Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Isotetronic Acids from an Oxidative Cyclization

Zhe Zhou,[a] Patrick M. Walleser[a] and Marcus A. Tius*[a,b]

[a]*Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822 (USA)* *E-mail: tius@hawaii.edu*

[b]*University of Hawaii Cancer Center, 701 Ilalo Street, Honolulu, HI 96813 (USA)*

Table of Contents

Experimental Section

General Information

Reactions were performed with anhydrous pyridine distilled over KOH. Sealed reaction tubes were purchased from Synthware and oven-dried before using. Air was not excluded from the reaction.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 MHz spectrometer at 500 MHz (^{1}H) and 126 MHz (^{13}C), respectively. Two of the ^{1}H spectra were collected with an Agilent DD2 300 MHz NMR spectrometer (300MHz, ^{1}H) as indicated in the characterization data. Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz).

Thin layer chromatography (TLC) was performed on Silicycle glass plates, UV 254, 250 µm thickness, particle size 5–17 µm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200–400 mesh or premium silica gel, 60 Å, 40 – 75 µm. Purity and homogeneity of all materials was determined from TLC, ^{1}H NMR and ^{13}C NMR.

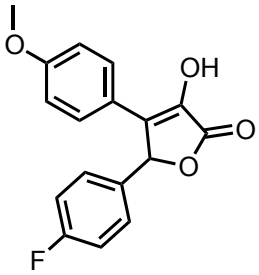
High resolution mass spectra were collected on an Agilent 6210 LC/MSD-TOF system (ESIMS).

General Procedure for the Oxidative Cyclization

Unless specifically indicated, reactions were conducted on a 300 mg scale based on ketone.

Ketones were synthesized using conventional aldol condensation methods.[1]

Ketone (1 eq.) and SeO_2 (2.2 eq.) were mixed with 5 mL distilled pyridine in a sealed tube. The reaction mixture was heated in an oil bath at 110ºC for 5 min. After 5 min, the reaction temperature was lowered to 90ºC and maintained for 12 h. After 12 h, the reaction mixture was allowed to cool to room temperature and was diluted with 50 mL EtOAc. The organic layer was washed with 1M HCl (2 x 100 mL) and brine (1 x 50 mL) before being dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel to give isotetronic acids. For the less polar **4-9**, 30% EtOAc/Hexanes was suitable for the mobile phase. For more polar products **10-15**, 60% EtOAc/Hexanes was used in the purification. Very non-polar **17a-b** were purified with 5% EtOAc/Hexanes, **19**, **21** and **24** were purified with 30% EtOAc/Hexanes. Yields and characterization data are indicated below for each product.

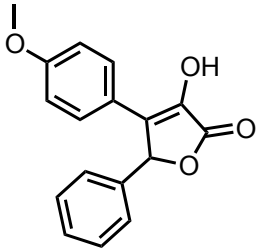


5-(4-fluorophenyl)-3-hydroxy-4-(4-methoxyphenyl)furan-2(5H)-one (4)
Yield: 67%, yellow solid. MP: 180.2-183.0ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.50 (d, *J* = 8.9 Hz, 2H), 7.34 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.16 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 169.81, (164.37, 162.39, d) 160.09, 136.00, 131.47 (d), 130.11 (d), 129.47, 127.88, 122.24, 116.18 (d), 114.20, 80.69, 55.25.

ESIMS: calculated for $C_{17}H_{13}FNaO_4$ ($M+Na^+$) 323.0696, found 323.0695.



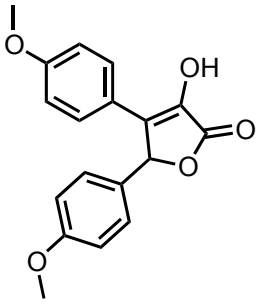
3-hydroxy-4-(4-methoxyphenyl)-5-phenylfuran-2(5H)-one (5)[2]

Yield: 55%, white solid. MP: 155.7-158.0ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.53 (d, *J* = 8.9 Hz, 2H), 7.40 - 7.32 (m, 5H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.17 (s, 1H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 170.06, 159.99, 135.96, 135.50, 129.74, 129.49, 129.09, 128.22, 128.17, 122.45, 114.13, 81.59, 55.23.

ESIMS: calculated for $C_{17}H_{14}NaO_4$ ($M+Na^+$) 305.0790, found 305.0799.



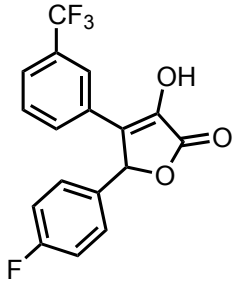
3-hydroxy-4,5-bis(4-methoxyphenyl)furan-2(5H)-one (6)[2]

Yield: 61%, yellow solid. MP: 166.6-168.1ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.54 (d, *J* = 8.9 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.14 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 170.42, 160.55, 159.90, 136.22, 129.64, 129.54, 128.34, 127.52, 122.65, 114.44, 114.06, 81.45, 55.26, 55.21.

ESIMS: calculated for $C_{18}H_{16}NaO_5$ ($M+Na^+$) 335.0895, found 335.0891.



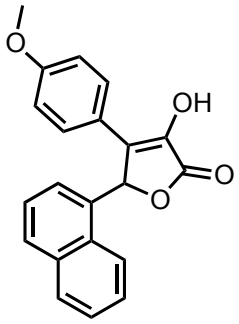
5-(4-fluorophenyl)-3-hydroxy-4-(3-(trifluoromethyl)phenyl)furan-2(5H)-one (7)

Yield: 75%, white solid. MP: 204.8-206.0ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.91 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.08 (t, *J* = 8.7 Hz, 2H), 6.24 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d): 169.39, (164.52, 162.53, d), 138.86, 131.22 (q), 130.51, 130.10, 130.03, 129.18, 125.94, 125.55 (q), 124.69, 122.52, 124.56 (q), 116.41 (d), 80.75.

ESIMS: calculated for $C_{34}H_{19}F_8Na_2O_6$ ($2M+2Na^+-H^+$) 721.0849, found 721.0842.



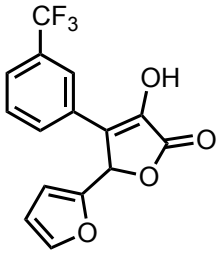
3-hydroxy-4-(4-methoxyphenyl)-5-(naphthalen-1-yl)furan-2(5H)-one (8)

Yield: 56%, white solid. MP: 206.5-208.2ºC

^{1}H NMR (300 MHz, Chloroform-d): 8.40 (d, *J* = 8.5 Hz, 1H), 8.00 - 7.85 (m, 2H), 7.75 - 7.48 (m, 4H), 7.39 - 7.22 (m, 2H), 7.05 (s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-d): 170.14, 160.03, 136.54, 133.93, 132.15, 131.15, 130.39, 129.66, 129.04, 128.02, 127.21, 126.70, 126.23, 125.34, 122.99, 122.88, 114.16, 77.33, 55.26.

ESIMS: calculated for $C_{21}H_{16}NaO_4$ ($M+Na^+$) 355.0946, found 355.0955.



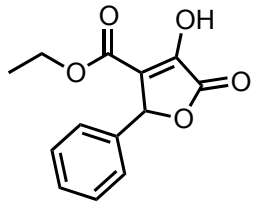
4-hydroxy-3-(3-(trifluoromethyl)phenyl)-[2,2'-bifuran]-5(2H)-one (9)

Yield: 73%, white solid. MP: 151.7-152.5ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.92 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 1.7, 0.8 Hz, 1H), 6.49 (d, *J* = 3.4 Hz, 1H), 6.38 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.33 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d): 169.61, 147.42, 144.29, 139.09, 131.16(q), 130.53, 130.25, 129.16, 125.50(q), (124.77, 122.61, d), 124.15(q), 124.03, 112.07, 110.97, 73.97.

ESIMS: calculated for $C_{15}H_9F_3NaO_4$ ($M+Na^+$) 333.0351, found 333.0347.



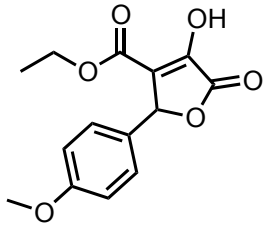
ethyl 4-hydroxy-5-oxo-2-phenyl-2,5-dihydrofuran-3-carboxylate (10)[3]

Yield: 60%, white solid. MP: 105.3-106.8ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.44 - 7.33 (m, 3H), 7.31 - 7.23 (m, 2H), 6.00 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 165.85, 164.38, 152.15, 134.26, 129.55, 128.65, 127.22, 118.76, 79.37, 61.81, 13.79.

ESIMS: calculated for $C_{13}H_{12}NaO_5$ ($M+Na^+$) 271.0582, found 271.0573.



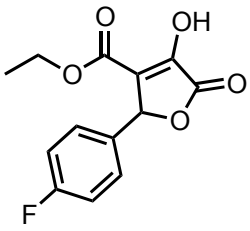
ethyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3-carboxylate (11)[3]

Yield: 66%, white solid. MP: 100.1-101.7ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.20 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.97 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 165.76, 164.45, 160.52, 152.07, 128.66, 126.06, 118.77, 114.08, 79.24, 61.84, 55.32, 13.87.

ESIMS: calculated for $C_{14}H_{14}NaO_6$ ($M+Na^+$) 301.0688, found 301.0688.



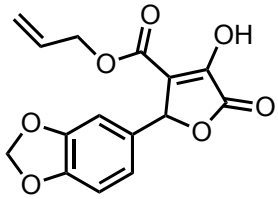
ethyl 2-(4-fluorophenyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-carboxylate (12)

Yield: 63%, white solid. MP: 123.5-124.4ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.26 (t, *J* = 8.4 Hz, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 5.98 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 165.58, 164.28, 163.35 (d), 152.45, 130.20, 129.16 (d), 126.74, 115.78 (d), 78.59, 61.89, 13.85.

ESIMS: calculated for $C_{13}H_{11}FNaO_5$ ($M+Na^+$) 289.0488, found 289.0491.



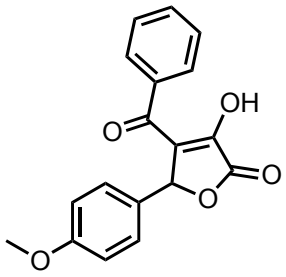
allyl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-carboxylate (13)

Yield: 58%, yellow oil.

^{1}H NMR (500 MHz, Chloroform-d): 6.85 - 6.77 (m, 2H), 6.69 (d, *J* = 1.7 Hz, 1H), 5.99 (s, 2H), 5.94 (s, 1H), 5.78 (ddt, *J* = 17.1, 10.3, 5.6 Hz, 1H), 5.21 (dd, *J* = 10.3, 1.2 Hz, 1H), 5.14 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.67 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d): 165.51, 163.99, 152.39, 148.78, 148.08, 130.44, 127.68, 121.88, 119.25, 118.19, 108.37, 107.13, 101.49, 79.31, 66.02.

ESIMS: calculated for $C_{15}H_{12}NaO_7$ ($M+Na^+$) 327.0481, found 327.0487.



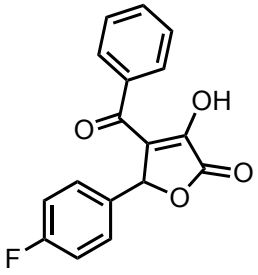
4-benzoyl-3-hydroxy-5-(4-methoxyphenyl)furan-2(5*H*)-one (14)[4]

Yield: 73%, white solid. MP: 200.6-202.0ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.70 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.57 - 7.48 (m, 1H), 7.39 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, cdcl$_3$): 190.98, 166.86, 160.56, 152.23, 136.07, 133.71, 129.07, 128.61, 128.58, 125.99, 123.47, 114.33, 81.17, 55.24.

ESIMS: calculated for $C_{18}H_{14}NaO_5$ ($M+Na^+$) 333.0739, found 333.0740.



4-benzoyl-5-(4-fluorophenyl)-3-hydroxyfuran-2(5*H*)-one (15)[5]

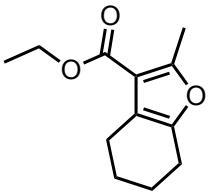
Yield: 70%, white solid. MP: 204.0-205.3ºC

^{1}H NMR (500 MHz, Chloroform-d): 7.71 - 7.67 (m, 2H), 7.57 - 7.51 (m, 1H), 7.41 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.26 - 7.21 (m, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 6.46 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d): 190.72, 166.84, (164.28, 162.29, d), 151.18, 136.08, 133.84, 129.77 (d), 129.45, 128.66, 128.53, 123.68 (d), 116.06 (d), 80.53.

ESIMS: calculated for $C_{17}H_{11}FNaO_4$ ($M+Na^+$) 321.0539, found 321.0546.

17a is a known compound, the spectroscopic data matches literature.[6]



ethyl 2-methyl-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (17b)

The reaction was done with 200mg of ketone. Yield: 36%, yellow oil.

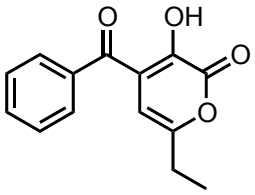
^{1}H NMR (500 MHz, Chloroform-d): 4.26 (q, *J* = 7.1 Hz, 2H), 2.58 (tt, *J* = 6.0, 2.0 Hz, 2H), 2.55 - 2.48 (m, 5H, tt & s overlap), 1.84 - 1.75 (m, 2H), 1.73 - 1.65 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 165.01, 157.51, 149.07, 117.30, 112.79, 59.62, 22.87, 22.82, 22.70, 22.26, 14.35, 13.96.

ESIMS: calculated for $C_{12}H_{16}NaO_3$ ($M+Na^+$) 231.0997, found 231.0991.

Structure was assigned based on HSQC and HMBC spectra. The assignment can be found along with the HSQC & HMBC spectra in this SI.

This is a known compound, no spectra were reported in the literature.[7]



4-benzoyl-6-ethyl-3-hydroxy-2*H*-pyran-2-one (19)

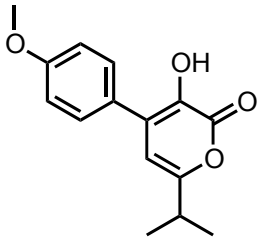
Yield: 49%, yellow oil.

^{1}H NMR (500 MHz, Chloroform-d): 7.89 - 7.83 (m, 2H), 7.74 - 7.66 (m, 1H), 7.57 (m, 2H), 6.45 (t, *J* = 0.9 Hz, 1H), 2.80 (q, *J* = 7.6, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): 194.46, 161.94, 157.21, 146.37, 136.74, 134.19, 129.60, 128.82, 127.38, 109.35, 21.39, 11.63.

LC-ESIMS: calculated for $C_{14}H_{13}O_4$ ($M+H^+$) 245.0814, found 245.0816.

Assignment based on HMBC is included.



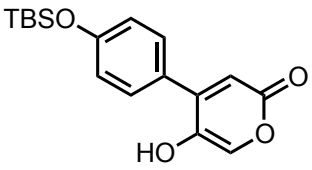
3-hydroxy-6-isopropyl-4-(4-methoxyphenyl)-2*H*-pyran-2-one (21)

Yield: 38%, yellow oil.

^{1}H NMR (300 MHz, Chloroform-d): 7.56 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.23 (s, 1H), 3.83 (s, 3H), 3.13 - 2.97 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-d): 165.84, 163.29, 159.56, 130.65, 128.90, 124.38, 114.07, 113.43, 108.59, 55.27, 28.10, 20.86.

ESIMS: calculated for $C_{15}H_{16}O_4$ ($M+H^+$) 261.1127, found 261.1144.



4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5-hydroxy-2*H*-pyran-2-one (24)

The reaction was done with 8 eq. of SeO_2. Yield: 13%, light yellow oil.

^{1}H NMR (500 MHz, Chloroform-d): 7.60 (d, *J* = 1.7 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 1.7 Hz, 1H), 1.00 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-d): 162.65, 156.14, 145.88, 137.50, 136.50, 130.68, 124.09, 119.67, 114.74, 25.63, 18.19, -4.38.

LC-ESIMS: calculated for $C_{17}H_{23}O_4Si$ ($M+H^+$) 319.1366, found 319.1343.

Assignment based on HSQC and HMBC is included.

Notes and references

1. Starting materials for **4-9** and ketone **20** were synthesized using conventional piperidine-catalyzed aldol reaction.
   (a) Ramachandran, S. and M. S. Newman, *Org. Synth., Coll. Vol. 5*, 1973, 486–489. (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc*, 1952, **74**, 4223–4251.
   Starting materials for **10-15** and ketone **18** were synthesized according to:
   G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti and A. Tolomelli, *Synthetic Commun.*, 2003, **33**, 1587–1594.
   Ketones **16a** and **16b** were synthesized according to:
   D. I. Magee, S. Ratshonka, J. McConaghy and M. Hood, *Can. J. Chem.*, 2012, **90**, 450–463.

2. (a) P. Cordier, *Bull. Soc. Chim. Fr.*, 1953, C37–C40. (b) P. Cagniant, *Ann. Chim.* (Paris), 1952, **7**, 457–470.

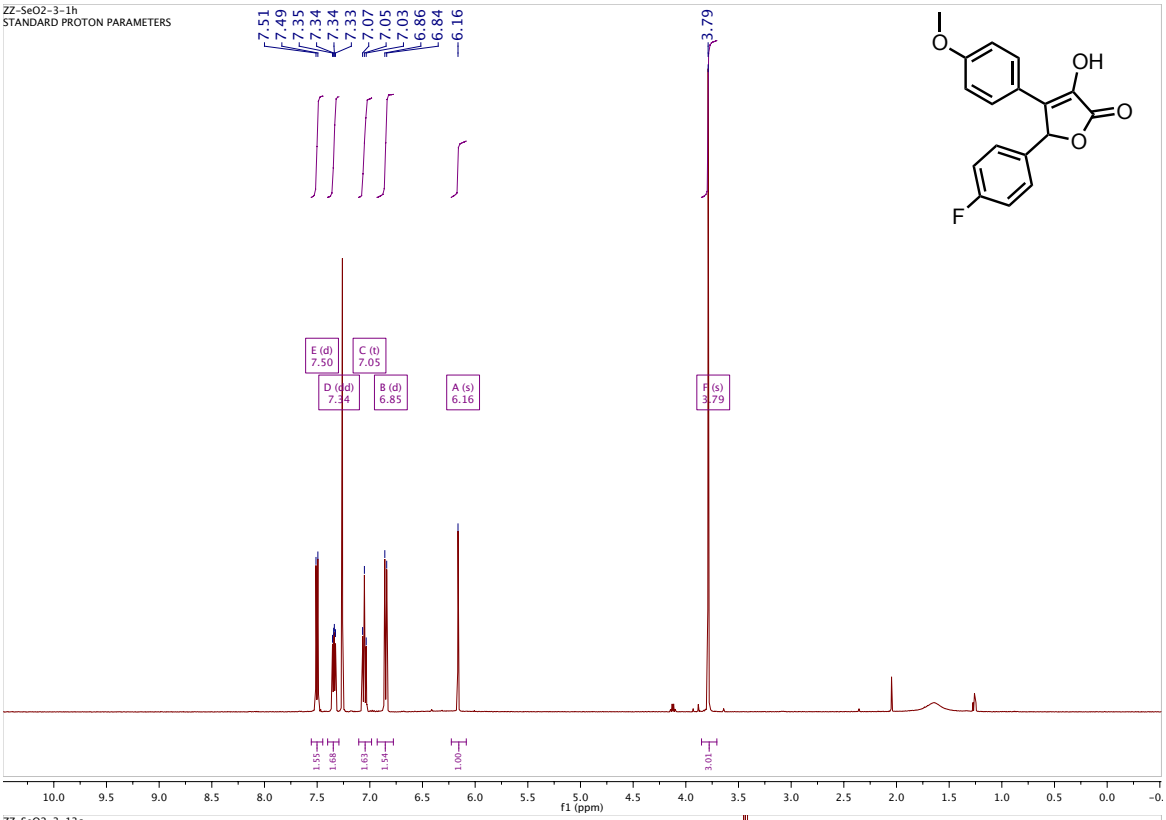
3. (a) R. Dede, L. Michaelis and P. Langer, *Tetrahedron Lett.*, 2005, **46**, 8129–8131. (b) R. Dede, L. Michaelis, D. Fuentes, M. A. Yawer, I. Hussain, C. Fischer and P. Langer, *Tetrahedron*, 2007, **63**, 12547–12561.

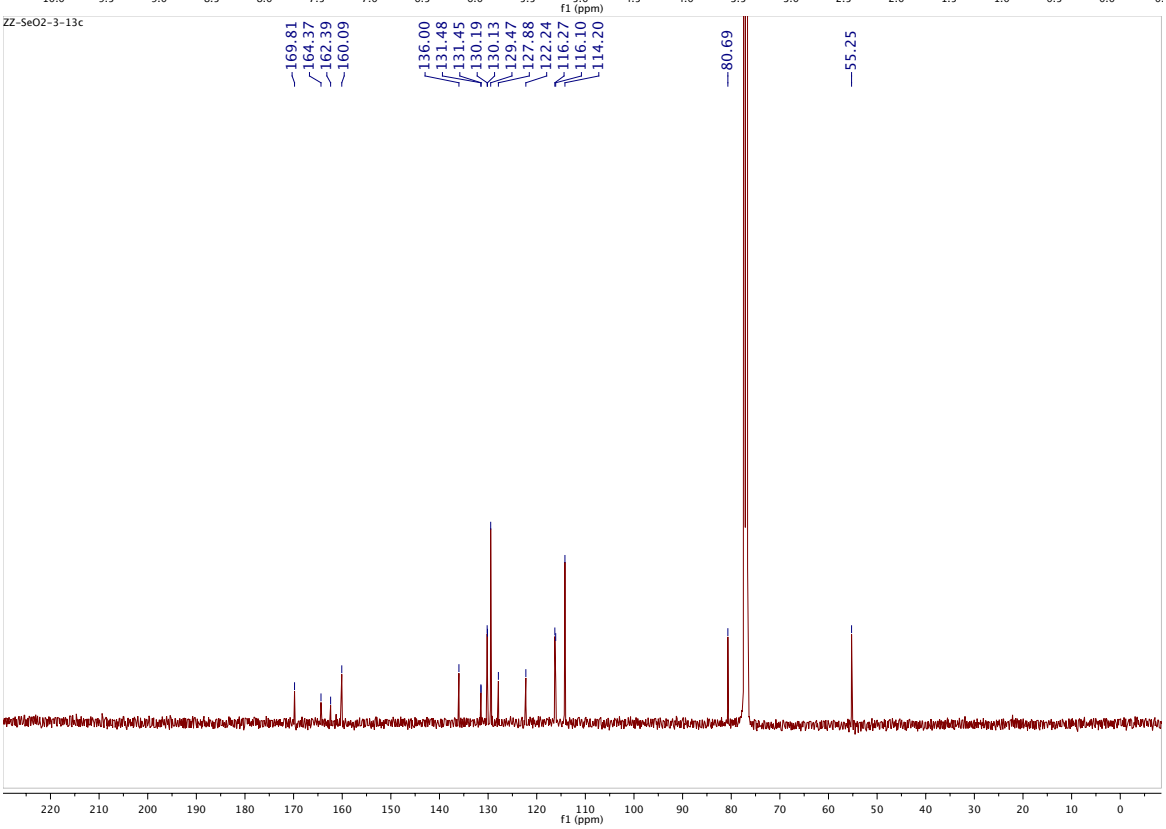
4. T. Kurihara, Y. Sakamoto, T. Kobayashi and M. Mori, *J. Het. Chem.*, 1978, **15**, 737–743. No spectroscopic data was reported.

