The Influence of Substitution on Thiol-Induced Oxanorbornadiene Fragmentation

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A. GENERAL METHODS

Unless otherwise noted, all reactions were carried out in oven-dried glassware under an atmosphere of dry argon. Dichloromethane, toluene, and tetrahydrofuran were dried by passage through activated alumina (MBraun solvent purification system). All commercially available reagents were purchased from Acros Organics, Alfa Aesar, Ark Pharm, Sigma Aldrich, Chem-Impex, Combi-Blocks, Fisher, Fluka, Frontier Scientific, J&W Pharmlab, Oakwood Chemical, OxChem, Strem Chemicals, or TCI Chemicals and were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories.

NMR spectra were obtained on Brüker AMX-400, DRX-500 or AMX-700 instruments. Chemical shifts are reported relative to the central line of residual solvent chloroform (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C) and methanol (3.31 ppm, ^{1}H; 49.00 ppm, ^{13}C). ^{13}C NMR were obtained with ^{1}H decoupling. High-resolution mass spectrometry was performed on an Agilent 6230 ESI-TOF LC/MS instrument (G6230B) operating at 4 GHz with internal reference. LC was performed on an Agilent 1260 HPLC with a mobile phase gradient from 2-100% acetonitrile/ water containing 0.1% formic acid on a Zorbax Extend-C18 Rapid Resolution HT (2.1 x 50mm, 1.8µm).

Analytical thin layer chromatography (TLC) was performed using MilliporeSigma aluminum plates coated with 0.25 mm silica gel containing PF 254 indicator, and the compounds were visualized with UV light and potassium permanganate stain. Flash chromatography was carried out with Silicycle SilicaFlash. F60 (particle size 40-63 µm) silica gel or it was performed on the Biotage® Automated Liquid Chromatography System Isolera One® using Biotage® SNAP KP-Sil 10-25g or ZIP 5g Si silica gel cartridges.

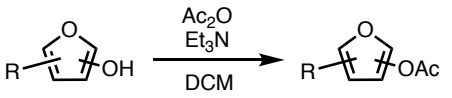
B. COMPUTATIONAL PROCEDURES

Theoretical calculations were performed using the software package Gaussian 16, Revision A.03.[1] Geometry optimizations and frequency analyses were performed using the M06-2X[2] density functional and the 6-311+G(d,p) basis set in chloroform (SMD) in combination with Grimme D3 empirical dispersion correction[3] without Becke-Johnson dampening as proposed by Grimme and coworkers.[4] Quasi-harmonic correction was performed by using the “Goodvibes” Python script by Robert Paton.[5] Single imaginary frequencies corresponding to the desired reaction coordinates were obtained only in the case of transition state calculations. No imaginary frequencies were obtained for all other structures. Table S1 shows the calculated energies. Coordinates are provided as *.xyz files.

Table S1. M06-2X-D3/6-311+G(d,p)(chloroform) calculated energies.

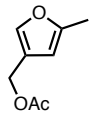
Structure	ΔE (hartree)	ZPE (hartree)	ΔH_{298} (hartree)	ΔG_{298} (hartree)
2a	-1602.963095	0.392363	-1602.543485	-1602.623120
2b	-1622.820640	0.379620	-1622.414074	-1622.493201
2c	-1853.844844	0.461888	-1853.351638	-1853.439182
2d	-1622.822577	0.380113	-1622.416029	-1622.493737
2e	-1622.819747	0.379805	-1622.412824	-1622.492296
2f	-1814.532883	0.433625	-1814.069496	-1814.154069
2g	-1929.048906	0.466213	-1928.550360	-1928.639830
2h	-2019.025407	0.435563	-2018.557060	-2018.647624
2i	-2151.586162	0.437702	-2151.114622	-2151.207206
2j	-1876.665032	0.382074	-1876.253504	-1876.337779
2k	-1668.655117	0.325608	-1668.304231	-1668.379856
2l	-1530.105294	0.304595	-1529.777459	-1529.848937
2m	-2296.898678	0.424630	-2296.439060	-2296.533461
2n	-2222.980884	0.443254	-2222.502689	-2222.597204
2o	-2544.000408	0.460204	-2543.501942	-2543.602599
2p	-1547.551412	0.375453	-1547.150797	-1547.226103
2q	-1622.779169	0.380168	-1622.373020	-1622.449582
8	-1432.826713	0.326289	-1432.477795	-1432.548116
9	-1432.825040	0.326470	-1432.476212	-1432.545906
10	-1432.830606	0.326991	-1432.481239	-1432.551048
11	-1432.832123	0.326811	-1432.482776	-1432.552815
12	-1538.854375	0.250734	-1538.582366	-1538.650356
13	-1538.854524	0.250810	-1538.582401	-1538.650275
14	-1538.852944	0.249724	-1538.581639	-1538.650015
15	1538.846246	0.249976	-1538.574972	-1538.642681
16	-1201.800981	0.245789	-1201.537479	-1201.598108
TS2a	-1602.913440	0.388204	-1602.497204	-1602.578359
TS2b	-1622.774043	0.375706	-1622.370697	-1622.451426
TS2c	-1853.793691	0.457853	-1853.304004	-1853.392656
TS2d	-1622.777333	0.375908	-1622.373978	-1622.453984
TS2e	-1622.774531	0.375793	-1622.371108	-1622.451338
TS2f	-1814.493067	0.429501	-1814.032986	-1814.118950
TS2g	-1929.010091	0.462885	-1928.514287	-1928.604681
TS2h	-2018.984392	0.432268	-2018.518977	-2018.610195
TS2i	-2151.545640	0.434697	-2151.077033	-2151.169835
TS2j	-1876.620683	0.378735	-1876.211541	-1876.297687
TS2k	-1668.611537	0.323378	-1668.262640	-1668.339018
TS2l	-1530.055689	0.301242	-1529.730712	-1529.803383
TS2m	-2296.842518	0.421887	-2296.385442	-2296.480073
TS2n	-2222.944787	0.439953	-2222.469401	-2222.565009
TS2o	-2543.963486	0.456884	-2543.467765	-2543.569700
TS2p	-1547.510662	0.372073	-1547.112569	-1547.189819
TS2q	-1622.737632	0.376875	-1622.334064	-1622.412208
TS8	-1432.786666	0.322158	-1432.441129	-1432.512805
TS9	-1432.784174	0.322949	-1432.438270	-1432.509373
TS10	-1432.785633	0.323236	-1432.439447	-1432.510541
TS11	1432.786964	0.323395	-1432.44059	-1432.511474
TS12	-1538.806516	0.246695	-1538.537901	-1538.607410
TS13	-1538.807307	0.246580	-1538.538744	-1538.608139
TS14	-1538.802382	0.246087	-1538.534093	-1538.603808
TS15	-1538.797052	0.246404	-1538.528742	-1538.598050
TS16	-1201.756382	0.241444	-1201.496401	-1201.558938

C. SYNTHETIC PROCEDURES



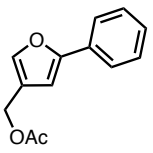
Acetate esters – general procedure: The furan (1 equiv) was dissolved in CH_2Cl_2. Acetic anhydride (3 equiv) and trimethylamine (5 equiv) were added. The mixture was stirred at room temperature overnight. Saturated NH_4Cl was added and the organic layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under vacuum. The residue obtained was purified by silica gel chromatography (20% ethyl acetate in hexanes).

(5-methylfuran-3-yl)methyl acetate, S1



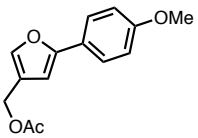
Colorless oil; yield 71% (112 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (s, 1H), 6.02 (s, 1H), 4.91 (s, 2H), 2.27 (d, J= 0.9 Hz, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 153.2, 139.7, 121.1, 106.5, 58.0, 21.0, 13.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_{10}O_3Na^+$ calc 177.0528; Found 177.0534.

(5-phenylfuran-3-yl)methyl acetate, S2



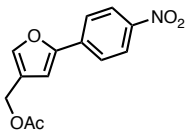
White solid; yield 92% (231 mg); ^{1}H NMR(500 MHz, $CDCl_3$): δ 7.66- 7.64 (m, 2H), 7.50 (s, 1H), 7.40- 7.37 (m, 2H), 7.29- 7.27 (m, 1H), 6.69 (s, 1H), 5.01 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.9, 154.8, 140.9, 130.5, 128.7, 127.6, 123.8, 122.4, 105.8, 57.8, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}O_3Na^+$ 239.0684; Found 239.0685.

(5-(4-methoxyphenyl)furan-3-yl)methyl acetate, S3



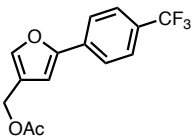
Pink solid; yield 88% (170 mg);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59-7.56 (dt, J= 2.8, 9.6 Hz, 2H), 7.45 (d, J= 0.7 Hz, 1H), 6.92- 6.89 (dt, J= 2.8, 9.7 Hz, 2H), 6.55- 6.54 (d, J= 0.5 Hz, 1H), 4.99 (s, 2H), 3.81 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 159.1, 154.7, 140.2, 125.2, 123.4, 122.2, 114.0, 104.1, 57.8, 55.1, 20.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}O_4Na^+$ 269.0790; Found 269.0788.

(5-(4-nitrophenyl)furan-3-yl)methyl acetate, S4



Yellow solid; yield 73% (25 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26- 8.23 (dt, J= 2.3, 9.3 Hz, 2H), 7.79- 7.76 (dt, J= 2.3, 9.3 Hz, 2H), 7.60 (d, J= 0.7 Hz, 1H), 6.91 (s, 1H), 5.01 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 152.4, 146.6, 142.9, 136.0, 124.3, 124.0, 123.2, 109.7, 57.4, 20.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}O_4Na^+$ 284.0535; Found 284.0542.

(5-(4-(trifluoromethyl)phenyl)furan-3-yl)methyl acetate, S5

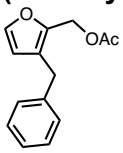


White solid; yield 87% (18 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75- 7.74 (d, J= 8.1 Hz, 2H), 7.64- 7.62 (d, J= 8.2 Hz, 2H), 7.55 (s, 1H), 6.80 (s, 1H), 5.01 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 153.2, 141.9, 133.6, 125.7- 125.7, 123.8, 122.8, 107.8, 57.6, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}F_3O_3H^+$ calc 285.0739; found 285.0734.

(4-methylfuran-3-yl)methyl acetate, S6

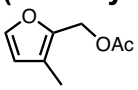
Colorless oil; yield 87% (24 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.19 (s, 1H), 4.95 (s, 2H), 2.07 (s, 3H) , 2.02 (d, J= 0.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 142.2, 140.1, 120.5, 119.7, 56.7, 20.9, 7.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_{11}O_3^+$ calc 177.0528; Found 177.0533.

(3-benzylfuran-2-yl)methyl acetate, S7

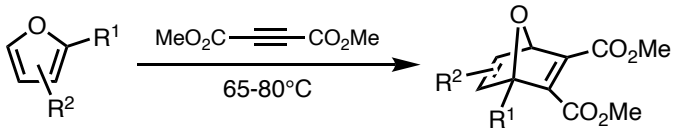


Colorless oil; yield 78% (19 mg); ^{1}H NMR (500 MHz, CD_3OD): 7.41- 7.40 (d, J= 1.8 Hz, 1H), 7.27-7.23 (m, 2H), 7.19- 7.16 (m, 3H), 6.21 (d, J= 1.8 Hz, 1H), 5.07 (s, 2H), 3.82 (s, 2H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 172.4, 146.8, 143.9, 141.7, 129.5, 129.4, 127.2, 125.4, 113.3, 57.2, 31.6, 20.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}O_3H^+$ 231.1021; Found 231.0833.

(3-methylfuran-2-yl)methyl acetate, S8

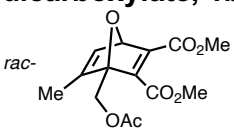


The NMR data agreed with the reported spectrum of this compound.[6]



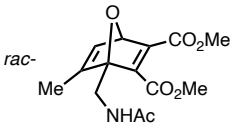
Diels-Alder reactions – general procedure: The furan (1 equiv) and dimethylacetylenedicarboxylate (1.2 equiv) with a few drops of acetonitrile were stirred in a sealed vial for 16 hours at 65-80°C (oil bath). The reaction mixture was purified by silica gel chromatography (gradient, 20-60% ethyl acetate in hexanes).

Dimethyl-1-(acetoxymethyl)-6-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1b



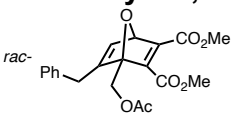
Yellow oil; yield 60% (5 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69- 6.69 (t, J= 1.9 Hz, 1H), 5.60 (d, J= 1.6 Hz, 1H), 4.90- 4.87 (d, J= 12.8 Hz, 1H), 4.63- 4.60 (d, J= 12.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.08 (s, 3H) , 1.97 (d, J= 1.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 164.27, 162.7, 153.4, 153.2, 152.7, 136.7, 96.2, 83.3, 60.3, 52.3, 20.5, 13.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_7Na^+$ calc 319.0794; Found 319.0786.

Dimethyl-1-(acetamidomethyl)-6-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1a



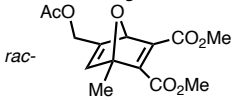
Yellow oil; yield 60% (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67- 6.66 (t, J= 1.9 Hz, 1H), 5.73 (br s, 1H), 5.57 (d, J= 1.6 Hz, 1H), 4.28- 4.24 (dd, J= 6.7, 14.7 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.76- 3.75 (d, J= 4.3 Hz, 1H), 1.97 (s, 3H) , 1.94 (d, J= 1.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 164.0, 162.5, 153.6, 153.5, 152.9, 136.5, 97.4, 82.8, 52.4, 52.2, 36.7, 22.9, 12.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{17}NO_6Na^+$ 318.0954; Found 318.0957.

Dimethyl-1-(acetoxymethyl)-6-benzyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1c



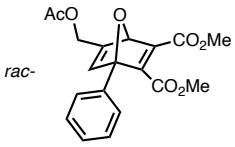
Yellow oil; yield 77% (40 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30- 7.27 (m, 2H), 7.24- 7.21 (m, 1H), 7.13- 7.12 (d, J= 7.2 Hz, 2H), 6.57- 6.56 (d, J= 1.6 Hz, 1H), 5.59 (s, 1H), 4.85- 4.82 (d, J= 12.7 Hz, 1H), 4.57- 4.54 (d, J= 12.8 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.67- 3.57 (q, J= 17.2 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 163.7, 162.8, 157.2, 153.5, 152.3, 137.8, 136.5, 129.0, 128.6, 126.8, 96.1, 83.4, 60.4, 52.4, 52.3, 34.2, 20.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{20}O_7Na^+$ 395.1107; Found 395.1101.

Dimethyl-5-(acetoxymethyl)-1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1d



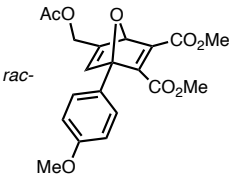
Yellow oil; yield 68% (52 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (s, 1H), 5.51 (s, 1H), 4.88- 4.85 (dd, J= 1.3, 14.2 Hz, 1H), 4.79- 4.76 (dd, J= 1.6, 14.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.06 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 164.7, 162.7, 156.2, 154.9, 150.8, 141.2, 94.4, 84.1, 60.0, 52.3, 52.3, 20.7, 15.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_7Na^+$ calc 319.0794; Found 319.0789.

Dimethyl-5-(acetoxymethyl)-1-phenyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1f



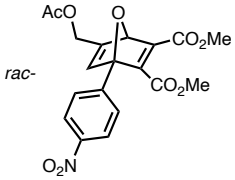
Yellow oil; yield 93% (107 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50- 7.48 (m, 2H), 7.42- 7.38 (m, 3H), 7.22- 7.21 (t, J= 1.5 Hz,1H), 5.74 (s, 1H), 4.96- 4.93 (dd, J= 1.5, 14.3 Hz, 1H), 4.88- 4.85 (dd, J= 1.6, 14.3 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.5, 164.8, 162.3, 158.4, 155.4, 148.6, 139.2, 133.5, 129.1, 128.6, 126.8, 98.5, 84.4, 60.1, 52.4, 52.3, 20.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}O_7Na^+$ 381.0950; Found 381.0957.

Dimethyl-5-(acetoxymethyl)-1-(4-methoxyphenyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1g



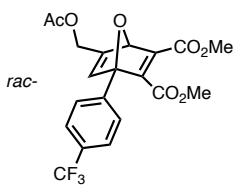
Yellow oil; yield 97% (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43- 7.40 (dt, J= 2.8, 9.6 Hz, 2H), 7.20 (t, J= 2.8, 9.7 Hz, 1H), 6.93- 6.90 (m, 2H), 5.71 (s, 1H), 4.95- 4.92 (dd, J= 1.6, 14.3 Hz, 1H), 4.87- 4.84 (dd, J= 1.6, 14.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 170.5, 165.0, 162.4, 160.1, 158.3, 155.4, 148.7, 139.1, 128.4, 125.5, 114.01, 98.4, 84.4, 60.1, 55.2, 52.4, 52.3, 20.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}O_7Na^+$ 411.1056; Found 411.1055.

Dimethyl (1S,4R)-5-(acetoxymethyl)-1-(4-nitrophenyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1h



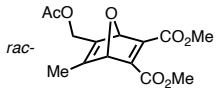
Yellow oil; Yield 76% (9 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29- 8.27 (m, 2H), 7.71- 7.69 (m, 2H), 7.18- 7.17 (q, J= 1.4 Hz, 1H), 5.78 (d, J= 0.8 Hz, 1H), 4.97- 4.93 (dd, J= 1.4, 14.5 Hz, 1H), 4.89- 4.86 (dd, J= 1.4, 14.5 Hz, 1H), 3.83 (d, J= 1.2 Hz, 3H), 3.69 (d, J= 1.2 Hz, 3H), 2.10 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.4, 164.1, 162.1, 156.8, 155.8, 149.3, 148.2, 140.5, 138.4, 127.7, 123.7, 97.2, 84.6, 59.9, 52.6, 52.5, 20.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{17}NO_9Na^+$ 426.0801; Found 426.0795.

Dimethyl-5-(acetoxymethyl)-1-(4-(trifluoromethyl)phenyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1i



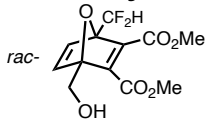
White solid; yield 60% (16 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68- 7.67 (d, J= 8.2 Hz, 2H), 7.64- 7.62 (d, J= 8.2 Hz, 2H), 7.18 (t, J= 1.7 Hz, 1H), 5.76 (s, 1H), 4.96- 4.93 (dd, J= 1.6, 14.4 Hz, 1H), 4.89- 4.86 (dd, J= 1.7, 14.4 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 170.4, 164.4, 162.2, 157.4, 155.6, 149.0, 138.7, 137.5, 131.0, 127.1, 125.6-125.5, 122.8, 97.6, 84.5, 60.0, 52.5, 52.4, 20.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}F_3O_7Na^+$ 449.0824; Found 449.0816.

Dimethyl-5-(acetoxymethyl)-6-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1e



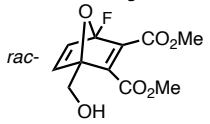
Colorless oil; yield 58% (10 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.60- 5.59 (d, J= 1.3 Hz, 1H), 5.40 (s, J= 1.7 Hz, 1H), 4.86- 4.83 (d, J= 12.9 Hz, 1H), 4.67- 4.65 (dd, J= 0.7, 12.9 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.04 (s, 3H) , 1.98 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.8, 163.3, 163.1, 153.4, 151.67, 151.5, 142.0, 88.9, 86.9, 57.8, 52.4, 20.8, 12.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_7Na^+$ 319.0794; Found 319.0786.

Dimethyl-1-(difluoromethyl)-4-(hydroxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1k



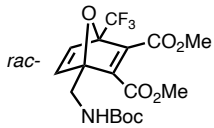
Reaction at 80°C, yellow oil; yield 60% (56 mg); ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.19 (br s, 2H), 6.56, 6.49, 6.41 (3 s, 1H), 4.31 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.67 (br s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 163.5, 163.1, 152.5, 151.7, 144.8, 141.2, 112.8, 111.4, 110.0, 97.9, 94.1, 94.0, 93.8, 59.6, 52.8, 52.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}F_2O_6Na^+$ 313.0494; Found 313.0496.

Dimethyl-1-fluoro-4-(hydroxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1l



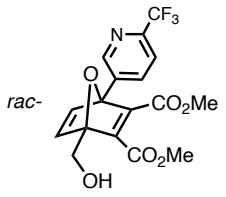
Reaction at 80°C for 24h, yellow oil; yield 52% (13 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (dd, J = 2.5, 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 4.29 (d, J = 7.0 Hz, 2H), 3.88 (s, 1H), 3.83 (s, 1H), 2.66 (t, J = 7.2 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 163.1, 162.0, 151.5, 151.3, 145.7- 145.6, 141.0, 140.9, 122.0, 120.5, 91.0, 59.7, 52.9, 52.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{11}F_1O_6Na^+$ 281.0432; Found 281.0428.

Dimethyl-1-(((tert-butoxycarbonyl)amino)methyl)-4-(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S9



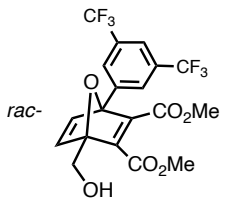
Reaction at 80°C for 6 days, yellow oil; yield 40% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.19 (m, 2H), 4.99 (br s, 1H), 4.10 (m, 1H, overlap with EtOAc), 3.97 (dd, J = 6.2, 15.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 162.2, 155.8, 152.6, 151.3, 145.9, 140.8, 123.3, 120.5, 97.3, 93.2, 92.9, 91.4, 80.0, 52.9, 52.8, 39.1, 28.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}F_3N_1O_7Na^+$ 430.1090; Found 430.1087.

Dimethyl-1-(hydroxymethyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S10



Reaction at 80°C for 2 days, yellow oil; yield 91% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 1.7, 8.1 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), 4.41 (d, J = 6.3 Hz, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 2.98 (t, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 163.6, 157.5, 149.9, 148.7, 148.3, 144.9, 144.5, 136.1, 132.9, 122.7, 120.1, 120.1, 97.3, 94.1, 59.9, 52.8, 52.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{14}F_3N_1O_6H^+$ 386.0851; Found 386.0855.

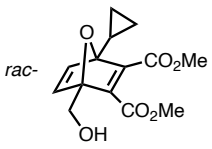
Dimethyl-1-(3,5-bis(trifluoromethyl)phenyl)-4-(hydroxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S11



Reaction at 80°C for 6 days, yellow oil; yield 56% (31 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 2H), 7.91 (br s, 1H), 7.41 (d, J = 5.2 Hz), 7.29 (d, J = 5.2 Hz, 1H), 4.41 (d, J = 6.2 Hz), 3.83 (s, 3H), 3.66 (s, 3H), 2.90 (t, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 163.7, 158.4, 149.5, 145.3,

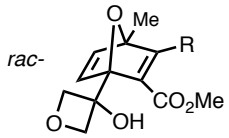
144.8, 136.6, 132.3, 131.9, 127.2, 124.5, 122.9, 121.8, 97.3, 95.4, 60.1, 53.0, 52.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{14}F_6O_6H^+$ calc 453.0773; Found 453.0771.

Dimethyl-1-(3,5-bis(trifluoromethyl)phenyl)-4-(hydroxymethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1p

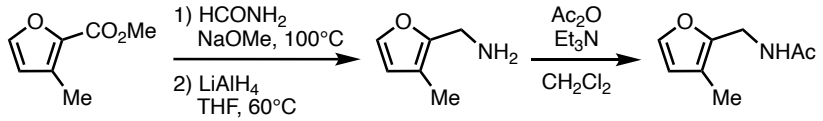


Reaction at 75°C, yellow oil; yield 94% (85 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (dd, J = 0.76, 5.3 Hz, 1H), 6.77 (d, J = 5.3 Hz, 1H), 4.21 (d, J = 4.9 Hz), 3.81 (s, 3H), 3.73 (s, 3H), 2.98 (t, J = 6.6 Hz, 1H), 1.42-1.52 (m, 1H), 0.56-0.71 (m, 3H), 0.47-0.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 163.9, 159.8, 148.9, 144.8, 143.6, 97.1, 95.8, 60.1, 52.5, 52.3, 9.3, 2.4, 2.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_6Na^+$ 303.0845; Found 303.0842.

Dimethyl-1-(2-hydroxyoxetan-2-yl)-4-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1q

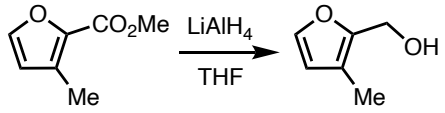


Reaction at 70°C, yellow oil; yield 87% (297 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, J = 5.2 Hz, 1H), 6.97 (d, J = 5.2 Hz, 1H), 4.73 (d, J = 7.3 Hz, 1H), 4.62 (d, J = 7.2 Hz, 2H), 4.56 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 164.2, 158.6, 149.9, 148.1, 143.0, 97.3, 92.8, 80.7, 80.1, 72.0, 52.6, 52.2, 15.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_7Na^+$ calc 319.0788; Found 319.0792.

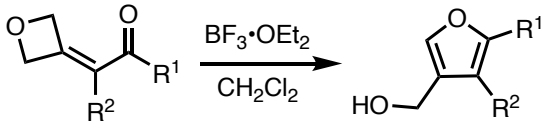


N-((3-methylfuran-2-yl)methyl)acetamide, S12: This compound was prepared according to a literature procedure.[7] The NMR data agreed with the reported spectrum of this compound.

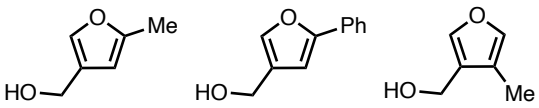
(3-methylfuran-2-yl)methanol, S13: This compound was prepared according to a literature procedure.[8] The NMR data agreed with the reported spectrum of this compound.



3-Hydroxymethylfurans – general procedure: Following the published procedure,[9] the enone (1 equiv) was dissolved in dichloromethane. A solution of $BF_3{\cdot}OEt_2$ (1% mol) in dichloromethane was added. The solution was stirred at room temperature for 2 min. The reaction mixture was purified by silica gel chromatography (50% diethyl ether in hexanes).

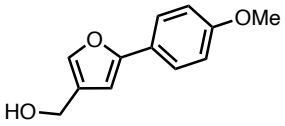


(5-methylfuran-3-yl)methanol (S14), **(5-phenylfuran-3-yl)methanol (S15)**, **(4-methylfuran-3-yl)methanol (S16)**



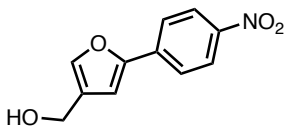
The NMR data agreed with the reported spectra of these compounds.[9]

(5-(4-methoxyphenyl)furan-3-yl)methanol, S17



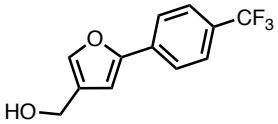
Pale pink solid; yield 76% (159 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.57 (dt, J= 2.8, 9.6 Hz, 2H), 7.41 (s, 1H), 6.93- 6.90 (dt, J= 2.8, 9.6 Hz, 2H), 6.57 (s, 1H), 4.58 (s, 2H), 3.83 (s, 3H), 1.56 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 154.8, 138.6, 127.1, 125.2, 123.7, 114.1, 103.5, 56.8, 55.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}O_3H^+$ 205.0865; Found 205.0863.

(5-(4-nitrophenyl)furan-3-yl)methanol, S18



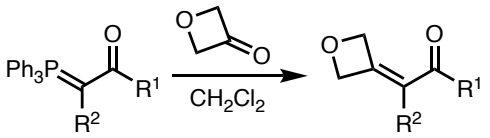
Yellow solid; yield 90% (27 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25-8.24 (d, J= 7.5 Hz, 2H), 7.78- 7.76 (d, J= 7.4 Hz, 2H), 7.55 (s, 1H), 6.92 (s, 1H), 4.63 (s, 2H), 1.63 (br s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 146.5, 141.2, 136.2, 127.9, 124.3, 124.0, 108.9, 56.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_9NO_4Na^+$ 242.0429; Found 242.0424.

(5-(4-(trifluoromethyl)phenyl)furan-3-yl)methanol, S19

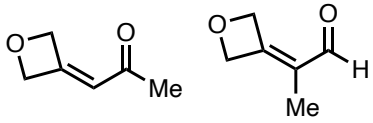


White solid; yield 96% (105 mg); ^{1}H NMR (500 MHz, $CDCl_3$): 7.74-7.72 (d, J= 8.2 Hz, 2H), 7.63- 7.61 (d, J= 8.4 Hz, 2H), 7.49 (s, 1H), 6.81 (s, 1H), 4.61 (s, 2H), 1.74 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 140.2, 133.7, 129.3, 129.0, 127.5, 125.7- 125.7, 123.8, 107.0, 56.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9F_3O_2H^+$ calc 243.0633; found 243.0631.

Wittig reaction – general procedure: Following the published procedure,[9] the phosphorane (1.4 equiv) was dissolved in dry dichloromethane. 3-oxetanone was added (1.0 equiv). The mixture was stirred at room temperature for 16 hours. The reaction mixture was purified by silica gel chromatography (50% diethyl ether in hexanes).

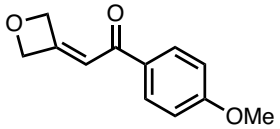


1-(oxetan-3-ylidene)propan-2-one (S20), **1-(oxetan-3-ylidene)propan-2-one (S21)**



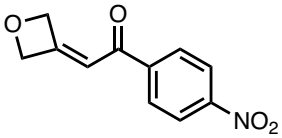
The NMR data agreed with the reported spectra of these compounds.[9]

1-(4-methoxyphenyl)-2-(oxetan-3-ylidene)ethan-1-one, S22



Pink solid; yield 98% (185 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91- 7.88 (dt, J= 2.7, 9.7 Hz, 2H), 6.95- 6.92 (m, J= 2.7, 9.7 Hz, 2H), 6.78- 6.77 (p, J= 2.3 Hz, 1H), 5.67- 5.65 (m, 2H), 5.40- 5.38 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 154.9, 138.6, 127.1, 125.3, 123.8, 114.1, 103.5, 56.9, 55.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}O_3Na^+$ 227.0684; Found 227.0681.

