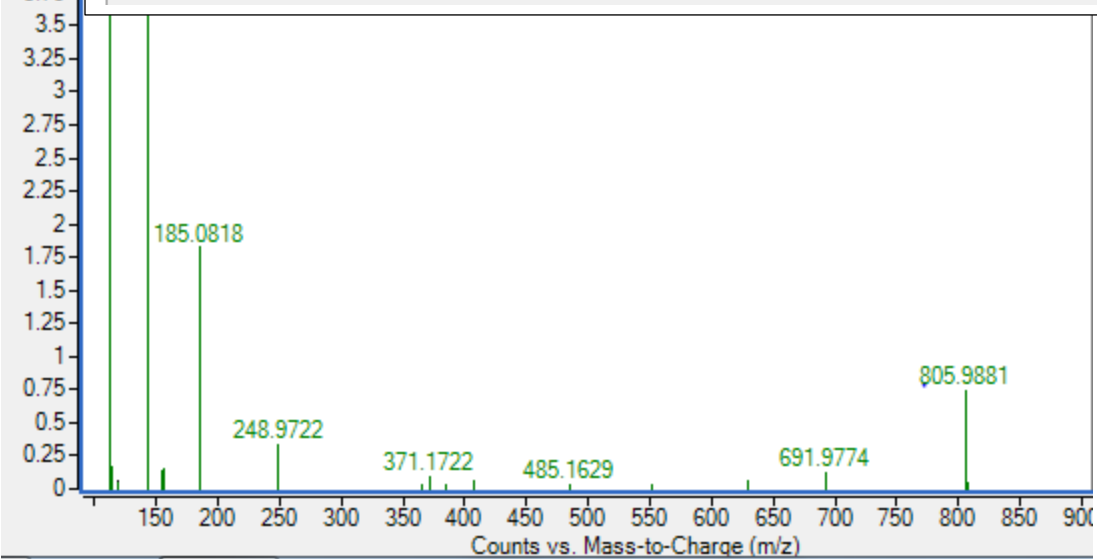




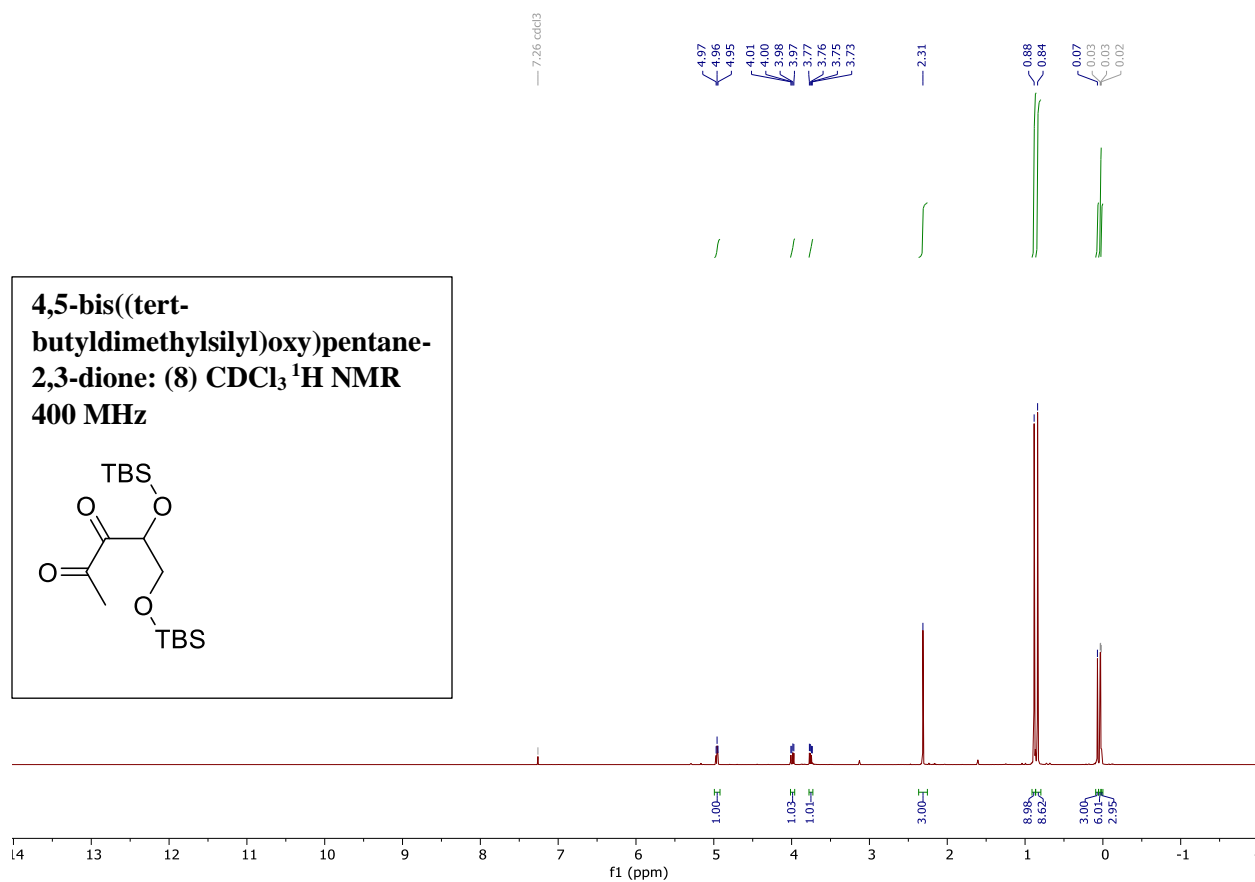
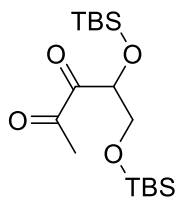