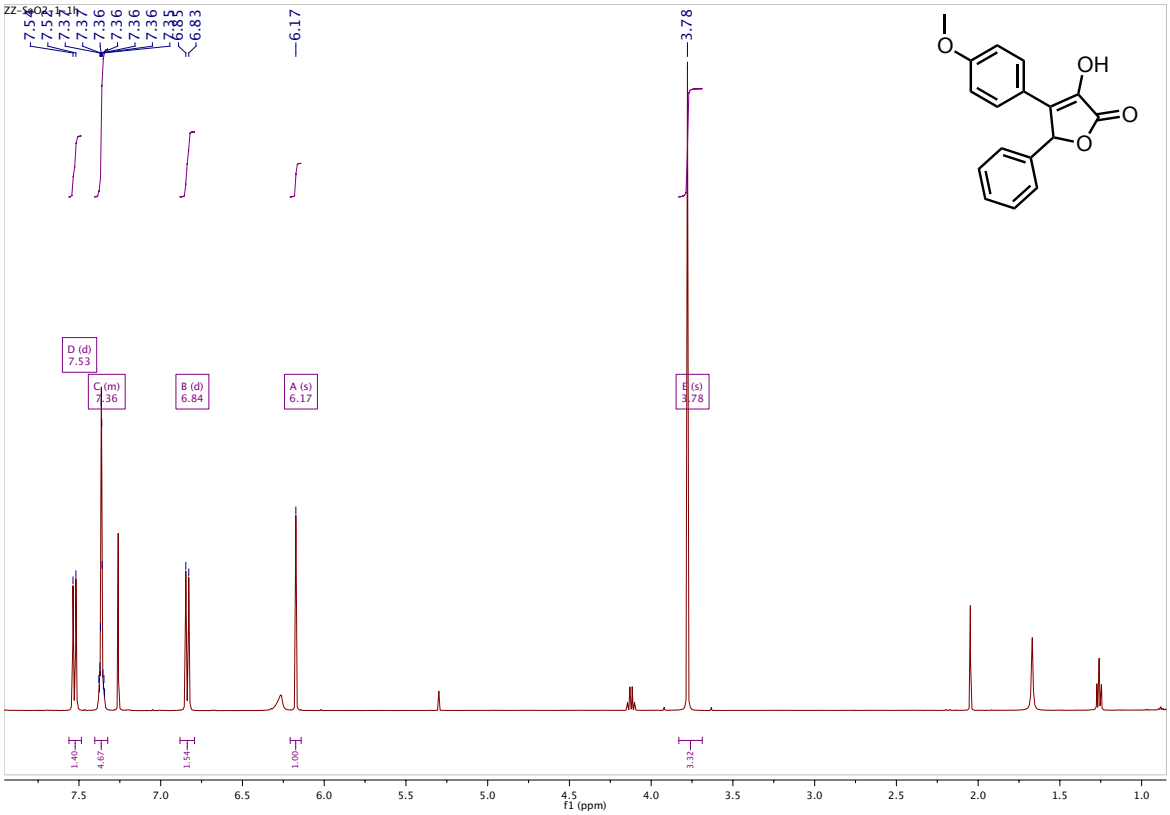
5. V. L. Gein, L. F. Gein, E. N. Bezmaternykh and E. V. Voronina, *Pharm. Chem. J.*, 2000, **34**, 254–256.

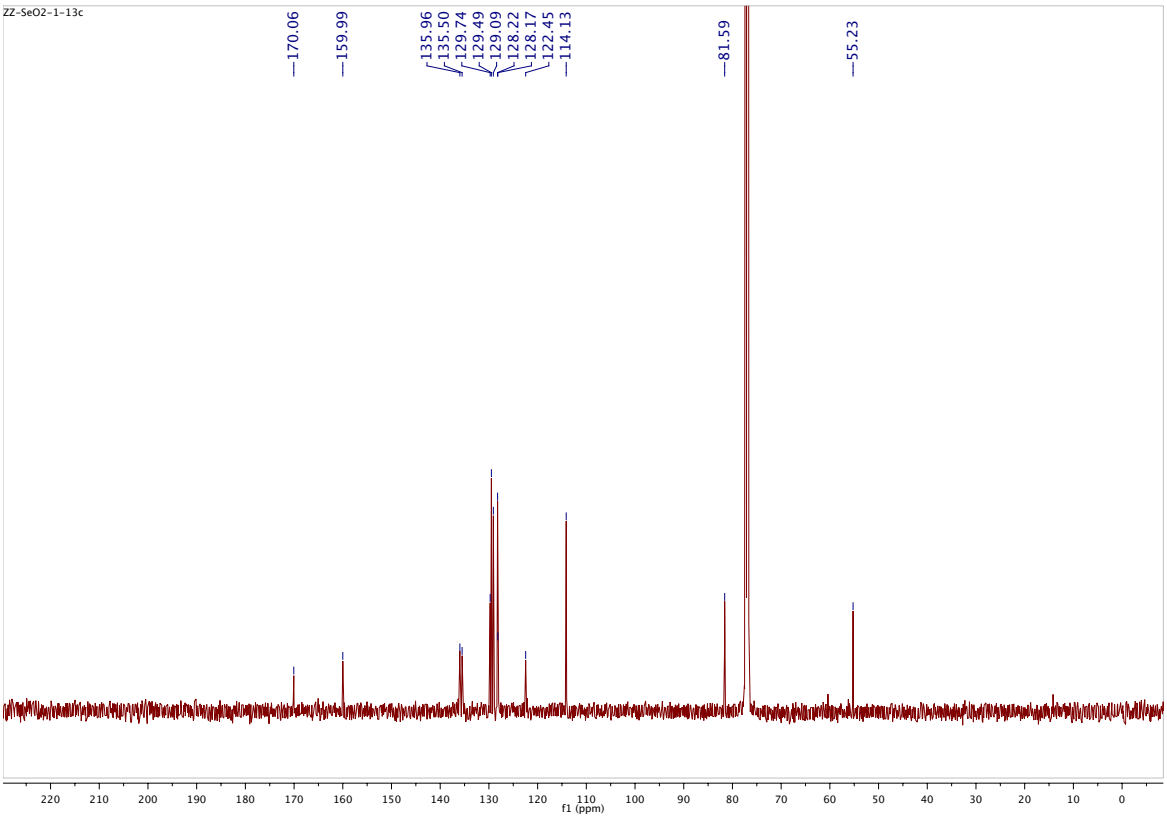
6. A. O. Chagarovsky, E. M. Budynina, O. A. Ivanova, E. V. Villemson, V. B. Rybakov, I. V. Trushkov and M. Y. Melnikov, *Org. Lett.*, 2014, **16**, 2830–2833.

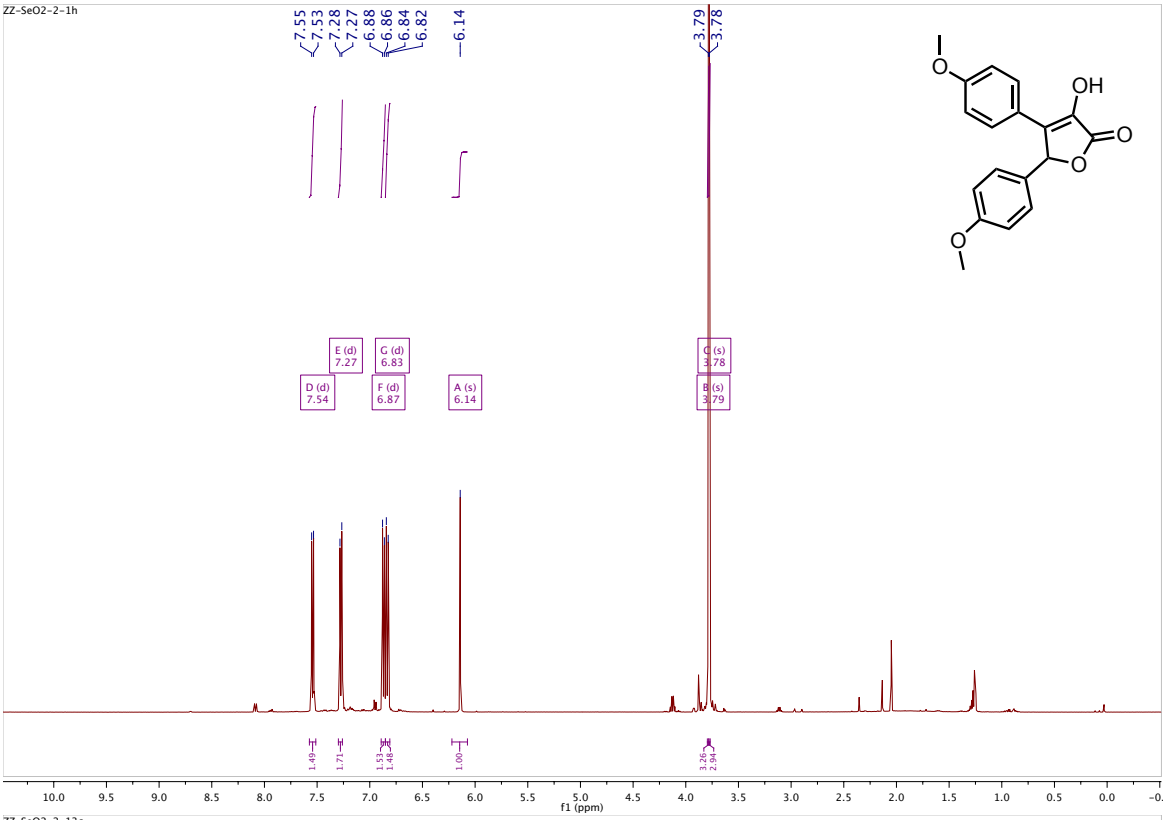
7. E. J. Corey and A. K. Ghosh, *Chem. Lett.*, 1987, 223–226. No spectroscopic data was reported.

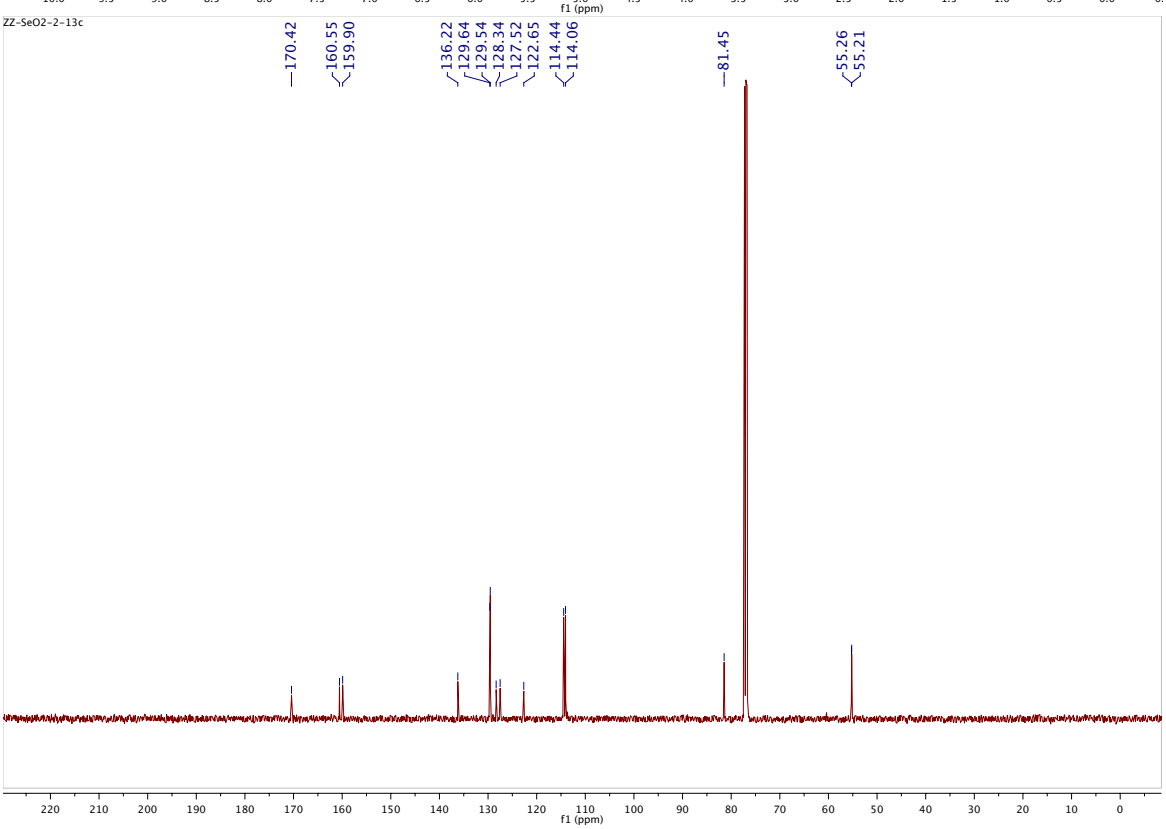

ZZ-SeO2-3-1h
STANDARD PROTON PARAMETERS
7.51
7.49
7.35
7.34
7.34
7.33
7.07
7.05
7.03
6.86
6.84
6.16
3.79
O
OH
O
O
F
E (d) 7.50
C (t) 7.05
D (dd) 7.24
B (d) 6.85
A (s) 6.16
F (s) 3.79
1.55
1.68
1.63
1.54
1.00
3.01
f1 (ppm)

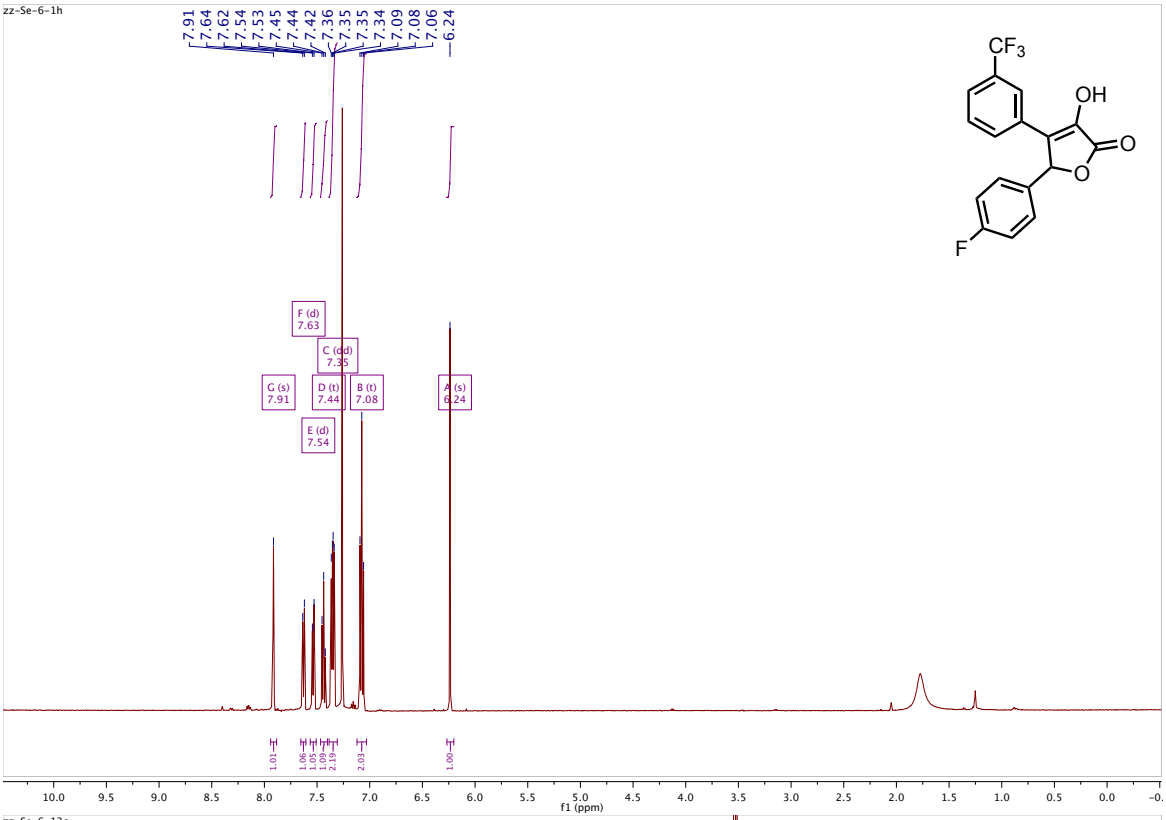

ZZ-SeO2-3-13c
169.81
164.37
162.39
160.09
136.00
131.48
131.45
130.19
130.13
129.47
127.88
122.24
116.27
116.10
114.20
80.69
55.25
f1 (ppm)

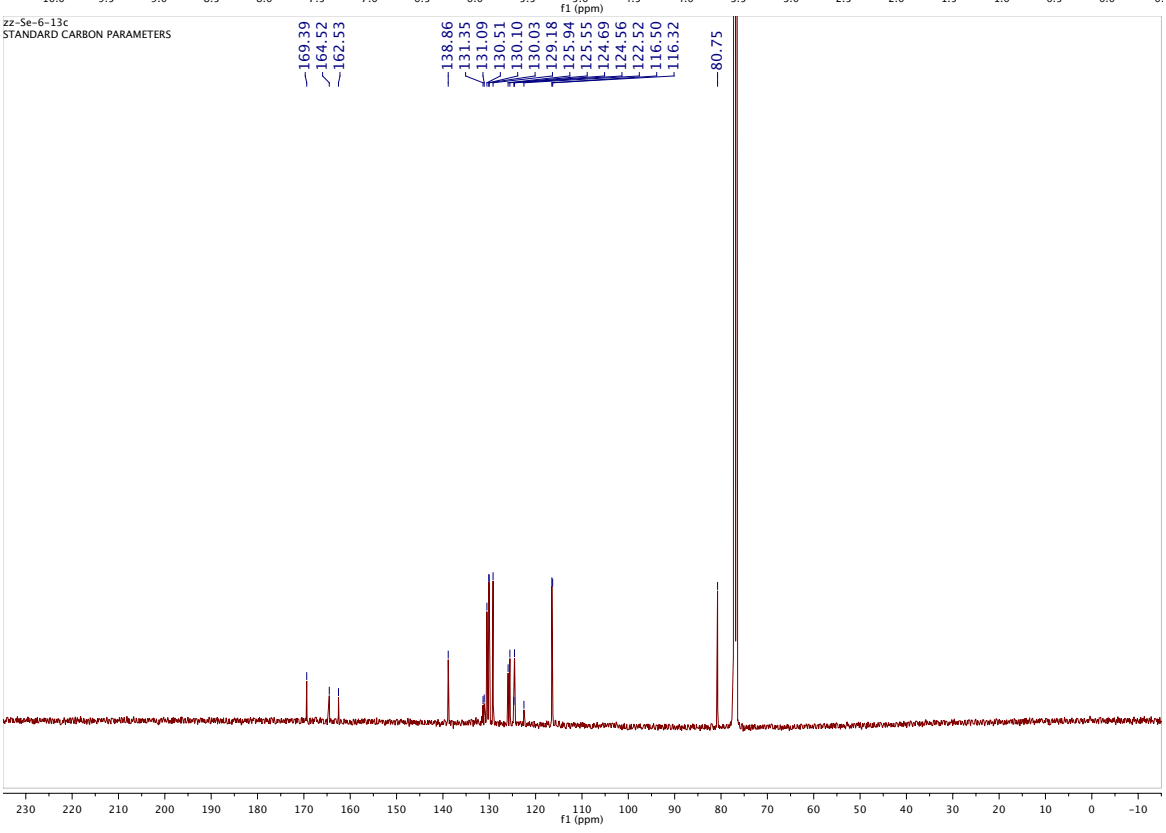

ZZ-SeO2-1-1H
7.53
7.52
7.37
7.36
6.84
6.83
6.17
3.78
OH
O
D (d) 7.53
C (m) 7.36
B (d) 6.84
A (s) 6.17
E (s) 3.78
1.40
4.67
1.54
1.00
3.32
f1 (ppm)