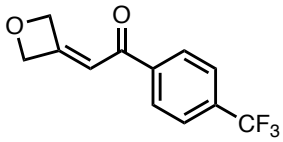
1-(4-nitrophenyl)-2-(oxetan-3-ylidene)ethan-1-one, S23



Yellow solid; yield 45% (102 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34-8.32 (dt, J= 2.2, 9.1 Hz, 2H), 8.08- 8.06 (dt, J= 2.2, 9.1 Hz, 2H), 6.85-6.83 (p, J= 2.3 Hz, 1H), 5.69- 5.67 (m, 2H), 5.46- 5.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.1, 164.5, 150.2, 142.1, 129.1, 123.9, 112.9, 82.5, 79.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for

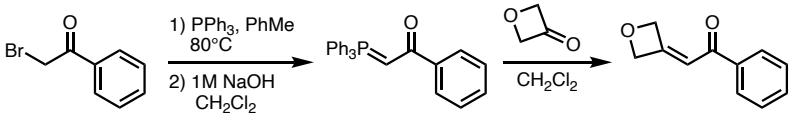
$C_{11}H_9NO_4Na^+$ 242.0429; Found 242.0434.

2-(oxetan-3-ylidene)-1-(4-(trifluoromethyl)phenyl)ethan-1-one, S24

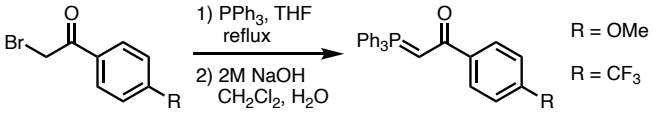


White solid; yield 43% (109 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02- 8.01 (d, J= 8.1 Hz, 2H), 7.75- 7.73 (d, J= 8.3 Hz, 2H), 6.83- 6.82 (p, J= 2.3 Hz, 1H), 5.69- 5.67 (m, 2H), 5.45- 5.43 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 184.5, 164.4, 141.9, 135.3, 130.0, 126.9- 124.1, 114.5, 83.5, 80.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9F_3O_2H^+$ calc 243.0633; Found 243.0631.

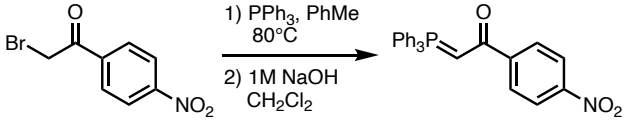
2-(oxetan-3-ylidene)-1-phenylethan-1-one, S25: This compound was prepared according to a literature procedure.[9] The NMR data agreed with the reported spectrum of this compound.



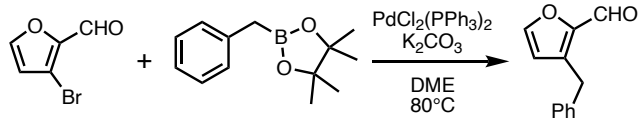
1-(4-Methoxyphenyl)-2-(triphenylphosphoranylidene)ethenone, **1-(4-(Trifluoromethyl)phenyl)-2-(triphenylphosphoranylidene)ethenone, S26**:
These compounds were prepared according to a literature procedure.[10] The NMR data agreed with their reported spectra.



1-(4-(Nitro)phenyl)-2-(triphenylphosphoranylidene)ethenone, S27: This compound was prepared according to a literature procedure.[11] The NMR data agreed with the reported spectrum of this compound.

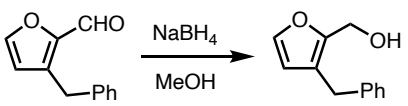


3-benzylfuran-2-carbaldehyde, S28: 3-bromo-2-furfuryl aldehyde (1 equiv), benzylboronic acid pinacol ester (1.2 equiv), potassium carbonate (3 equiv) and bis(triphenylphosphine)palladium(II) dichloride (10% mol) were added to a vial. The vial was evacued and backfilled with nitrogen three times. The solvent, dimethoxyethane, was added as well as water and the solution was heated at 80°C (oil bath). Saturated NH_4Cl was added until the solution reached a pH of 7 and the organic layer was extracted with ethyl acetate three times. The combined organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under vacuum. The residue obtained was purified by silica gel chromatography (10% ethyl acetate in hexanes) to give a yellow oil (58 mg, 30% yield).



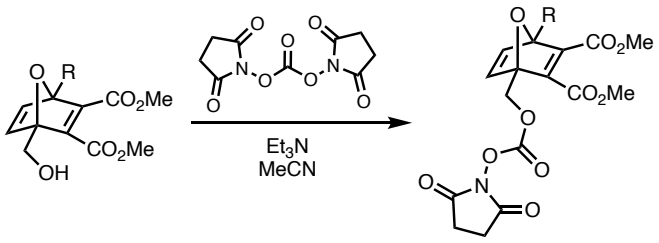
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.55- 7.55 (d, J= 1.5 Hz, 1H), 7.33- 7.30 (m, 2H), 7.25- 7.22 (m, 3H), 6.37- 6.37 (d, J= 1.6 Hz, 1H), 4.17 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 148.3, 147.3, 138.6, 128.7, 128.6, 126.7, 114.6, 30.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}O_2H^+$ 187.0759; Found 187.0754.

(3-benzylfuran-2-yl)methanol, S29: 3-benzylfuran-2-carbaldehyde (1 equiv) was dissolved in methanol and sodium borohydride (1.5 equiv) was added. The solution was stirred at room temperature for two hours. Saturated NH4Cl was added and the organic layer was extracted with dichloromethane three times. The combined organic

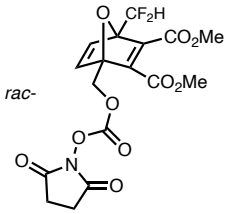


layer was washed with brine, dried over sodium sulfate and the solvent was removed under vacuum. The residue obtained was purified by silica gel chromatography (gradient, 10-30% ethyl acetate in hexanes) to give a colorless oil (32 mg, 70% yield.)
^{1}H NMR (500 MHz, $CDCl_3$): 7.33- 7.33 (d, J= 1.8 Hz, 1H), 7.31- 7.28 (m, 2H), 7.22- 7.19 (m, 3H), 6.20- 6.20 (d, J= 1.8 Hz, 1H), 4.60 (s, 2H), 3.81 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 141.9, 140.3, 128.5, 128.3, 126.2, 121.4, 112.3, 55.4, 30.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}O_2Na^+$ 211.0735; Found 211.0736.

Activation of 2-hydroxymethyl group – general procedure: A solution of di(N-succinimidyl) carbonate (DSC, 1.5 equiv) and triethylamine (2 equiv) in acetonitrile were stirred for 5 minutes at 0°C. Then a solution of OND alcohol (1 equiv) in acetonitrile was added dropwise at 0°C to the reaction mixture. The ice bath was removed and the reaction mixture was stirred until the consumption of OND starting material (as monitored by TLC, 3h). The solvent was removed under vacuum and the residue obtained was purified by silica gel chromatography (gradient, 30-70% ethyl acetate in hexanes)

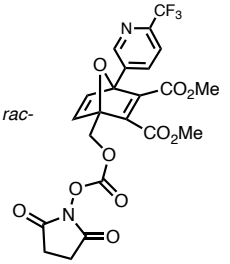


Dimethyl (1R,4R)-1-(difluoromethyl)-4-(((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)methyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S30



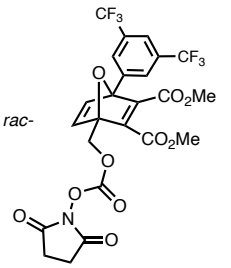
White solid; yield 43% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24- 7.23 (d, J = 5.3 Hz, 1H), 7.16- 7.15 (d, J = 5.2 Hz, 1H), 6.55, 6.44, 6.34 (3 s, 1H), 5.11- 5.04 (q, J = 10.6 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.80 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 162.9, 162.1, 152.7, 151.7, 1511, 149.8, 143.6, 141.9, 113.1, 111.2, 109.2, 94.2, 66.4, 52.8, 58.8, 25.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}F_2N_1O_{10}H^+$ 432.0742; Found 432.0745.

Dimethyl (1R,4S)-1-(((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)methyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S31

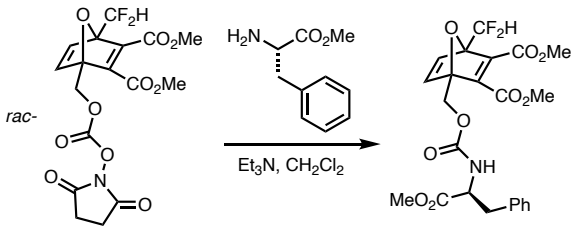


Yellow oil; yield 59% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, J = 2.0 Hz, 1H), 8.07 (d, J = 1.7, 8.2 Hz), 7.75 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 5.19 (s, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 2.83 (s, 4H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 168.2, 163.6, 162.3, 157.6, 151.4, 148.3- 148.2, 145.4, 143.4, 136.2, 132.4, 125.9, 123.5, 120.3, 109.7, 94.4, 93.7, 66.8, 52.9, 52.7, 25.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{17}F_3N_2O_{10}H^+$ 527.0914; Found 527.0917.

Dimethyl-1-(3,5-bis(trifluoromethyl)phenyl)-4-(((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)methyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, S32

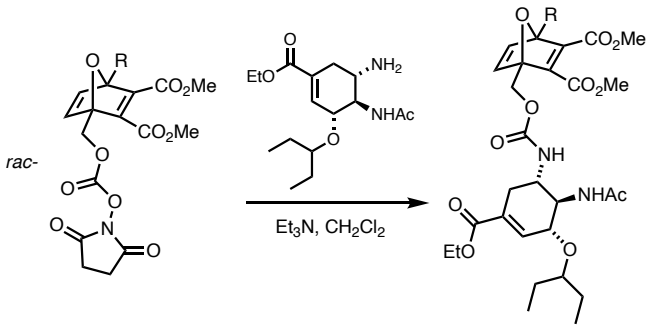


Yellow oil; Yield 49% (19 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 2H), 7.95 (br s, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.27 (t, J = 5.2 Hz, 1H), 5.23 (s, 2H), 3.87 (s, 3H), 3.70 (s, 3H), 2.86 (s, 4H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 168.2, 163.6, 162.2, 158.1, 151.4, 147.9, 145.5, 144.6, 135.9, 132.1- 132.9, 127.1, 123.79, 123.0, 122.2, 95.5, 93.7, 66.9, 52.9, 52.5, 25.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{17}F_6N_1O_{10}H^+$ 594.0835; Found 594.0838.

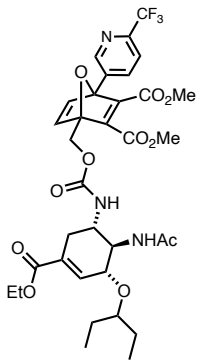


Dimethyl-1-(difluoromethyl)-4-(((((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)oxy)methyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1j: A solution of phenylalanine methyl ester hydrochloride (1 equiv) and triethylamine (2.5 equiv) in dichloromethane was cooled to -20 °C. Then a solution of OND N-hydroxysuccinimidyl carbonate (1.1 to 1.2 equiv) in dichloromethane was added dropwise and the reaction mixture was allowed to reach to room temperature in about 1.5 h. Solvent was removed under vaccum and the residue obtained was patitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to obtain the crude product which was purified by silica gel chromatography (40% ethyl acetate in hexanes) and yield product as a pale yellow solid (37 mg, 69%, mixture of diastereomers).
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.27-7.31 (m, 2H), 7.23-7.26 (m, 1H), 7.20 (dd, J = 1.2, 5.4 Hz), 7.07-7.14 (m, 3H), 6.60, 6.59, 6.53, 6.52, 6.45, 6.44 (6 s, 1H), 5.29, 5.27 (2 d, J = 8.3 Hz, 1H), 4.84, 4.83 (2 s, 2H), 4.60-4.66 (m, 1H), 3.84, 3.83 (2 s, 3H), 3.78, 3.75 (2 s, 3H), 3.72, 3.71 (2 s, 3H), 3.14, 3.12 (2 d, J = 5.7 Hz, 1H), 3.17-3.09 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 171.7, 171.7, 163.0, 162.8, 162.7, 155.0, 154.9, 152.3, 152.1, 151.7, 151.4, 144.6, 144.5, 141.8, 141.7, 135.7, 135.6, 129.4, 129.4, 128.8, 127.3, 127.3, 112.8, 111.5, 110.1, 95.8, 95.7, 94.3, 94.2, 94.0, 61.3, 61.2, 55.1, 55.1, 52.9, 52.8, 52.7, 52.5, 52.5, 38.3, 38.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{23}F_2N_1O_9Na^+$ 518.1233; Found 518.1239.

Oseltamivir conjugates – general procedure: A solution of oseltamivir phosphate (1 equiv) and triethylamine (2.5 equiv) in dichloromethane was cooled to -20 °C. Then a solution of OND N-hydroxysuccinimidyl carbonate (1.1 to 1.2 equiv) in dichloromethane was added dropwise and the reaction mixture was allowed to reach to room temperature in about 1.5 h. Solvent was removed under vaccum and the residue obtained was patitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to obtain the crude product which was purified by silica gel chromatography (gradient, 40-70% ethyl acetate in hexanes).



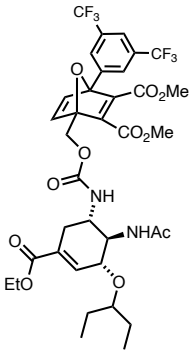
Dimethyl-1-(((((1S,5R,6R)-6-acetamido-3-(ethoxycarbonyl)-5-(pentan-3-yloxy)cyclohex-3-en-1-yl)carbamoyl)oxy)methyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1n



Pale yellow solid; yield 65% (14 mg, mixture of diastereomers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.00-8.10 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.44 (dd, J = 1.6, 4.8 Hz, 1H), 7.20 (dd, J = 1.0, 5.0 Hz, 1H), 6.80 (br s, 1H), 5.54-5.71 (m, 2H), 4.92, 4.88 (ABq, J = 12.6Hz, 2H), 4.15-4.26 (m, 2H), 4.05-4.14 (m, 1H), 3.94-4.04 (m, 1H), 3.86-3.94 (m, 1H), 3.83, 3.82 (2s, 3H), 3.67 (s, 3H), 3.34-3.42 (m, 1H), 2.75 (2dt, J = 5.1 Hz, 1H), 2.34-2.41 (m, 1H), 1.95 (s, 3H), 1.44-1.58 (m, 4H), 1.29 (td, J = 1.0, 6.9 Hz, 3H), 0.83-0.92 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 170.9, 165.9, 163.6, 163.5, 162.8, 156.0, 156.0, 155.8, 155.8, 150.4, 150.3, 148.5, 144.6, 144.6, 144.5, 144.4, 136.8, 136.7, 136.35, 136.29, 132.88, 129.39, 122.41, 120.16, 95.00, 94.98, 94.16,

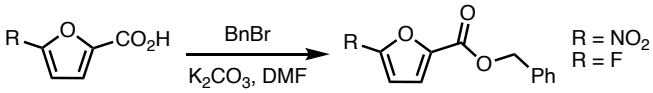
82.07, 82.0, 75.1, 74.9, 61.2, 61.1, 61.0, 53.3, 53.1, 52.7, 52.6, 52.5, 49.7, 49.6, 30.4, 30.3, 26.1, 26.1, 25.7, 23.3, 23.3, 14.1, 9.4, 9.3, 9.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{41}F_3N_3O_{11}H^+$ 724.2688; Found 724.2684.

Dimethyl-1-(((((1S,5R,6R)-6-acetamido-3-(ethoxycarbonyl)-5-(pentan-3-yloxy)cyclohex-3-en-1-yl)carbamoyl)oxy)methyl)-4-(3,5-bis(trifluoromethyl)phenyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1o

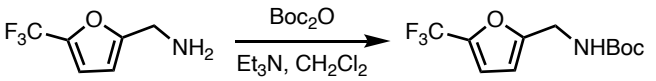


White solid; yield 60% (17 mg, mixture of diastereomers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br s, 2H), 7.91 (br s, 1H), 7.42 (d, J = 5.2 Hz, 1H), 7.21 (dd, J = 1.2, 5.2 Hz), 6.81 (br s, 1H), 5.48-5.73 (m, 2H), 4.93, 4.89 (ABq, J = 13.0 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.06-4.15 (m, 1H), 3.97-4.05 (m, 1H), 3.86-3.96 (m, 1H), 3.83, 3.81 (2s, 3H), 3.65 (s, 3H), 3.34-3.40 (m, 1H), 2.78, 2.73 (2t, J = 6.2 Hz, 1H), 2.33-2.44 (m, 1H), 1.97 (2s, 3H), 1.45-1.56 (m, 4H), 1.23-1.32 (m, 3H), 0.84-0.92 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.9, 165.9, 163.63, 162.7, 156.6, 155.7, 144.7, 144.5, 144.6, 136.9, 136.7, 136.4, 132.0, 131.8, 129.4, 127.3, 124.1, 122.8, 122.0, 95.2, 94.9, 82.1, 82.0, 75.1, 74.9, 61.3, 61.2, 61.0, 53.3, 53.1, 52.7, 52.6, 52.4, 49.6, 49.5, 30.5, 30.3, 29.7, 26.1, 25.7, 23.3, 14.2, 9.4, 9.3, 9.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{41}F_6N_2O_{11}H^+$ 791.2609; Found 791.2606.

Benzyl 5-nitrofuran-2-carboxylate[12] **(S33)** and **benzyl 5-fluorofuran-2-carboxylate**[13] **(S34)**: Prepared according to literature procedures; the NMR data agreed with the reported spectra.

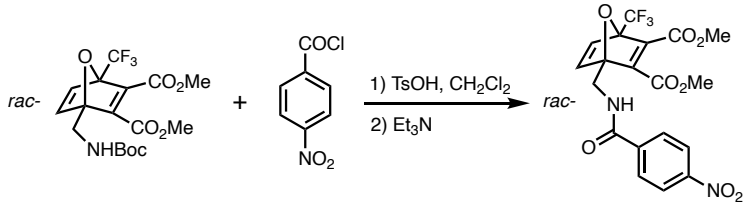


tert-butyl ((5-(trifluoromethyl)furan-2-yl)methyl)carbamate (S35): The furan (0.63 mmol) was dissolved in DCM (3 mL). Triethyl amine (1 equiv) was added, followed by di-tert-butyl dicarbonate (Boc_2O, 1.1 equiv). The reaction was stirred at room temperature overnight. Water and ethyl acetate were added. The organic layer was washed with water and 0.5M HCl, dried over sodium sulfate, filtered and concentrated under vacuum. White solid. 82% yield (155 mg).



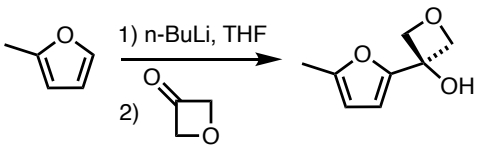
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (m, 1H), 6.29 (s, 1H), 4.94 (br s, 1H), 4.34- 4.33 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 155.1, 141.7- 140.6, 120.0, 117.9, 112.4, 107.7, 80.1, 37.5, 28.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{14}F_3NO_3Na^+$ 288.0823; Found 288.0825.

Dimethyl-1-((4-nitrobenzamido)methyl)-4-(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 1m: The OND (0.12 mmol) was dissolved in DCM (0.7 mL). p-toluenesulfonic acid (TsOH, 1.5 equiv) was added and the reaction was stirred at room temperature overnight. Triethyl amine (5 equiv) and 4-nitrobenzoyl chloride (1.1 equiv) were added. The reaction was stirred at room temperature for 16 hours. The organic layer was washed with sat. NaHCO3 (x 2), dried over sodium sulfate, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (50% ethyl acetate in hexanes) to yield product as a yellow oil (21 mg, 38% yield).

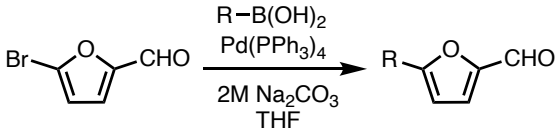


^{1}H NMR (700 MHz, $CDCl_3$): δ 8.31 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 7.21-7.24 (m, 2H), 6.90 (t, J = 5.7 Hz, 1H), 4.48 (dd, J = 6.0, 15.0 Hz, 1H), 4.36 (dd, J = 6.0, 15.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 165.5, 162.43, 162.3, 153.2, 150.3, 149.8, 145.7, 140.9, 139.3, 128.3, 123.9, 96.4, 53.0, 53.0, 38.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}F_3N_2O_8H^+$ 457.0854; Found 457.0851.

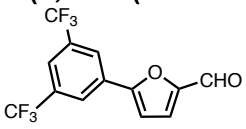
3-(5-methylfuran-2-yl)oxetan-3-ol, S36: This compound was prepared according to a literature producure.[14] The NMR data agreed with the reported spectrum of this compound.



5-Substituted furan carboxaldehydes – general procedure: 5-bromofuran-2-carbaldehyde (1 equiv), boronic acid (1.05 equiv), 2M sodium carbonate (5 equiv) and Tetrakis(triphenylphosphine)palladium(0) (0.035 equiv) were added to a vial. The solvent, THF, was added and the solution was heated at 80°C (oil bath) overnight. The reaction was then cooled to room temperature and concentrated under vacuum. Water and ethyl acetate were added. The organic layer was extracted twice with ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (15% ethyl acetate in hexanes).

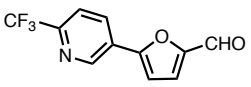


5-(3,5-bis(trifluoromethyl)phenyl)furan-2-carbaldehyde, S37



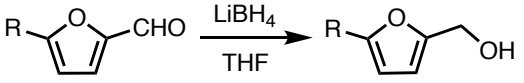
Pale yellow solid; yield 90% (760 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.22 (br s, 2H), 7.88 (br s, 1H), 7.37 (d, J = 3.8 Hz, 1H), 7.04 (d, J = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 155.5, 152.9, 132.8, 132.5, 131.0, 125.0, 122.7, 121.6, 109.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_6F_6O_2H^+$ 309.0350; Found 309.0549.

5-(6-(trifluoromethyl)pyridin-3-yl)furan-2-carbaldehyde, S38

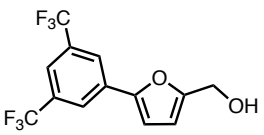


Pale yellow solid; yield 62% (156 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 9.12 (d, J = 2.0 Hz, 1H), 8.29 (dd, J = 2.0, 8.0 Hz, 1H), 7.78 (dd, J = 0.6, 8.2 Hz, 1H), 7.37 (d, J = 3.8 Hz, 1H), 7.07 (d, J = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 154.4, 153.2, 146.5, 133.3, 127.7, 122.5, 120.7, 120.7, 119.9, 110.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_6F_3N_1O_2H^+$ 242.0429; Found 242.0435.

Furan carboxyaldehyde reduction – general procedure: Lithium borohydride (1 equiv) was dissolved in THF and cooled to 0°C. The furan (1 equiv) was added dropwise at 0°C. The reaction was stirred and allowed to reach room temperature over 18 hours. Water was added to quench the reaction. The organic layer was extracted with DCM, washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum.

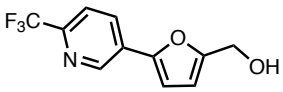


(5-(3,5-bis(trifluoromethyl)phenyl)furan-2-yl)methanol, S39



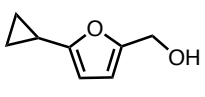
Pale yellow solid; yield 74% (92 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 2H), 7.74 (br s, 1H), 6.81 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 3.3 Hz, 1H), 4.72 (d, J = 6.1 Hz, 2H), 1.80 (t, J = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 151.0, 132.5, 132.4, 132.1, 124.3, 123.5, 122.2, 120.5, 110.3, 108.6, 57.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_8F_6O_2H^+$ 311.0507; Found 311.0514.

(5-(6-(trifluoromethyl)pyridin-3-yl)furan-2-yl)methanol, S40



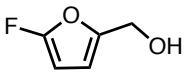
Pale yellow solid; yield 44% (40 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (d, J = 1.9 Hz, 1H), 8.09- 8.07 (dd, J = 1.6, 8.2 Hz, 1H), 7.69- 7.68 (d, J = 8.2 Hz, 1H), 6.83- 6.82 (d, J = 3.4 Hz, 1H), 6.46- 6.45 (d, J = 3.4 Hz, 1H), 4.71 (s, 2H), 1.88 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 149.5, 146.0, 145.2, 131.4, 129.1, 120.6, 120.5 -120.5, 110.3, 109.2, 57.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_8F_3N_1O_2H^+$ 244.0585; Found 244.0579.

(5-cyclopropylfuran-2-yl)methanol, S41



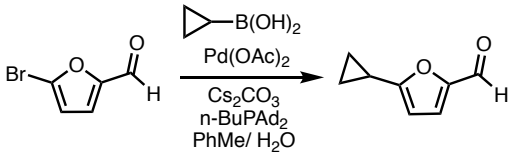
Yellow oil; yield 100% (44 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17- 6.16 (d, J = 3.1 Hz, 1H), 5.89- 5.88 (d, J = 3.1 Hz, 1H), 4.53 (s, 2H), 1.90- 1.85 (m, 1H), 1.25 (br s, 1H), 0.89-0.85 (m, 2H), 0.78-0.76 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 151.8, 108.7, 104.1, 57.6, 8.8, 6.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_{10}O_2H^+$ 139.0759; Found 139.0756.

(5-fluorofuran-2-yl)methanol, S42



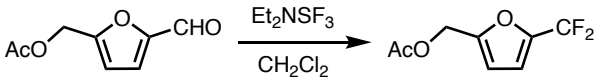
Reaction used 9 equiv of lithium borohydride, yellow oil; yield 65% (16 mg); The product is volatile and so the crude mixture was used for the next step without purification. The NMR signals of desired product were suppressed by excess benzyl alcohol. HRMS (ESI-TOF) m/z: $[2M + H]^+$ Calcd for $C_{10}H_{10}F_2O_4H^+$ 233.0625; Found 233.0627.

5-cyclopropylfuran-2-carbaldehyde, S43: 5-bromofuran-2-carbaldehyde (1 equiv), cyclopropylboronic acid (2 equiv), cesium carbonate (3 equiv), di(1-adamantyl)-n-butylphosphine (3% mol) and Palladium(II) acetate (2% mol) were added to a vial. Toluene and water (10:1) were added and the solution was heated at 100°C (oil bath) overnight. The reaction was then cooled to room temperature. Water and CH_2Cl_2 were added. The organic layer was extracted three times with DCM, dried over sodium sulfate, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (10% ethyl acetate in hexanes). Yellow oil. 74% yield (40 mg).

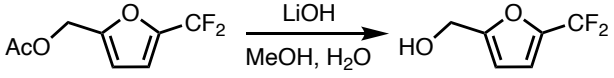


^{1}H NMR (500 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.16 (d, J = 3.6 Hz, 1H), 1.94-2.01 (m, 1H), 0.93-1.05 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 165.1, 151.1, 106.8, 9.5, 8.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_8O_2H^+$ 137.0603; Found 137.0601.

(5-(difluoromethyl)furan-2-yl)methyl acetate, S44: This compound was prepared according to a literature producure.[15] The NMR data agreed with the reported spectrum of this compound.



(5-(difluoromethyl)furan-2-yl)methanol, S45: This compound was prepared according to a literature producure.[15] The NMR data agreed with the reported spectrum of this compound.