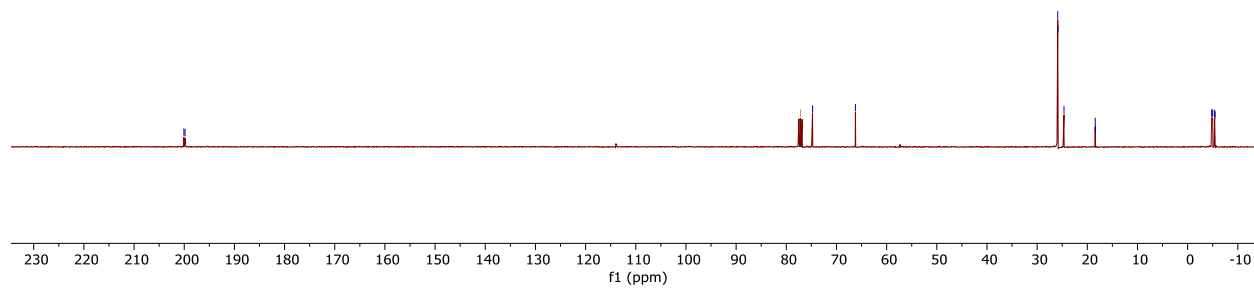
¹³C NMR

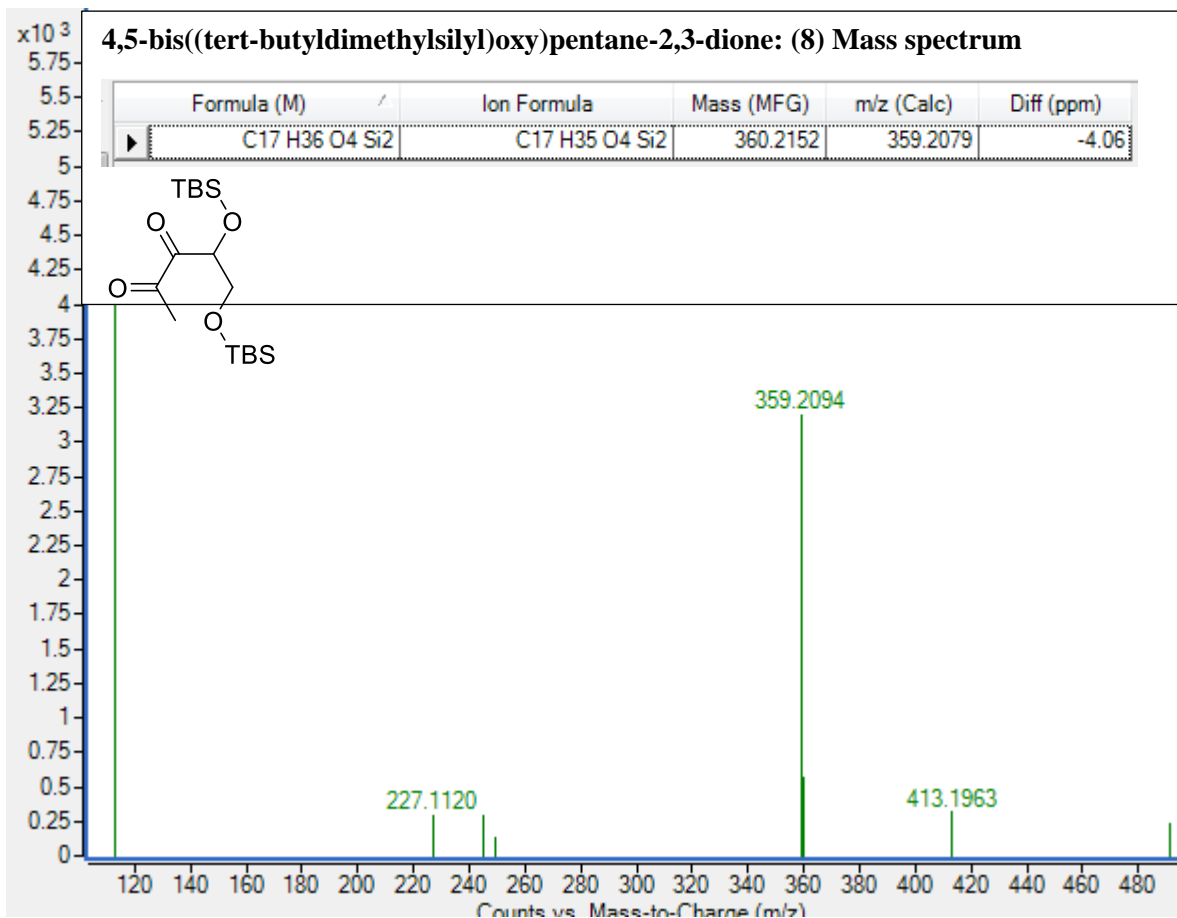
Formula (M)	Ion Formula	Mass (MFG)	m/z (Calc)	Diff (ppm)