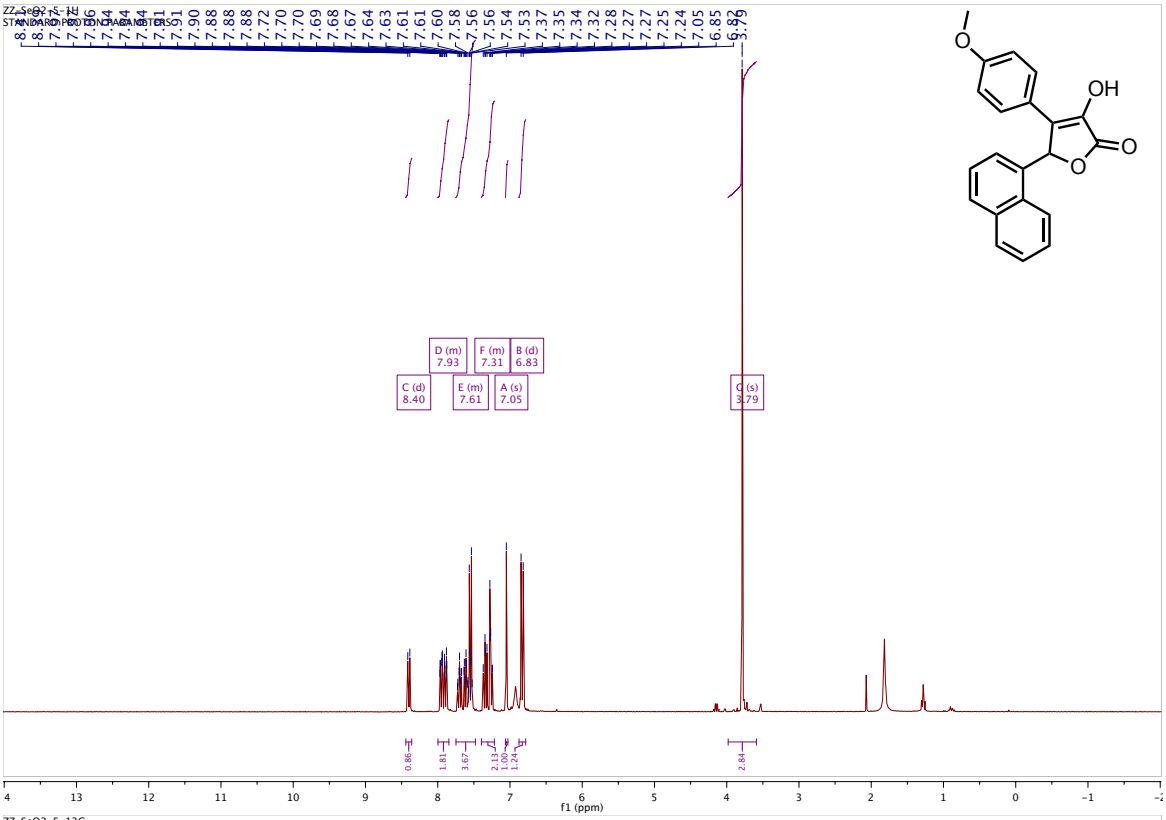

ZZ-SeO2-1-13c
170.06
159.99
135.96
135.50
129.74
129.49
129.09
128.22
128.17
122.45
114.13
81.59
55.23
f1 (ppm)

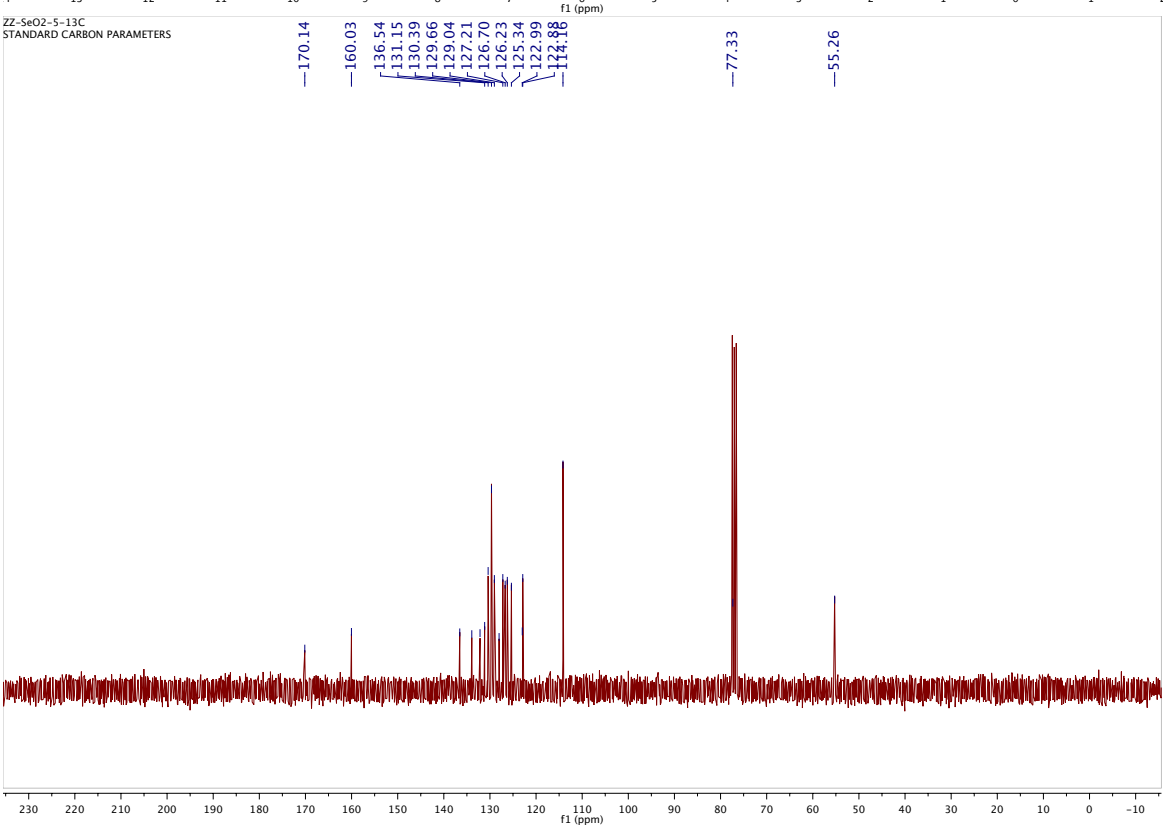

ZZ-SeO2-2-1h
7.55
7.53
7.28
7.27
6.88
6.86
6.84
6.82
6.14
3.79
3.78
OH
O
O
O
O
E (d) 7.27
G (d) 6.83
C (s) 3.78
D (d) 7.54
F (d) 6.87
A (s) 6.14
B (s) 3.79
1.49
1.71
1.53
1.48
1.00
3.26
2.94
f1 (ppm)

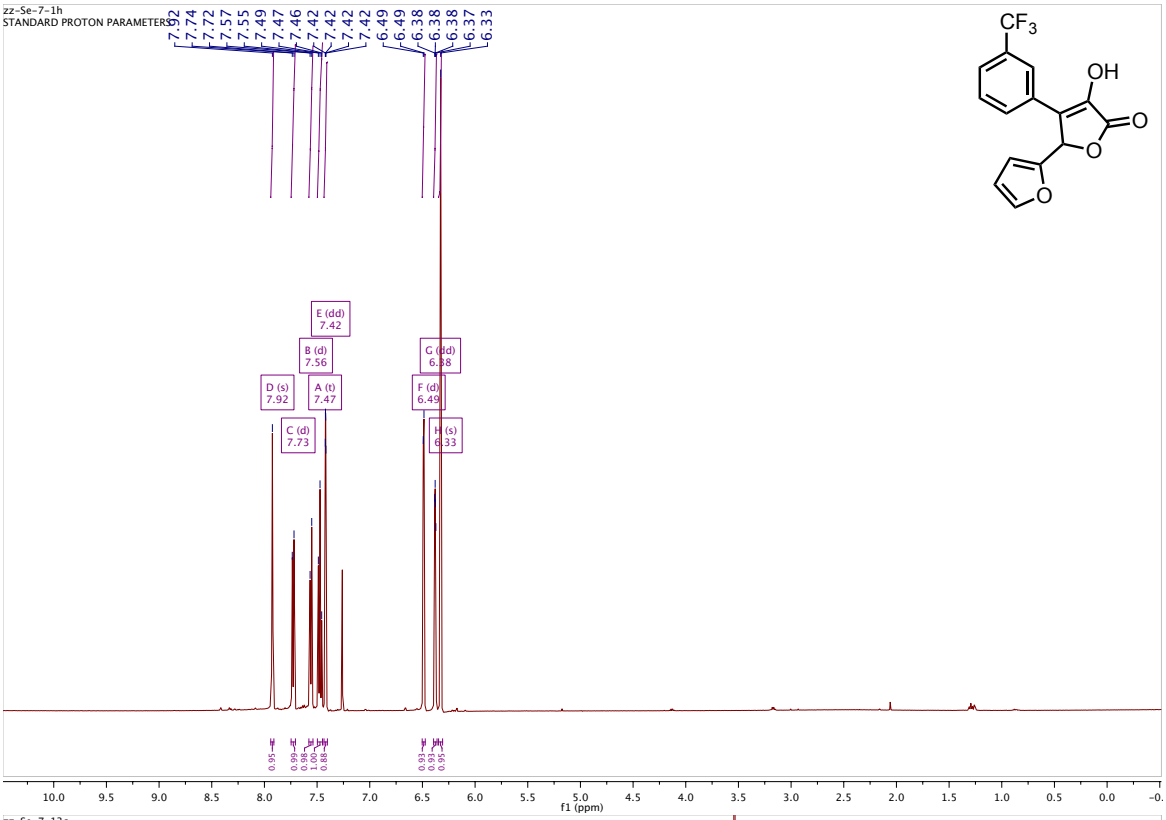

ZZ-SeO2-2-13c
170.42
160.55
159.90
136.22
129.64
129.54
128.34
127.52
122.65
114.44
114.06
81.45
55.26
55.21
f1 (ppm)

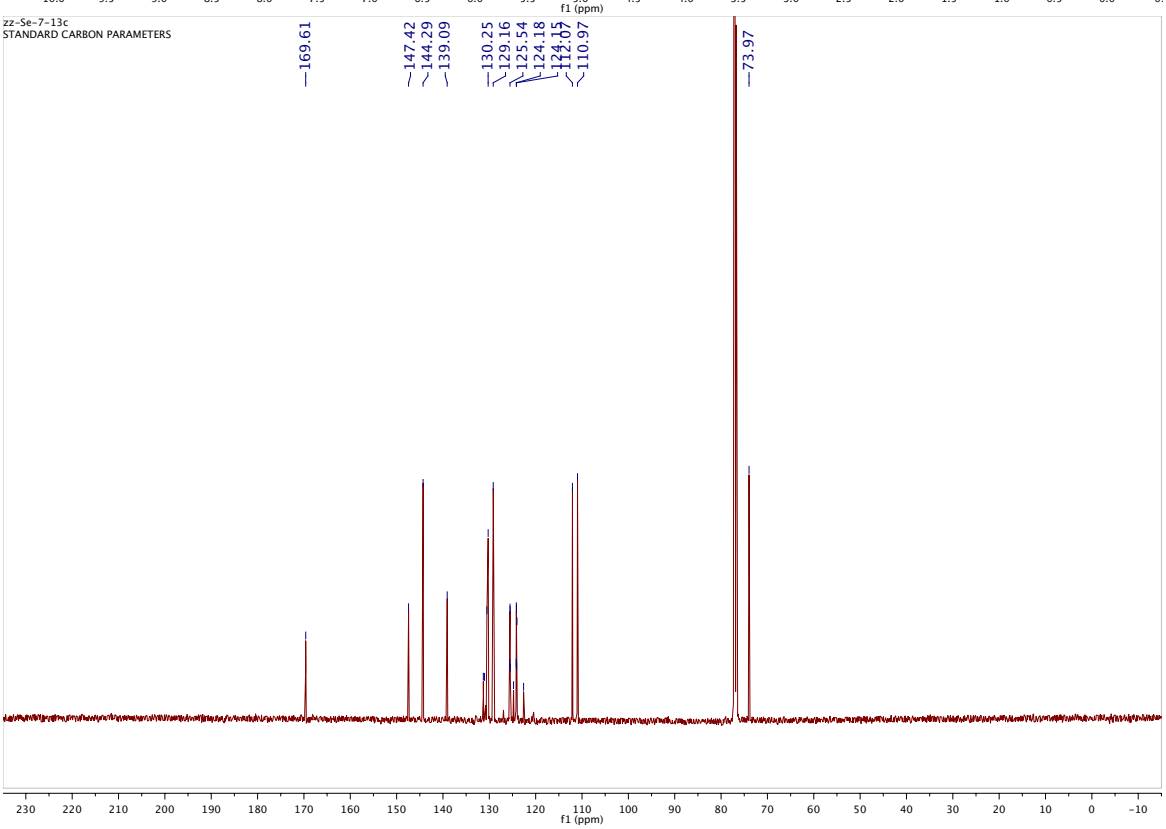

zz-Se-6-1h
7.91
7.64
7.62
7.54
7.53
7.45
7.44
7.42
7.36
7.35
7.35
7.34
7.09
7.08
7.06
6.24
CF3
OH
O
O
F
F (d) 7.63
C (dd) 7.35
G (s) 7.91
D (t) 7.44
B (t) 7.08
A (s) 6.24
E (d) 7.54
1.01
1.06
1.05
1.09
2.19
2.03
1.00
f1 (ppm)

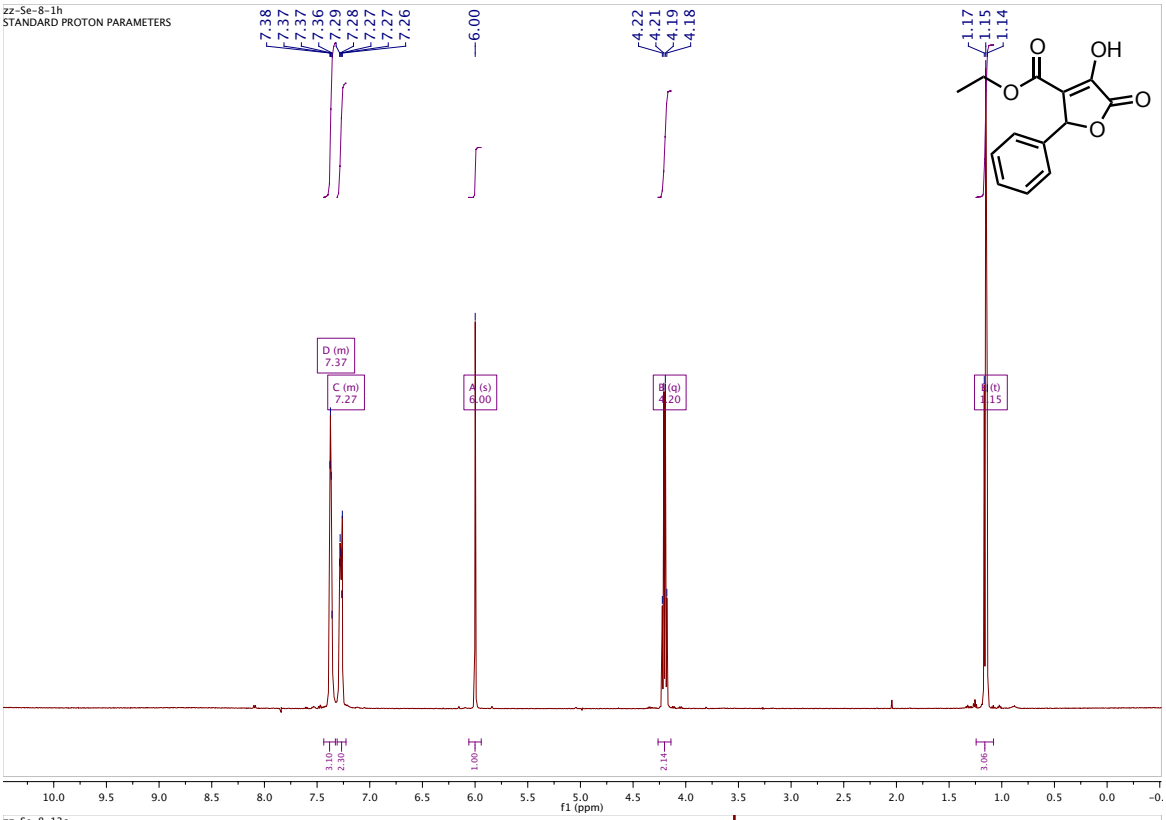

zz-Se-6-13c
STANDARD CARBON PARAMETERS
169.39
164.52
162.53
138.86
131.35
131.09
130.51
130.10
130.03
129.18
125.94
125.55
124.69
124.56
122.52
116.50
116.32
80.75
f1 (ppm)

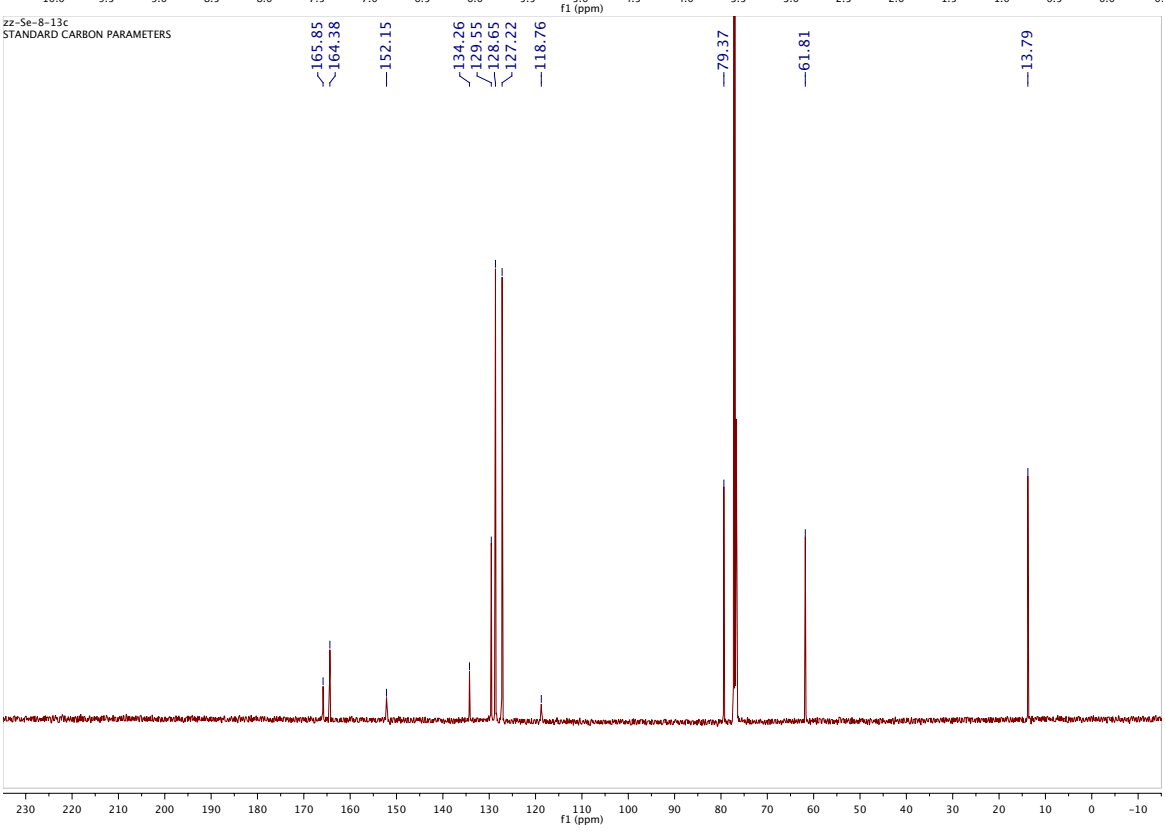

ZZ-SeO2-5-1H
STANDARD PROTON PARAMETERS
D (m) 7.93
F (m) 7.31
B (d) 6.83
C (d) 8.40
E (m) 7.61
A (s) 7.05
G (s) 3.79
f1 (ppm)

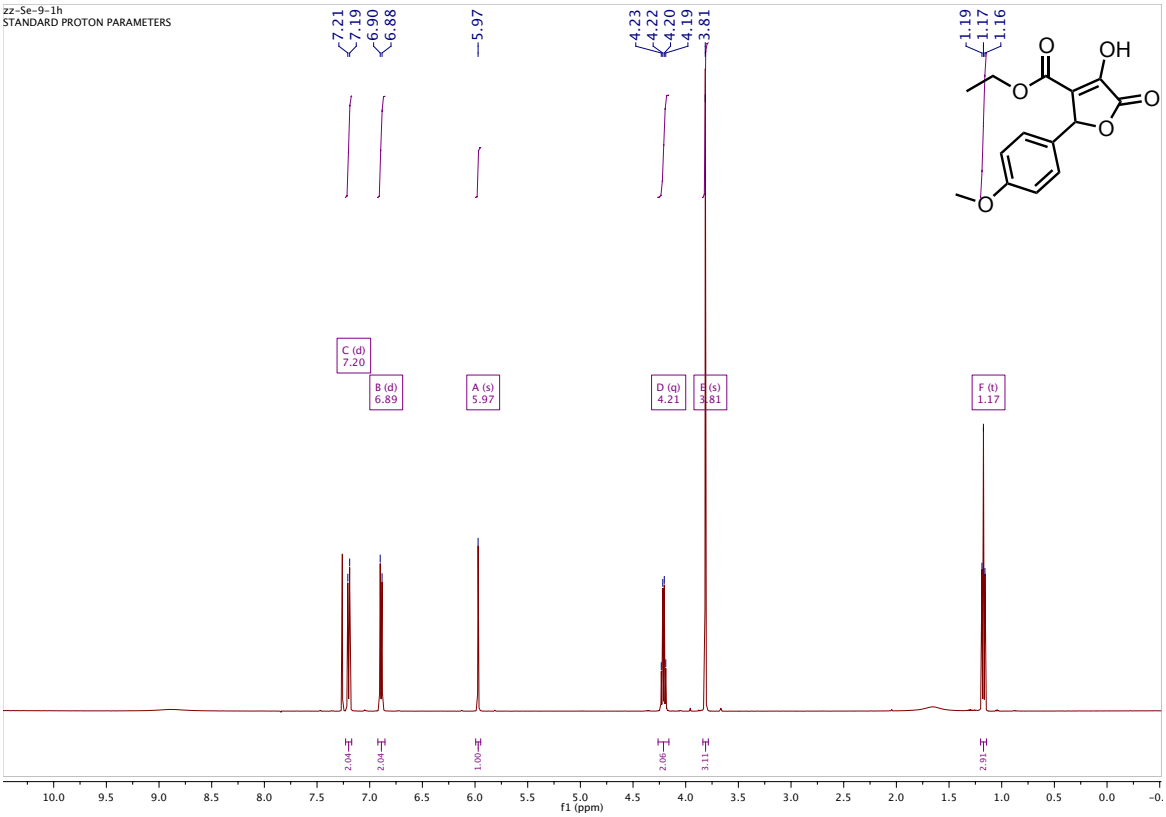

ZZ-SeO2-5-13C
STANDARD CARBON PARAMETERS
170.14
160.03
136.54
131.15
130.39
129.66
129.04
127.21
126.70
126.23
125.34
122.99
77.33
55.26
f1 (ppm)