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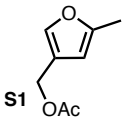
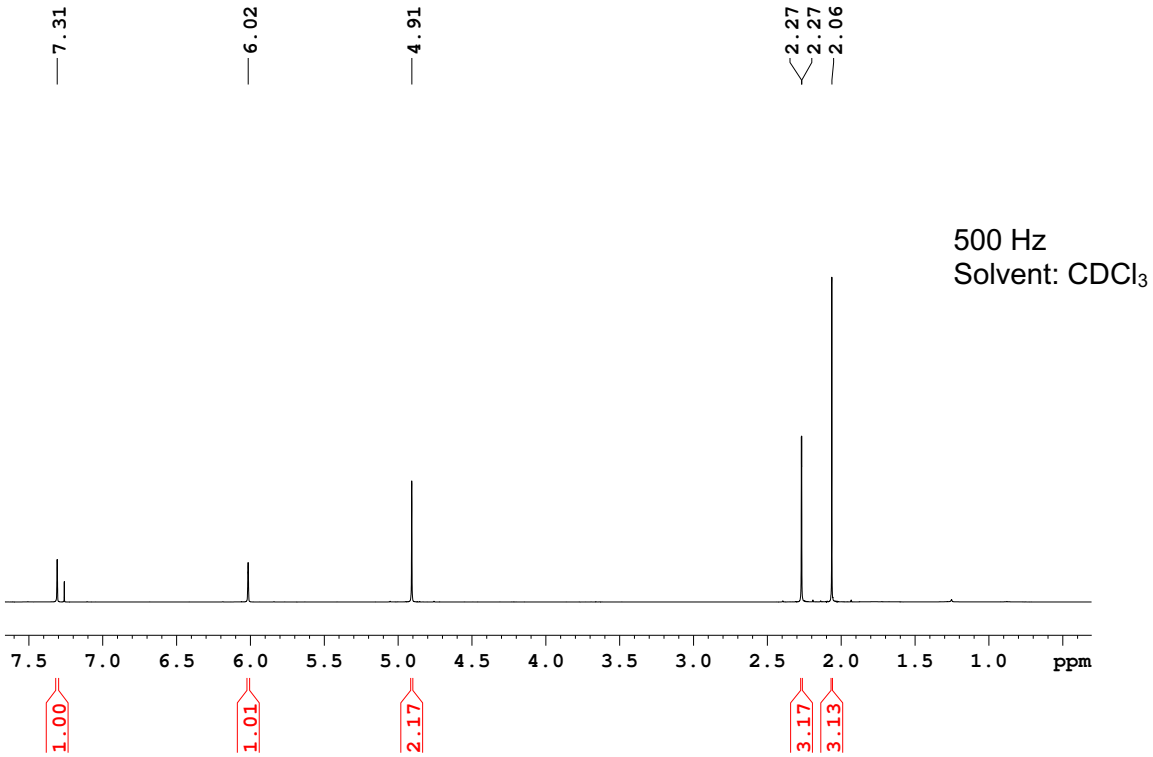
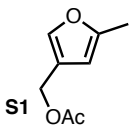
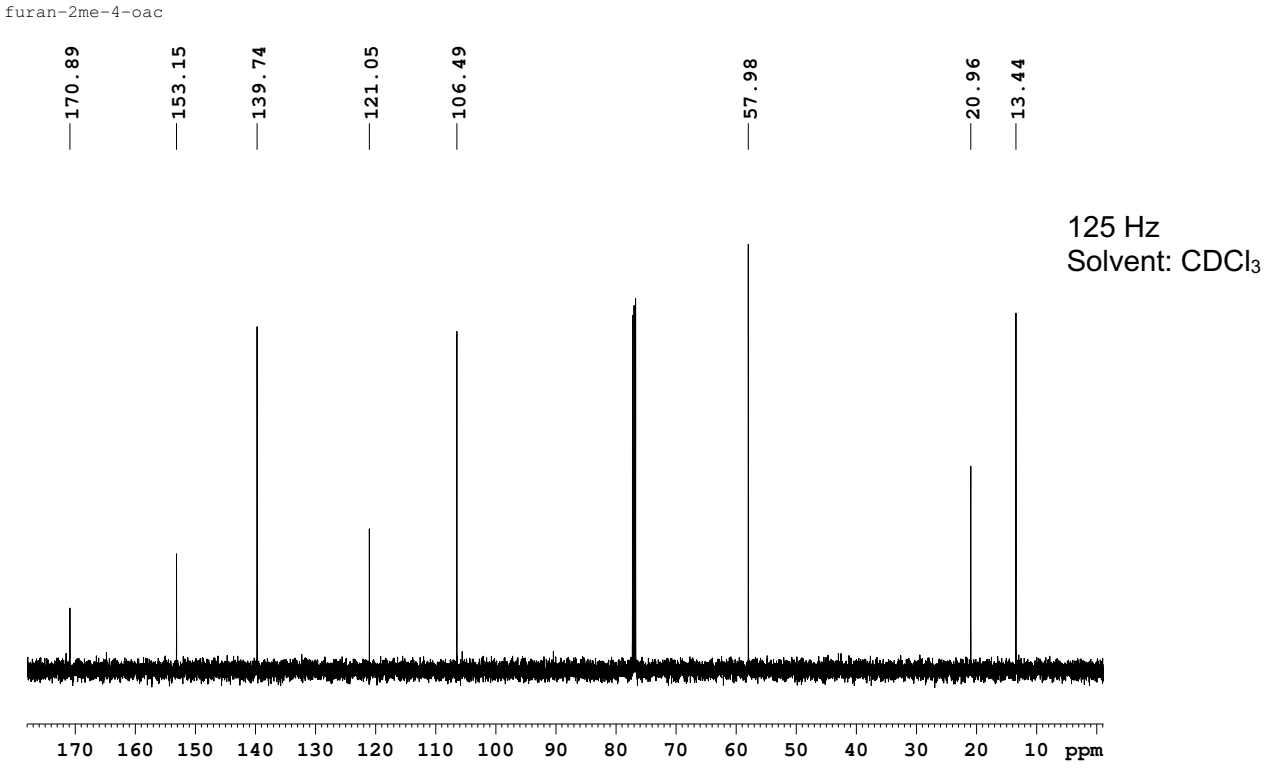
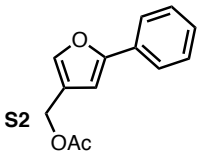
D. NMR SPECTRA



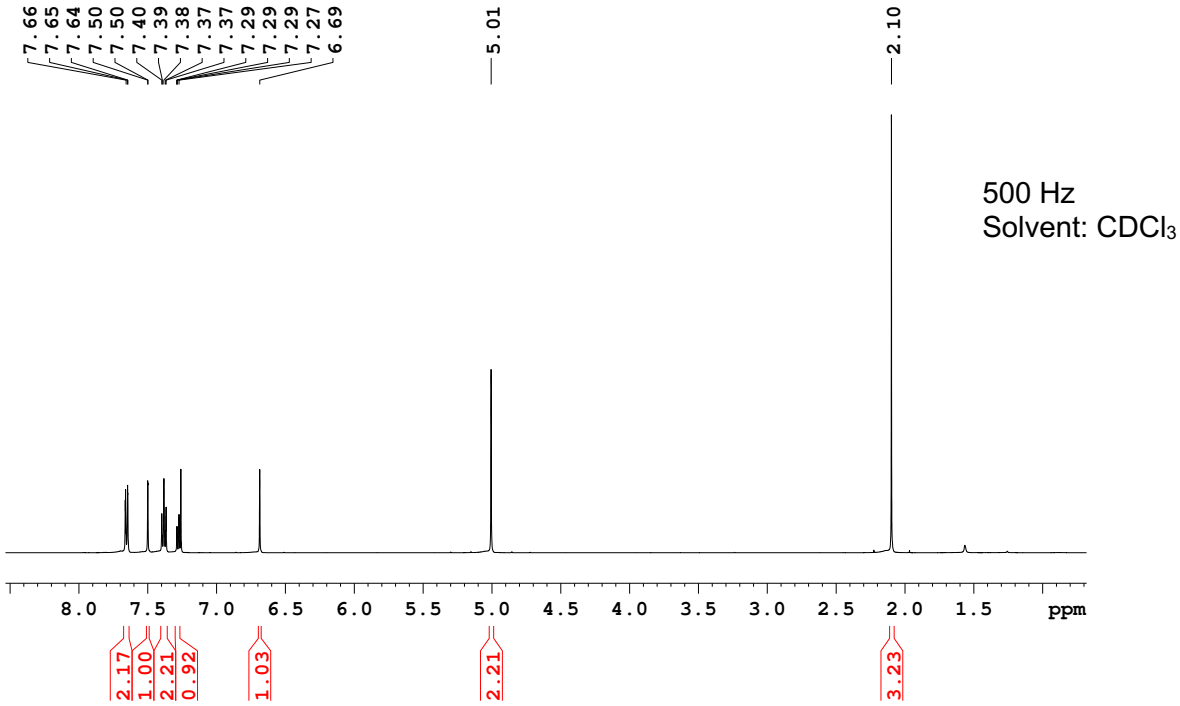



O
S1
OAc


furan-2me-4-oac
170.89
153.15
139.74
121.05
106.49
57.98
20.96
13.44
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
S2
OAc

fur-4oac-2ph


7.66
7.65
7.64
7.50
7.50
7.40
7.39
7.38
7.37
7.37
7.29
7.29
7.29
7.27
6.69
5.01
2.10
500 Hz
Solvent: CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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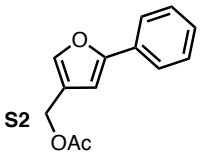
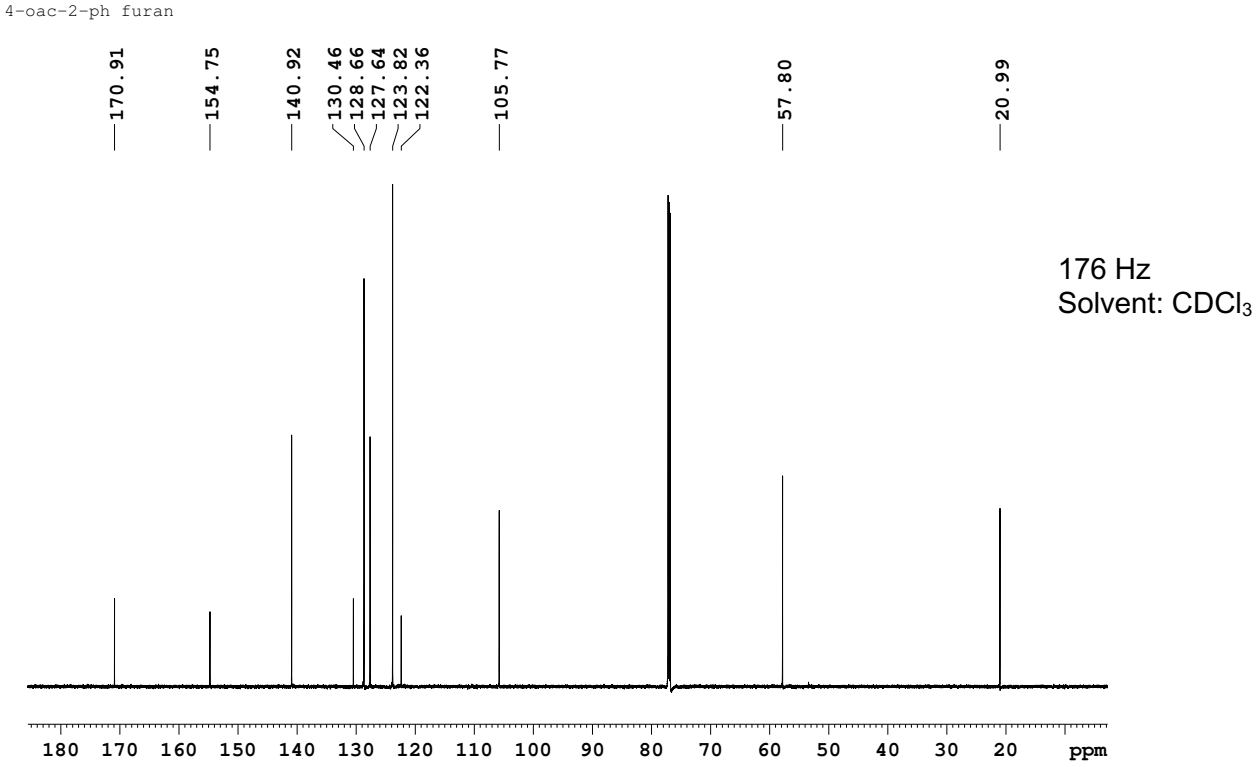
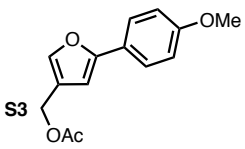
1.00
2.21
0.92
1.03
2.21
3.23

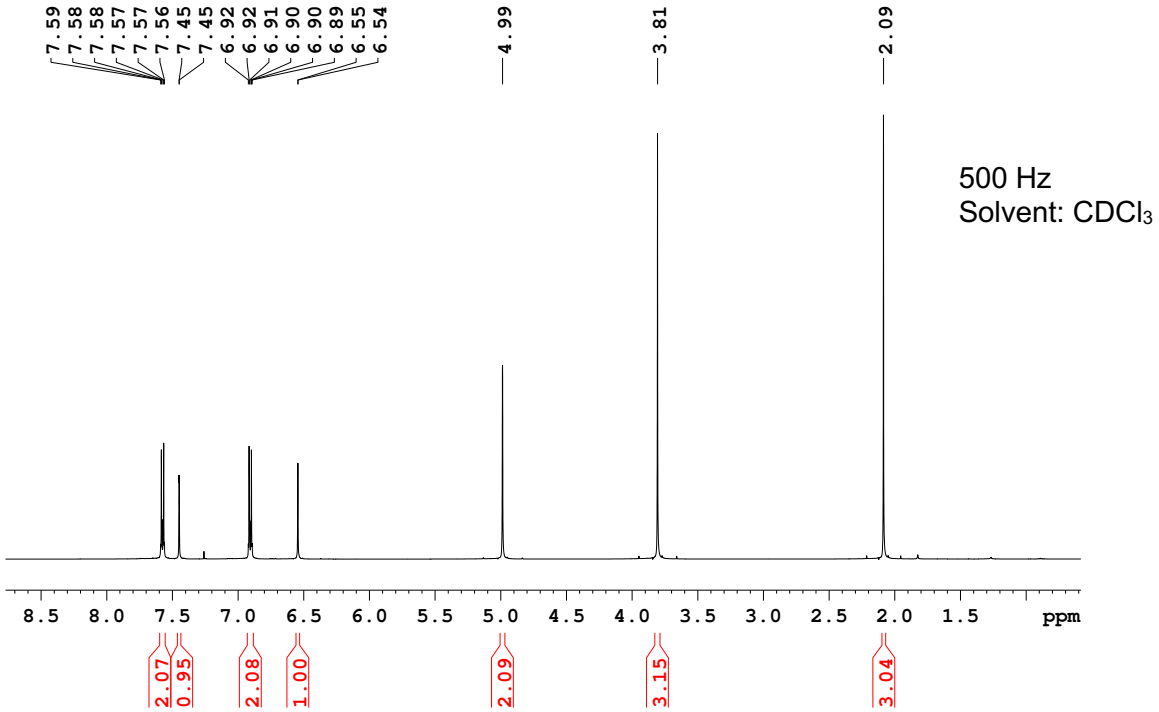


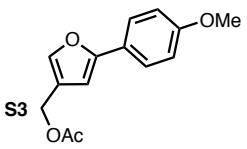


176 Hz
Solvent: $CDCl_3$

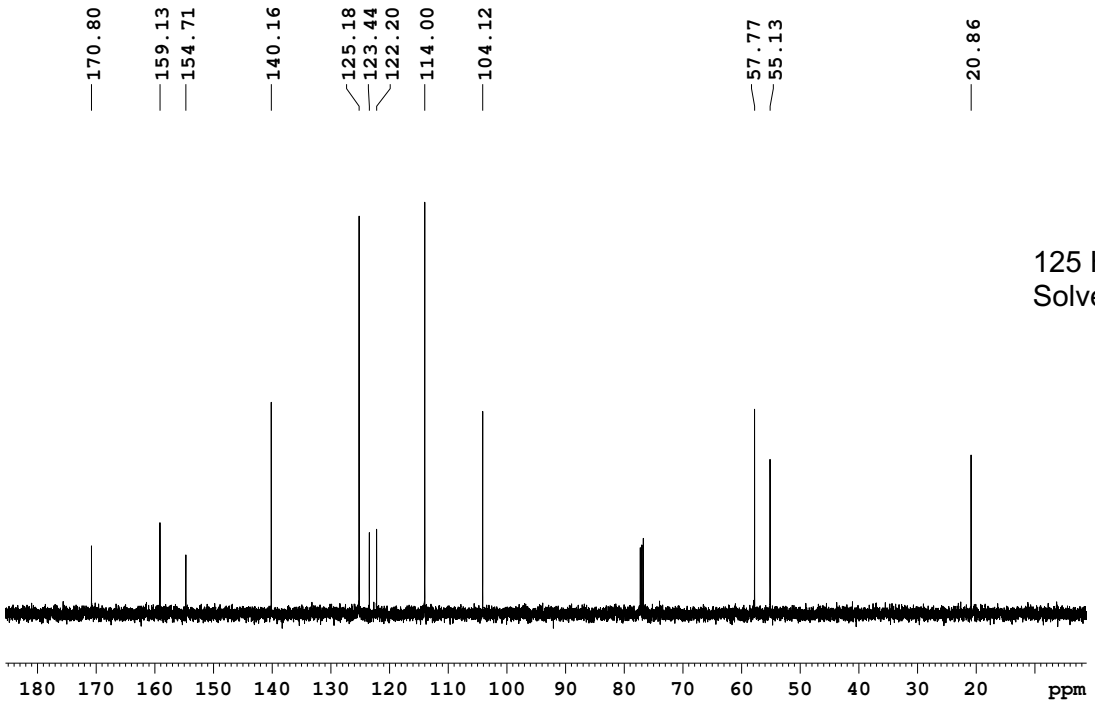


furan-2ph-ome-4oac

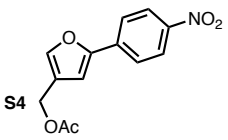


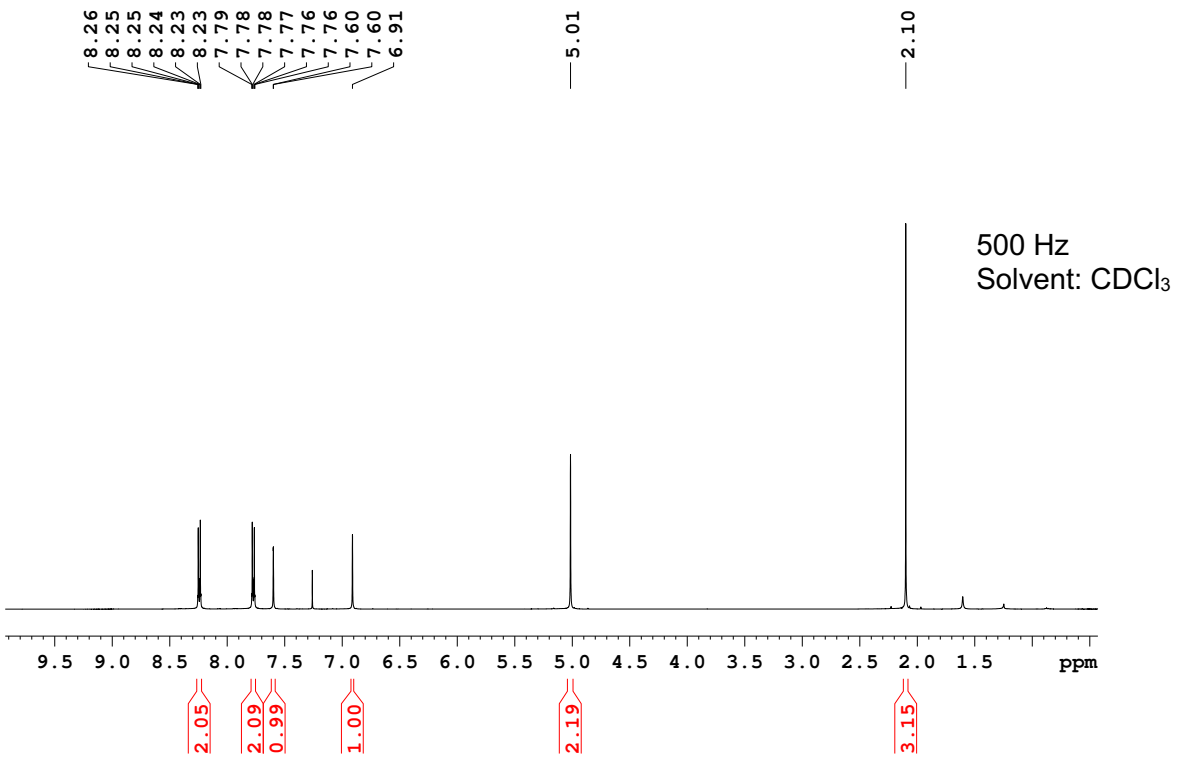


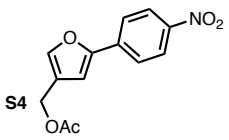
furan-2ph-ome-4oac

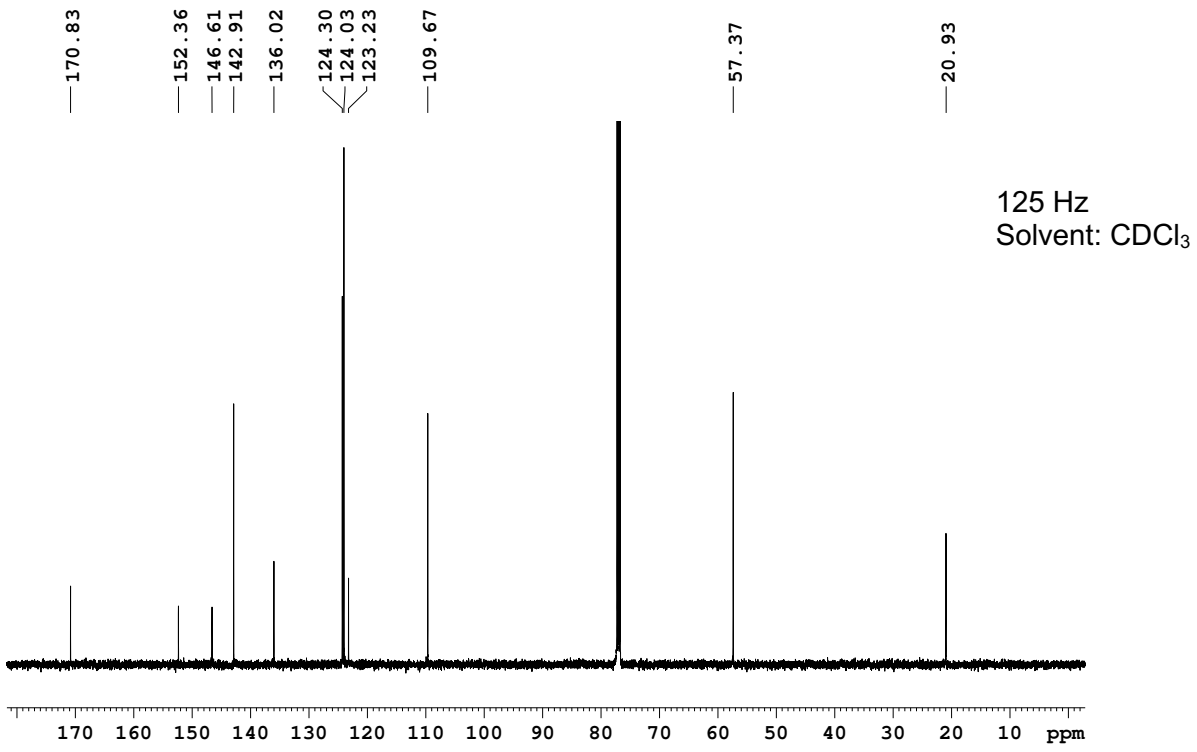


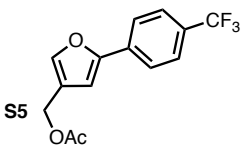
125 Hz
Solvent: $CDCl_3$


NO2
O
S4
OAc

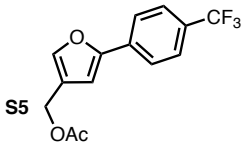

8.26
8.25
8.25
8.24
8.23
8.23
7.79
7.78
7.78
7.77
7.76
7.76
7.60
7.60
6.91
5.01
2.10
500 Hz
Solvent: CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
2.05
2.09
0.99
1.00
2.19
3.15

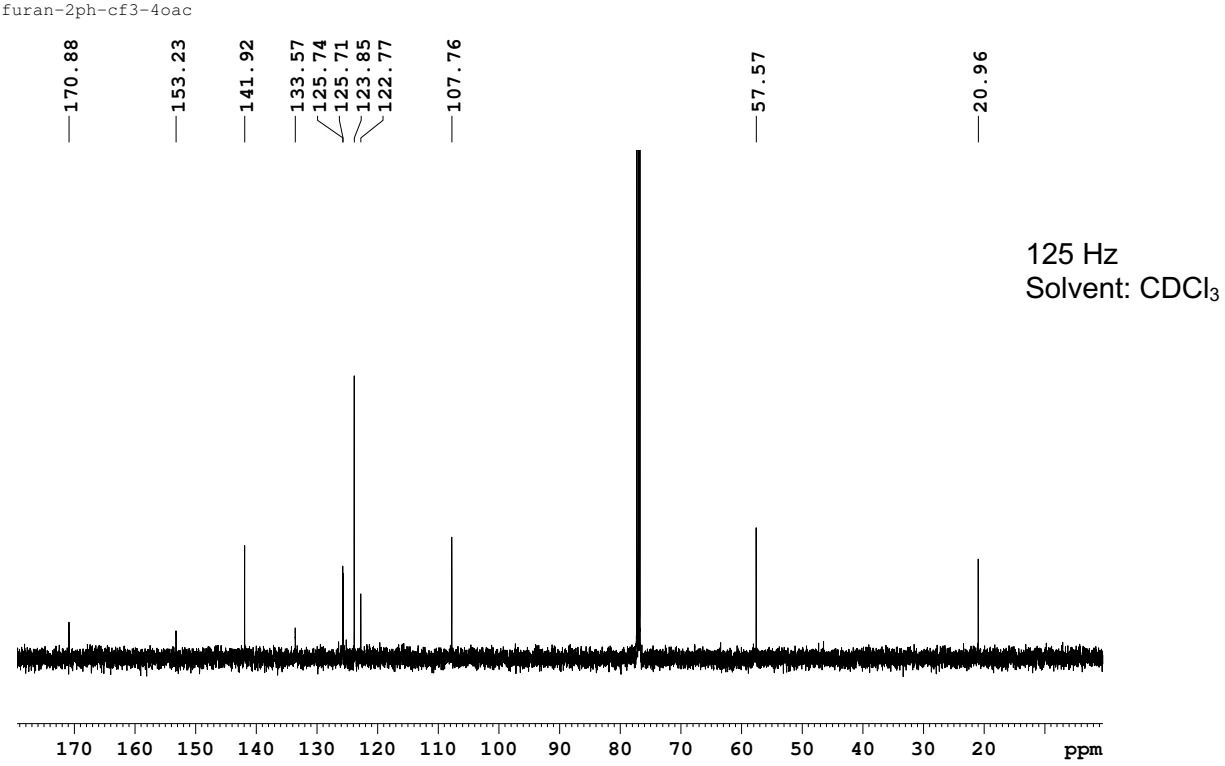

NO2
O
S4
OAc

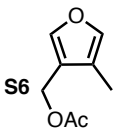

170.83
152.36
146.61
142.91
136.02
124.30
124.03
123.23
109.67
57.37
20.93
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


S5
O
CF3
OAc

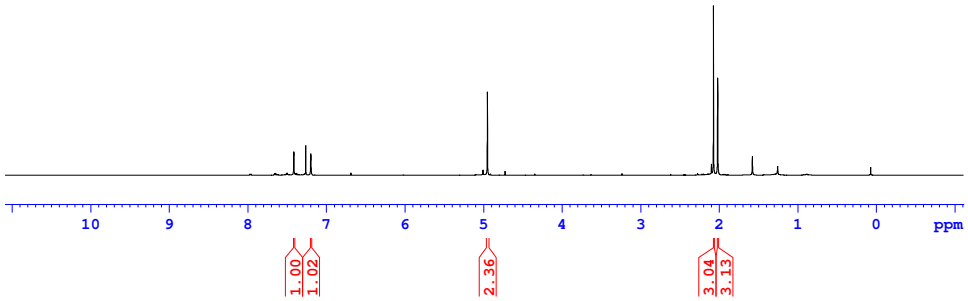
7.75
7.74
7.64
7.62
7.55
7.55
6.80
5.01
2.10
500 Hz
Solvent: CDCl3
11 10 9 8 7 6 5 4 3 2 1 0 −1 ppm
2.14
2.13
0.98
1.00
2.15
3.12
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 ppm

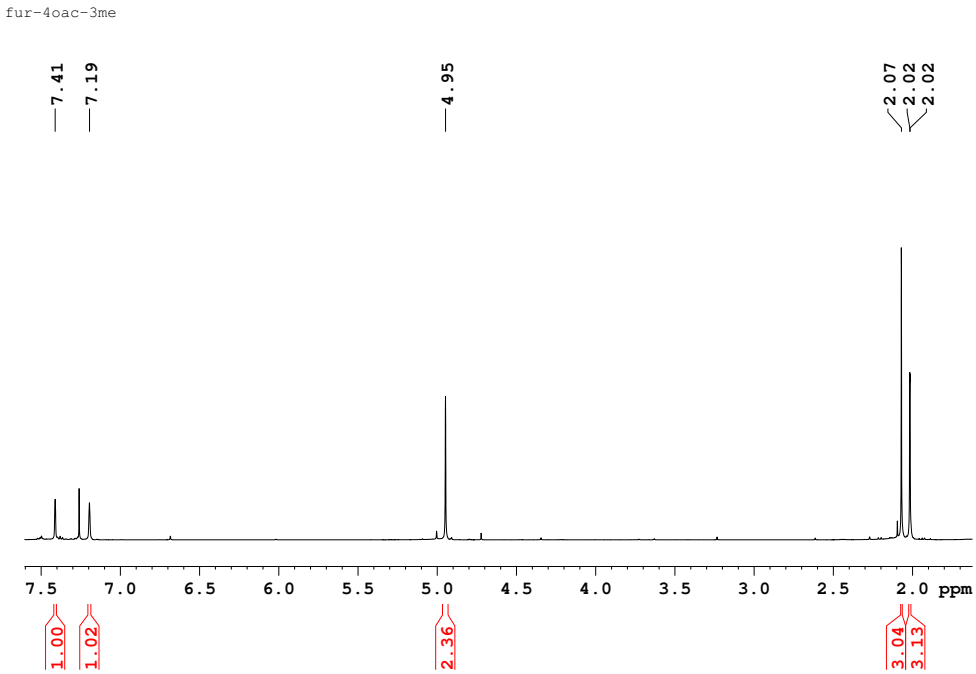

CF3
O
S5
OAc

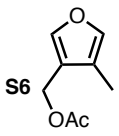

furan-2ph-cf3-4oac
170.88
153.23
141.92
133.57
125.74
125.71
123.85
122.77
107.76
57.57
20.96
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