C9 H14 O4	C9 H13 O4	186.0892	185.0819	0.71



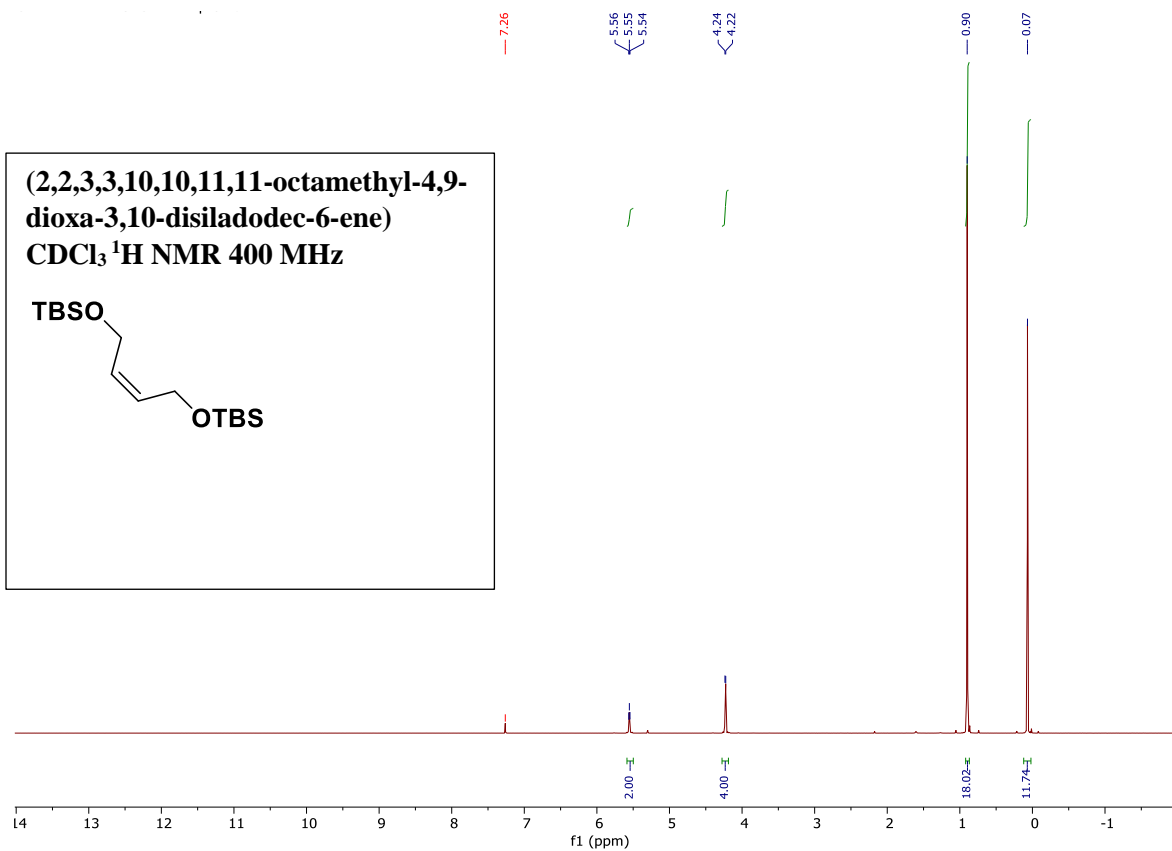
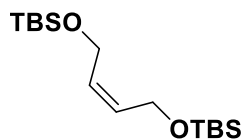
4,5-bis((tert-butyl)dimethylsilyl)oxy)pentane-2,3-dione: (8) CDCl₃ ¹H NMR 400 MHz



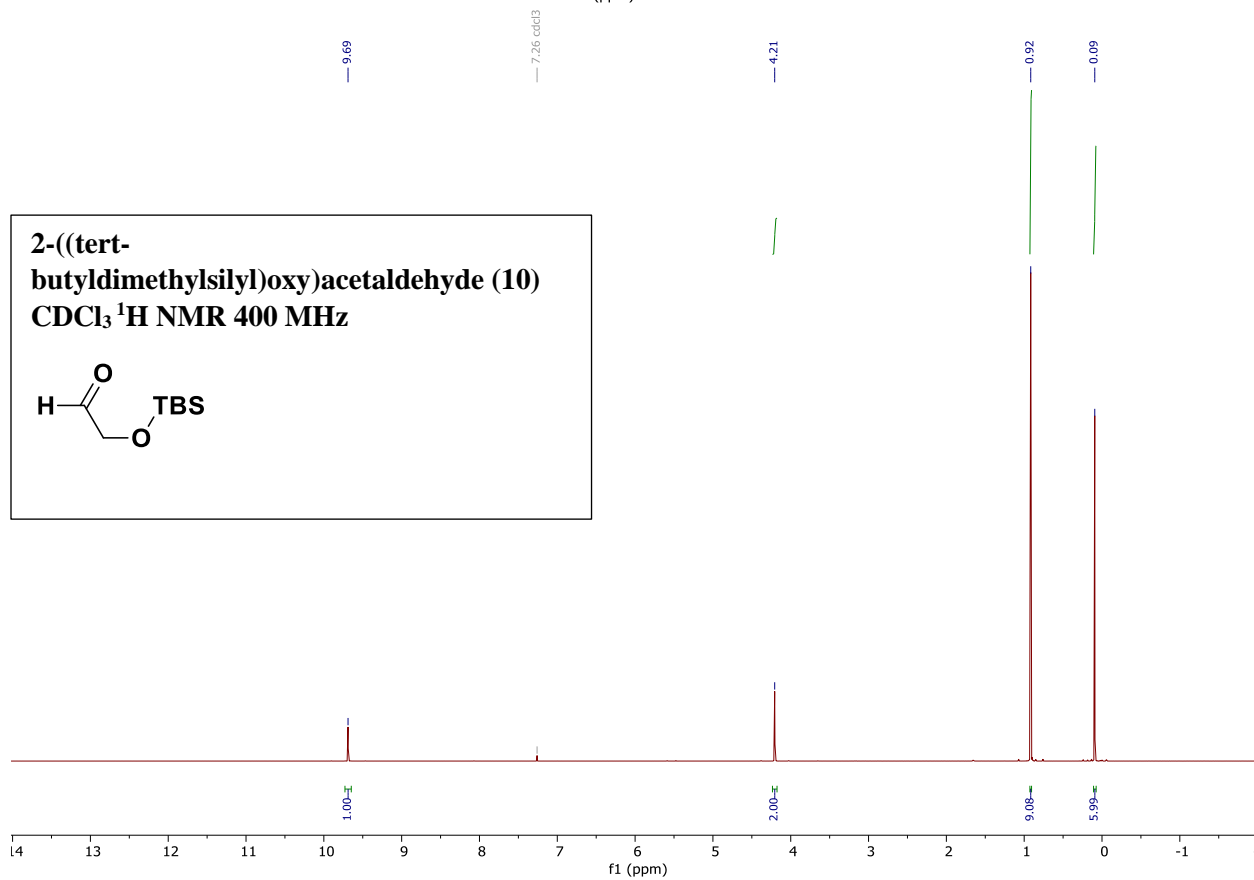
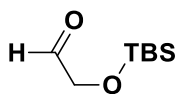