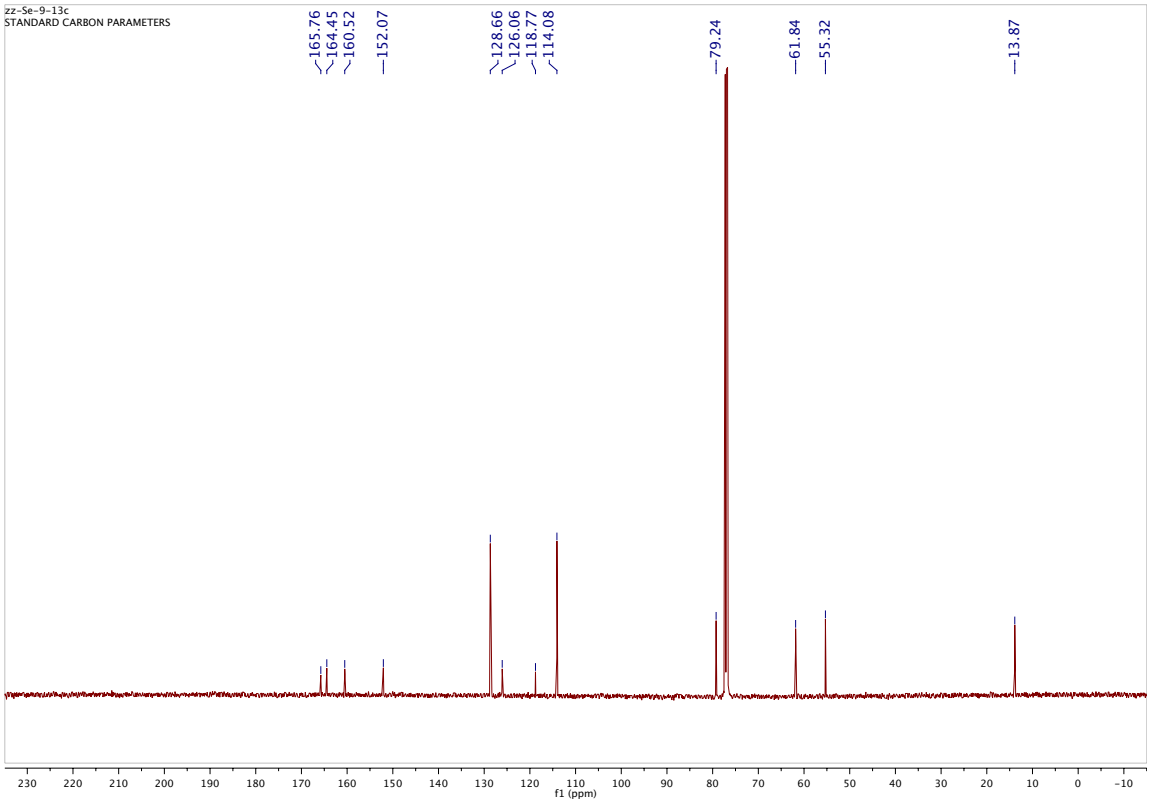

zz-Se-7-1h
STANDARD PROTON PARAMETERS
7.92
7.74
7.72
7.57
7.55
7.49
7.47
7.46
7.42
7.42
7.42
7.42
6.49
6.49
6.38
6.38
6.38
6.37
6.33
CF3
OH
O
O
O
E (dd)
7.42
B (d)
7.56
G (dd)
6.38
D (s)
7.92
A (t)
7.47
F (d)
6.49
C (d)
7.73
H (s)
6.33
0.95
0.99
0.98
0.94
0.88
0.93
0.93
0.95
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

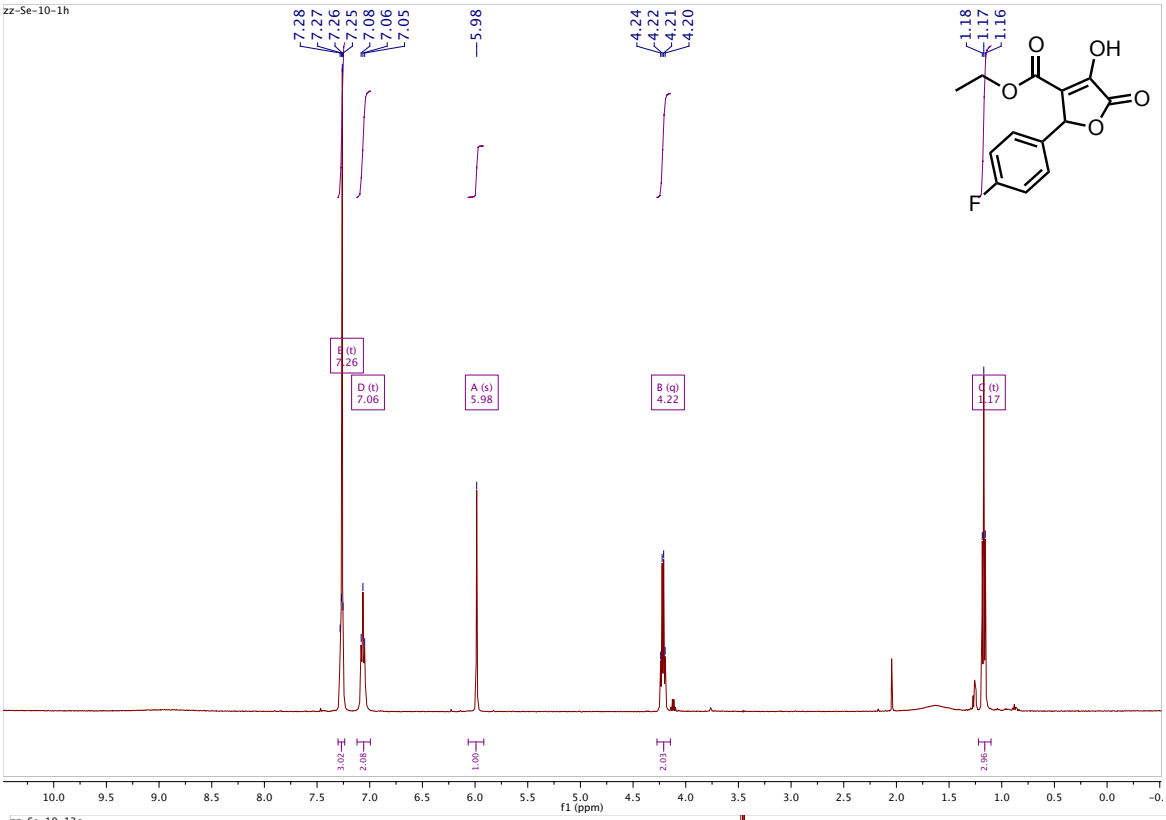

zz-Se-7-13c
STANDARD CARBON PARAMETERS
169.61
147.42
144.29
139.09
130.25
129.16
125.54
124.18
112.07
110.97
73.97
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

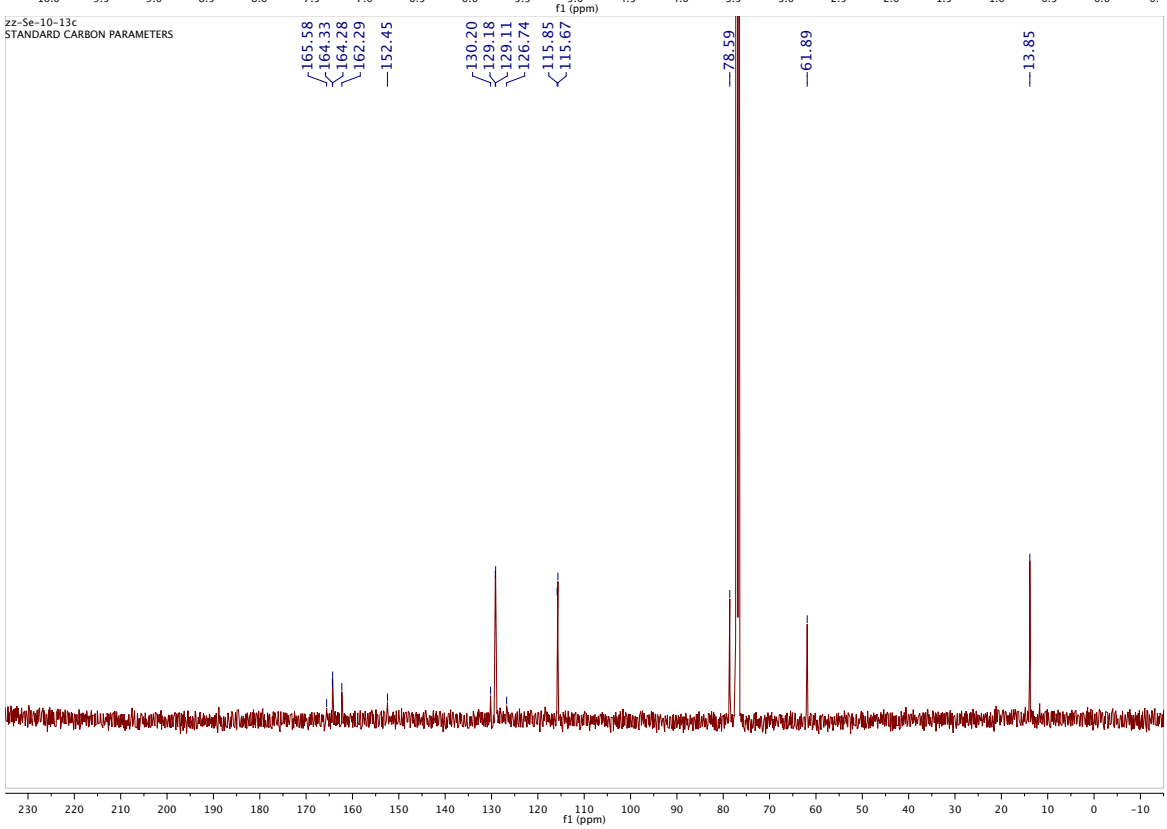

zz-Se-8-1h
STANDARD PROTON PARAMETERS
7.38
7.37
7.37
7.36
7.29
7.28
7.27
7.27
7.26
6.00
4.22
4.21
4.19
4.18
1.17
1.15
1.14
OH
O
O
O
O
D (m)
7.37
C (m)
7.27
A (s)
6.00
B (q)
4.20
E (t)
1.15
3.10
2.10
1.00
2.14
3.06
f1 (ppm)

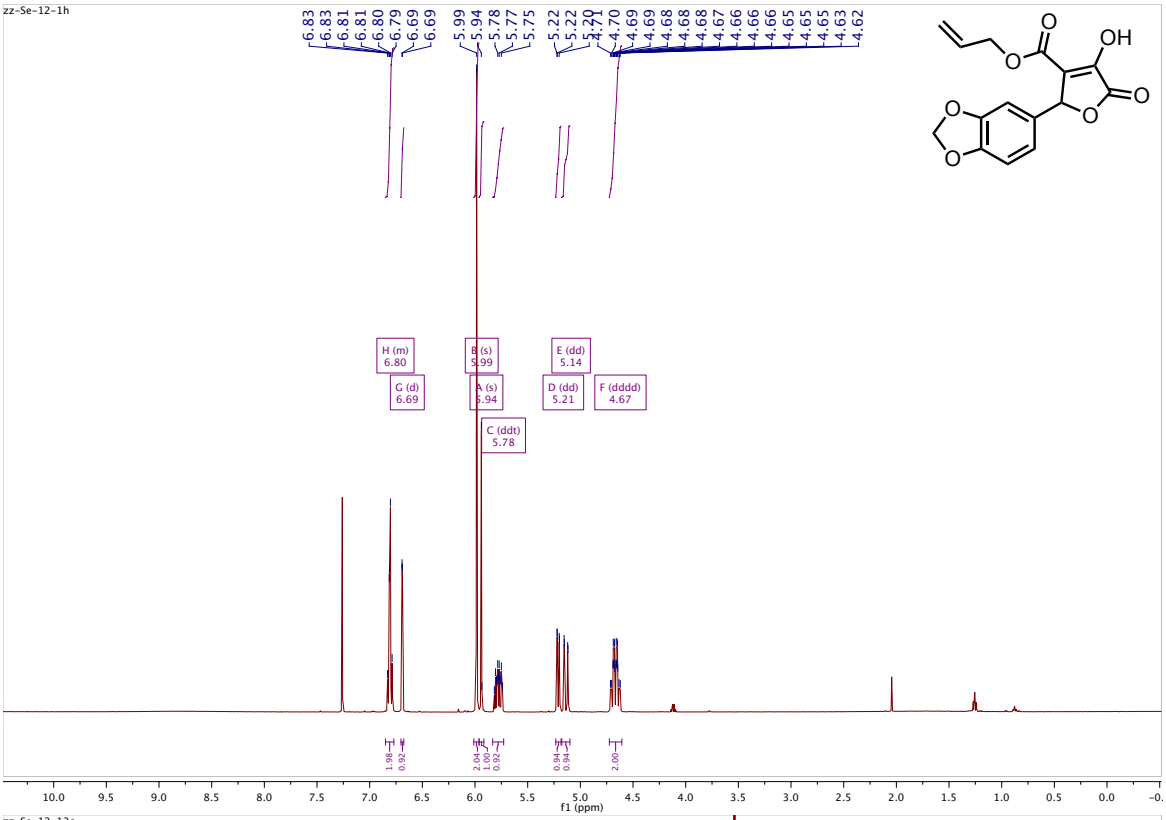

zz-Se-8-13c
STANDARD CARBON PARAMETERS
165.85
164.38
152.15
134.26
129.55
128.65
127.22
118.76
79.37
61.81
13.79
f1 (ppm)

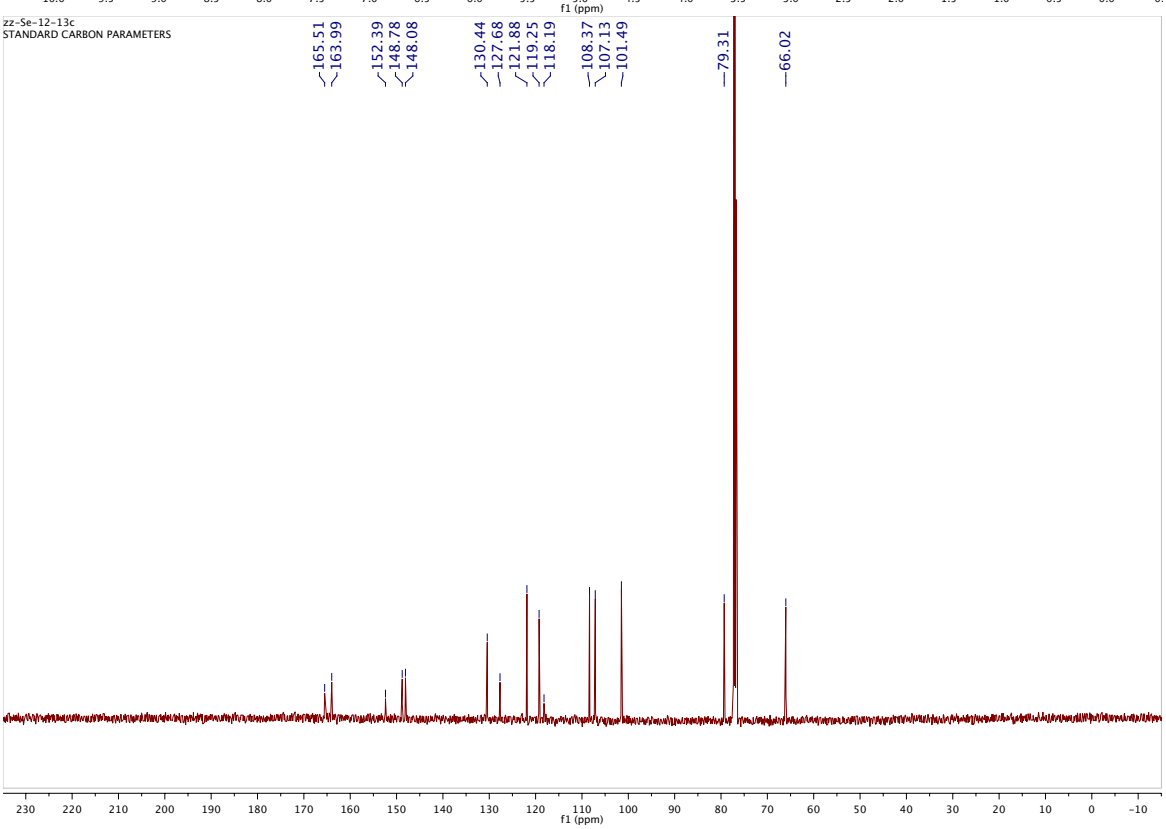

zz-Se-9-1h
STANDARD PROTON PARAMETERS
7.21
7.19
6.90
6.88
5.97
4.23
4.22
4.20
4.19
3.81
1.19
1.17
1.16
OH
O
C (d)
7.20
B (d)
6.89
A (s)
5.97
D (q)
4.21
E (s)
3.81
F (t)
1.17
2.04
2.04
1.00
2.06
3.11
2.91
f1 (ppm)

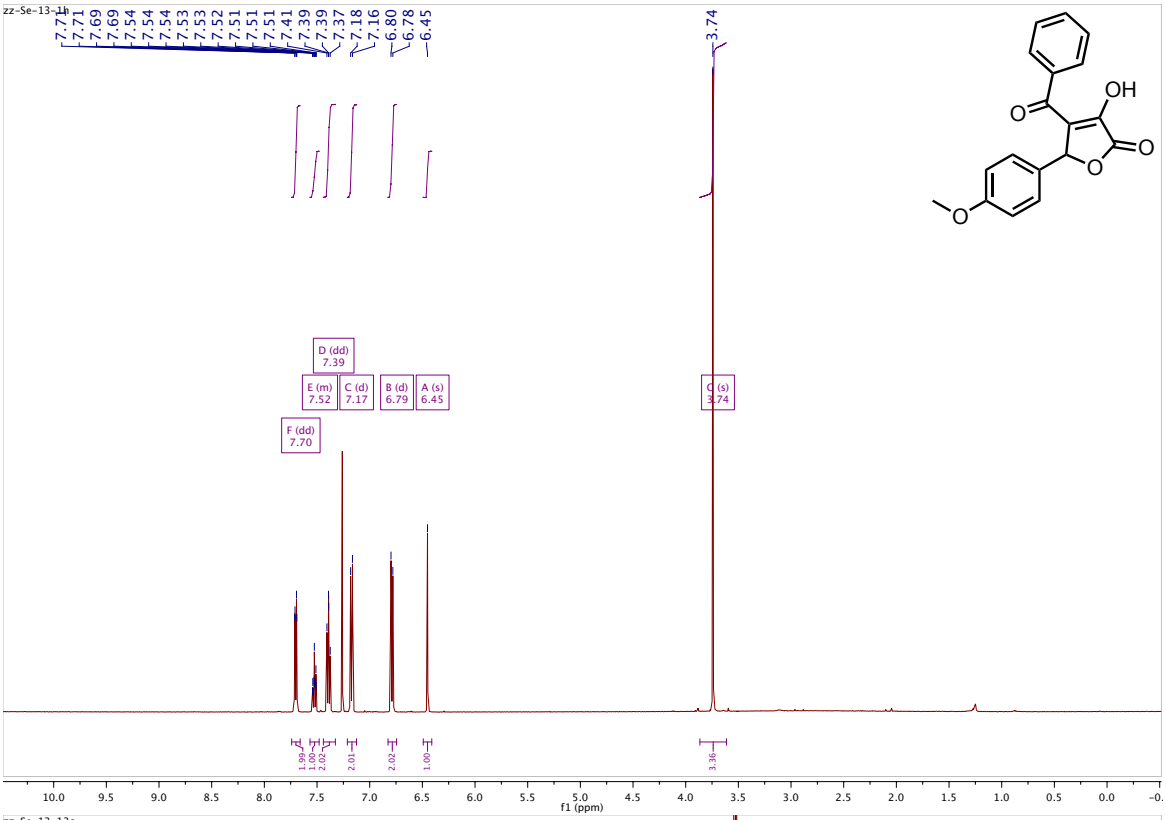

zz-Se-9-13c
STANDARD CARBON PARAMETERS
165.76
164.45
160.52
152.07
128.66
126.06
118.77
114.08
79.24
61.84
55.32
13.87
f1 (ppm)

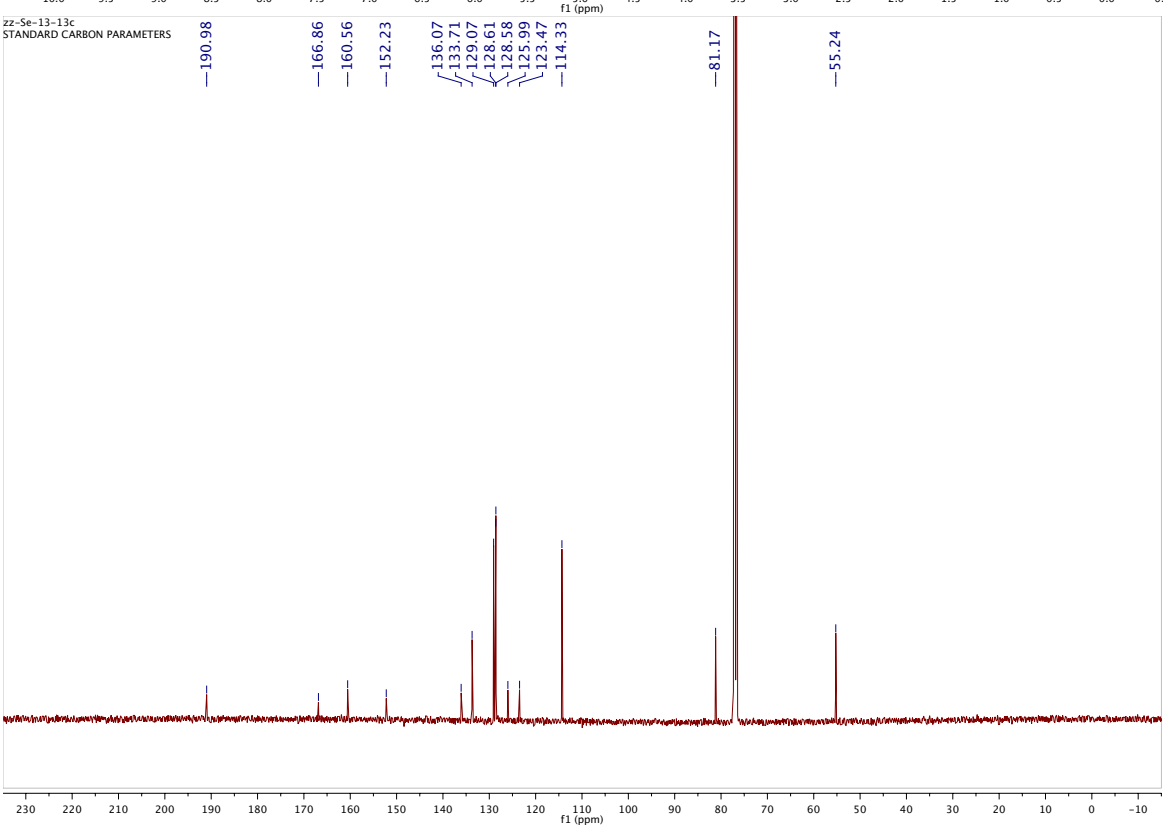

zz-Se-10-1h
7.28
7.27
7.26
7.25
7.08
7.06
7.05
5.98
4.24
4.22
4.21
4.20
1.18
1.17
1.16
OH
O
O
O
O
F
B (t)
7.26
D (t)
7.06
A (s)
5.98
B (q)
4.22
C (t)
1.17
3.02
2.08
1.00
2.03
2.96
f1 (ppm)