500 Hz
Solvent: $CDCl_3$

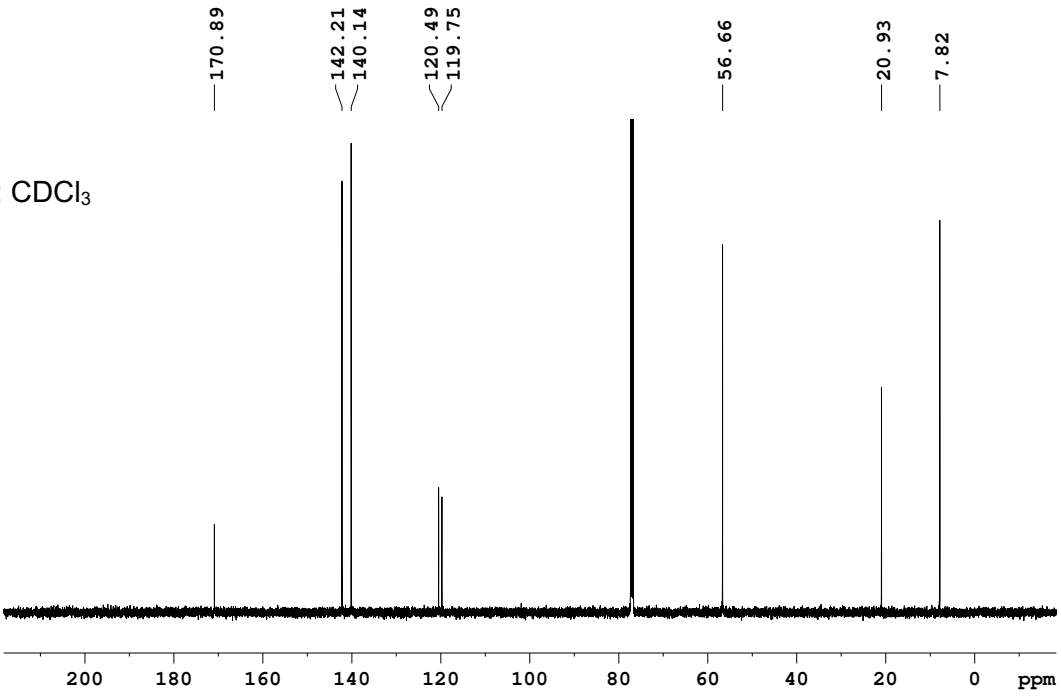


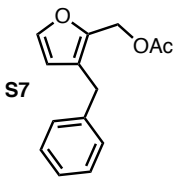




4oac-3me furan

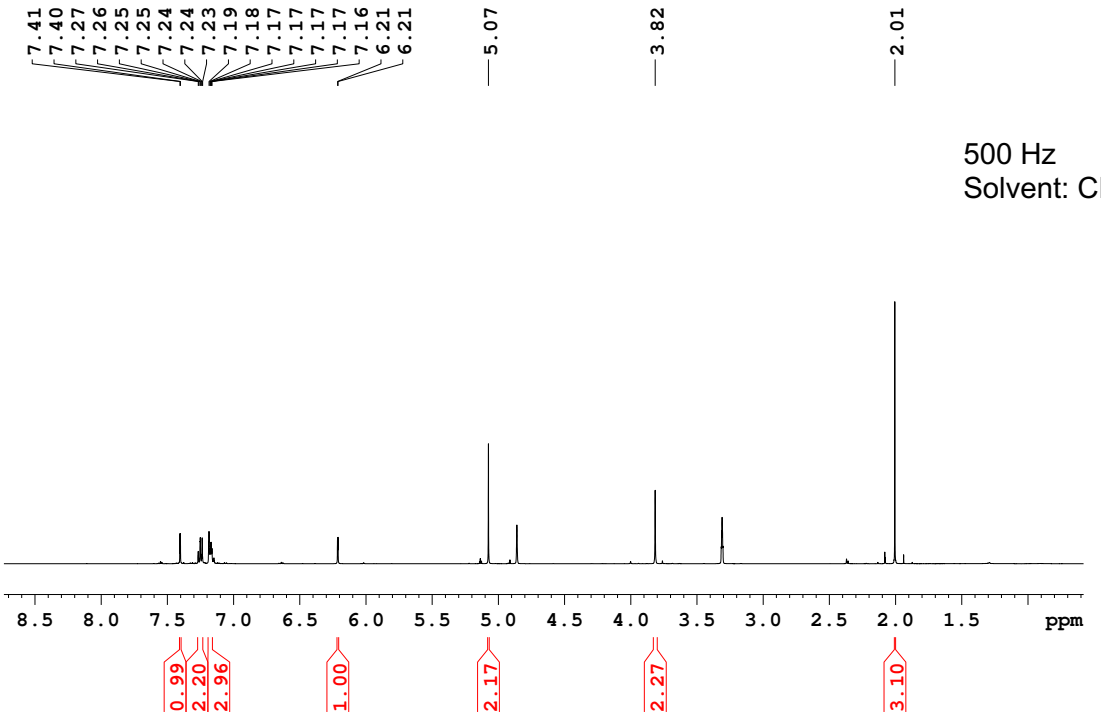
125 Hz
Solvent: $CDCl_3$

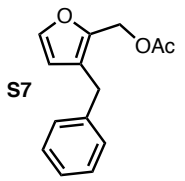




S7

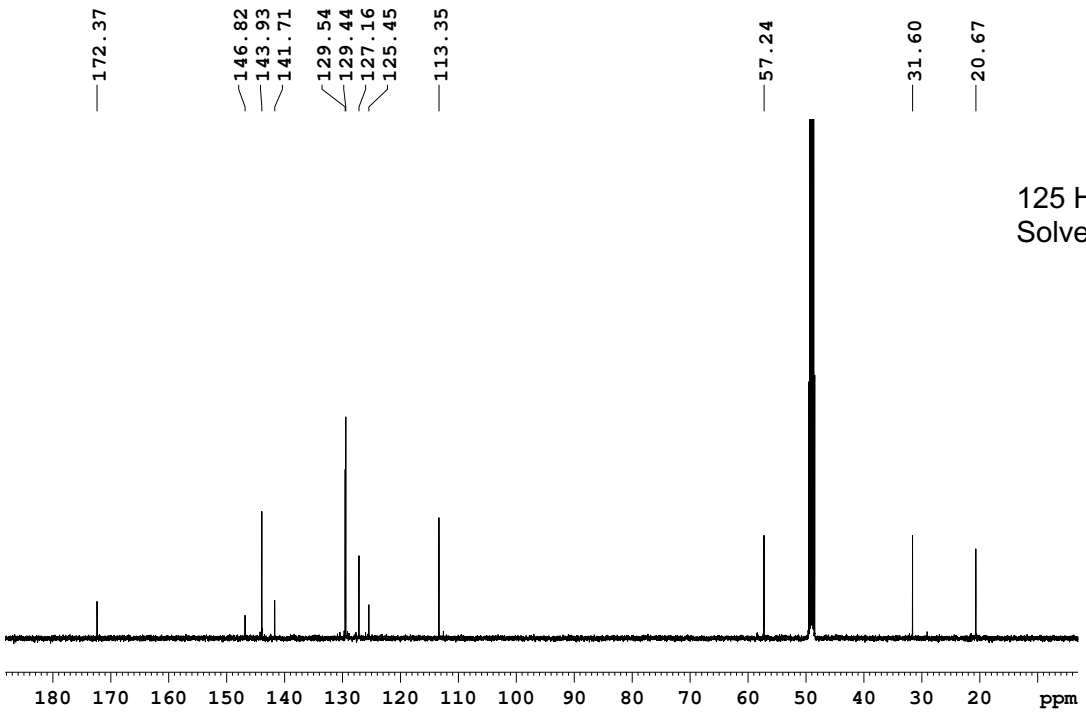
fur-2-oac-3bz



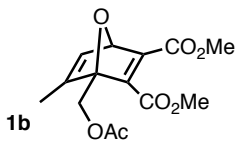


S7

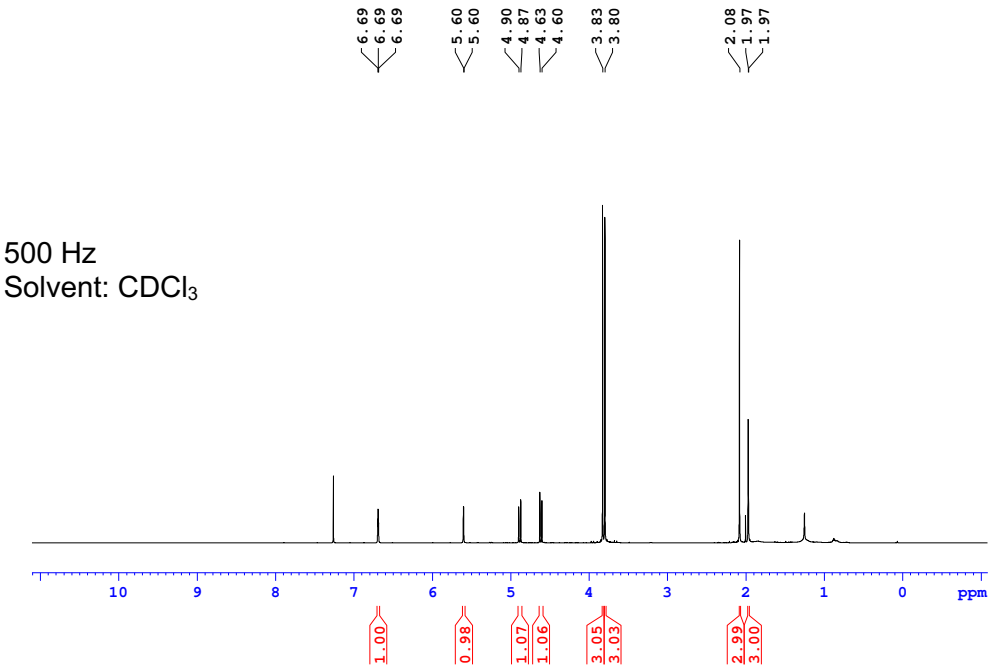
fur-2-oac-3bz

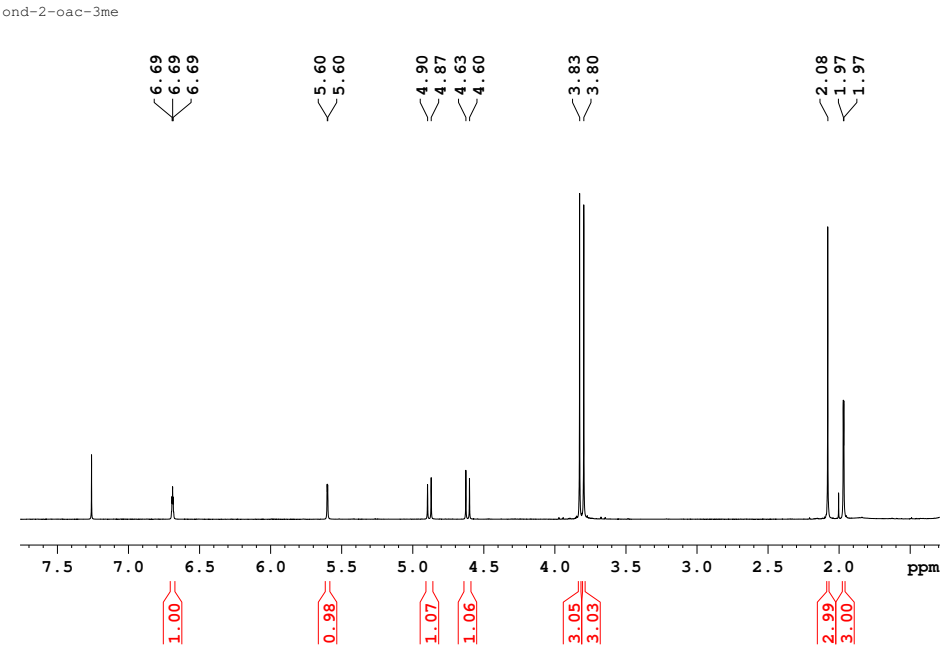


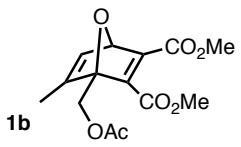
125 Hz
Solvent: CD_3OD


O
CO2Me
CO2Me
OAc

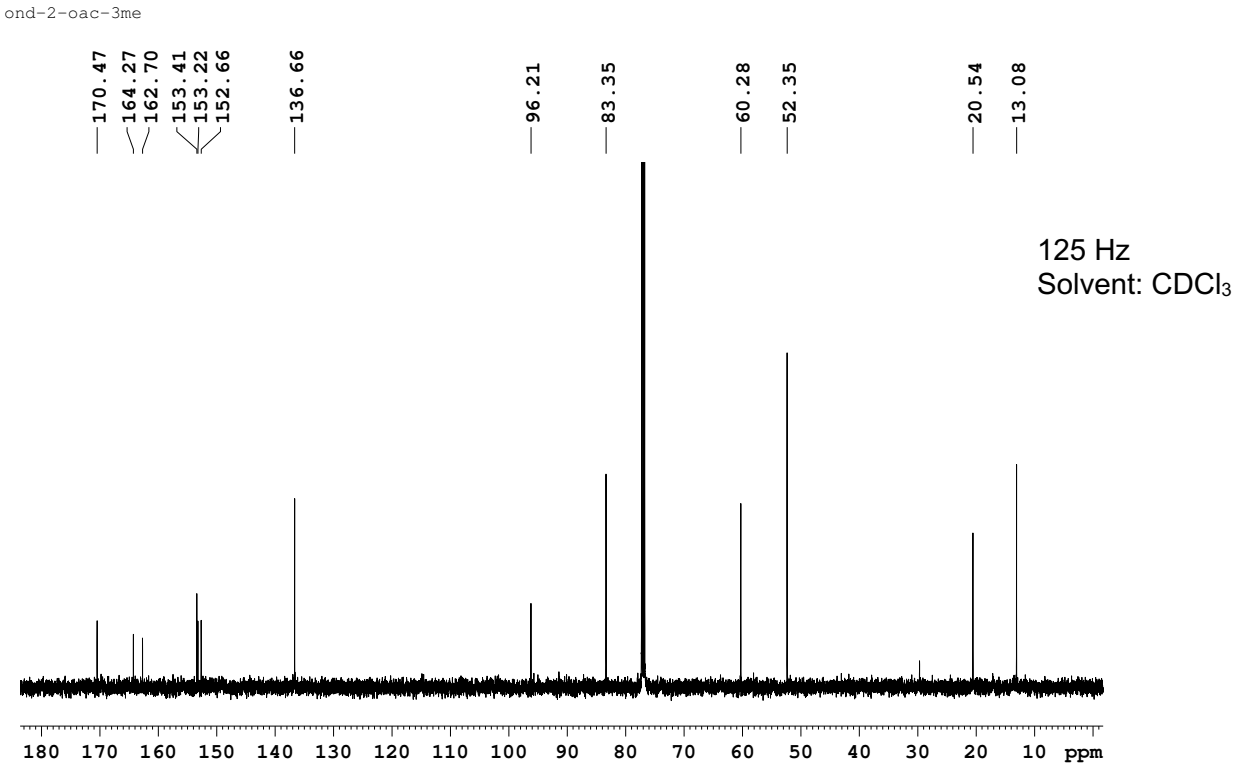
1b

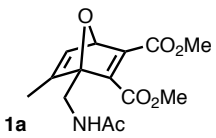

6.69
6.69
6.69
5.60
5.60
4.90
4.87
4.63
4.60
3.83
3.80
2.08
1.97
1.97
500 Hz
Solvent: CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.98
1.07
1.06
3.05
3.03
2.99
3.00


ond-2-oac-3me
6.69
6.69
6.69
5.60
5.60
4.90
4.87
4.63
4.60
3.83
3.80
2.08
1.97
1.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.00
0.98
1.07
1.06
3.05
3.03
2.99
3.00


O
CO2Me
CO2Me
OAc

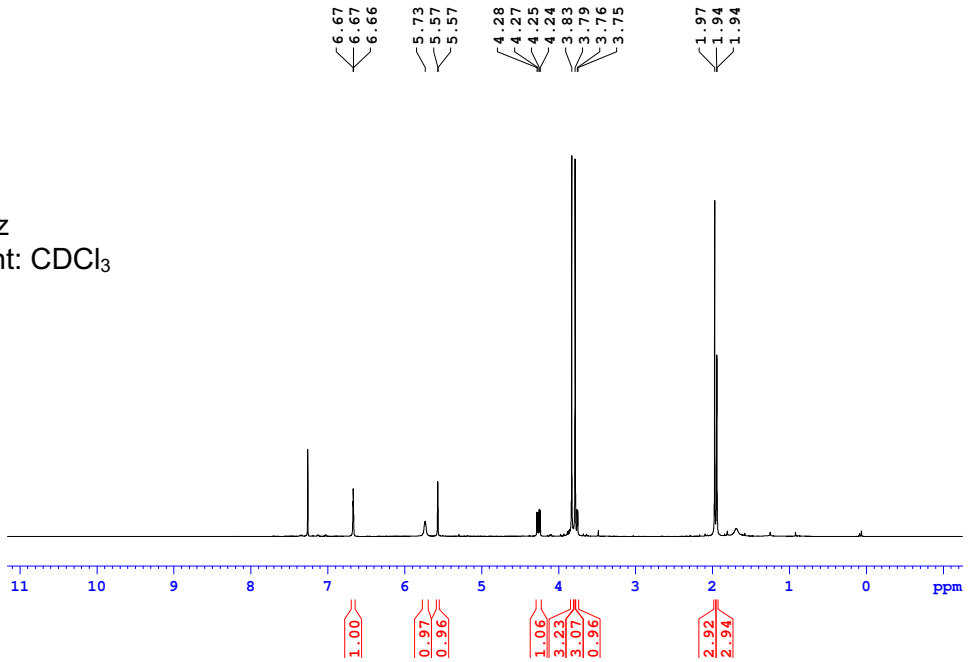
1b

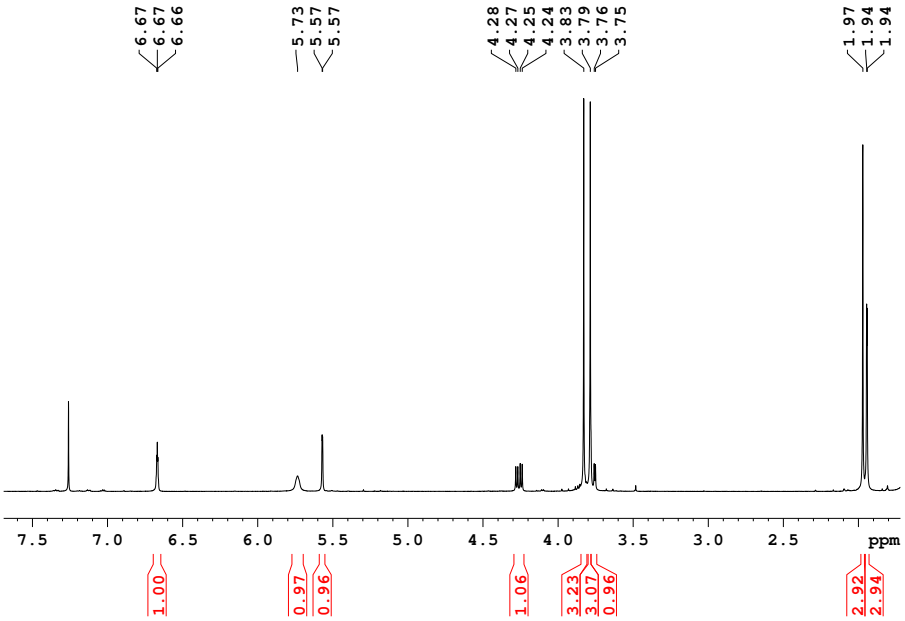

ond-2-oac-3me
170.47
164.27
162.70
153.41
153.22
152.66
136.66
96.21
83.35
60.28
52.35
20.54
13.08
125 Hz
Solvent: CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

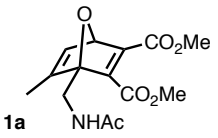


1a

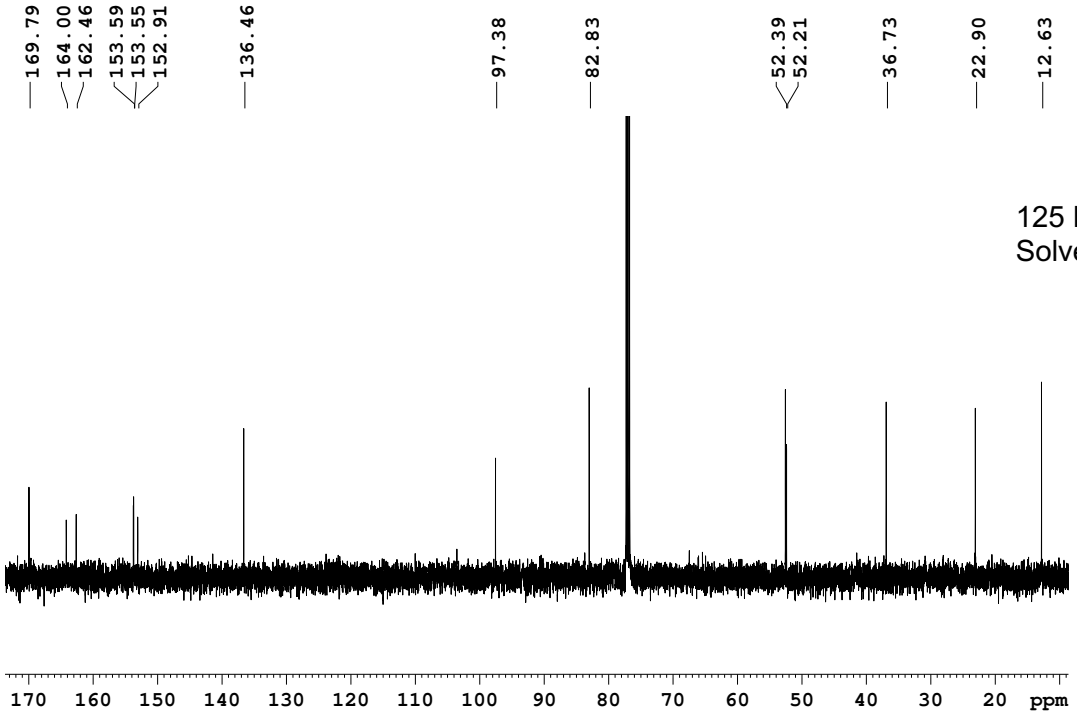
500 Hz
Solvent: $CDCl_3$

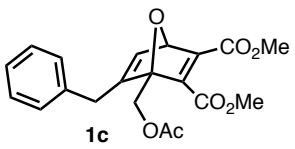





O
CO2Me
CO2Me
NHAc

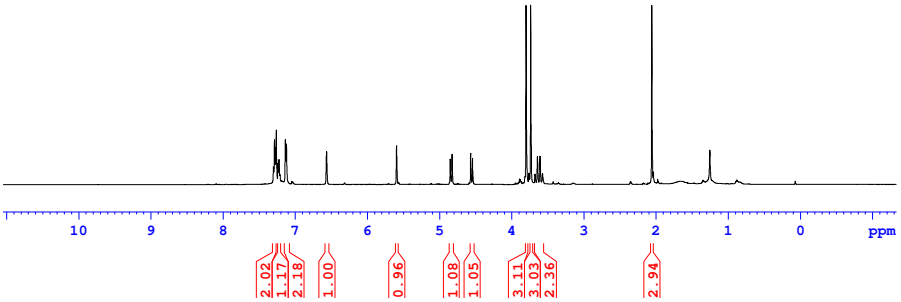
1a


169.79
164.00
162.46
153.59
153.55
152.91
136.46
97.38
82.83
52.39
52.21
36.73
22.90
12.63
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