CC(=O)OC(=O)C1OC(C1)OSi(C)(C)C(C)(C)C

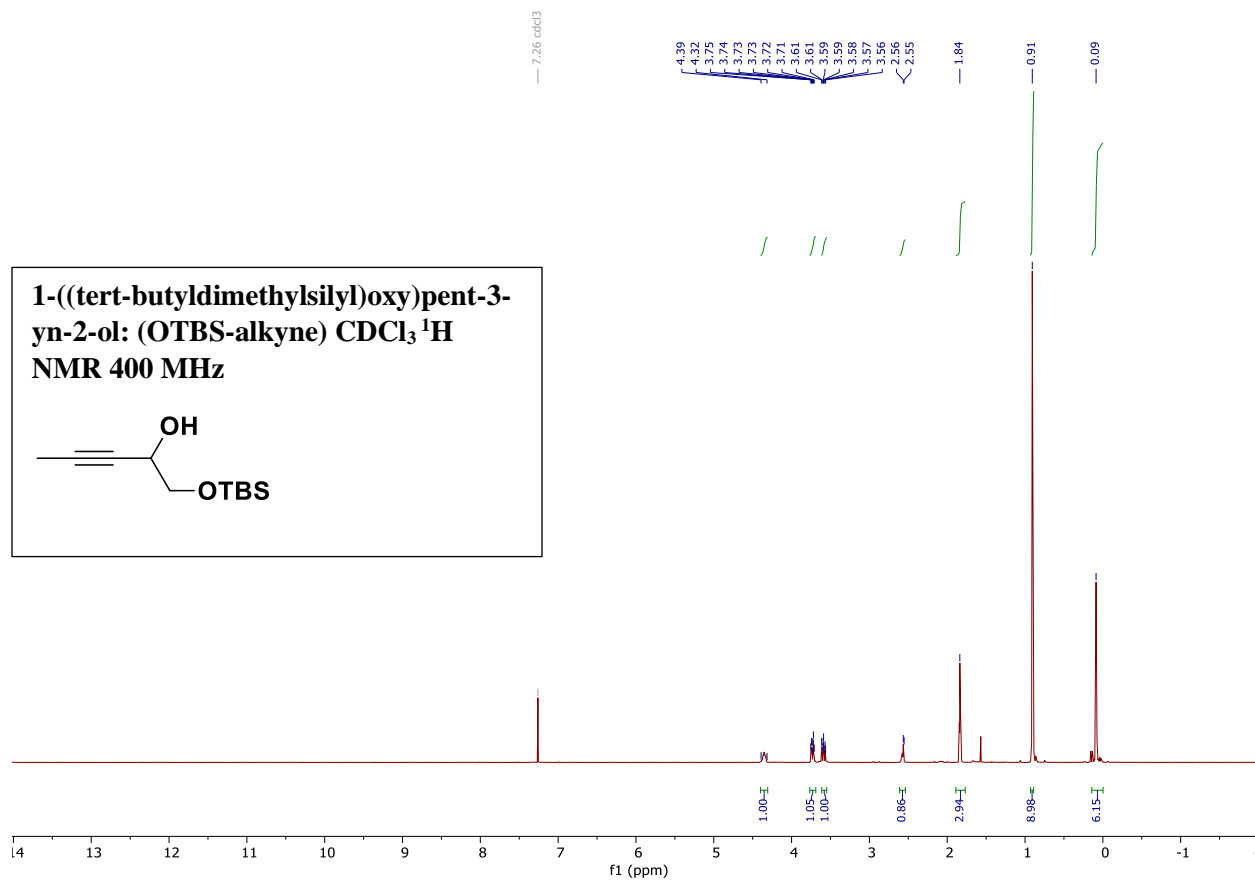


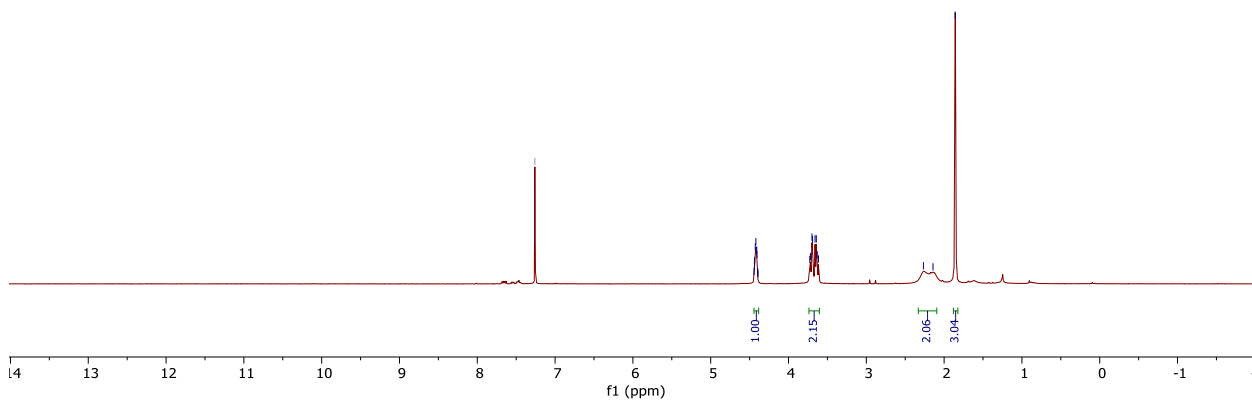
(2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene)
CDCl₃ ¹H NMR 400 MHz



2-((tert-butyltrimethylsilyl)oxy)acetaldehyde (10)
CDCl₃ ¹H NMR 400 MHz



CC#CC(O)COTBS

C#CC(O)COC#CC(O)CO