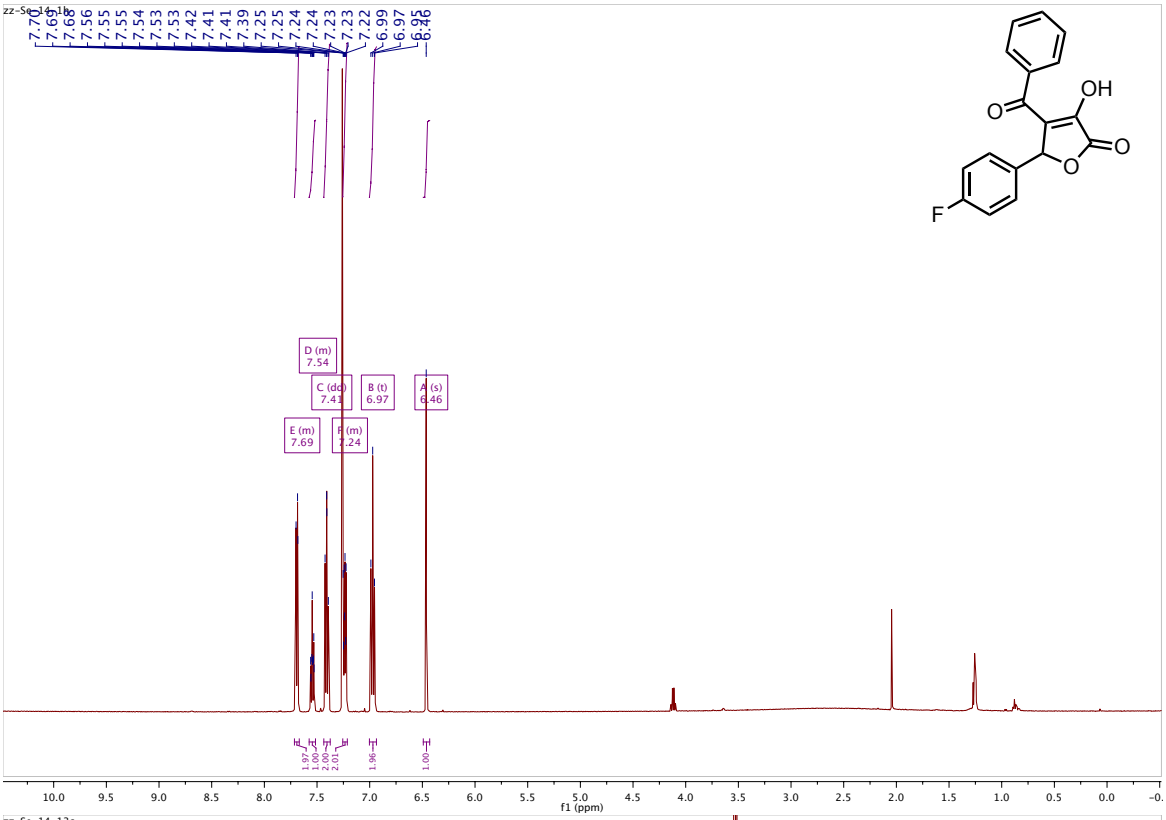

zz-Se-10-13c
STANDARD CARBON PARAMETERS
165.58
164.33
164.28
162.29
152.45
130.20
129.18
129.11
126.74
115.85
115.67
78.59
61.89
13.85
f1 (ppm)

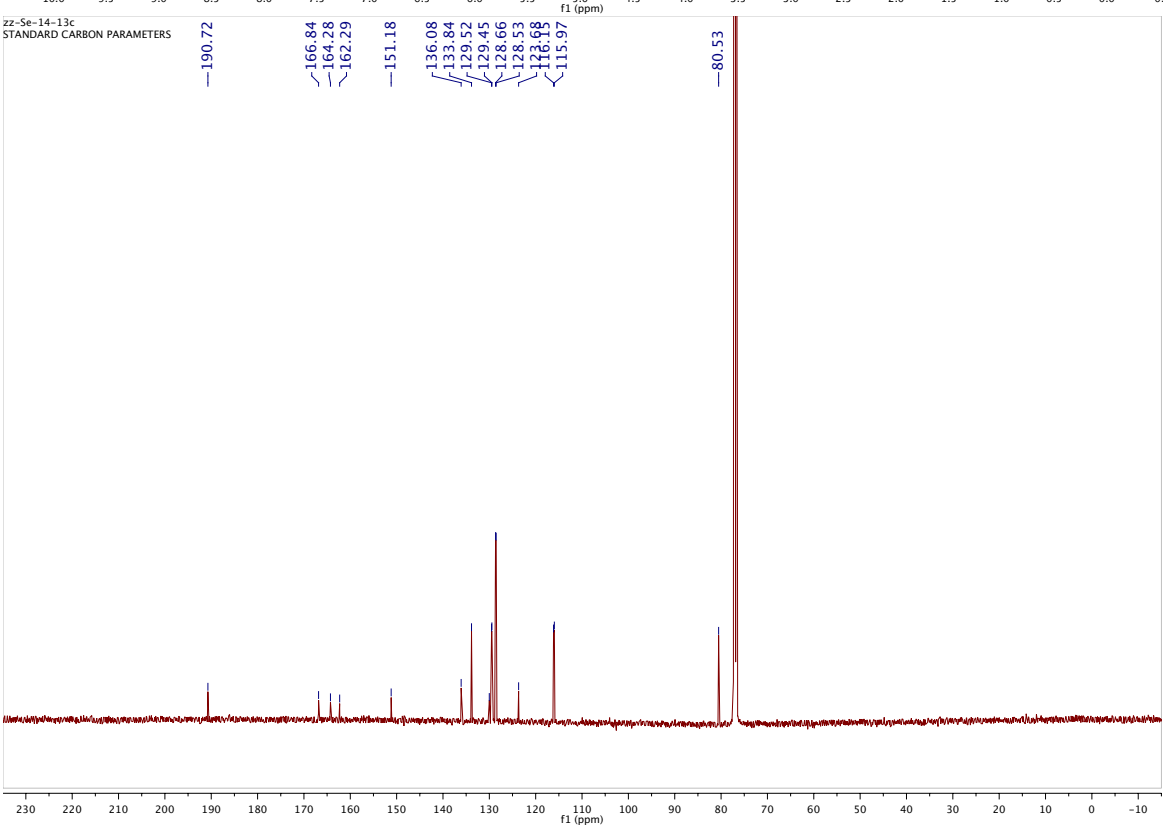

zz-Se-12-1h
6.83
6.83
6.81
6.81
6.80
6.79
6.69
6.69
5.99
5.94
5.78
5.77
5.75
5.22
5.22
5.20
4.71
4.70
4.69
4.69
4.68
4.68
4.68
4.67
4.66
4.66
4.66
4.65
4.65
4.65
4.63
4.62
H (m) 6.80
G (d) 6.69
B (s) 5.99
A (s) 5.94
C (ddt) 5.78
E (dd) 5.14
D (dd) 5.21
F (dddd) 4.67
1.98
0.92
2.04
1.00
0.92
0.94
0.94
2.00
f1 (ppm)

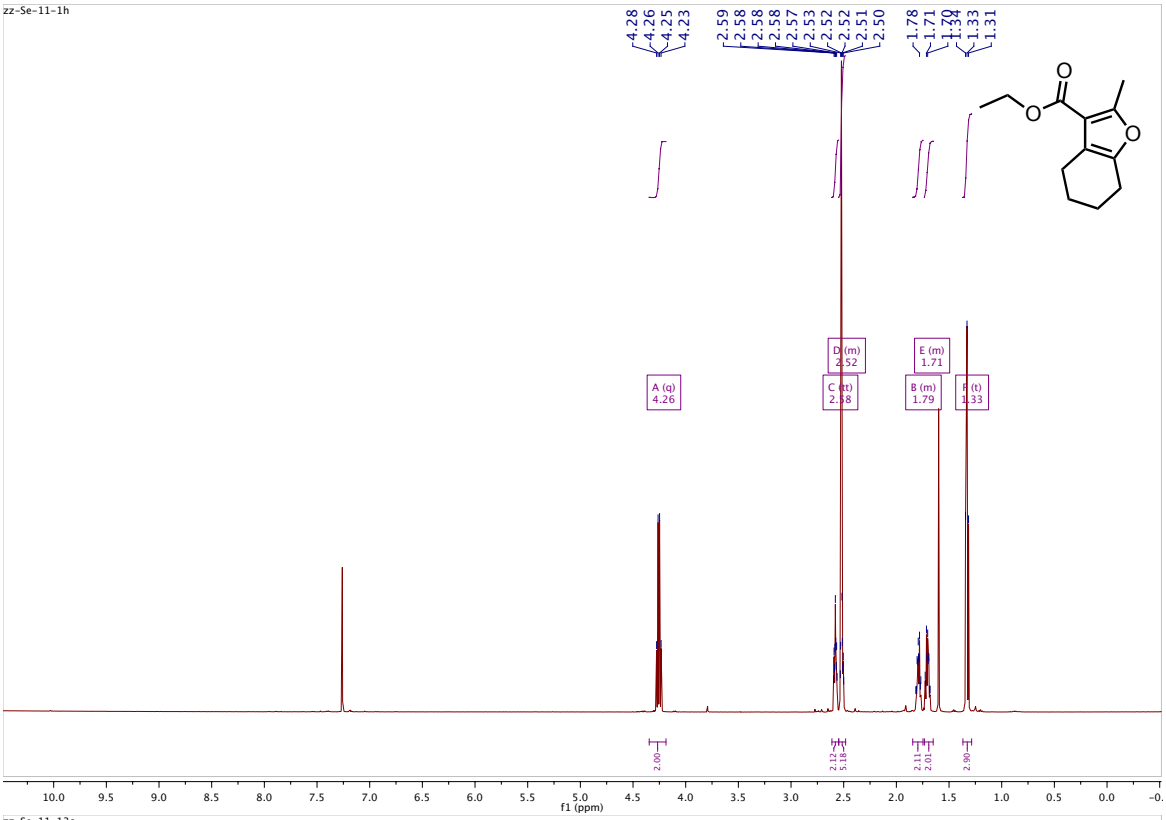

zz-Se-12-13c
STANDARD CARBON PARAMETERS
165.51
163.99
152.39
148.78
148.08
130.44
127.68
121.88
119.25
118.19
108.37
107.13
101.49
79.31
66.02
f1 (ppm)

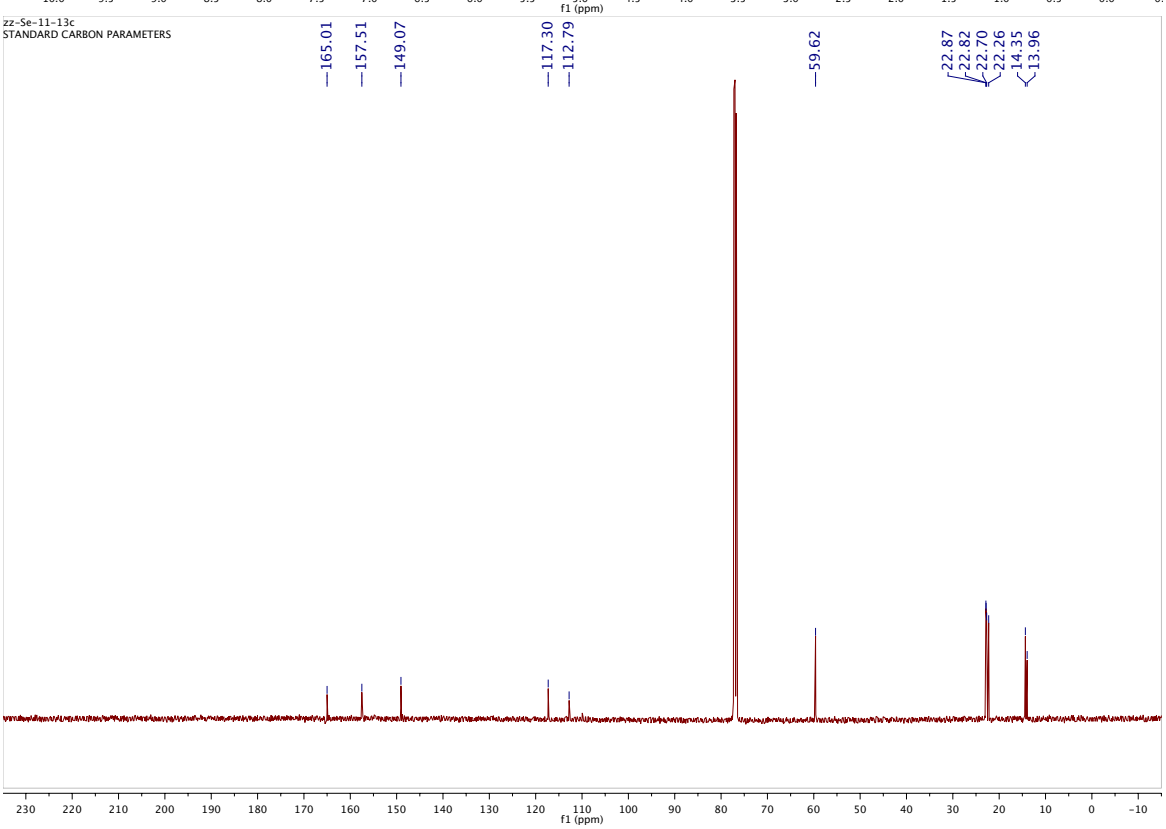

zz-Se-13-1h
7.71
7.71
7.69
7.69
7.54
7.54
7.54
7.53
7.53
7.52
7.51
7.51
7.51
7.41
7.39
7.39
7.37
7.18
7.16
6.80
6.78
6.45
3.74
OH
O
O
O
O
D (dd) 7.39
E (m) 7.52
C (d) 7.17
B (d) 6.79
A (s) 6.45
F (dd) 7.70
C (s) 3.74
1.99
1.09
2.02
2.01
2.02
1.00
3.36
f1 (ppm)

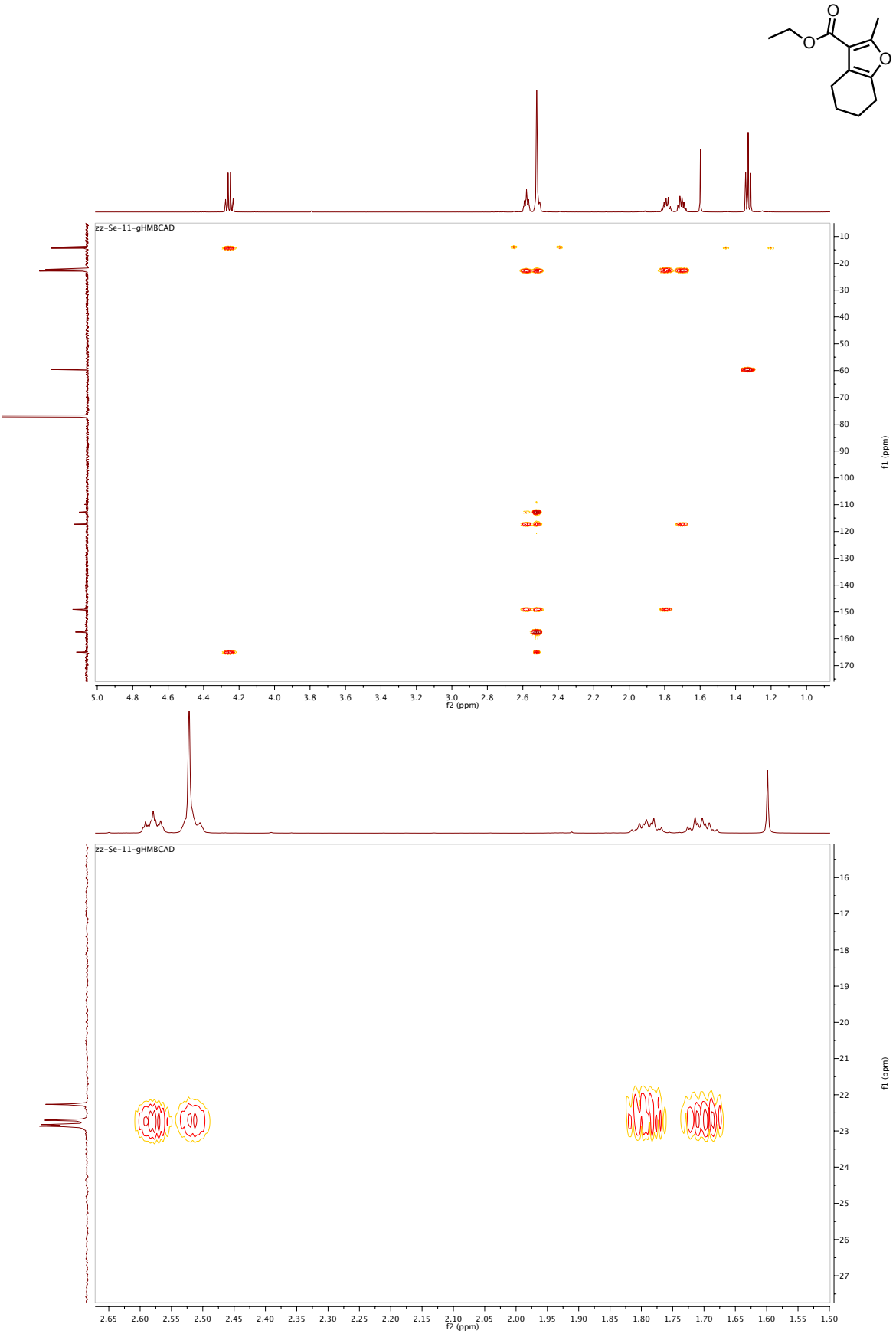

zz-Se-13-13c
STANDARD CARBON PARAMETERS
190.98
166.86
160.56
152.23
136.07
133.71
129.07
128.61
128.58
125.99
123.47
114.33
81.17
55.24
f1 (ppm)

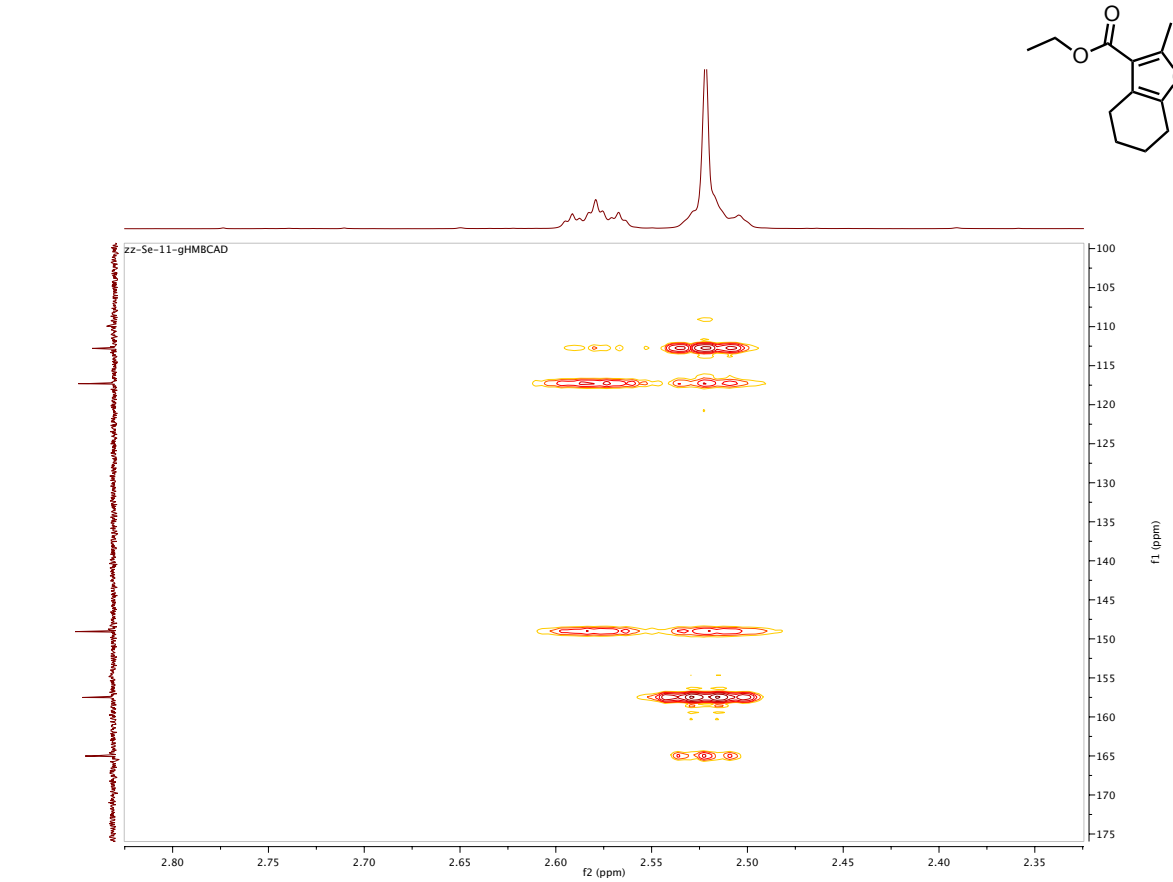

zz-Se-14-1h
7.70
7.69
7.68
7.56
7.55
7.55
7.54
7.53
7.53
7.42
7.41
7.41
7.39
7.25
7.25
7.24
7.24
7.23
7.23
7.22
6.99
6.97
6.95
6.46
D (m) 7.54
C (dd) 7.42
B (t) 6.97
A (s) 6.46
E (m) 7.69
F (m) 2.24
1.97
1.99
2.00
2.01
1.96
1.00
OH
O
O
O
F
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