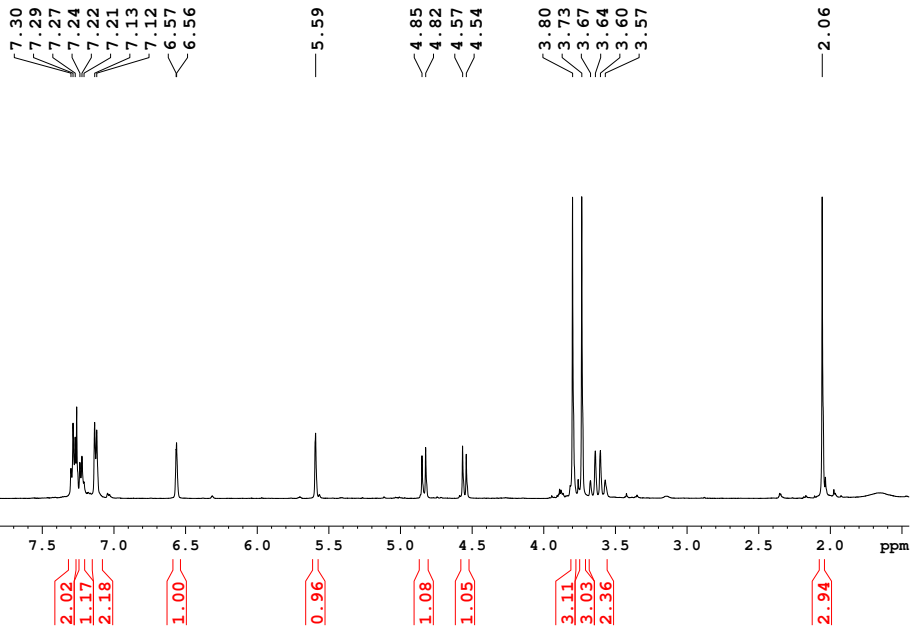


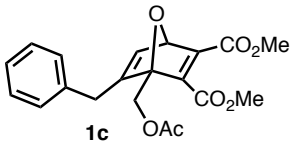
1c

500 Hz
Solvent: $CDCl_3$



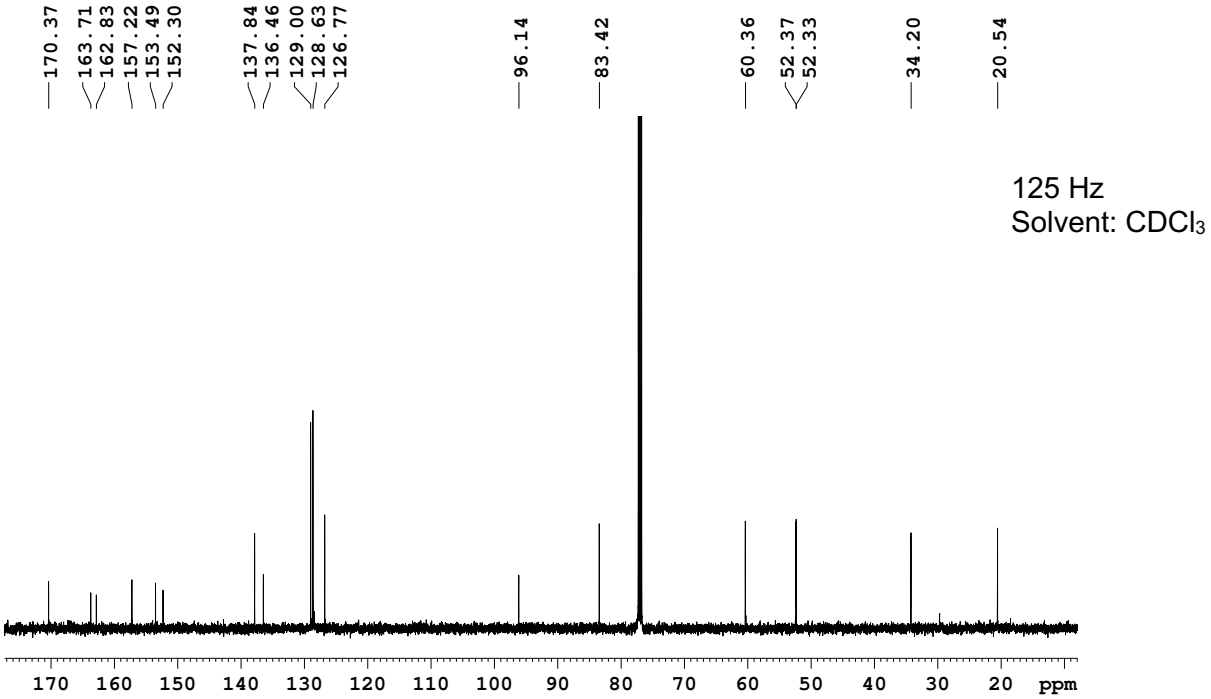
ond-2-oac-3-bz

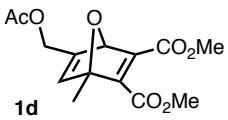




1c

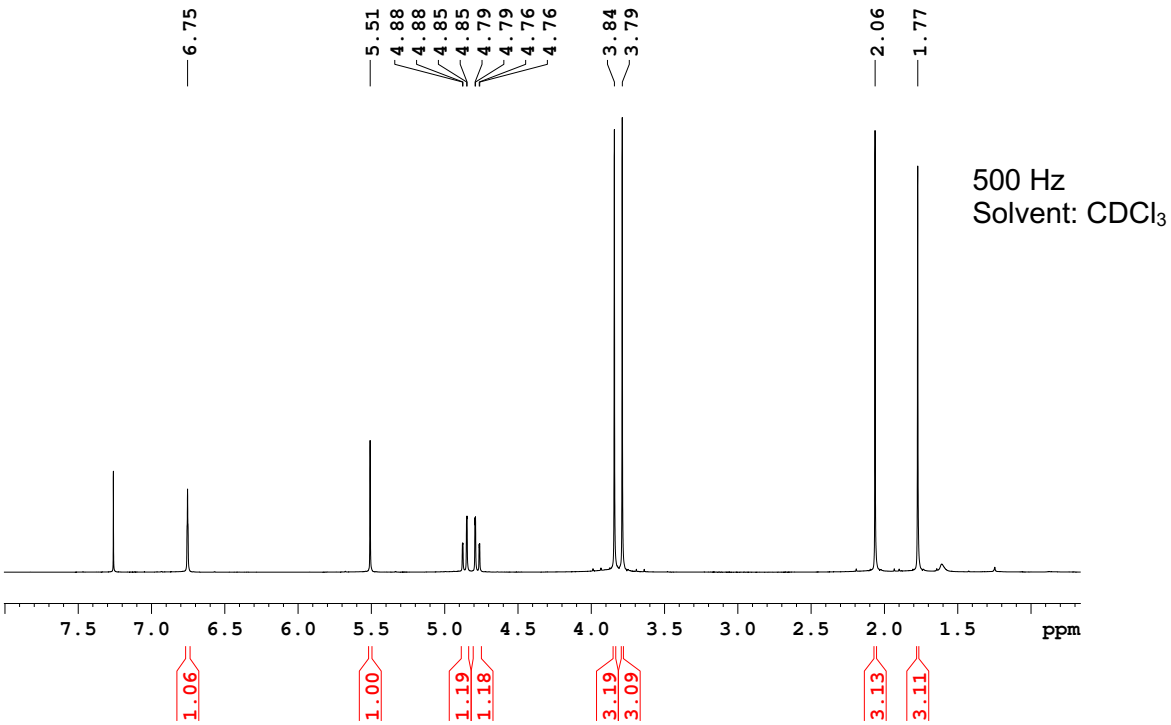
ond-2-oac-3-bz

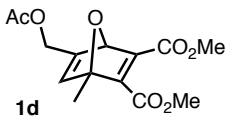




1d

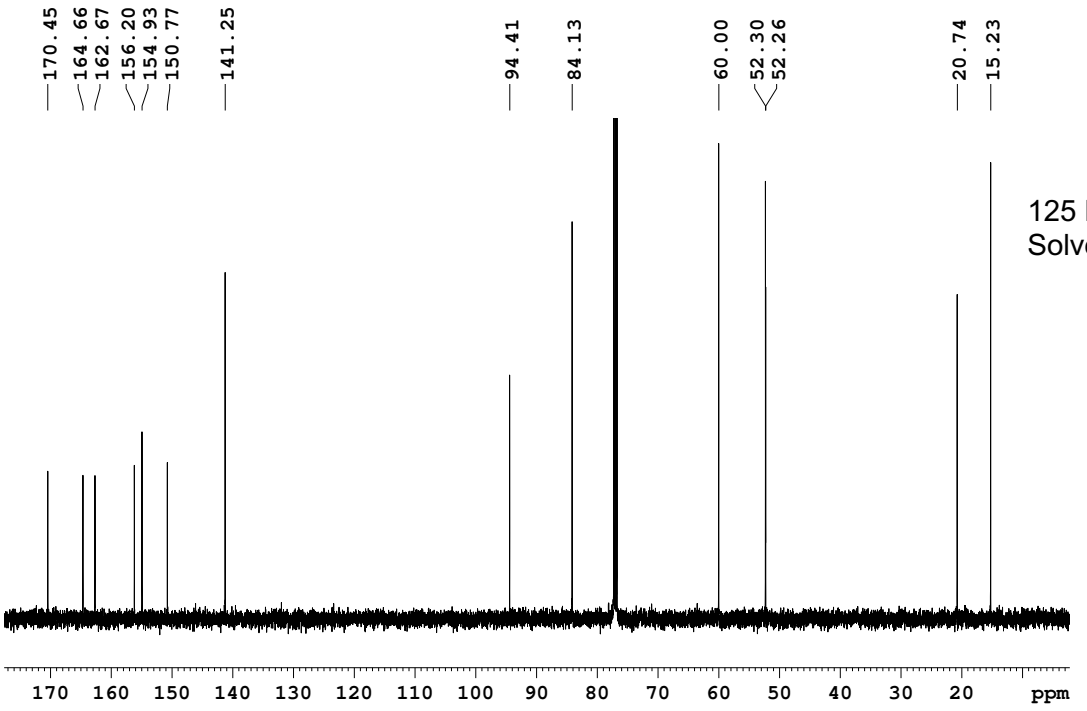
4oac-2me ond



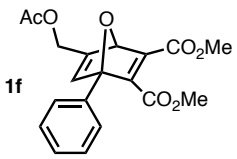


1d

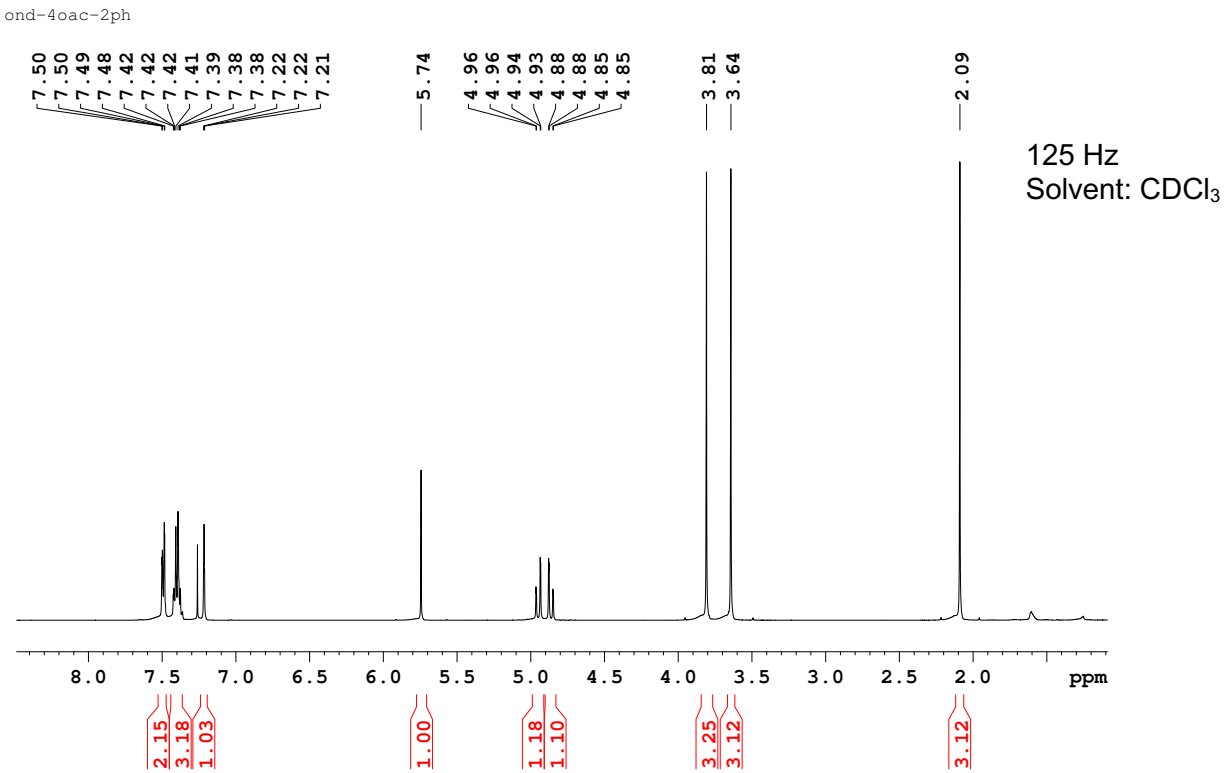
ond-2-me-4oac

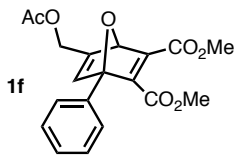


125 Hz
Solvent: $CDCl_3$


AcO
O
CO2Me
CO2Me

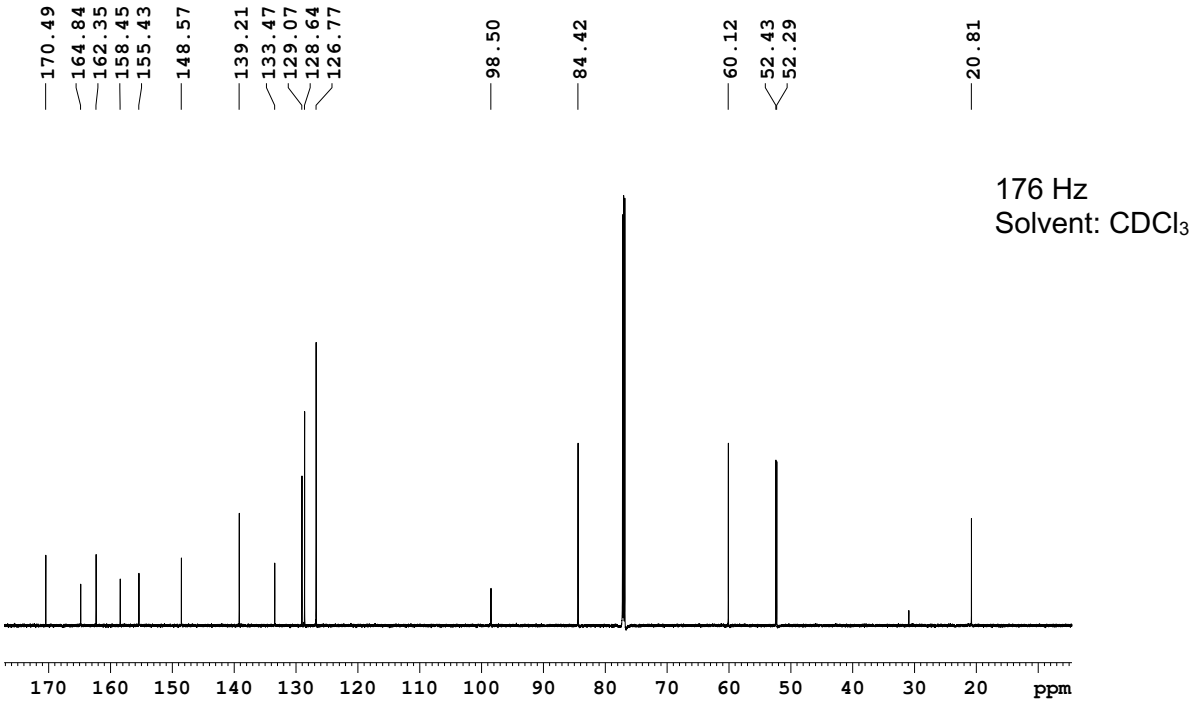
1f

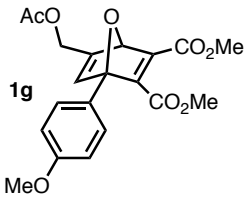

ond-4oac-2ph
7.50
7.50
7.49
7.48
7.42
7.42
7.42
7.41
7.39
7.38
7.38
7.22
7.22
7.21
5.74
4.96
4.96
4.94
4.93
4.88
4.88
4.85
4.85
3.81
3.64
2.09
125 Hz
Solvent: CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.15
3.18
1.03
1.00
1.18
1.10
3.25
3.12
3.12