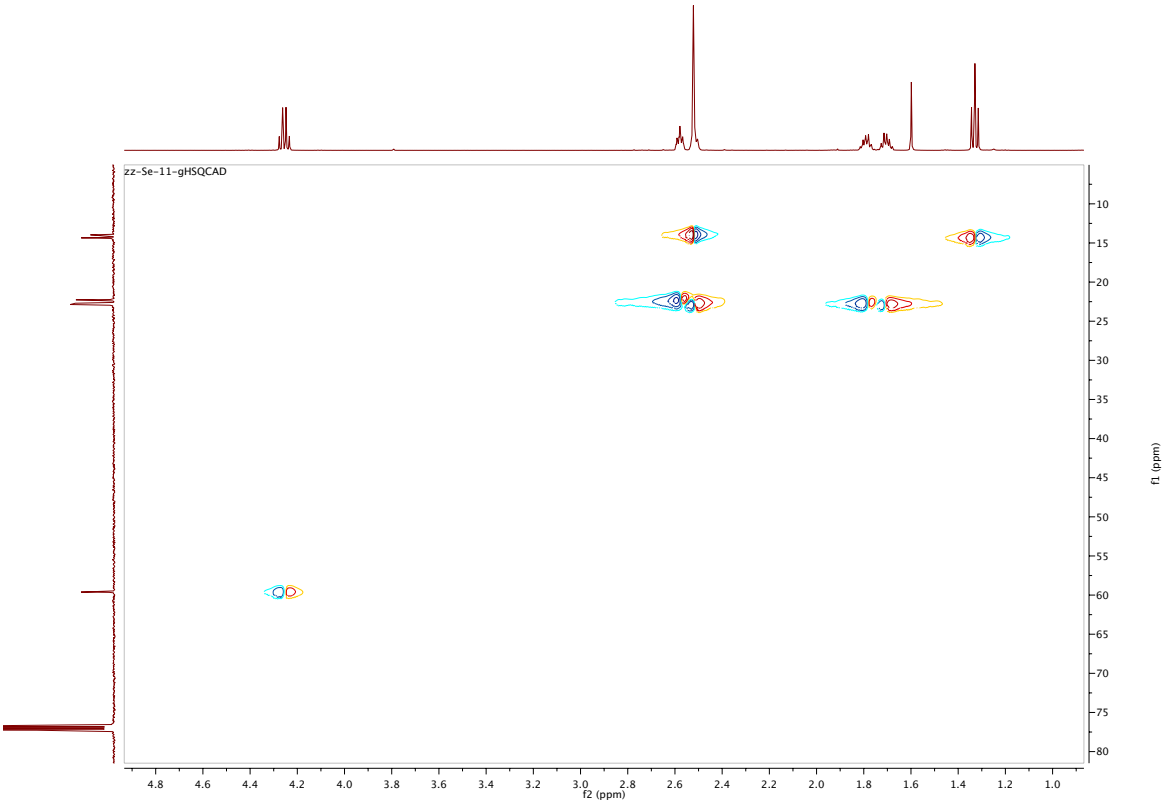

zz-Se-14-13c
STANDARD CARBON PARAMETERS
190.72
166.84
164.28
162.29
151.18
136.08
133.84
129.52
129.45
128.66
128.53
123.68
116.15
115.97
80.53
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

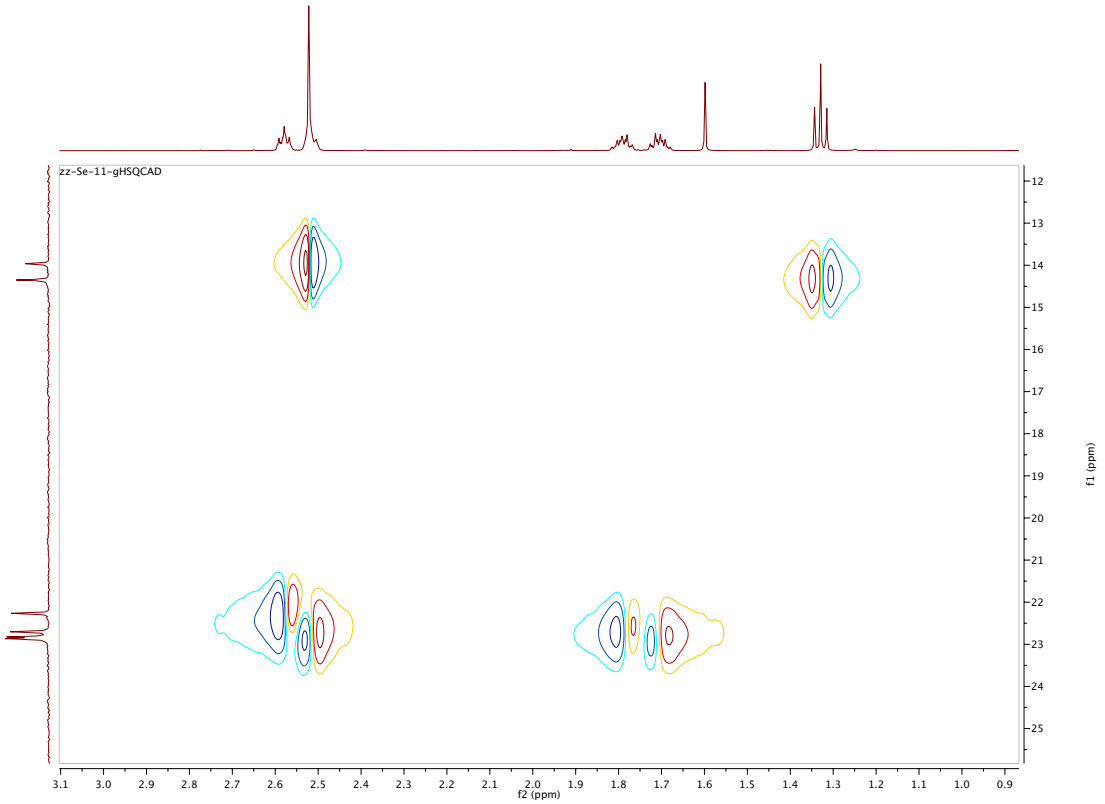

zz-Se-11-1h
4.28
4.26
4.25
4.23
2.59
2.58
2.58
2.58
2.57
2.53
2.52
2.52
2.51
2.50
1.78
1.71
1.70
1.34
1.33
1.31
O
O
O
A (q)
4.26
D (m)
2.52
C (tt)
2.18
E (m)
1.71
B (m)
1.79
F (t)
1.33
2.00
2.12
5.18
2.11
2.01
2.90
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

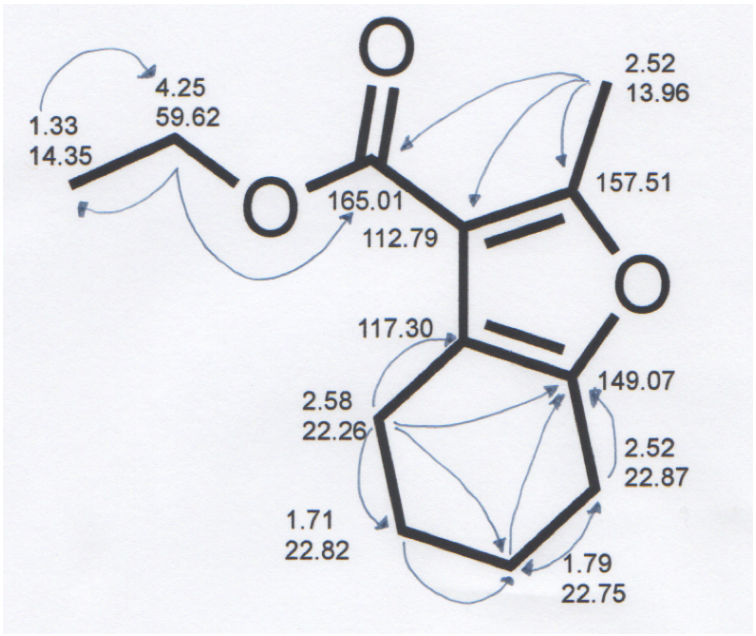

zz-Se-11-13c
STANDARD CARBON PARAMETERS
165.01
157.51
149.07
117.30
112.79
59.62
22.87
22.82
22.70
22.26
14.35
13.96
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

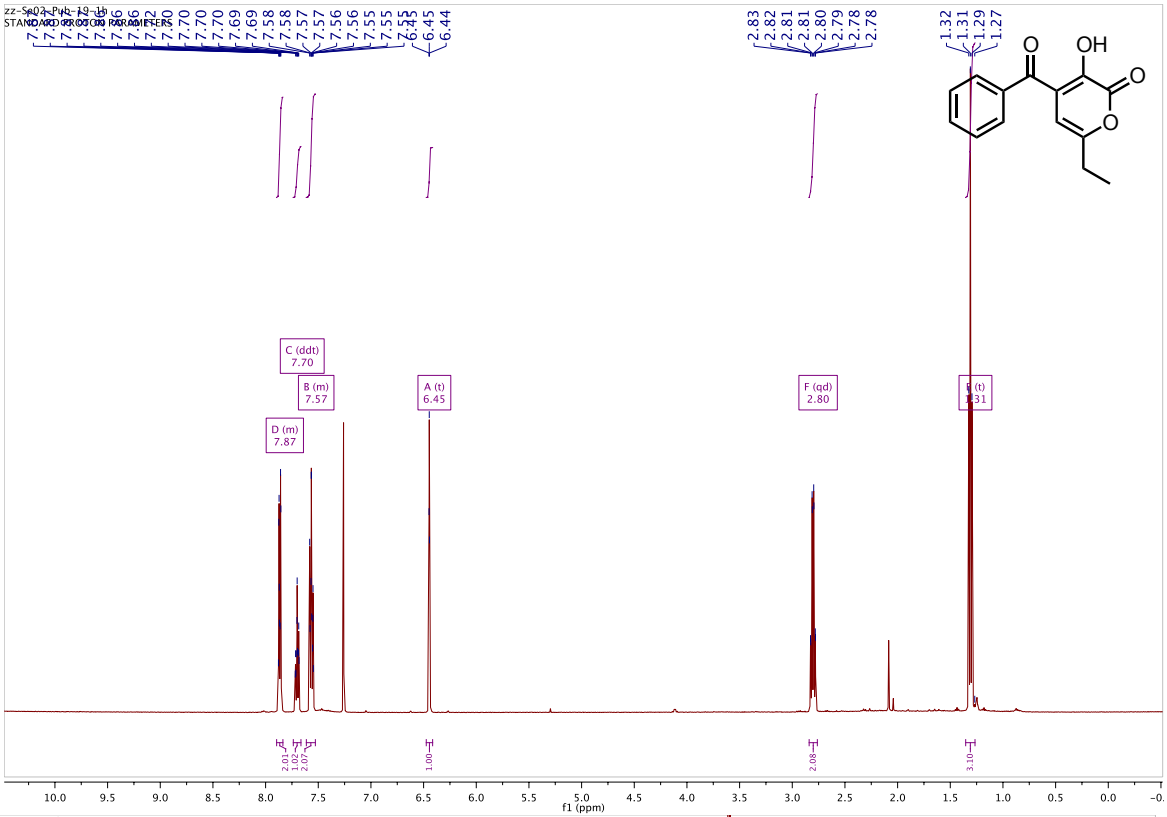

zz-Se-11-gHMBCAD
f2 (ppm)
f1 (ppm)
zz-Se-11-gHMBCAD
f2 (ppm)
f1 (ppm)

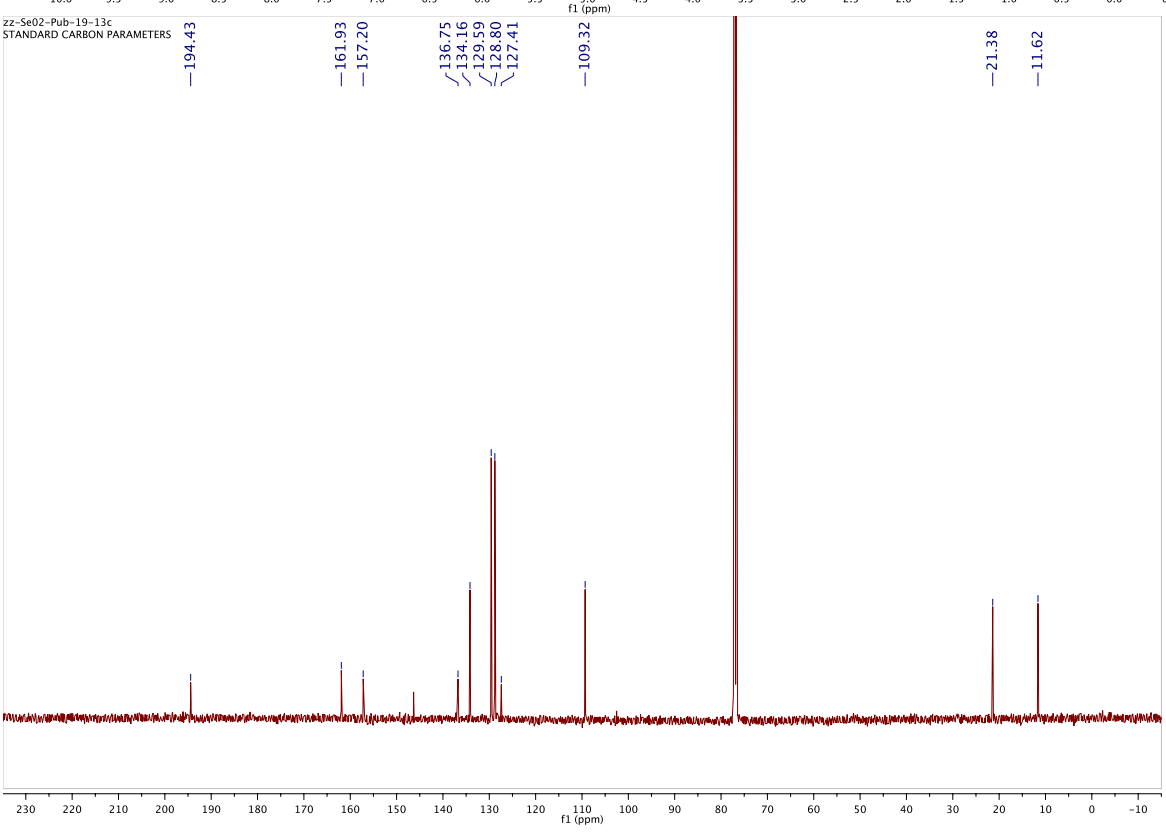

zz-Se-11-gHMBCAD
f2 (ppm)
f1 (ppm)

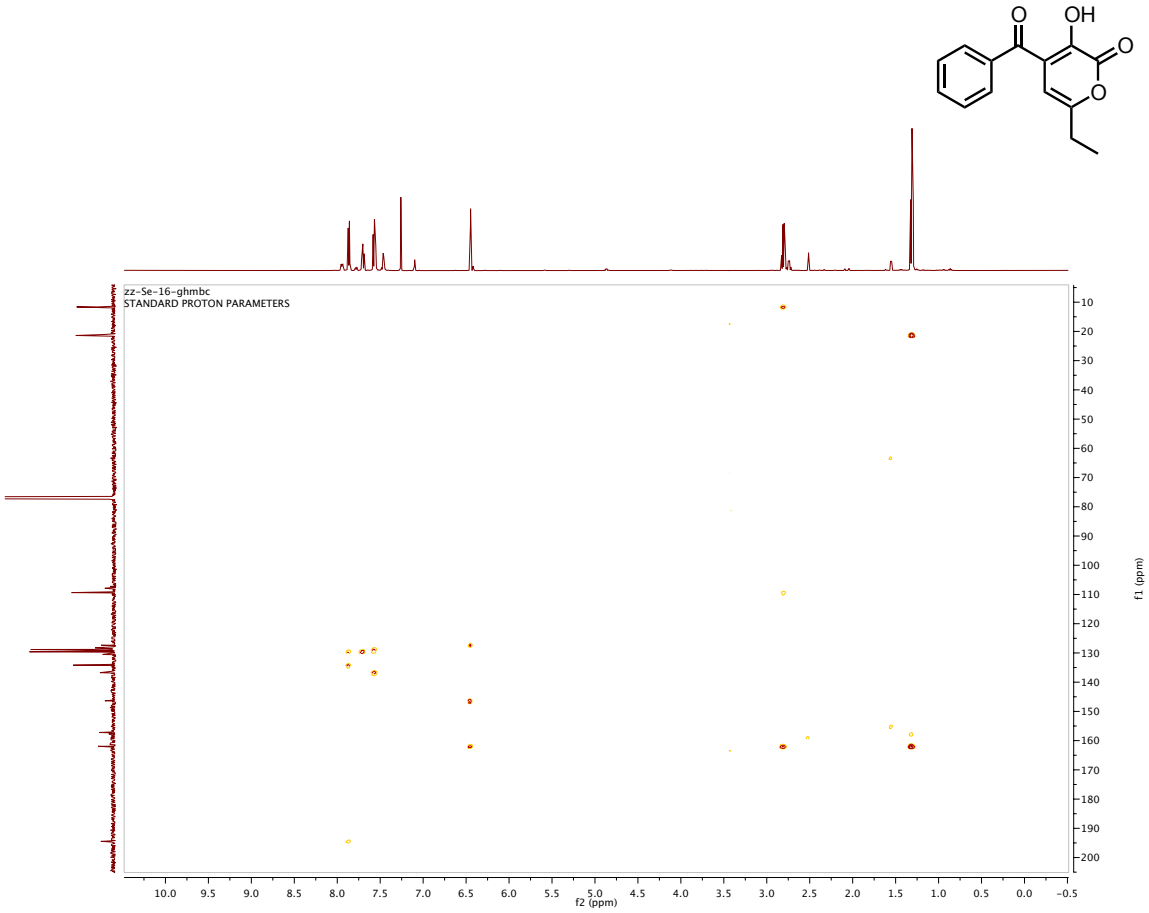

zz-Se-11-gHSQCAD
f2 (ppm)
f1 (ppm)

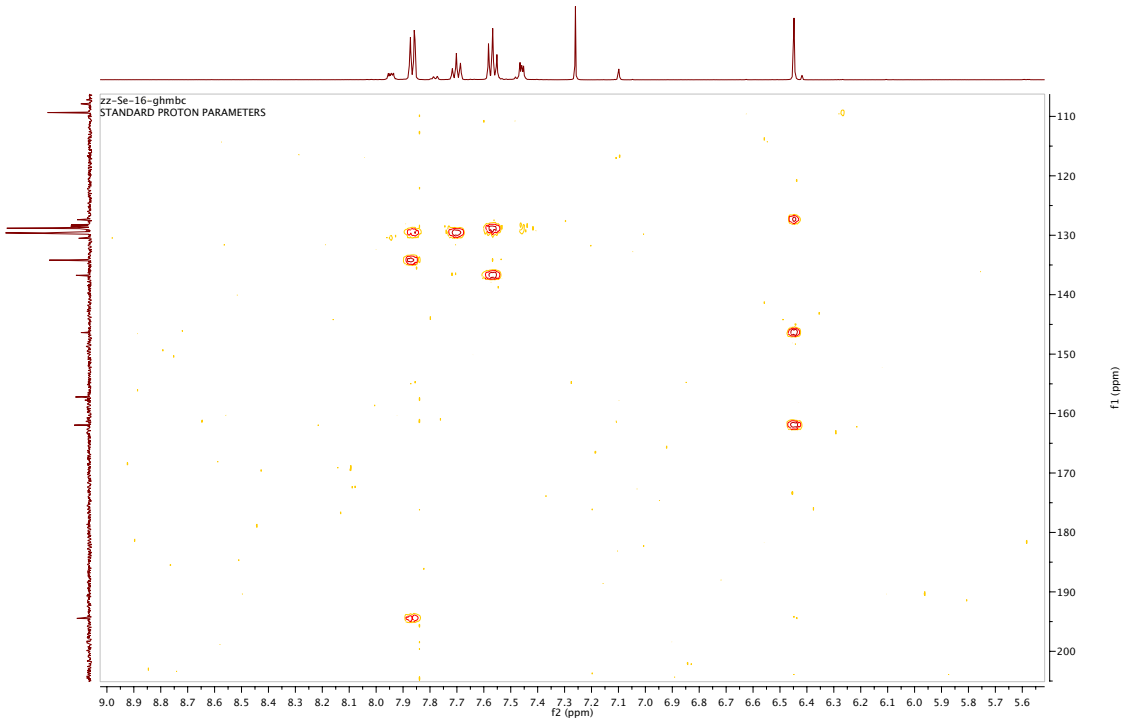

zz-Se-11-gHSQCAD
f2 (ppm)
f1 (ppm)