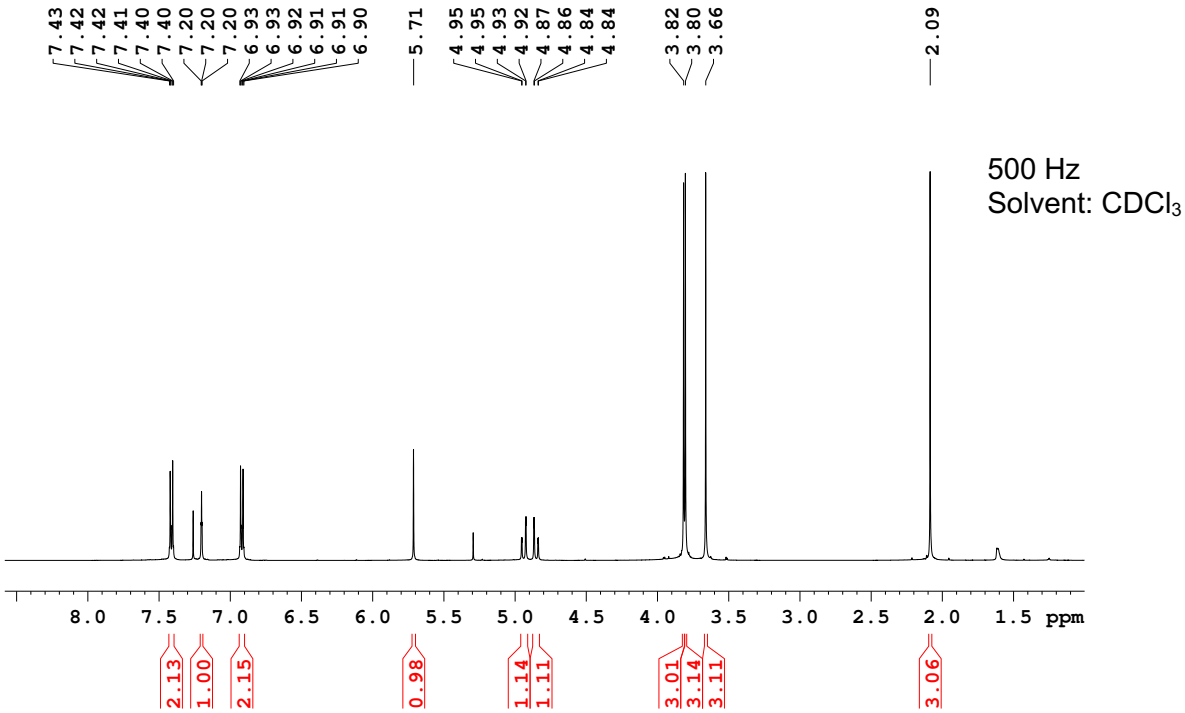
1f

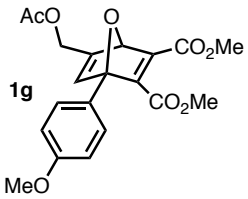
4-oac-2-ph ond

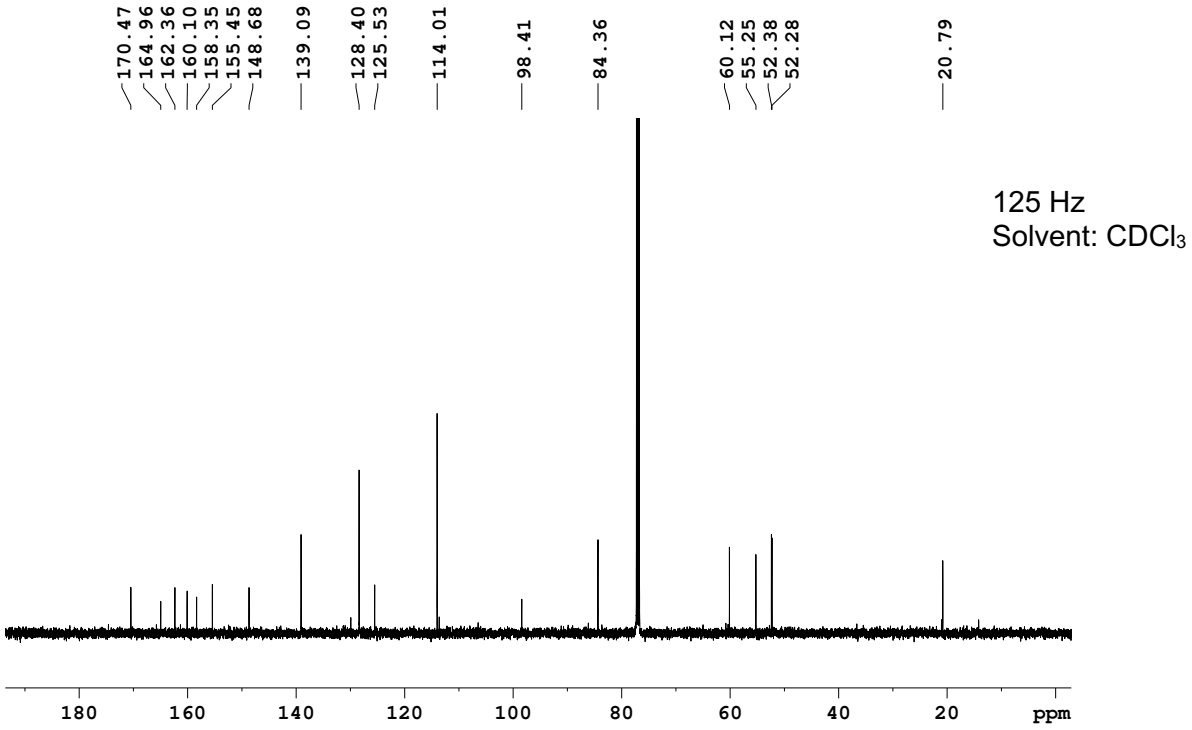




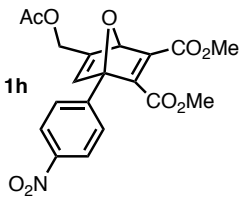
ond-2ph-ome-4oac





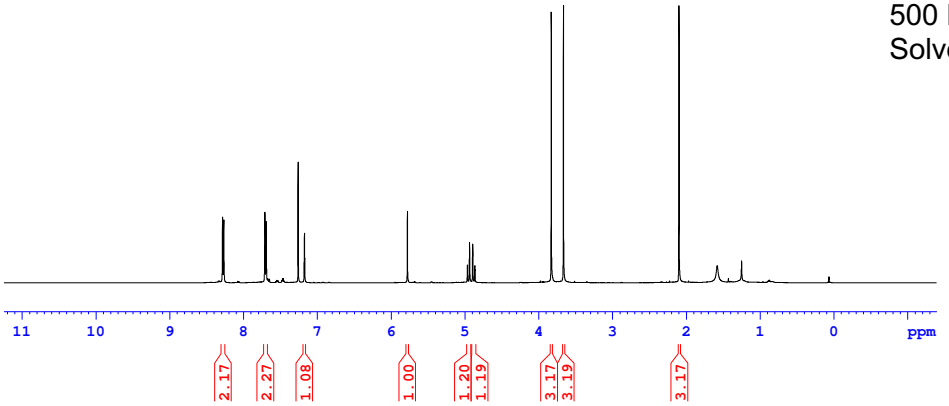


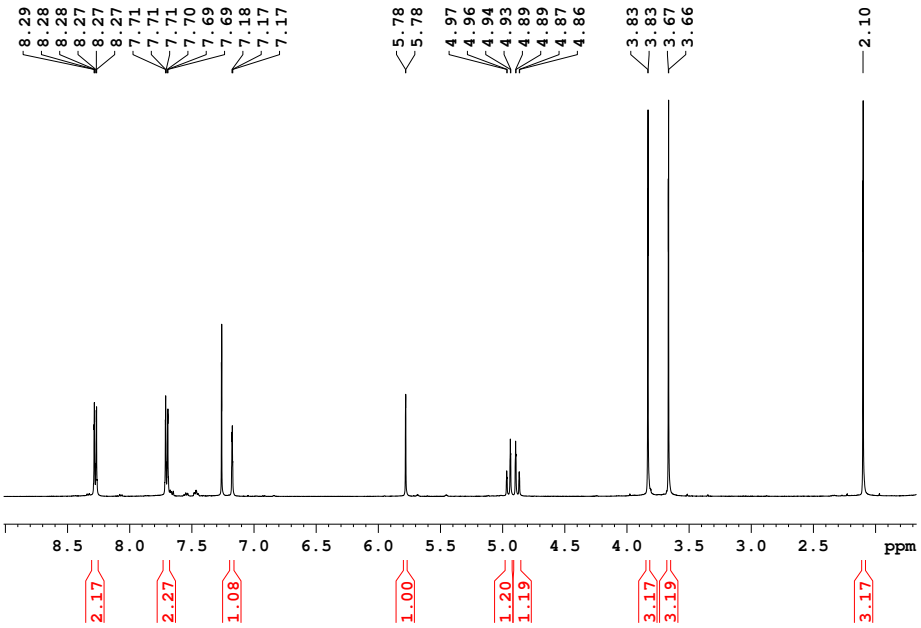
125 Hz
Solvent: $CDCl_3$

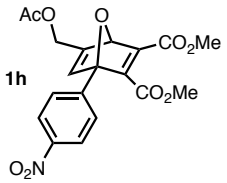


1h

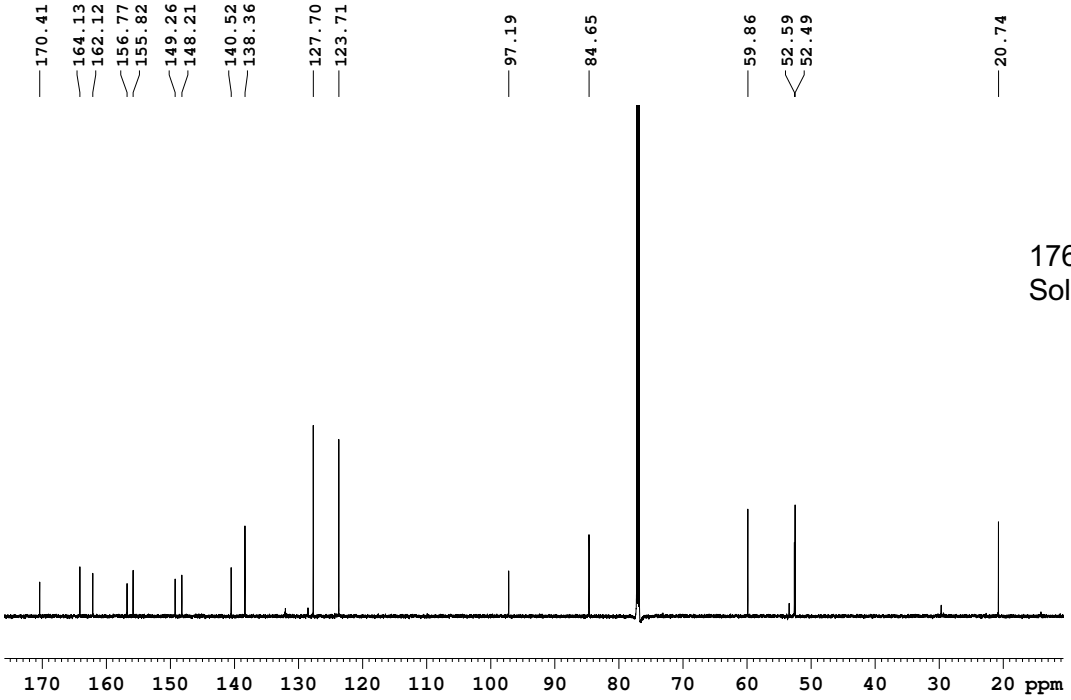
500 Hz
Solvent: $CDCl_3$



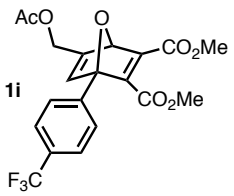




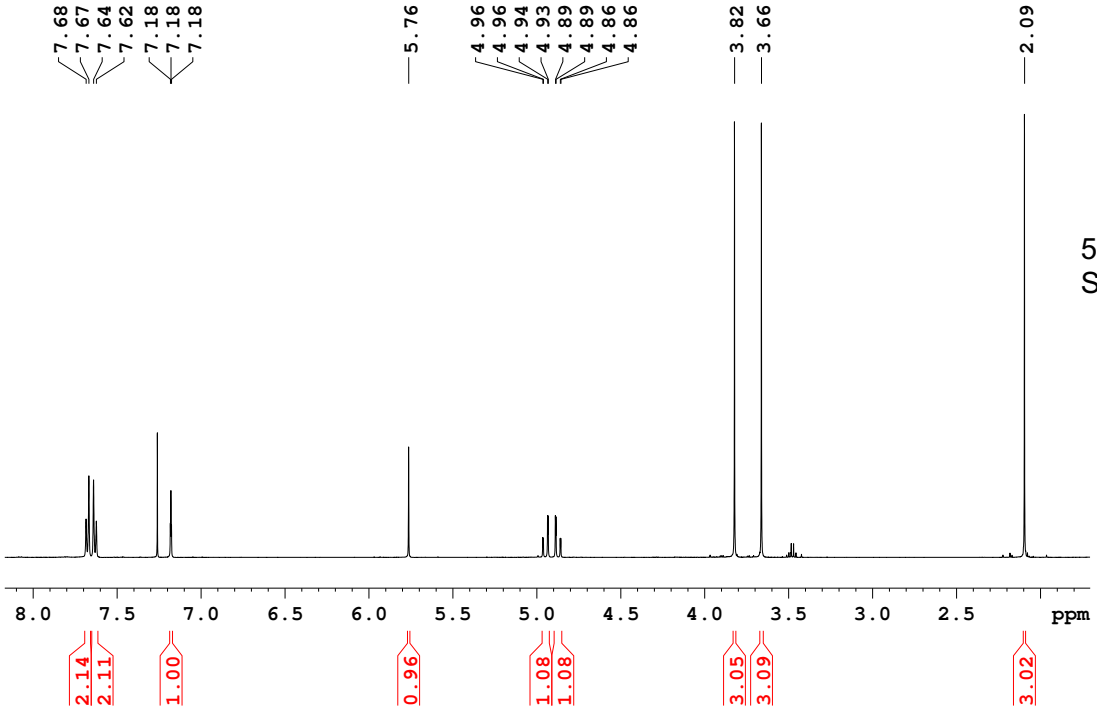
4oac-2phno2 ons



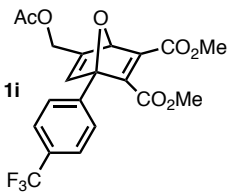
176 Hz
Solvent: $CDCl_3$



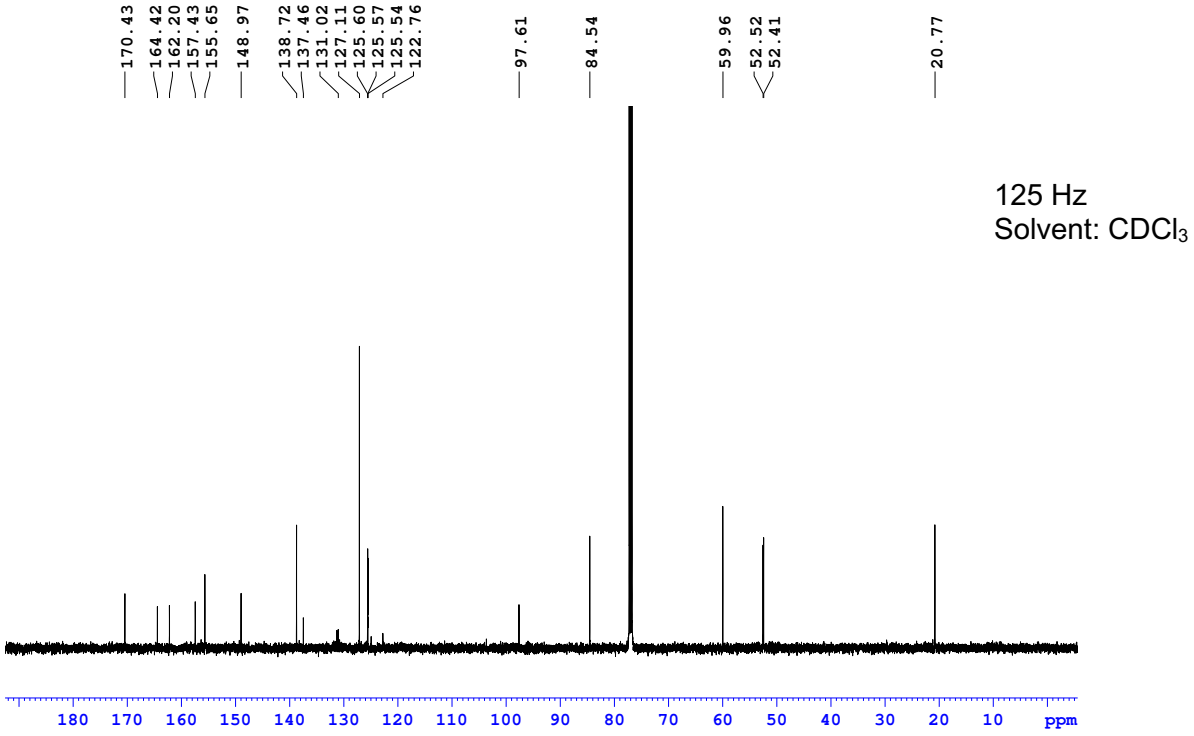
ond-2-ph-cf3-4-oh



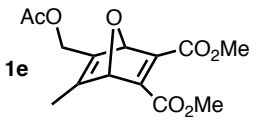
500 Hz
Solvent: $CDCl_3$



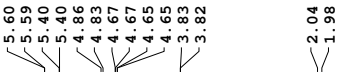
1i



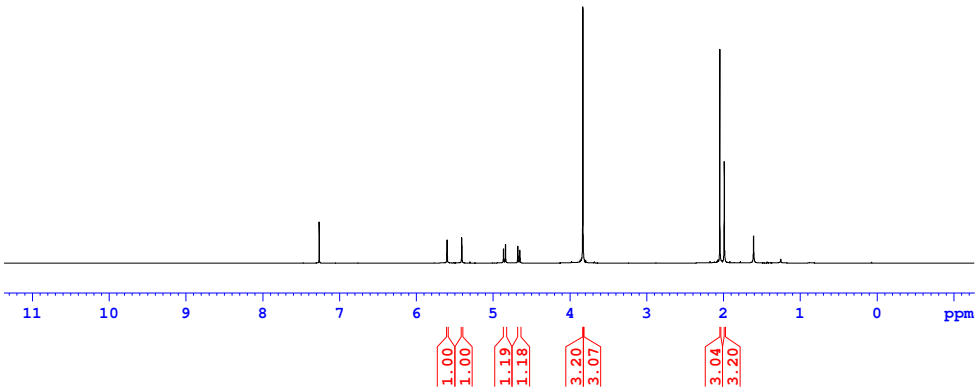
125 Hz
Solvent: $CDCl_3$



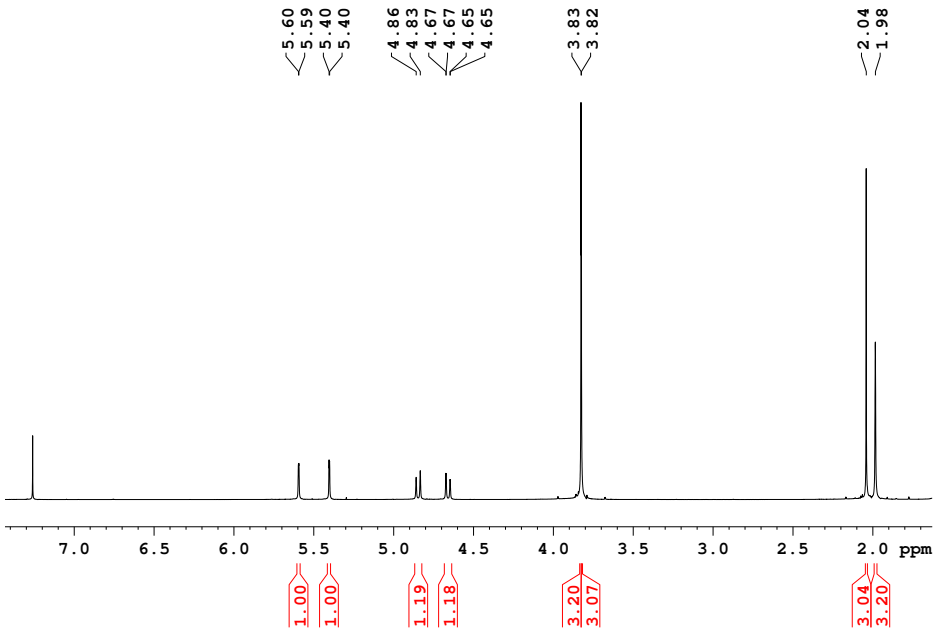
1e

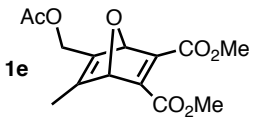


500 Hz
Solvent: $CDCl_3$



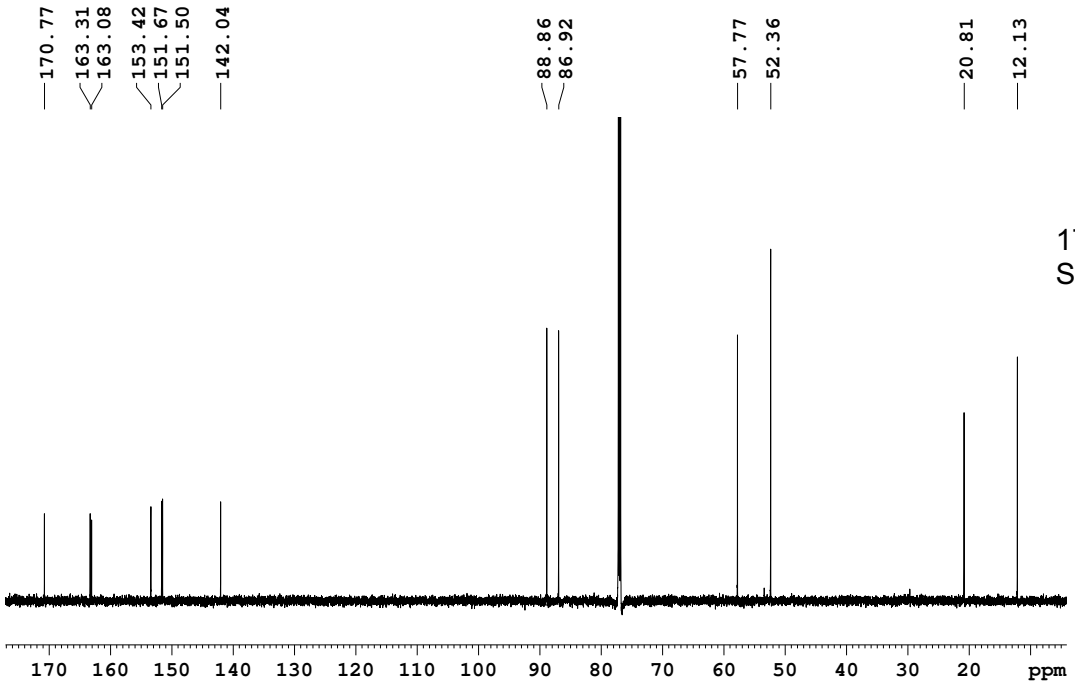
4oac-3me ond



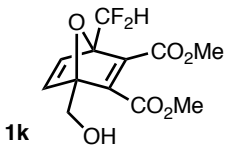


1e

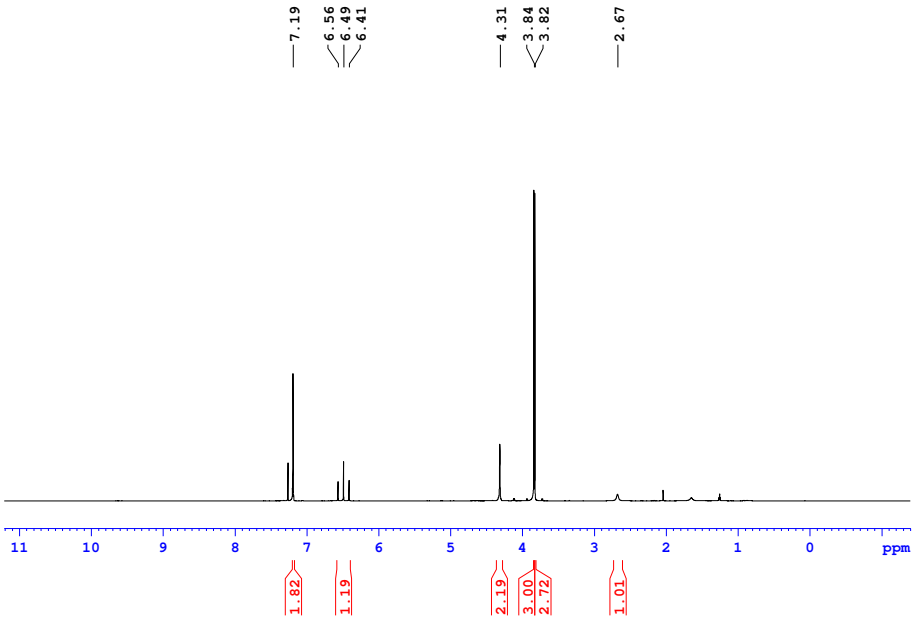
4-oac-3-me ond



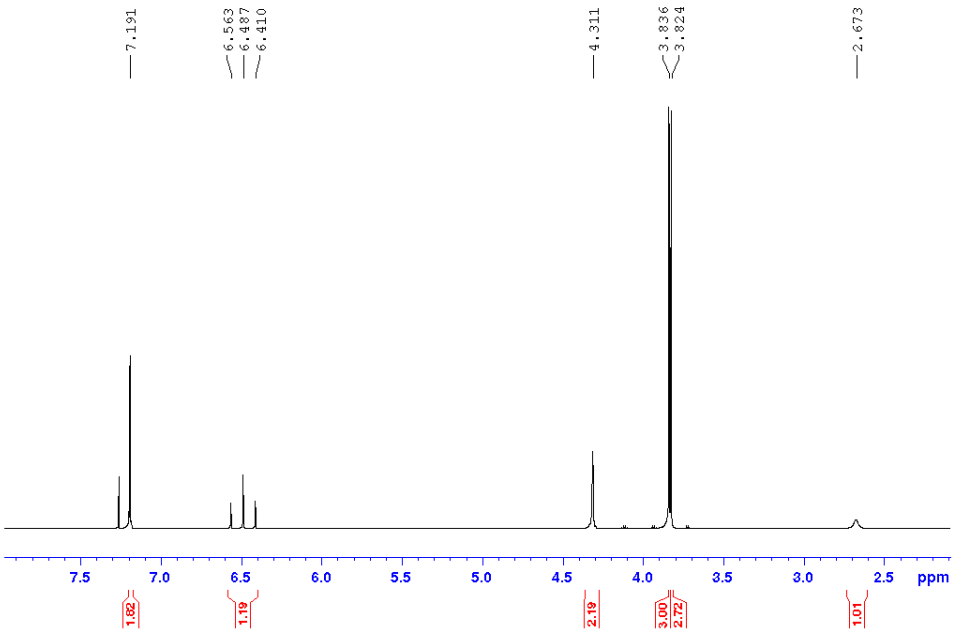
176 Hz
Solvent: $CDCl_3$

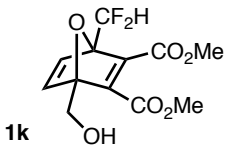


1k

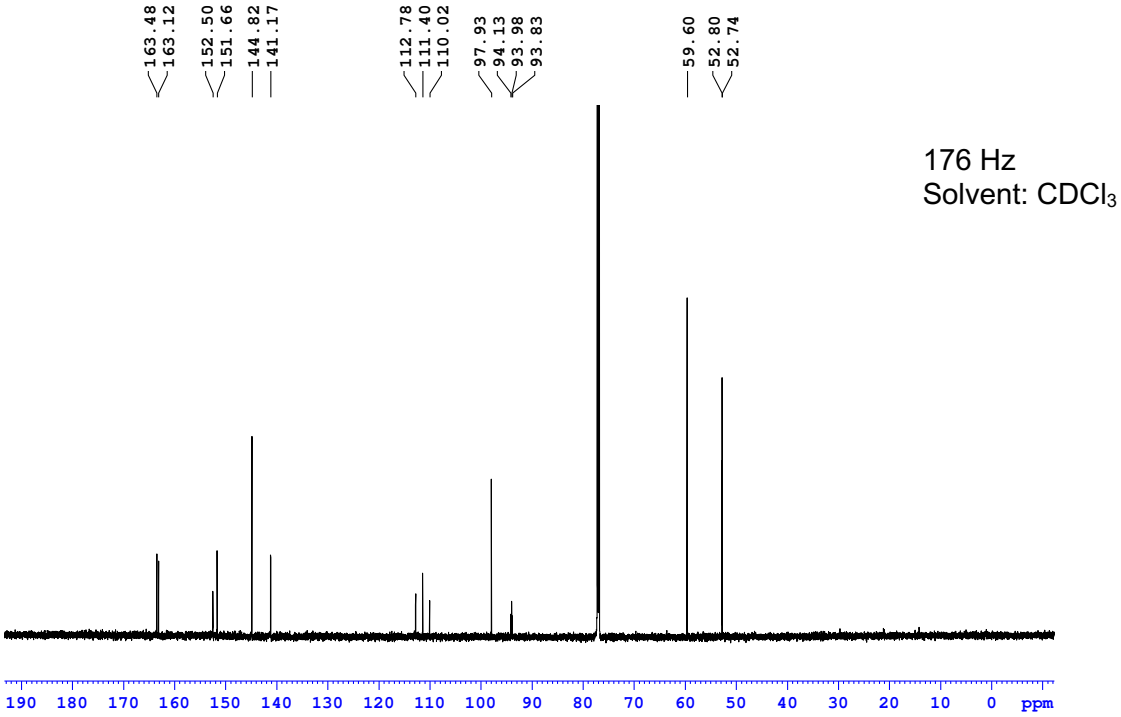


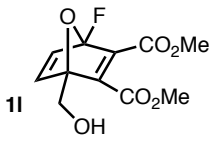
700 Hz
Solvent: $CDCl_3$




O
CF2H
CO2Me
CO2Me
OH

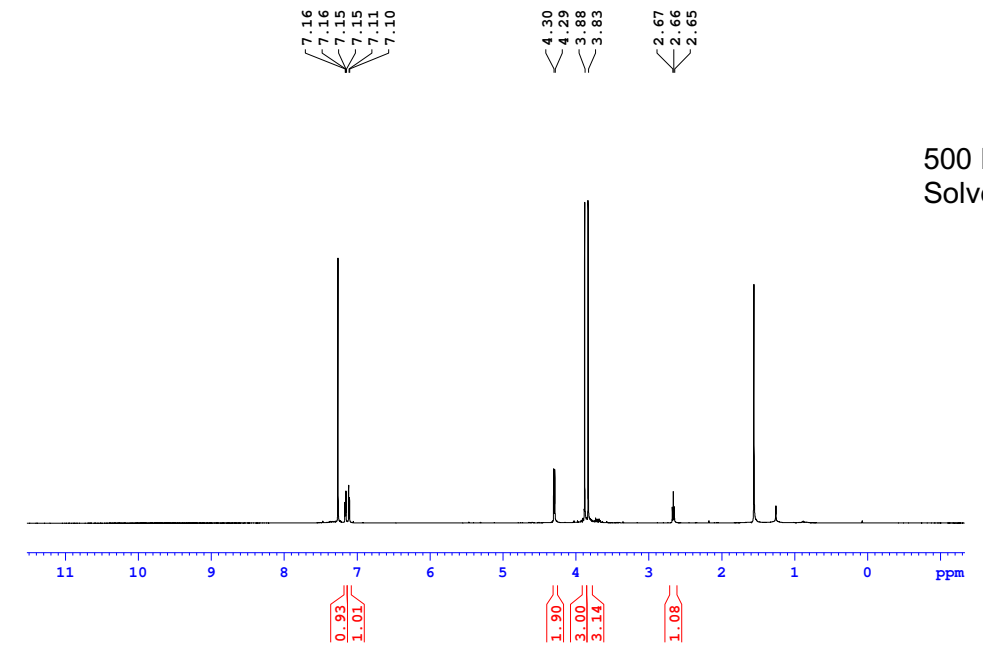
1k

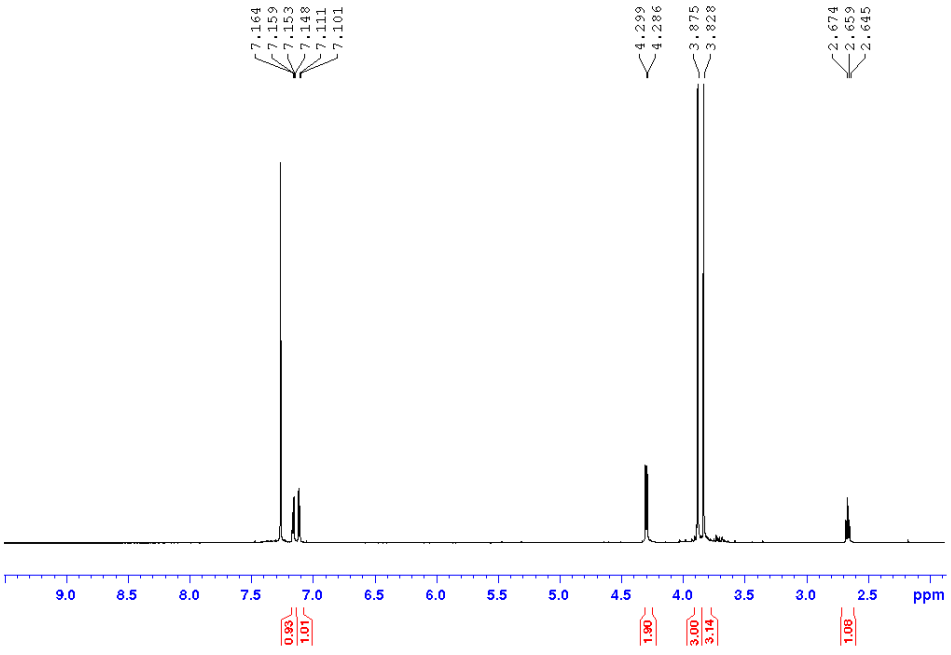

163.48
163.12
152.50
151.66
144.82
141.17
112.78
111.40
110.02
97.93
94.13
93.98
93.83
59.60
52.80
52.74
176 Hz
Solvent: CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

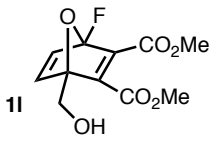


1l

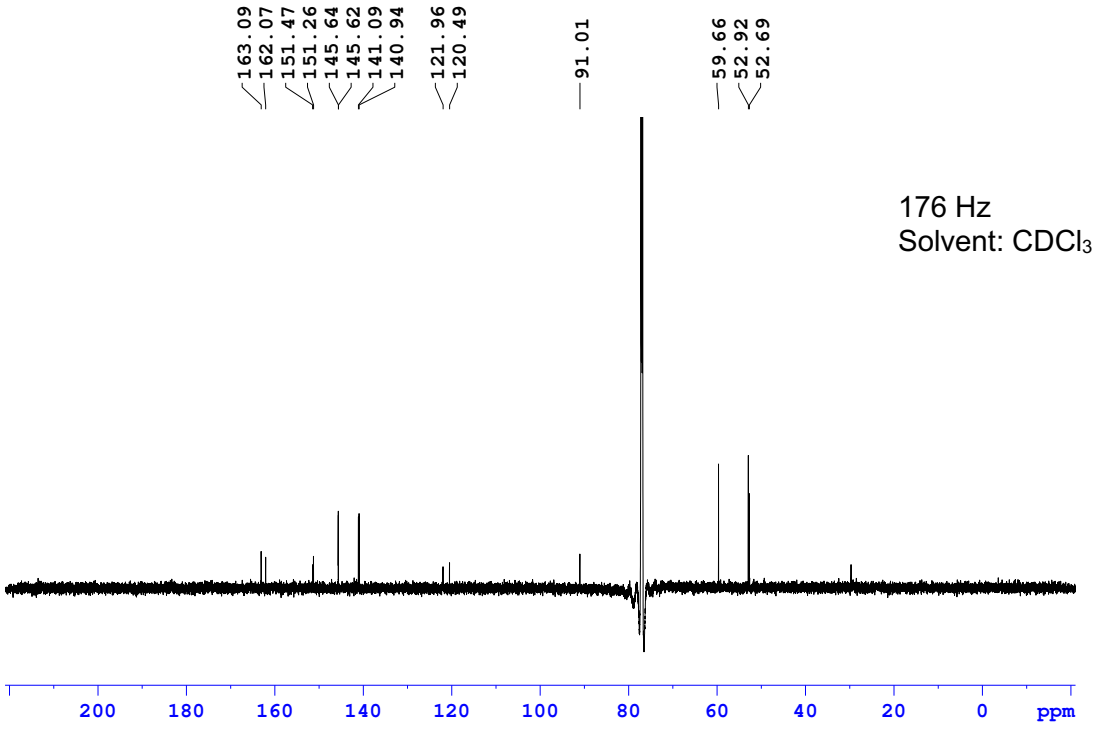
500 Hz
Solvent: $CDCl_3$

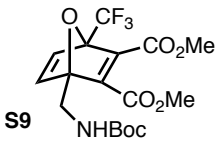





O
F
CO2Me
CO2Me
OH

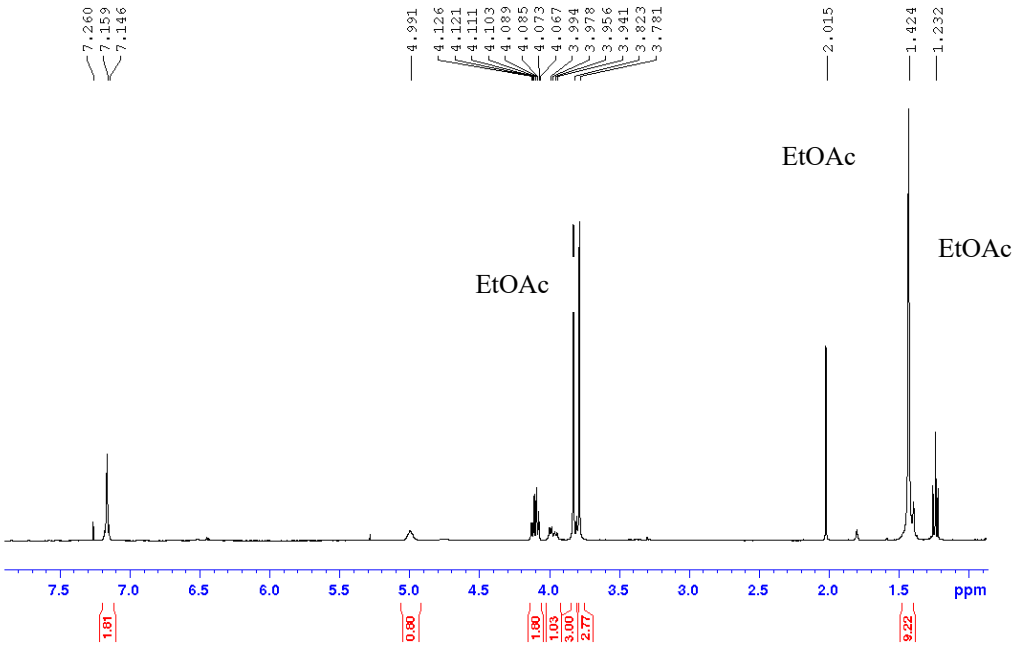
1l

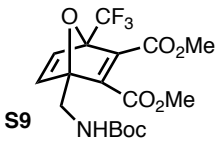

163.09
162.07
151.47
151.26
145.64
145.62
141.09
140.94
121.96
120.49
91.01
59.66
52.92
52.69
176 Hz
Solvent: CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm



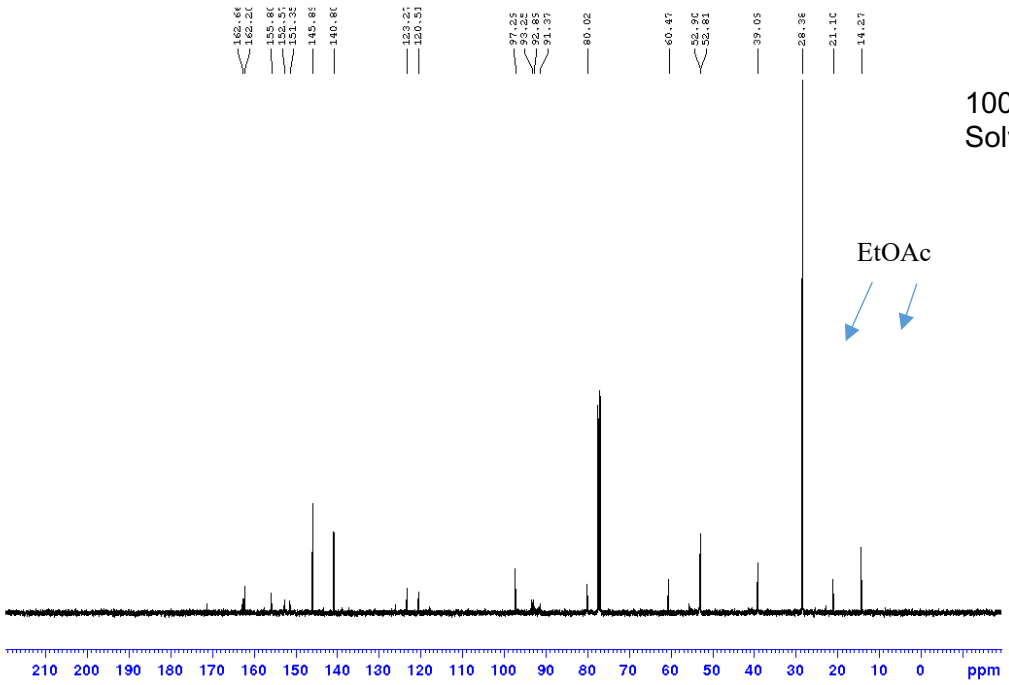
S9

400 Hz
Solvent: $CDCl_3$

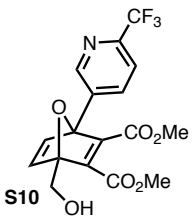




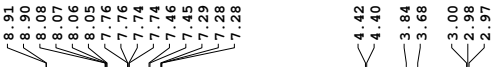
S9



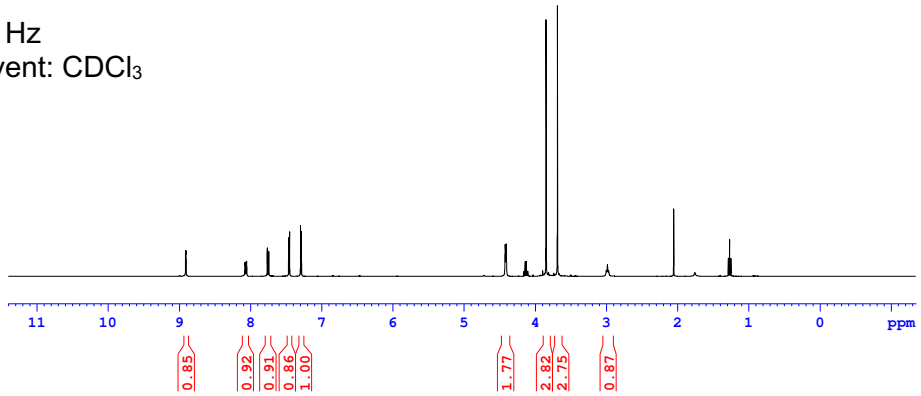
100 Hz
Solvent: $CDCl_3$

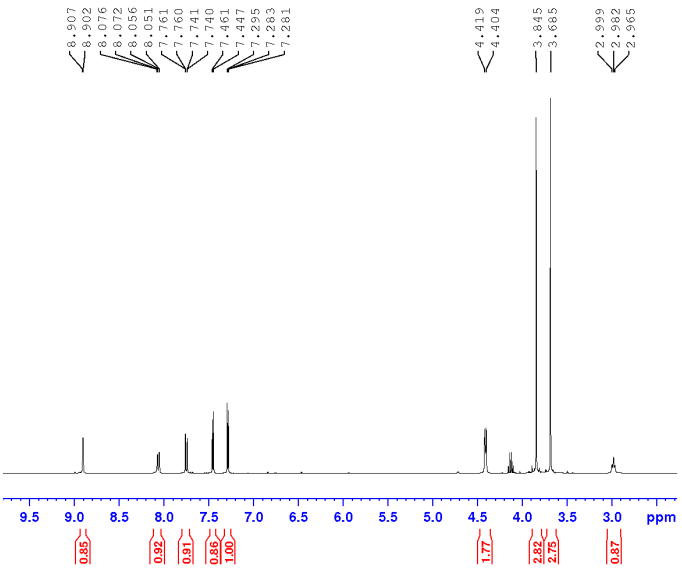


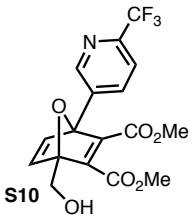
S10



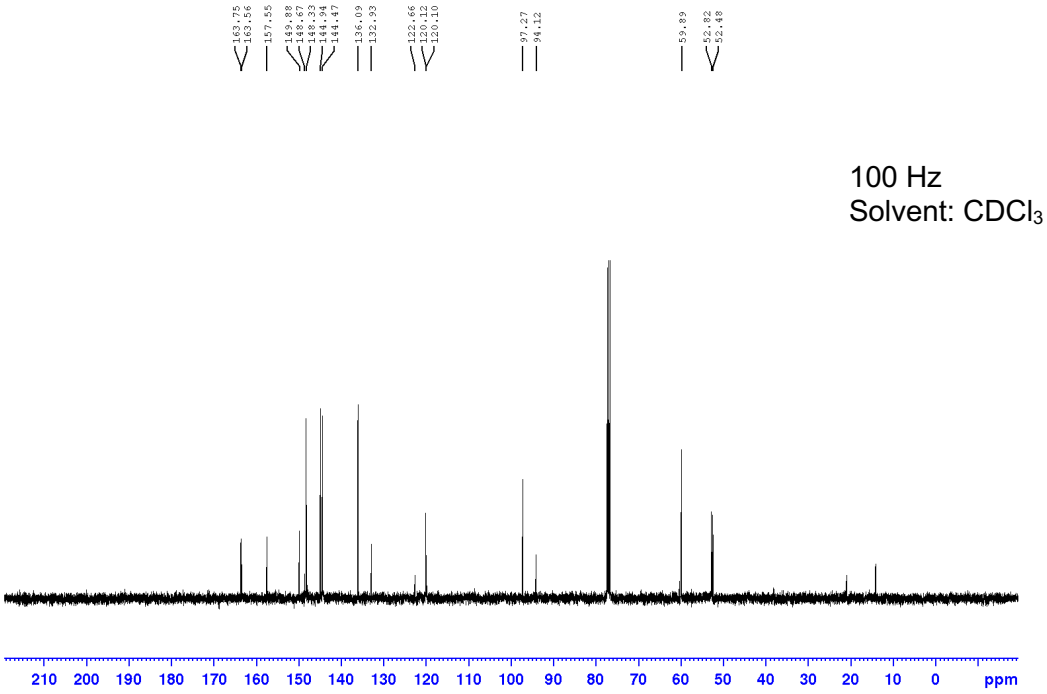
400 Hz
Solvent: $CDCl_3$

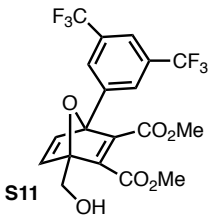




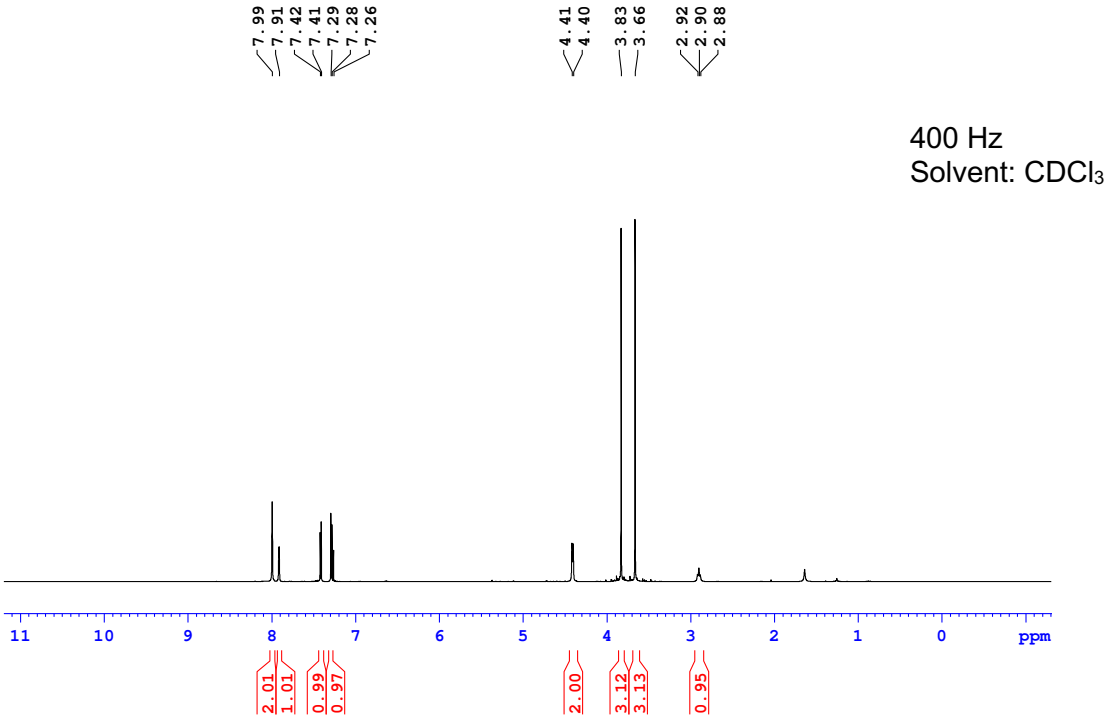

CF3
N
O
CO2Me
CO2Me
OH

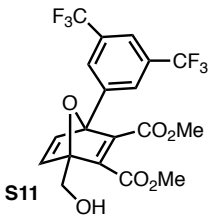
S10


163.75
163.56
157.55
149.88
148.67
148.33
144.94
144.47
136.09
132.93
122.66
120.12
120.10
97.27
94.12
59.89
52.82
52.48
100 Hz
Solvent: CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