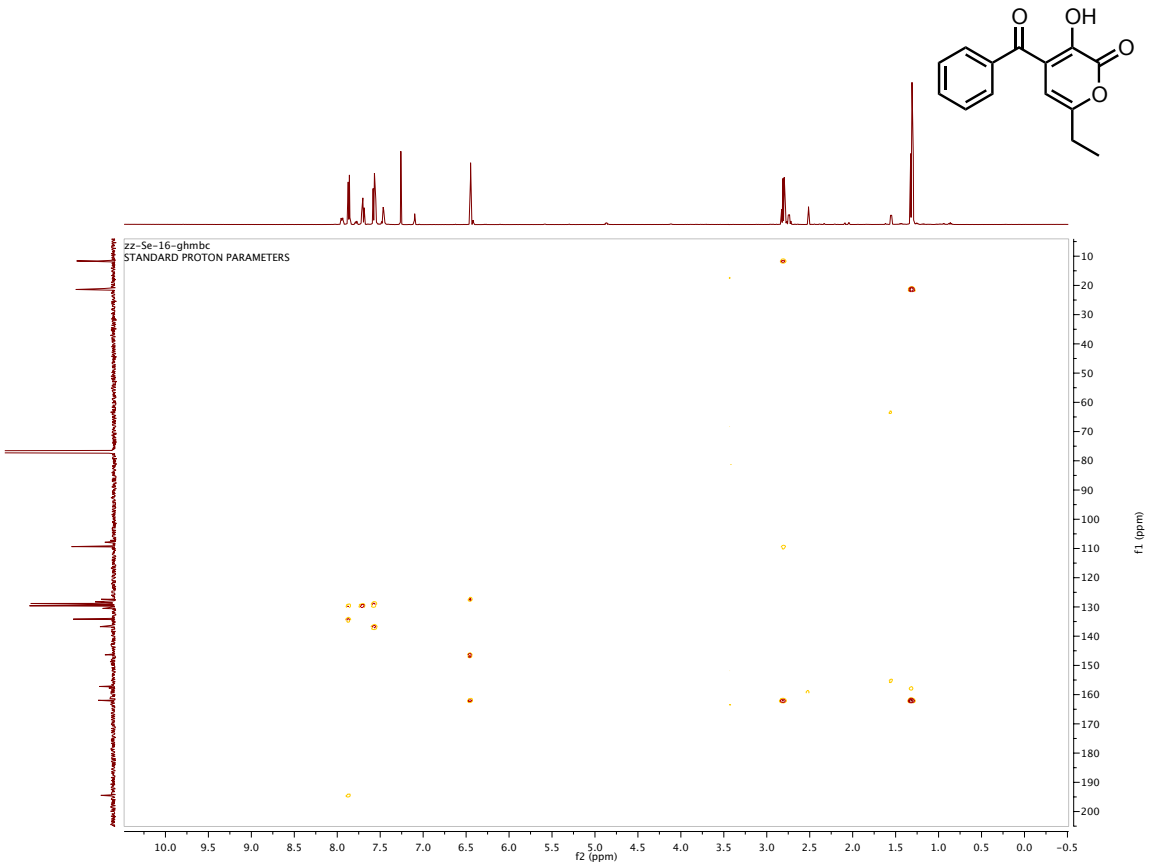

4.25
59.62
1.33
14.35
165.01
112.79
2.52
13.96
157.51
117.30
149.07
2.58
22.26
2.52
22.87
1.71
22.82
1.79
22.75

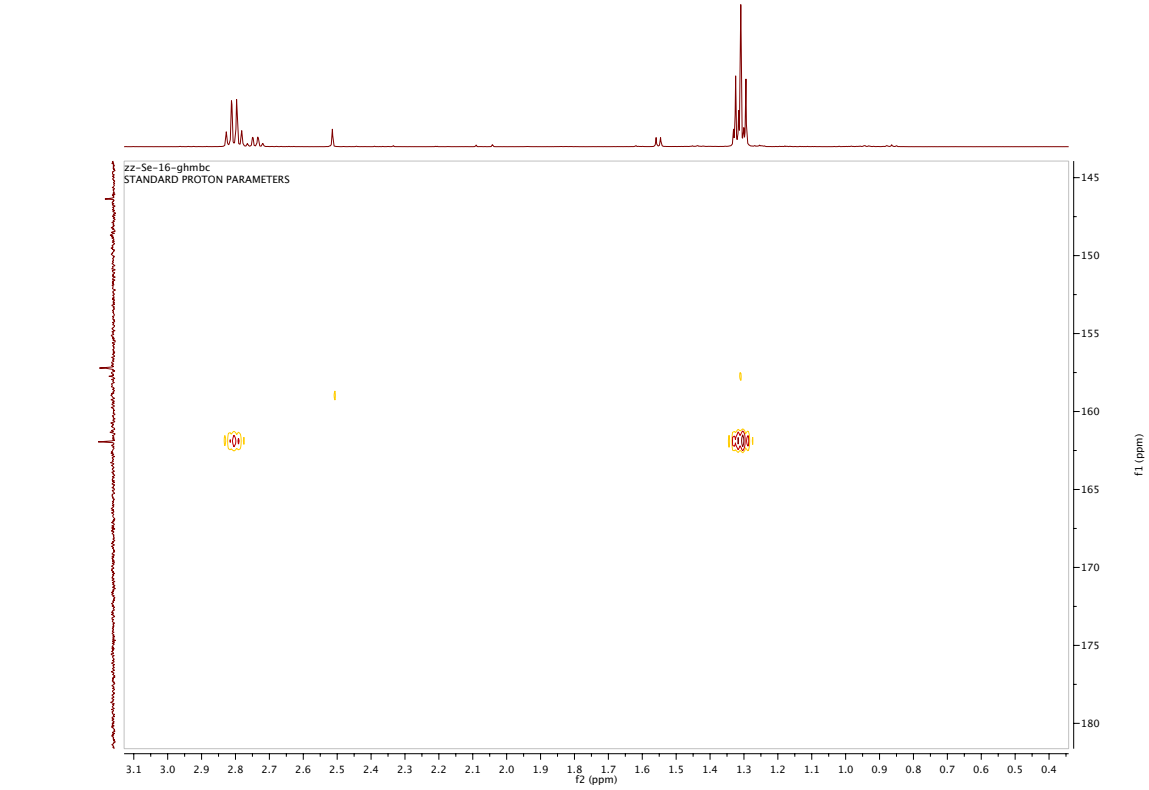

OH
O
O
O
C (ddt)
7.70
B (m)
7.57
A (t)
6.45
F (qd)
2.80
D (m)
7.87
f1 (ppm)

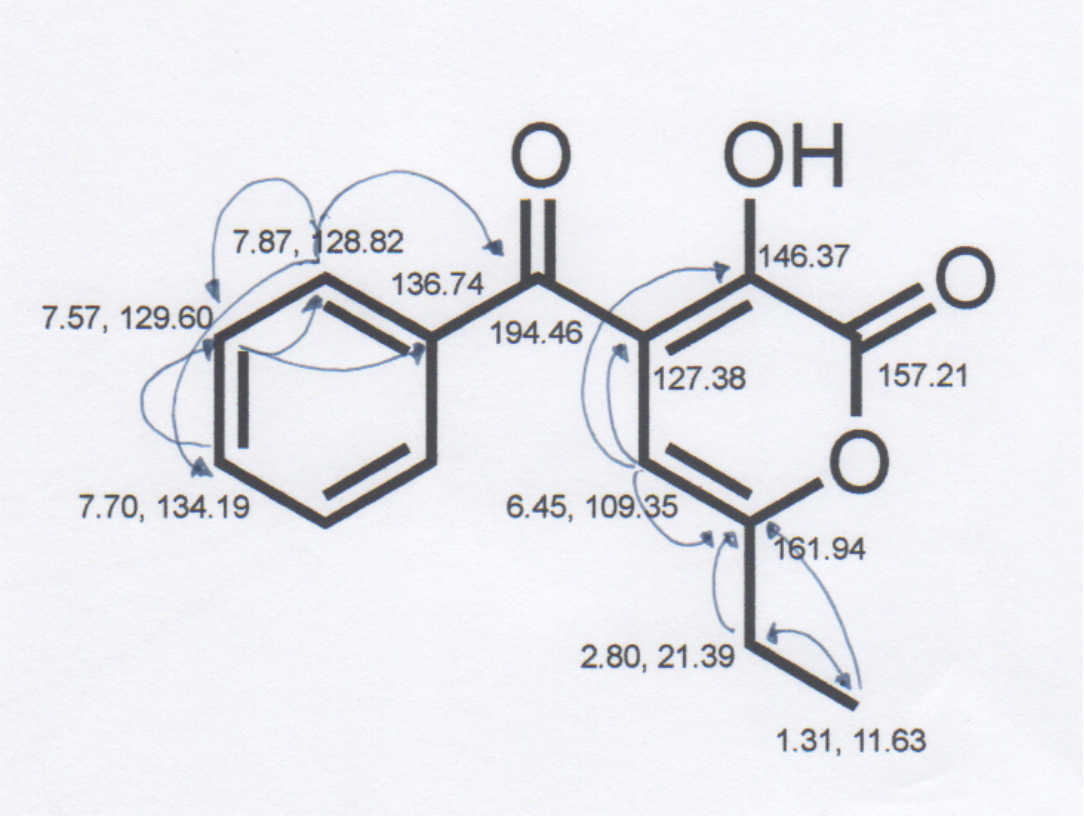

zz-Se02-Pub-19-13c
STANDARD CARBON PARAMETERS
194.43
161.93
157.20
136.75
134.16
129.59
128.80
127.41
109.32
21.38
11.62
f1 (ppm)

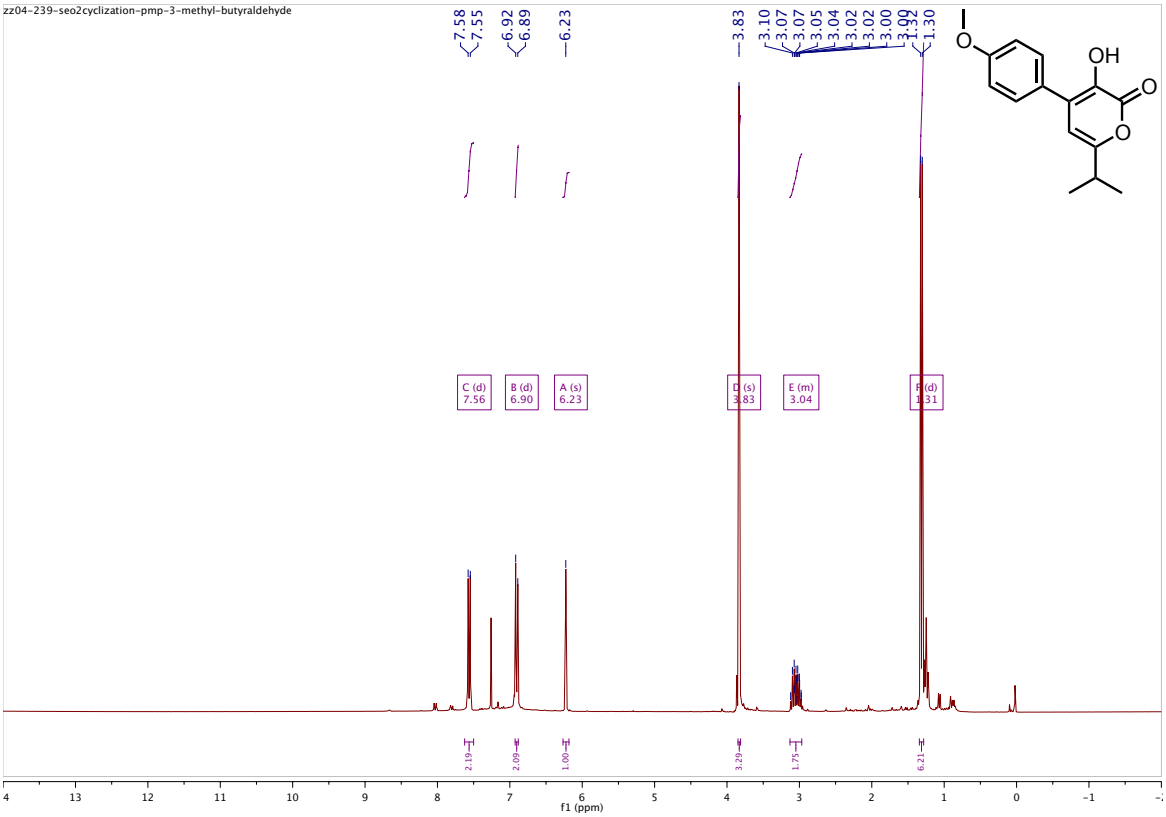

zz-Se-16-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

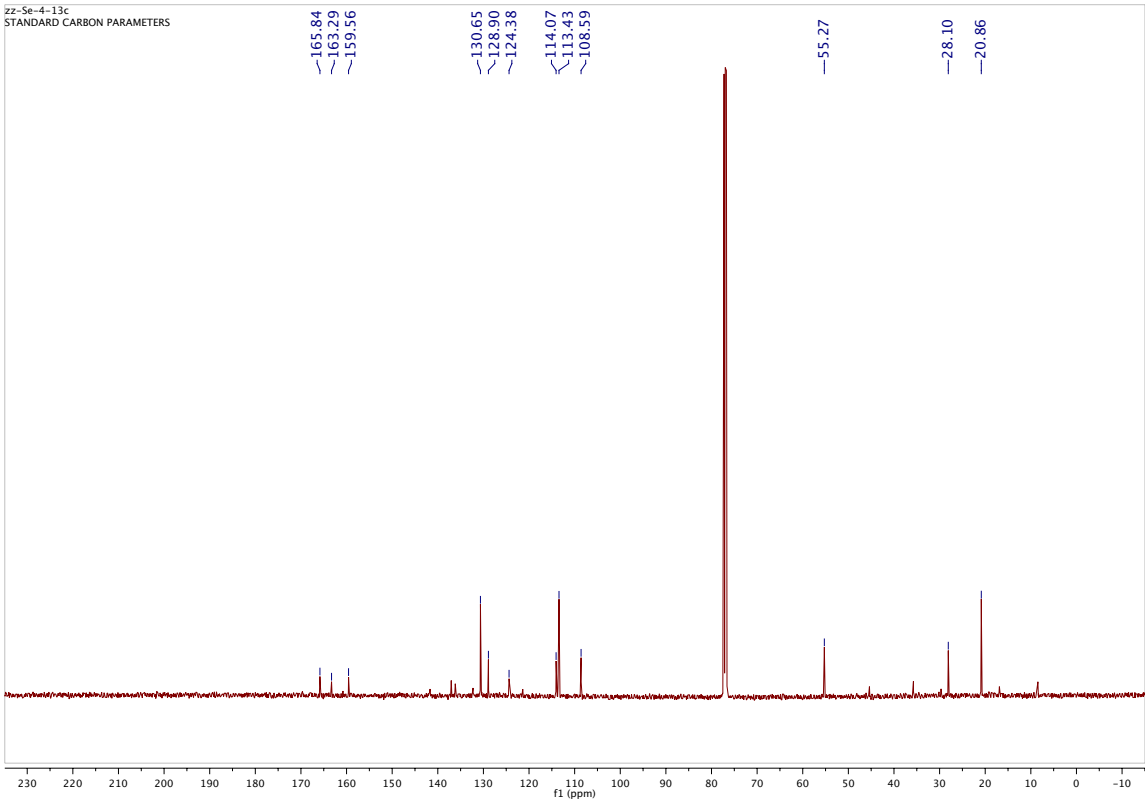

zz-Se-16-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

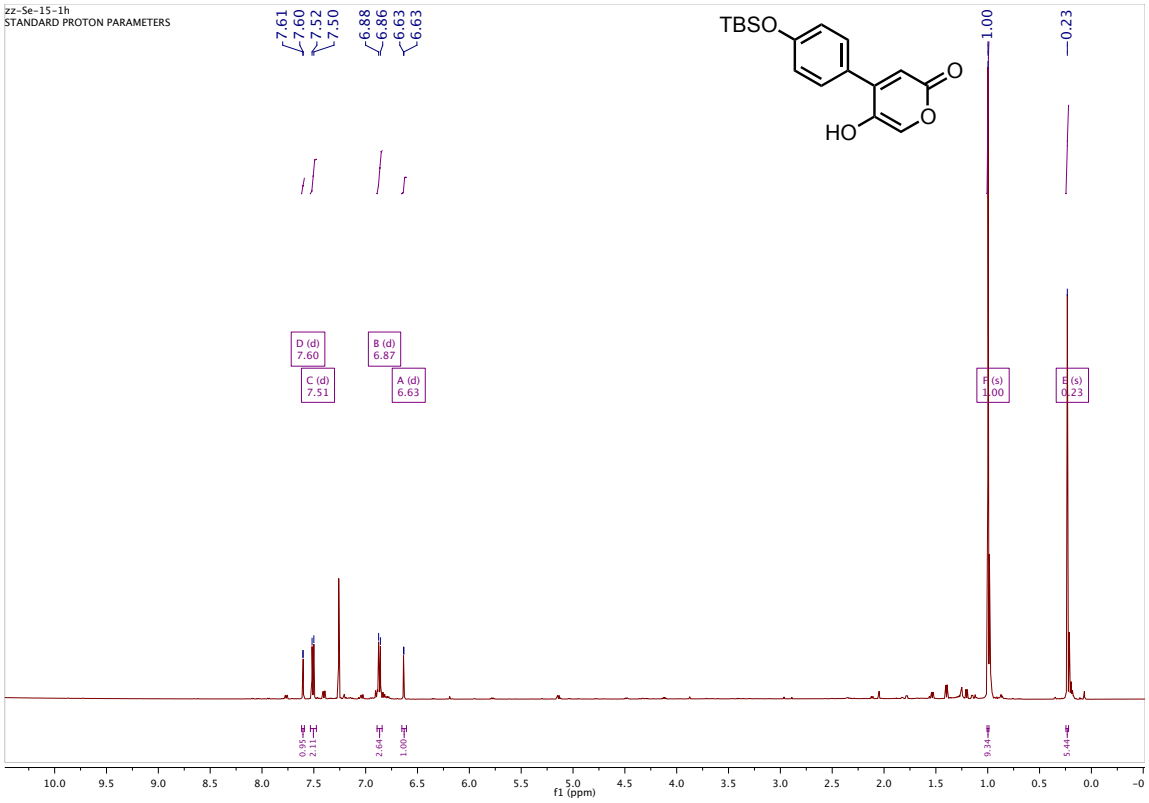

zz-Se-16-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

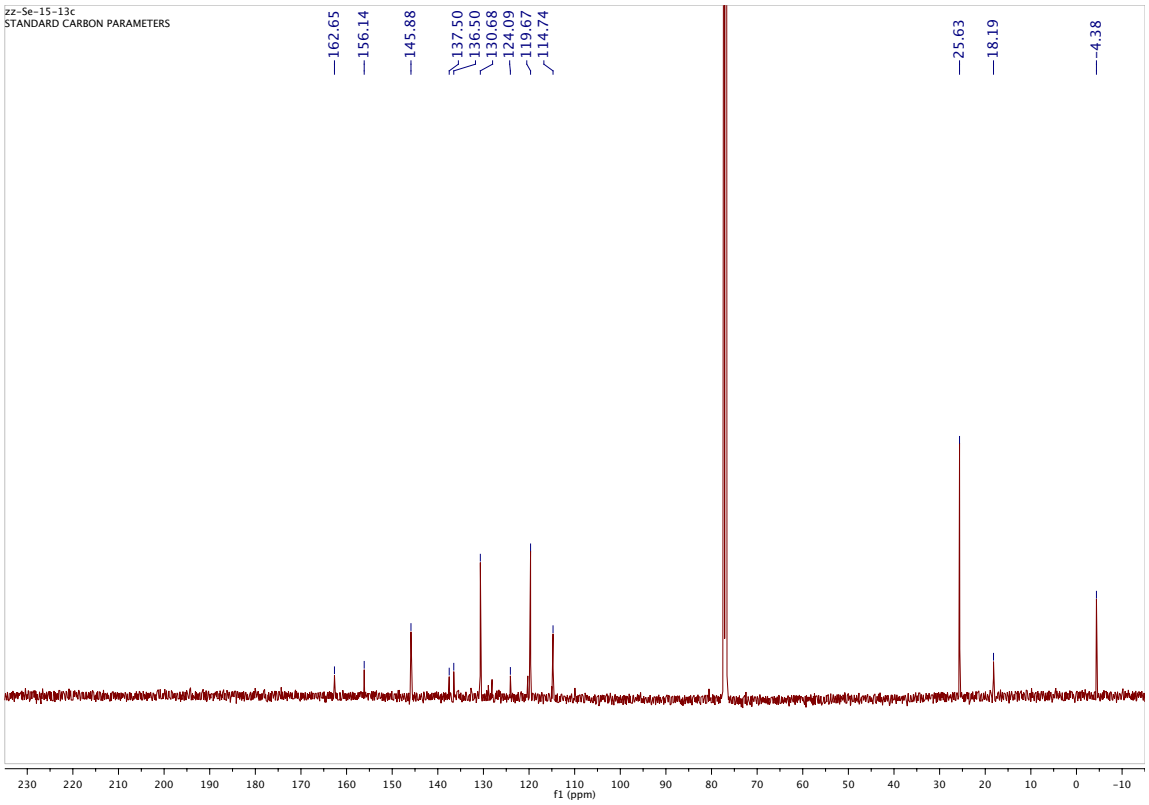

zz-Se-16-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

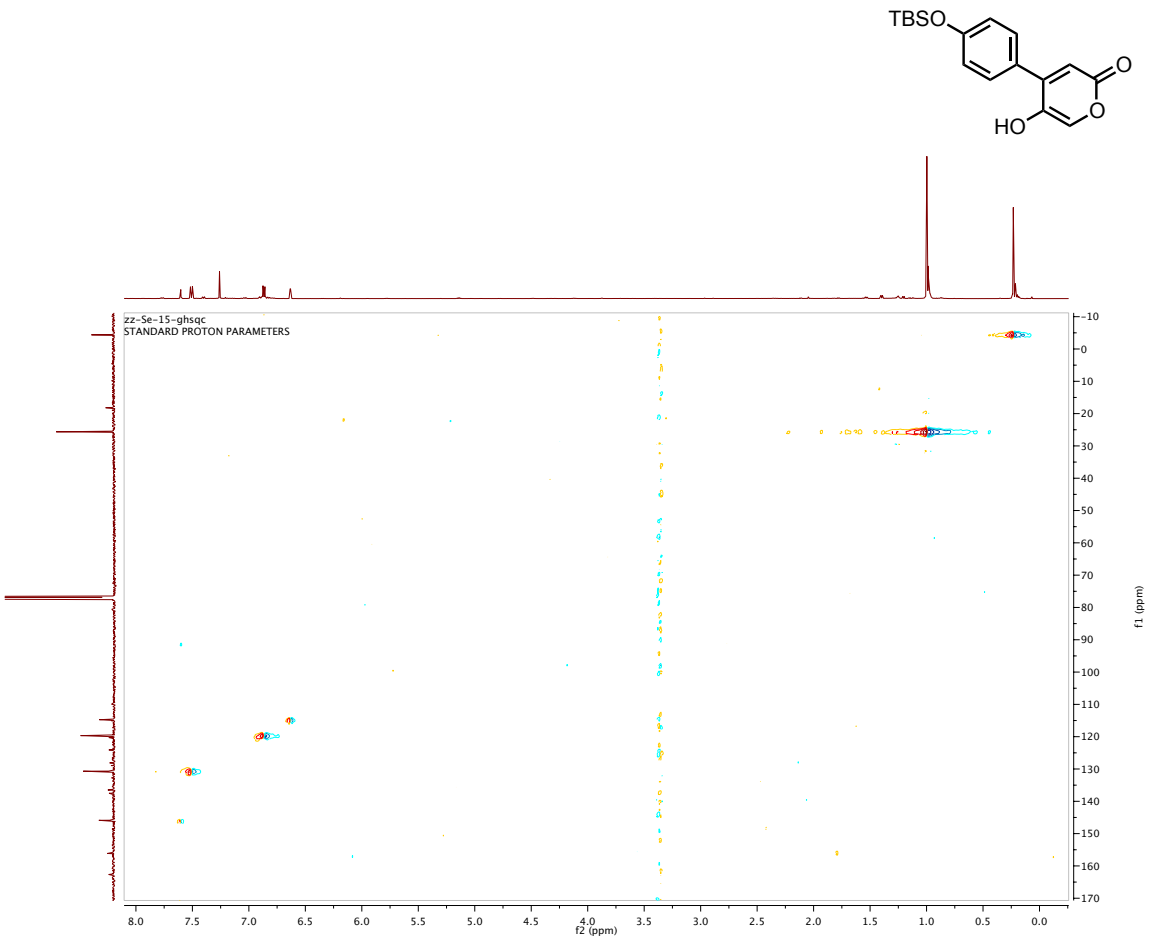

O
OH
7.87, 128.82
136.74
146.37
O
7.57, 129.60
194.46
127.38
157.21
O
7.70, 134.19
6.45, 109.35
161.94
2.80, 21.39
1.31, 11.63