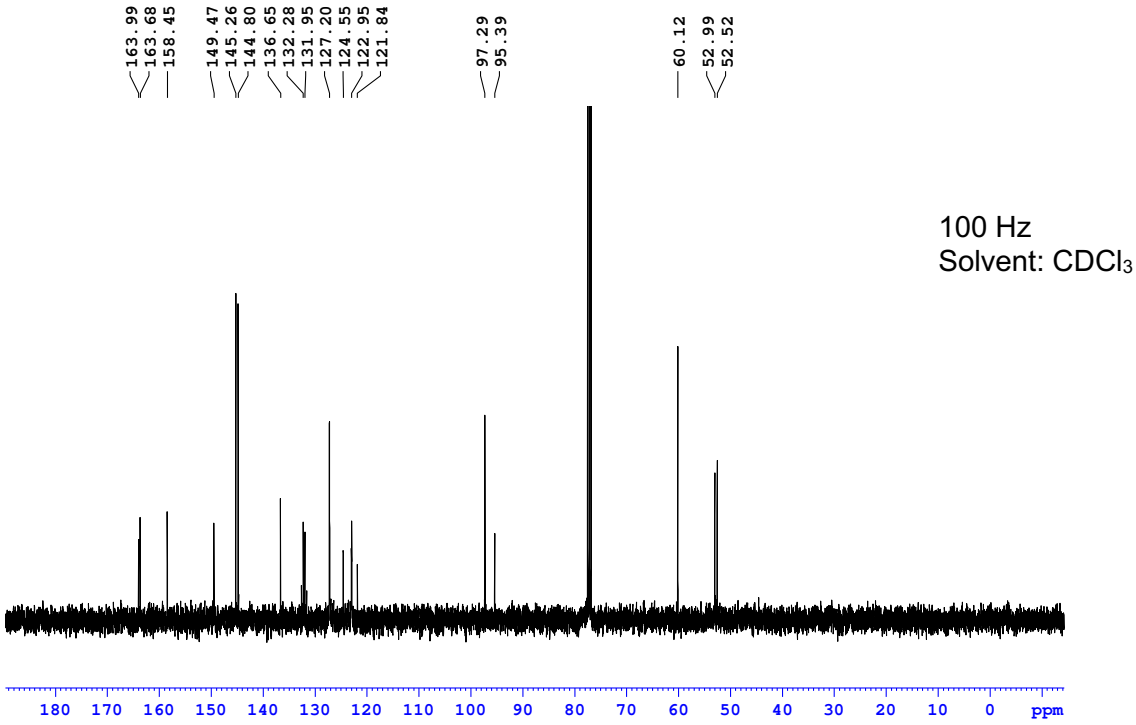

F3C
CF3
O
CO2Me
CO2Me
OH

S11

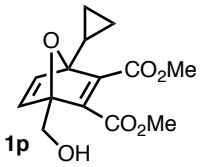

7.99
7.91
7.42
7.41
7.29
7.28
7.26
4.41
4.40
3.83
3.66
2.92
2.90
2.88
400 Hz
Solvent: CDCl3
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.01
1.01
0.99
0.97
2.00
3.12
3.13
0.95



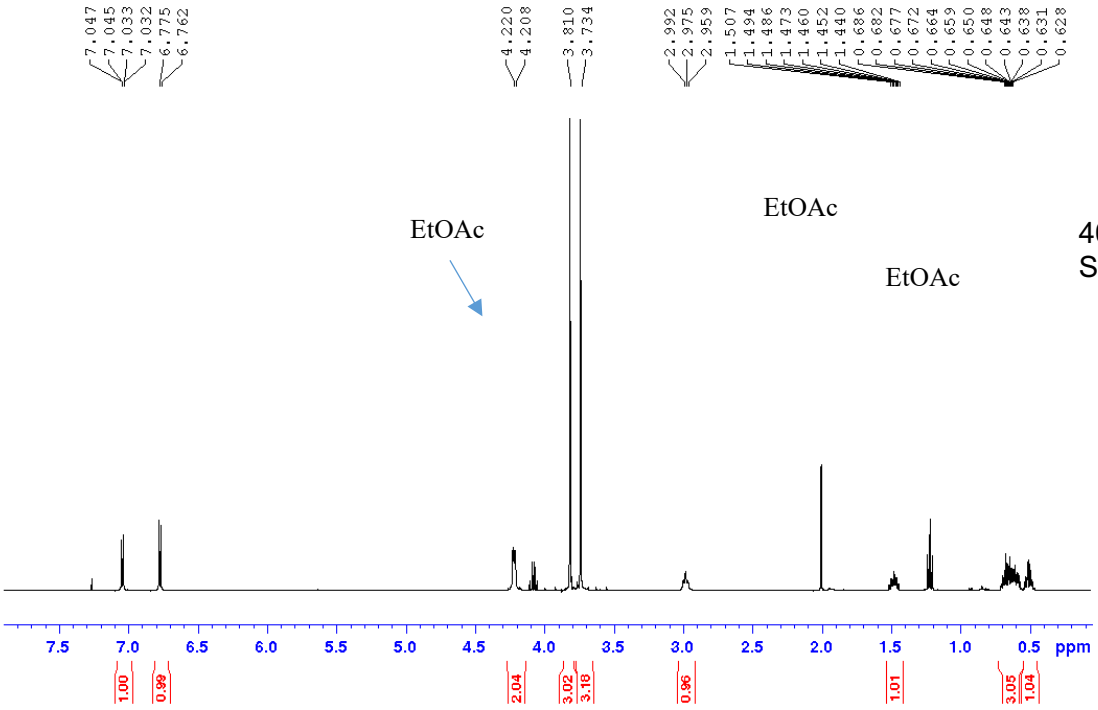
S11



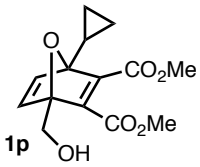
100 Hz
Solvent: $CDCl_3$



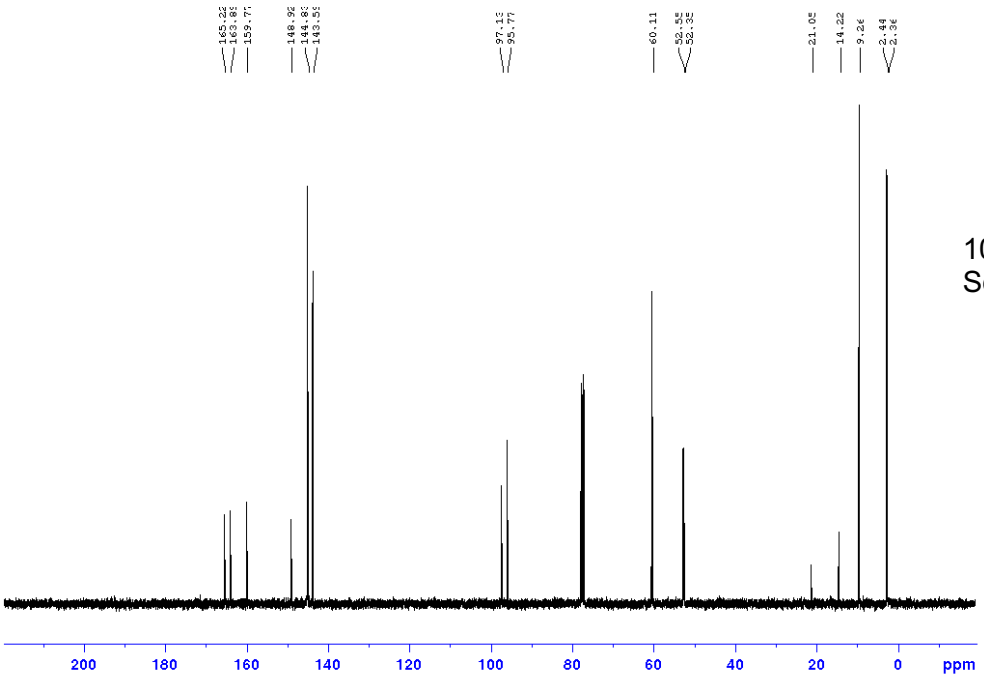
1p



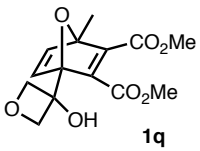
400 Hz
Solvent: $CDCl_3$



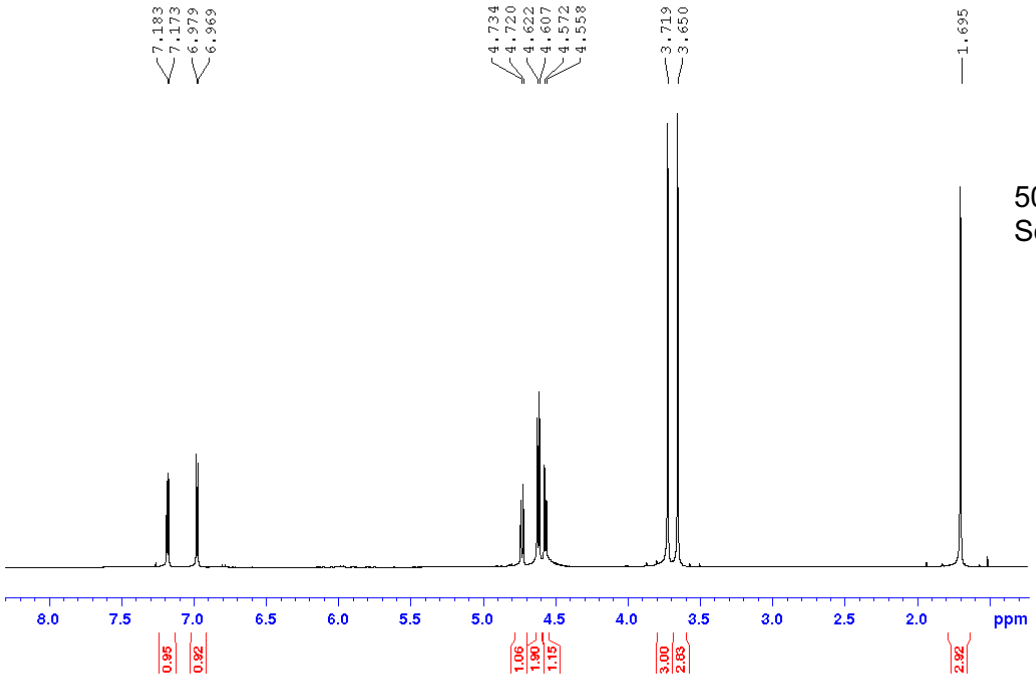
1p



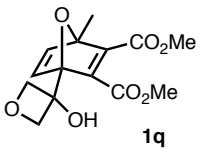
100 Hz
Solvent: $CDCl_3$



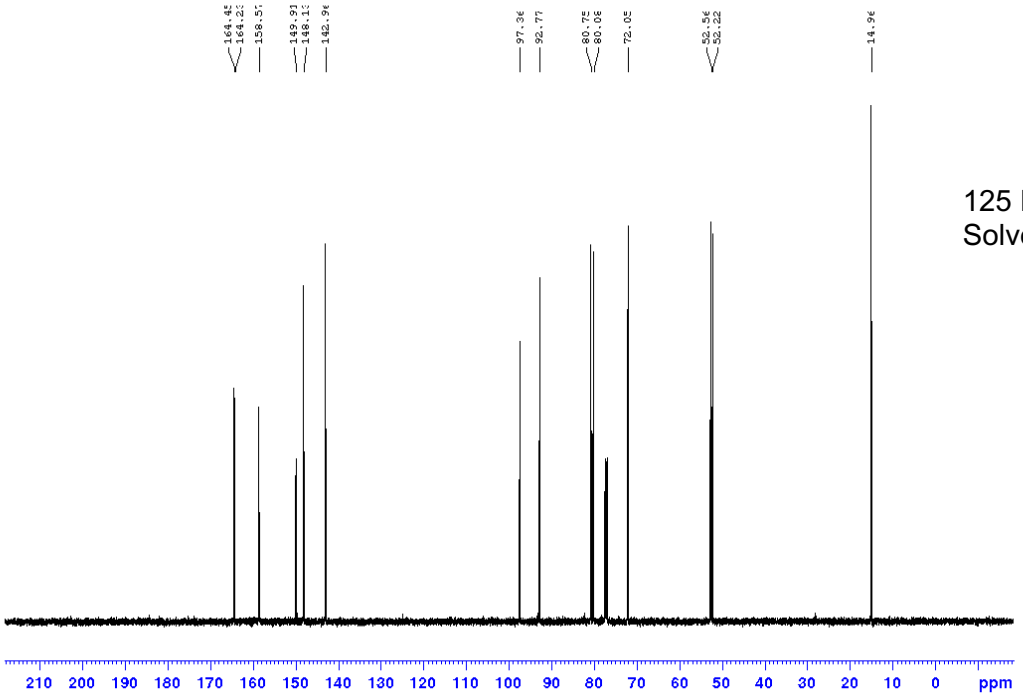
1q



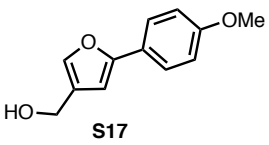
500 Hz
Solvent: $CDCl_3$



1q

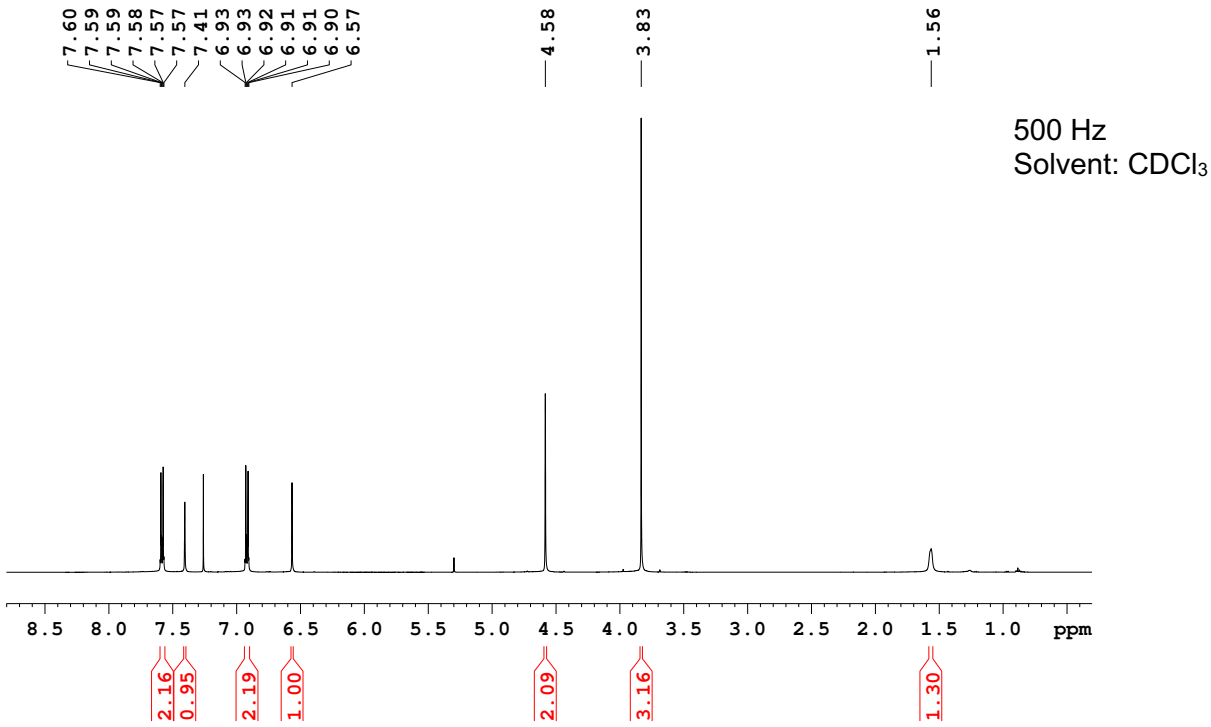


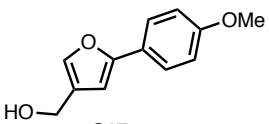
125 Hz
Solvent: $CDCl_3$



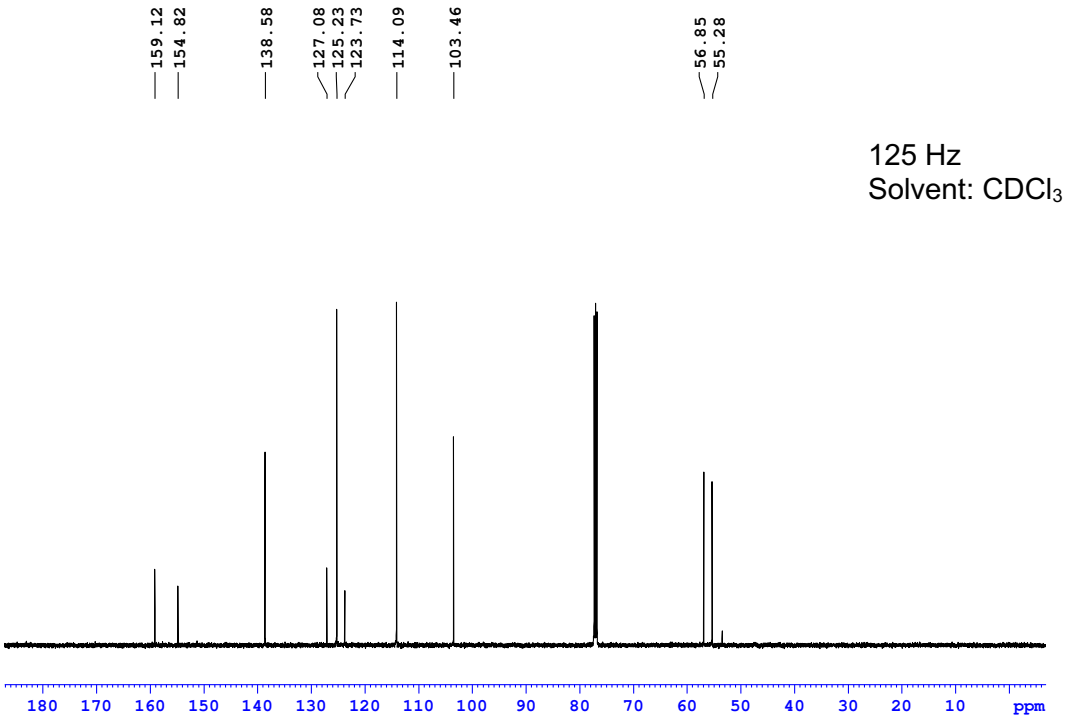
S17

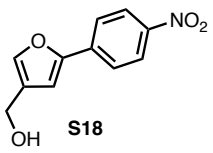
furan-2phome-4oh



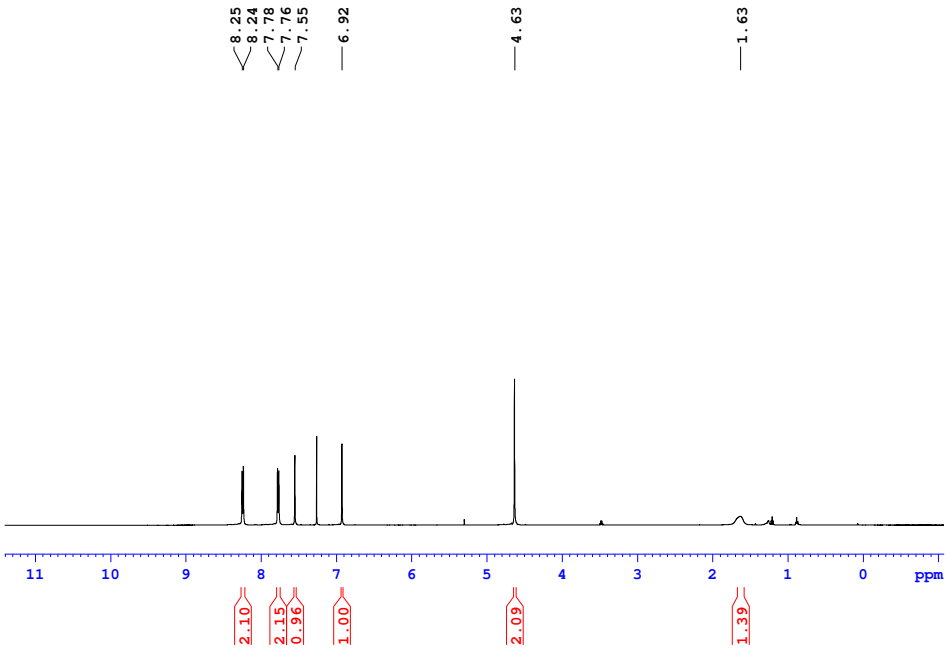

OMe
O
HO

S17

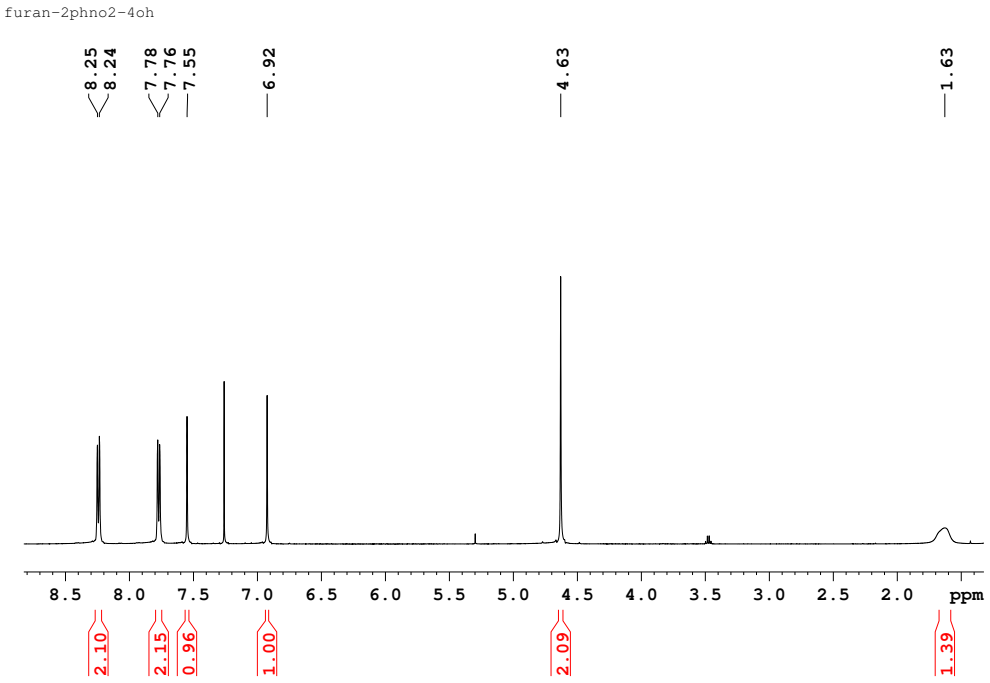

159.12
154.82
138.58
127.08
125.23
123.73
114.09
103.46
56.85
55.28
125 Hz
Solvent: CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