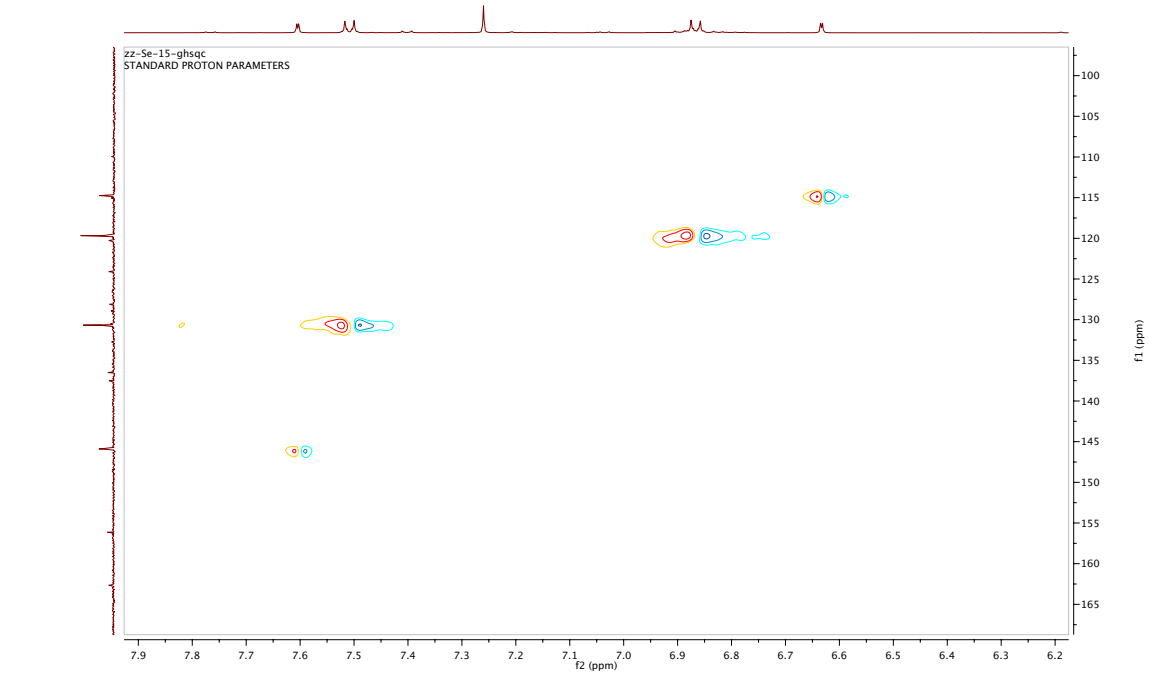

zz04-239-seo2cyclization-pmp-3-methyl-butyraldehyde
7.58
7.55
6.92
6.89
6.23
3.83
3.10
3.07
3.07
3.05
3.04
3.02
3.02
3.00
1.32
1.30
OH
O
O
O
C (d) 7.56
B (d) 6.90
A (s) 6.23
D (s) 3.83
E (m) 3.04
F (d) 1.31
2.19
2.09
1.00
3.29
1.75
6.21
f1 (ppm)

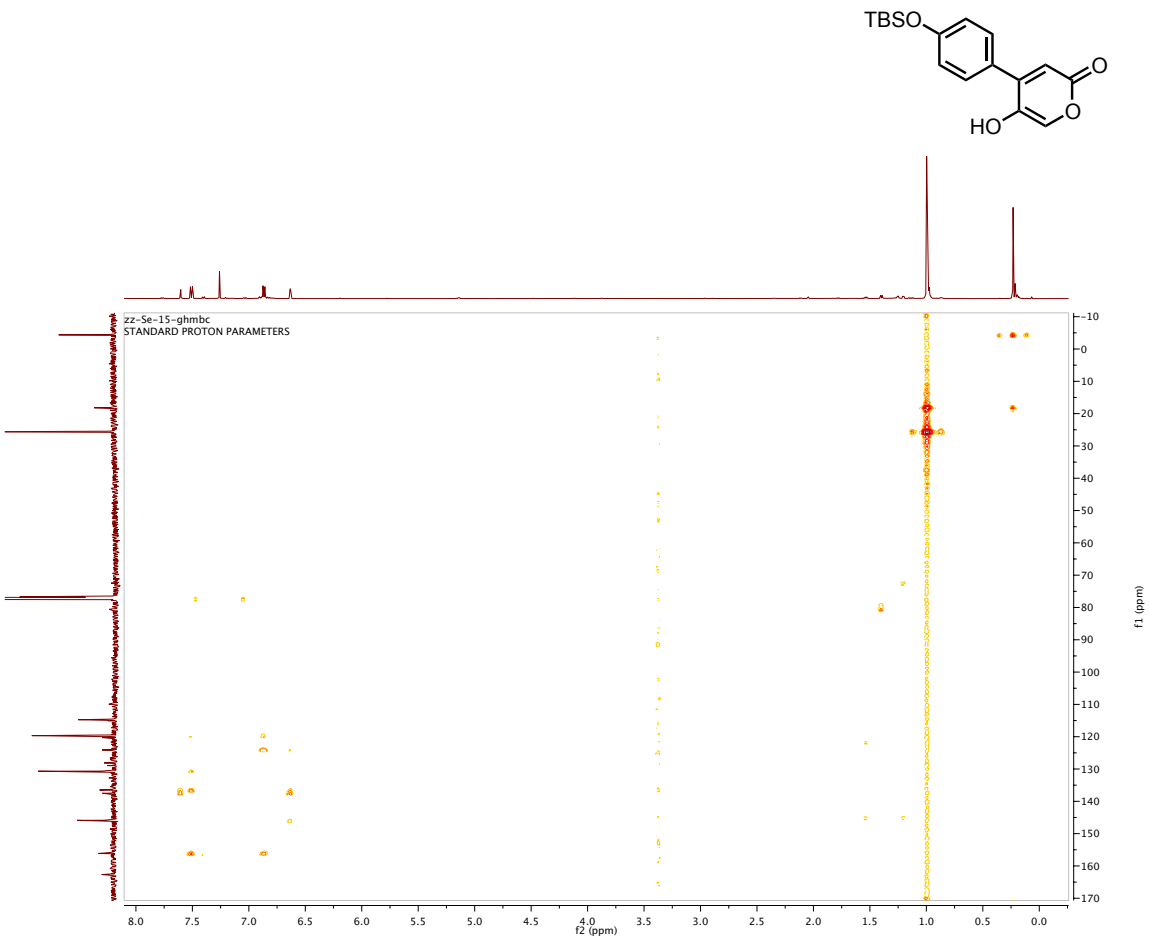

zz-Se-4-13c
STANDARD CARBON PARAMETERS
165.84
163.29
159.56
130.65
128.90
124.38
114.07
113.43
108.59
55.27
28.10
20.86
f1 (ppm)

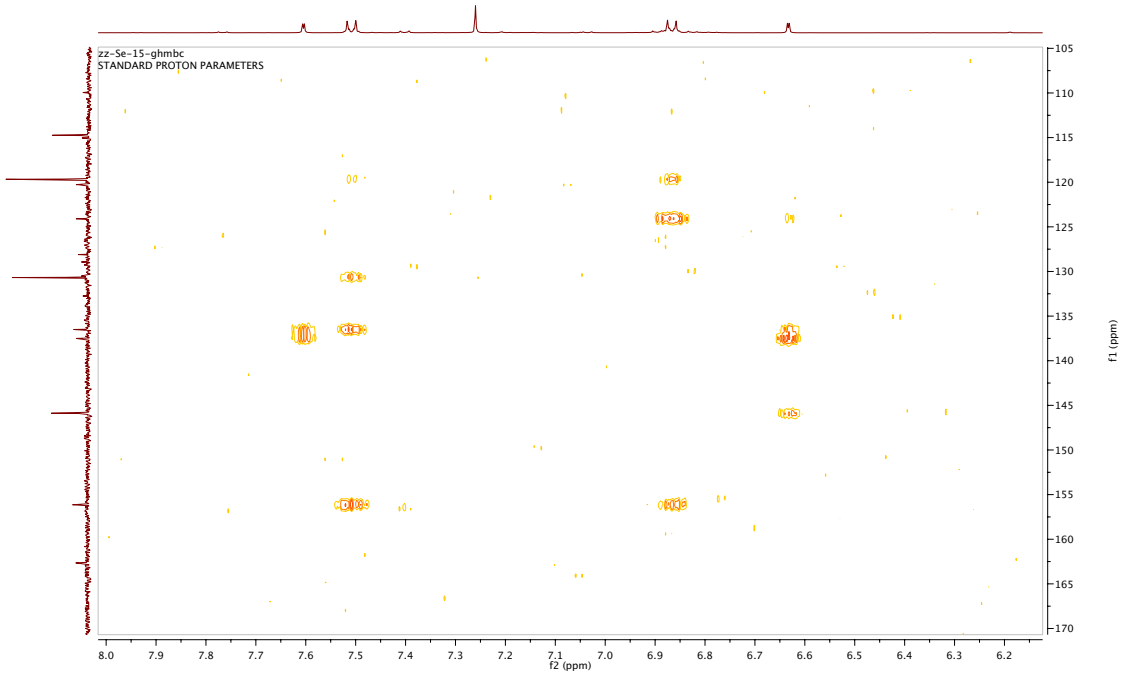

zz-Se-15-1h
STANDARD PROTON PARAMETERS
7.61
7.60
7.52
7.50
6.88
6.86
6.63
6.63
TBSO
O
O
HO
1.00
0.23
D (d) 7.60
C (d) 7.51
B (d) 6.87
A (d) 6.63
F (s) 1.00
E (s) 0.23
0.95
2.11
2.64
1.00
9.34
5.44
f1 (ppm)

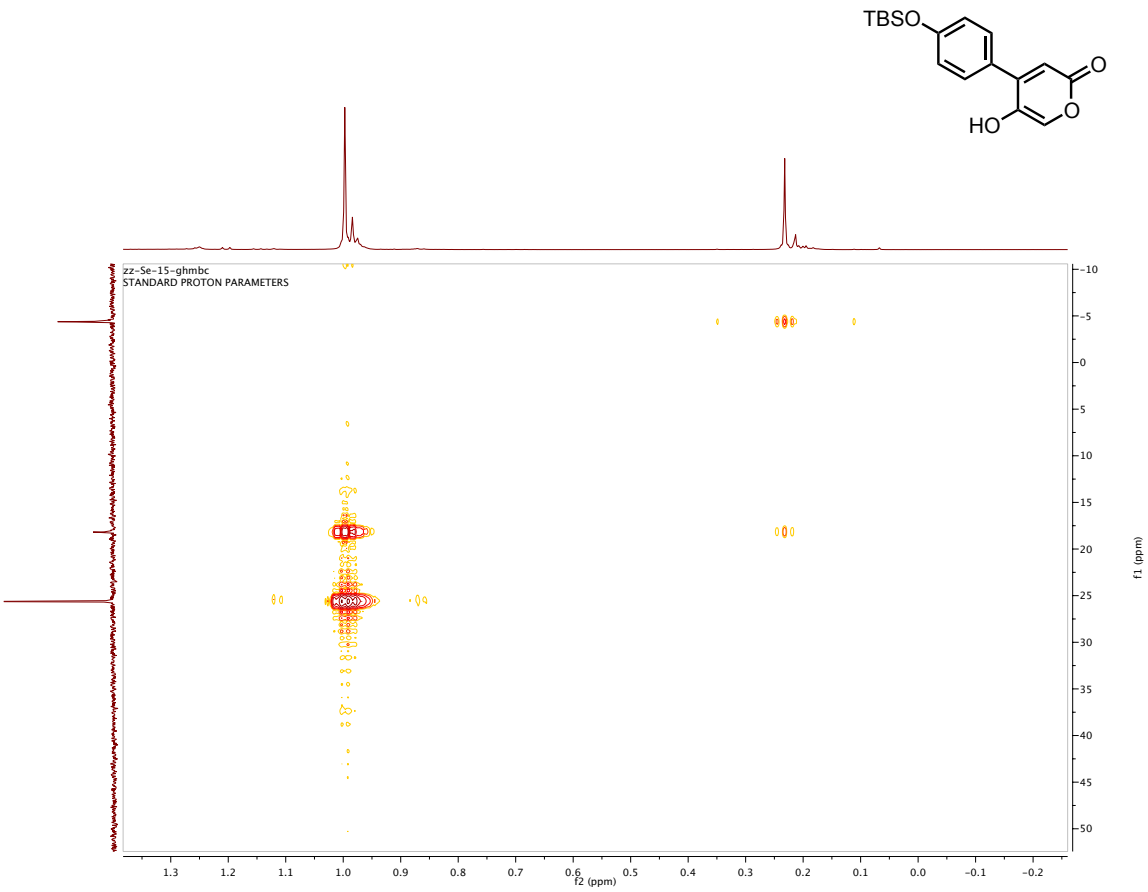

zz-Se-15-13c
STANDARD CARBON PARAMETERS
162.65
156.14
145.88
137.50
136.50
130.68
124.09
119.67
114.74
25.63
18.19
-4.38
f1 (ppm)

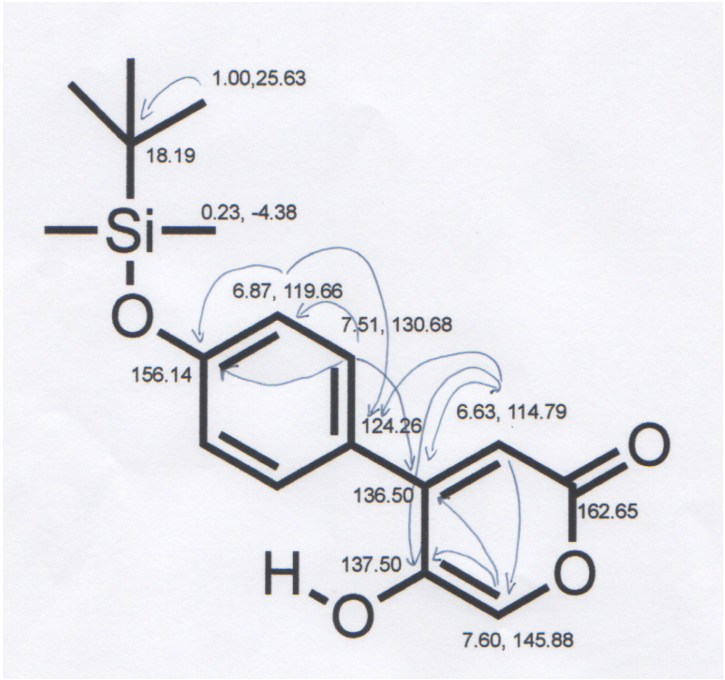

TBSO
O
O
HO
zz-Se-15-ghsqc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)


zz-Se-15-ghsqc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)


TBSO
O
O
HO
zz-Se-15-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)


zz-Se-15-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)


TBSO
O
HO
O
zz-Se-15-ghmbc
STANDARD PROTON PARAMETERS
f2 (ppm)
f1 (ppm)

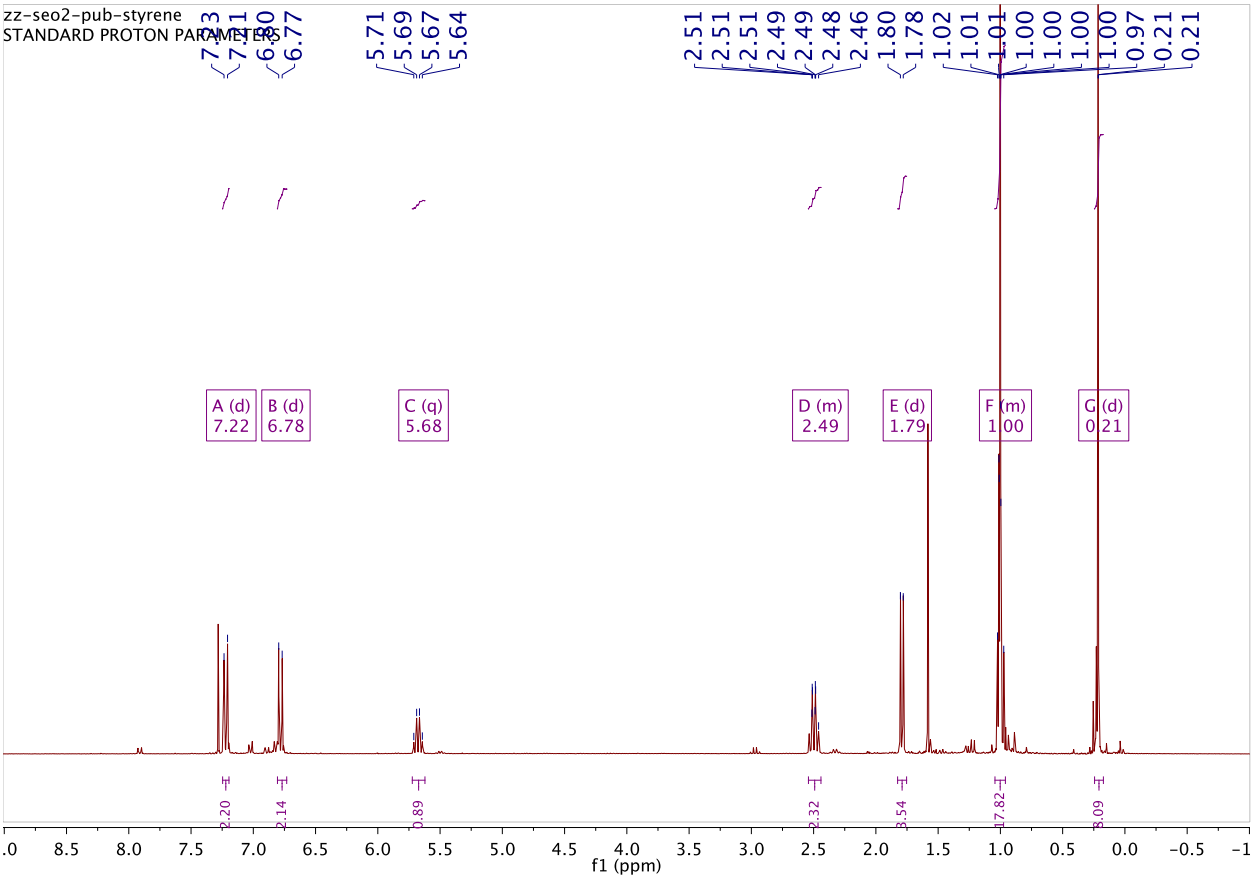

1.00,25.63
18.19
Si
0.23, -4.38
O
6.87, 119.66
7.51, 130.68
156.14
124.26
6.63, 114.79
O
136.50
162.65
137.50
H
O
O
7.60, 145.88

Based on comments from the referees, we decided to perform the following reactions to validate our hypotheses concerning eq (6)

Compound **22** (180 mg, 0.61 mmol, 1 eq.) was dissolved in 5 mL DCM and to this solution was added iPr_2NEt (197 mg, 1.53 mmol 2.5 eq.) and $MeSO_2Cl$ (140 mg, 1.22 mmol, 2.0 eq.) at room temperature. After 14 h, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was extracted with DCM (15 mL x 3) and the combined organic layer was dried over Na_2SO_4 before being concentrated under reduced pressure. The residue was purified by silica gel chromatography (2% EtOAc in Hexanes) to yield **23** (108 mg, 64% yield), which was then treated with 4 eq. of SeO_2 according to the general procedure described on page 3 of this document to give 34 mg of **24** (30% yield). The overall yield of **24** was 19%, whereas the one pot procedure gave product in 13% yield.

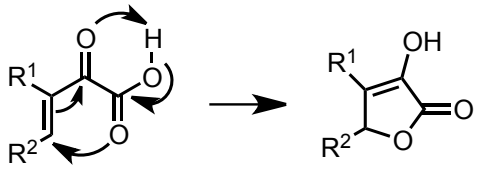
It is our opinion that these results validate our hypotheses.

The ^1H spectrum of **23** is attached below. It appears to have high diastereomeric purity.



Mechanistic Hypothesis

Oxa-Michael Addition with Simultaneous Proton Transfer



Oxa-Nazarov Mechanism