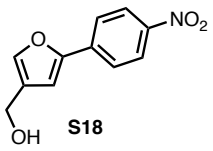


S18



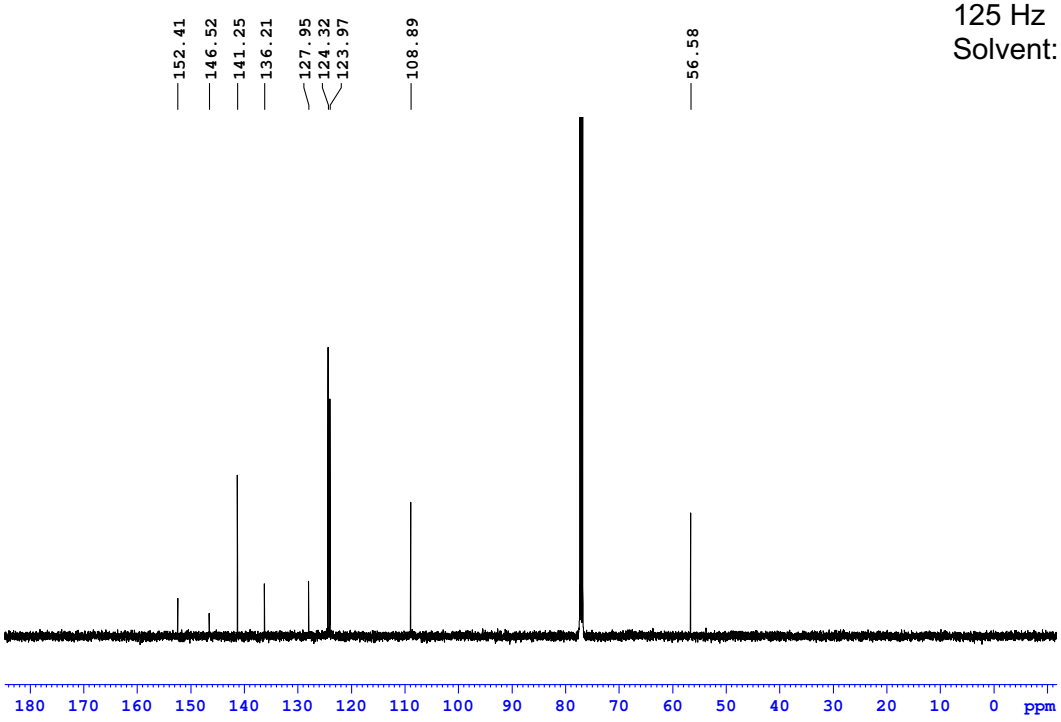
500 Hz
Solvent: $CDCl_3$

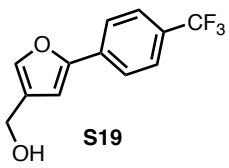




S18

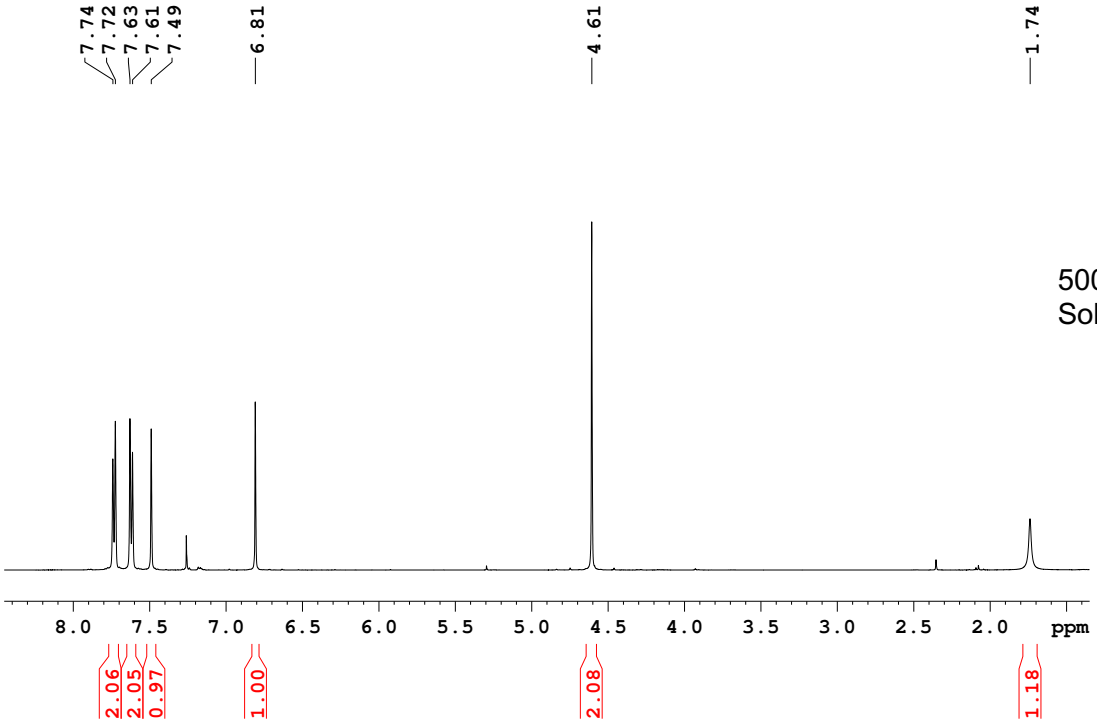
125 Hz
Solvent: $CDCl_3$



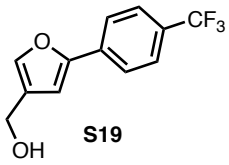


S19

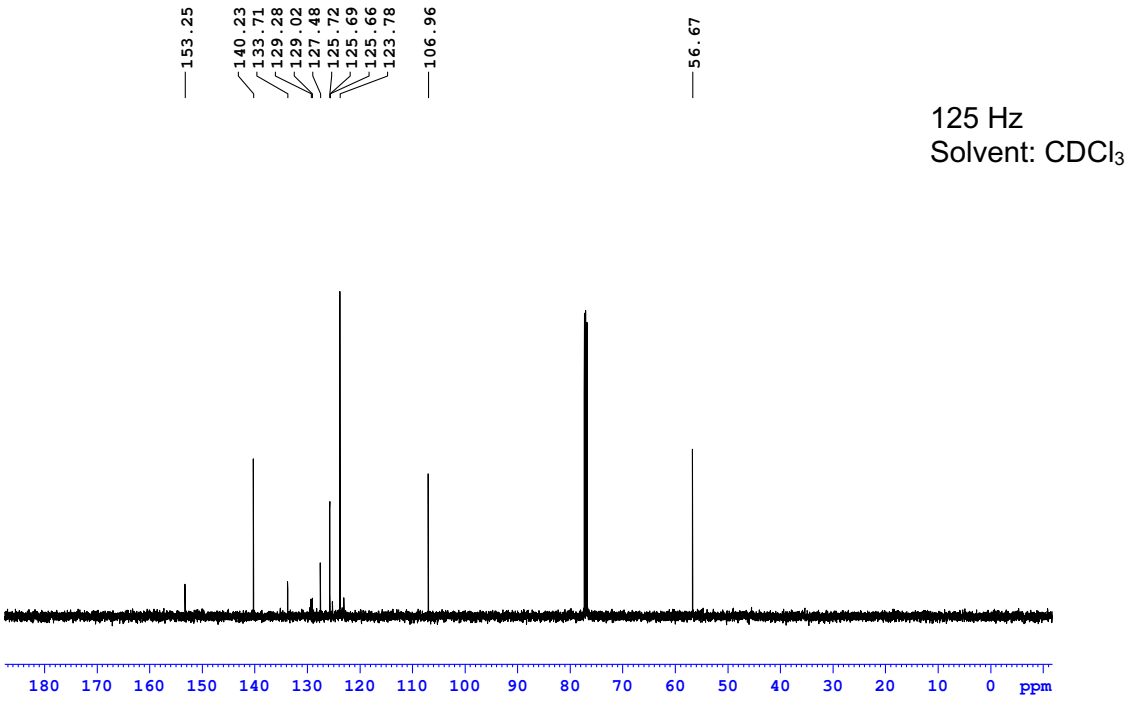
furan-2ph-cf3-4oh



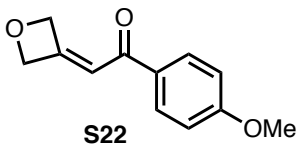
500 Hz
Solvent: $CDCl_3$



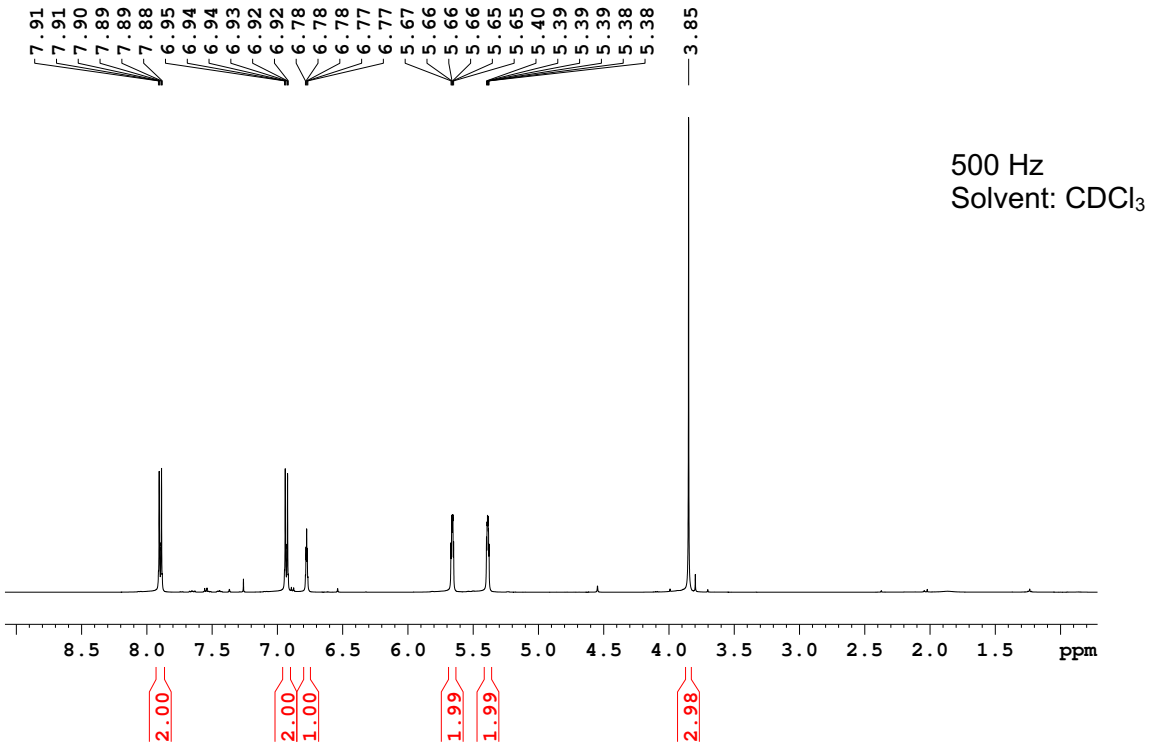
S19

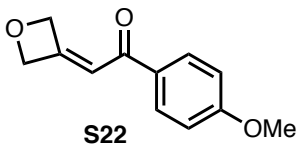


125 Hz
Solvent: $CDCl_3$

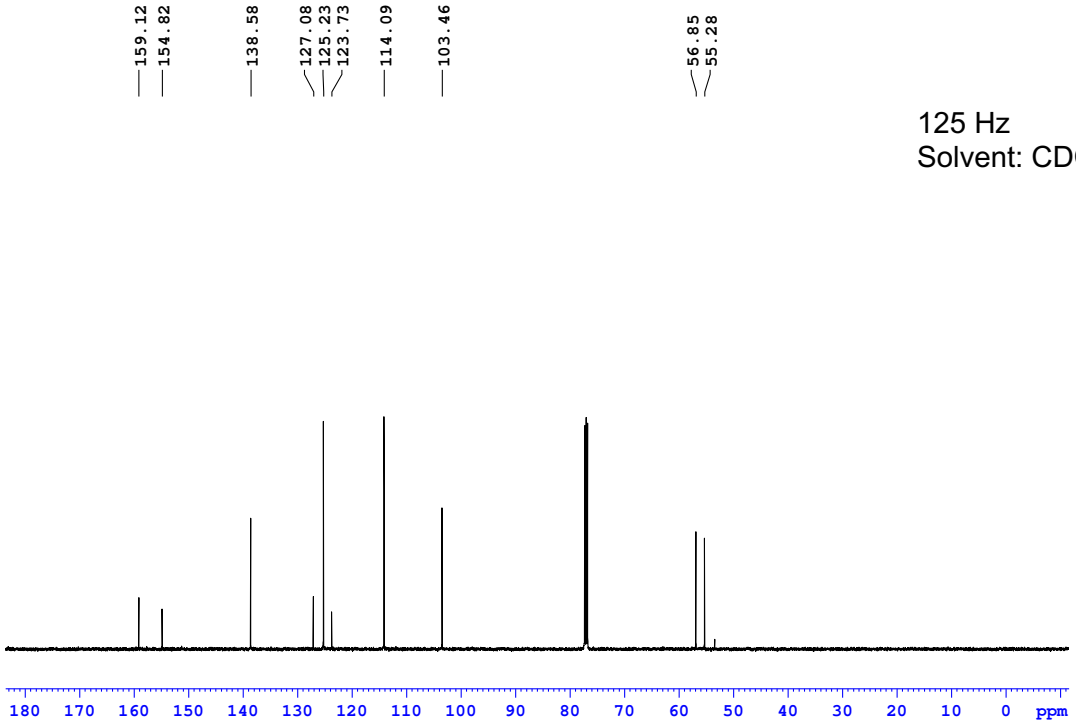

O
O
OMe

S22

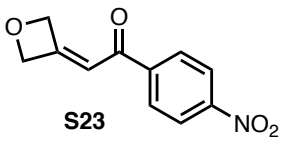

7.91
7.91
7.90
7.89
7.89
7.88
6.95
6.94
6.94
6.93
6.92
6.92
6.78
6.78
6.78
6.77
6.77
5.67
5.66
5.66
5.66
5.65
5.65
5.40
5.39
5.39
5.39
5.38
5.38
3.85
500 Hz
Solvent: CDCl3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.00
2.00
1.00
1.99
1.99
2.98



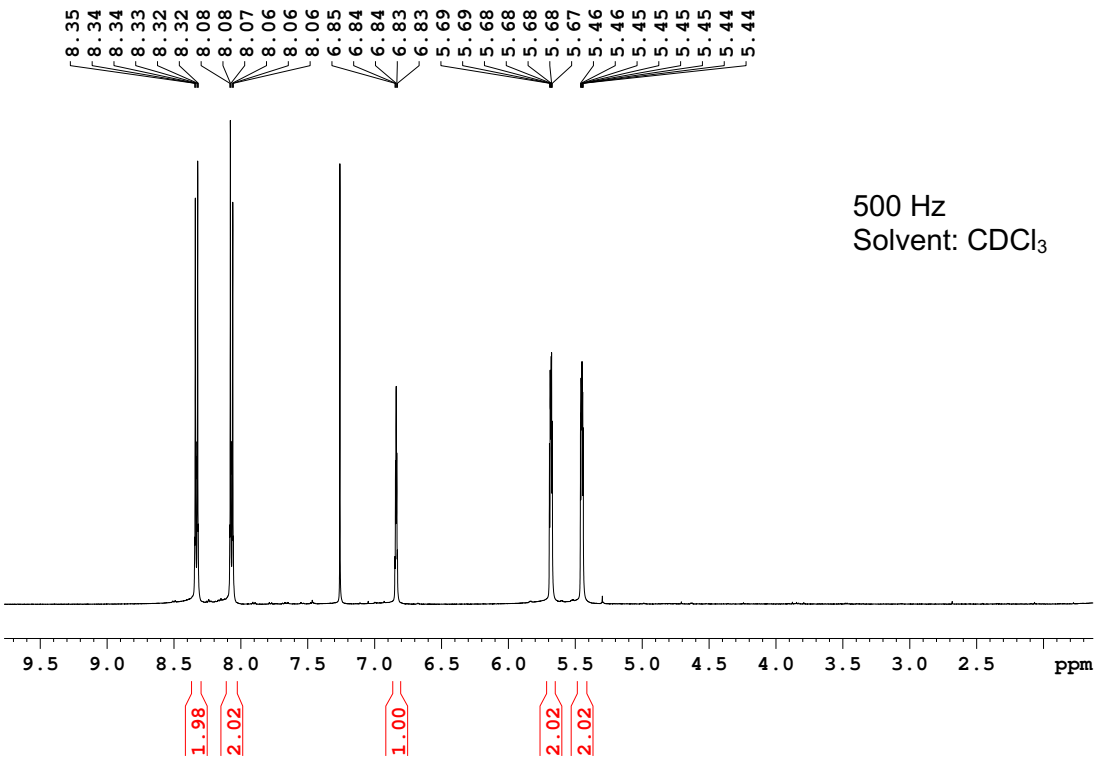
S22

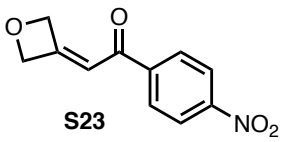


125 Hz
Solvent: $CDCl_3$

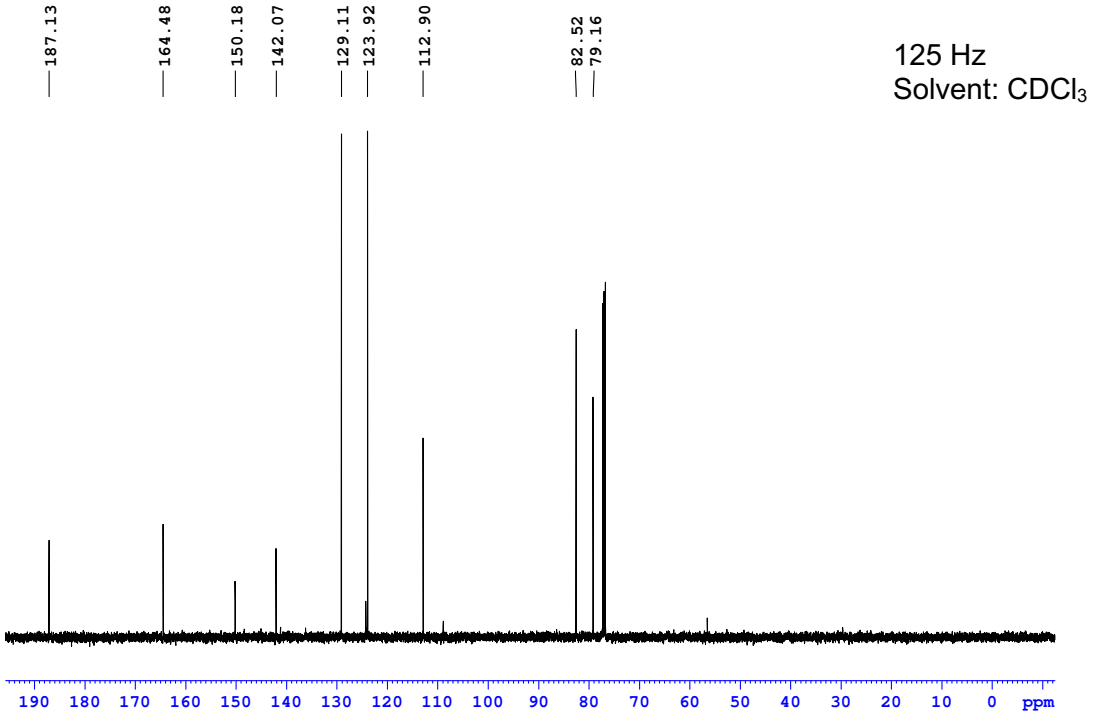

O
O
NO2

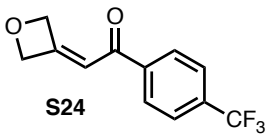
S23


8.35
8.34
8.34
8.33
8.32
8.32
8.08
8.08
8.07
8.06
8.06
8.06
6.85
6.84
6.84
6.83
6.83
5.69
5.69
5.68
5.68
5.68
5.67
5.46
5.46
5.45
5.45
5.45
5.45
5.44
5.44
500 Hz
Solvent: CDCl3
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
ppm
1.98
2.02
1.00
2.02
2.02

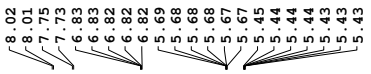

O
O
NO2

S23

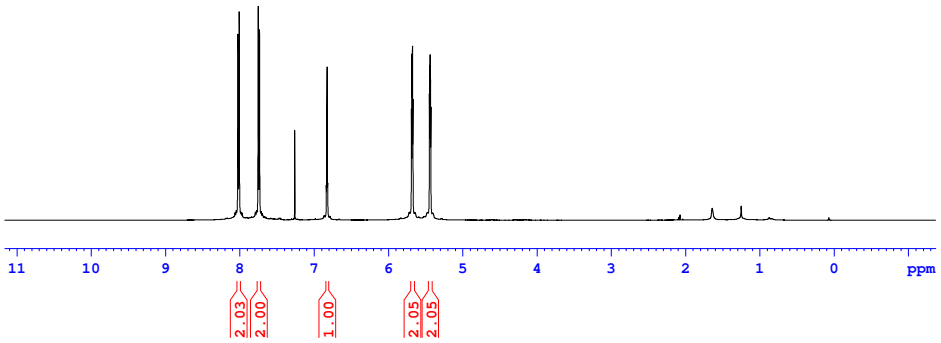

187.13
164.48
150.18
142.07
129.11
123.92
112.90
82.52
79.16
125 Hz
Solvent: CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

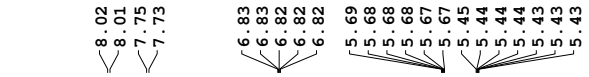


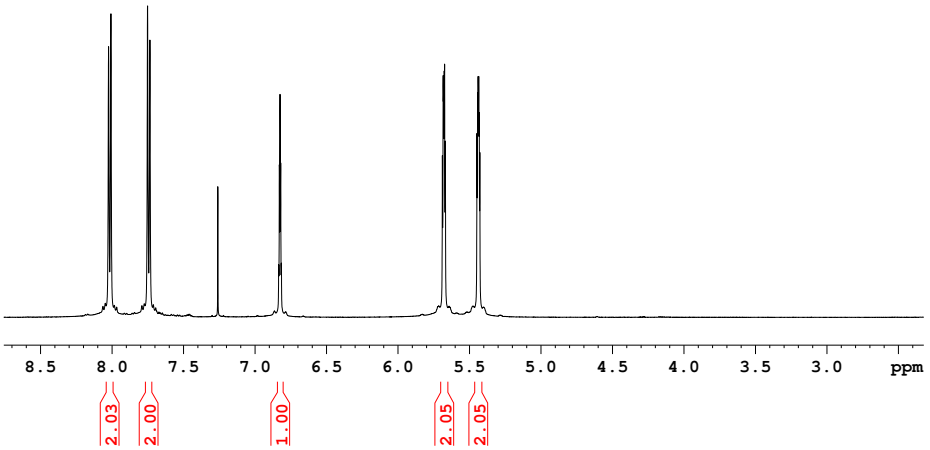
S24

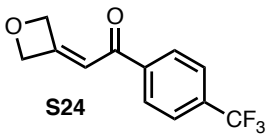


500 Hz
Solvent: $CDCl_3$

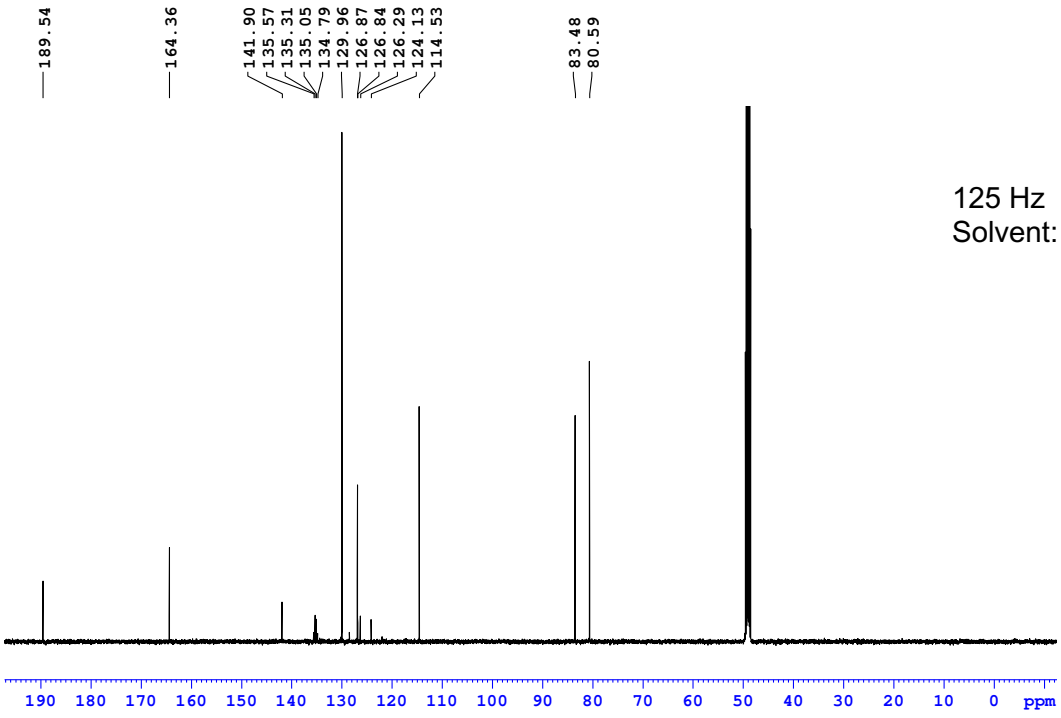




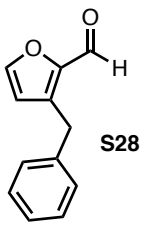




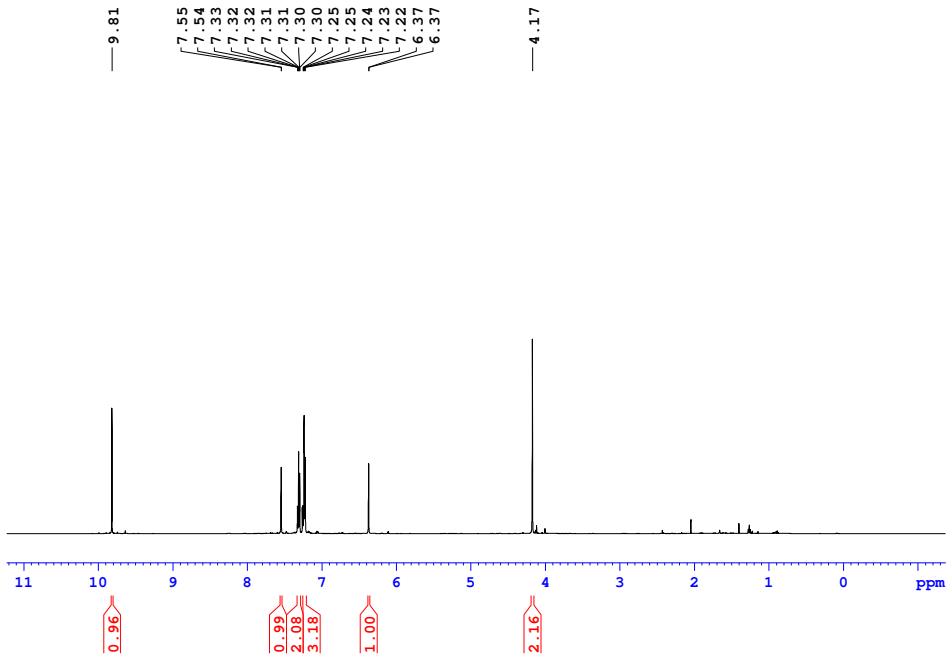
S24



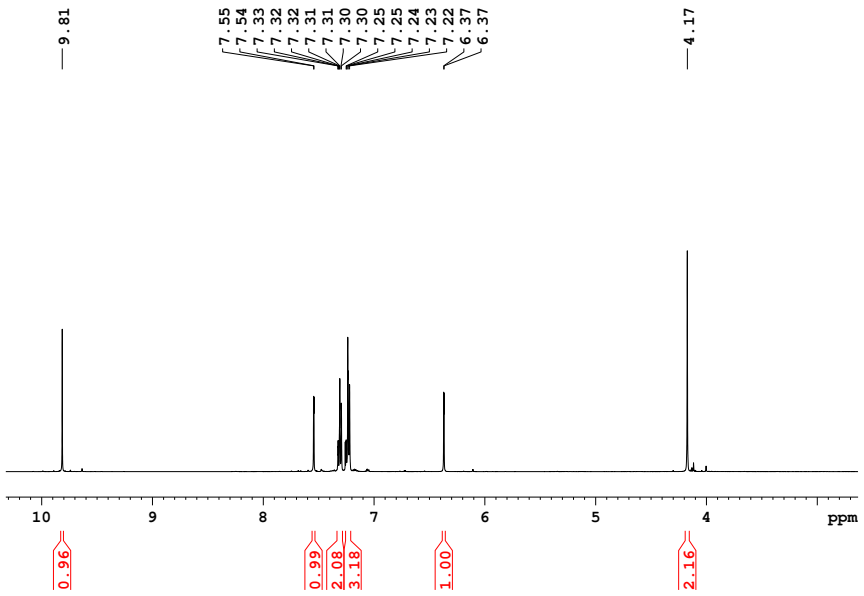
125 Hz
Solvent: CD_3OD

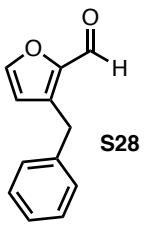


S28

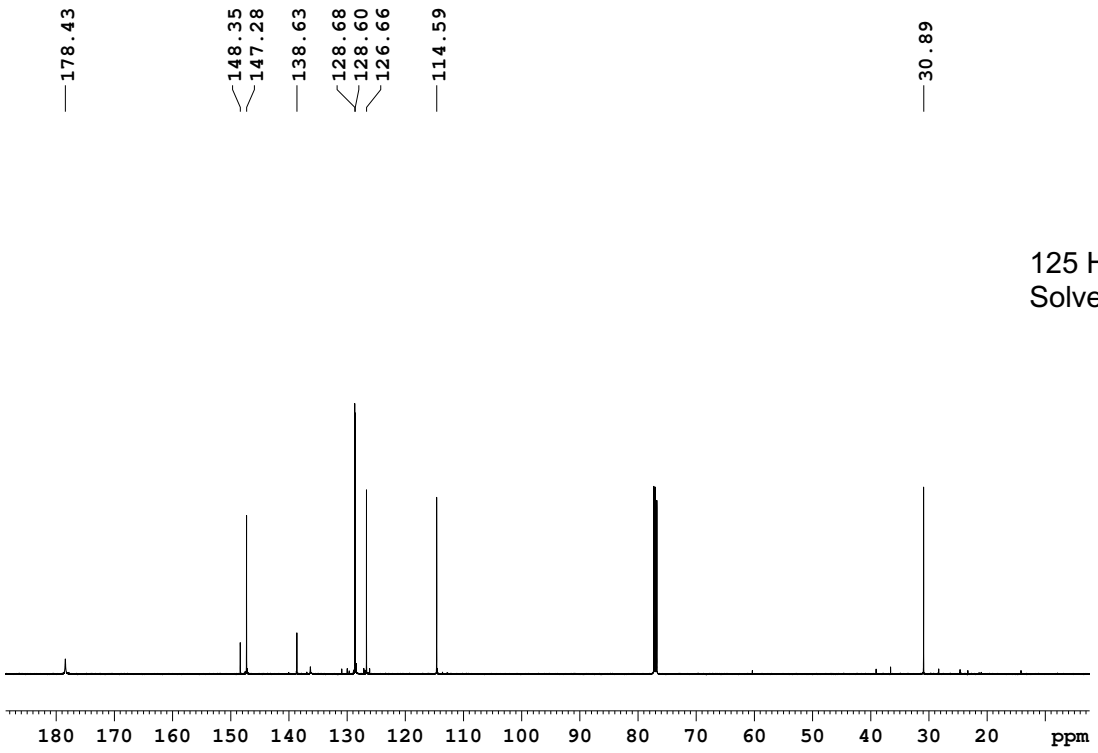


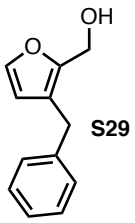
500 Hz
Solvent: $CDCl_3$



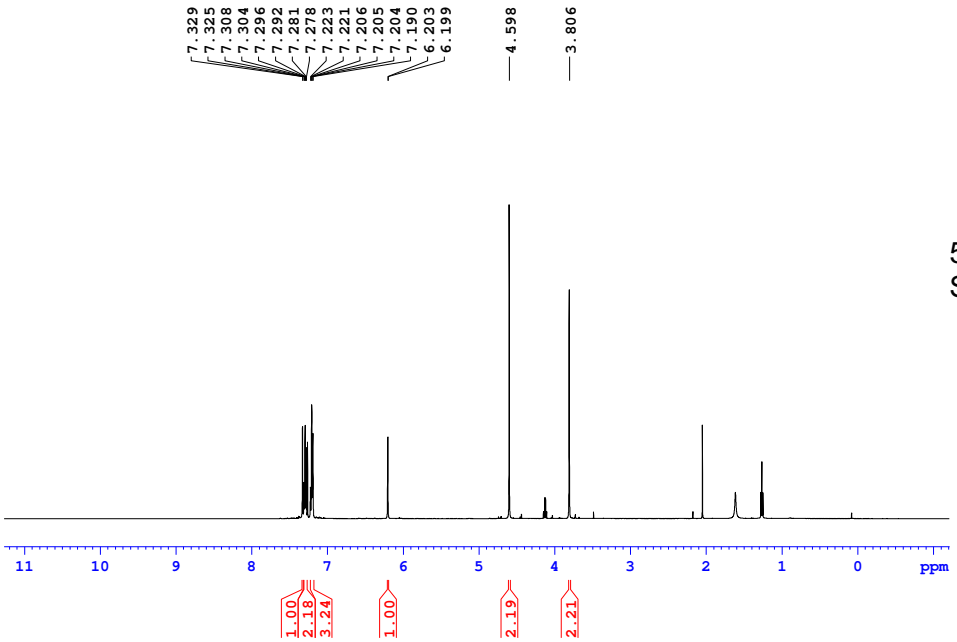

O
O
H

S28

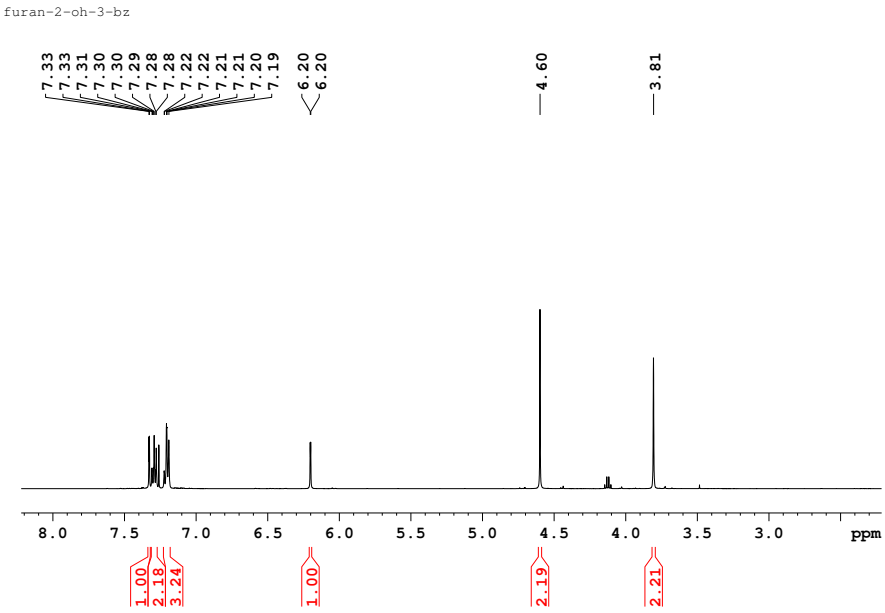

178.43
148.35
147.28
138.63
128.68
128.60
126.66
114.59
30.89
125 Hz
Solvent: CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

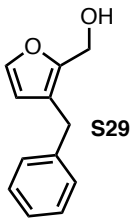


S29

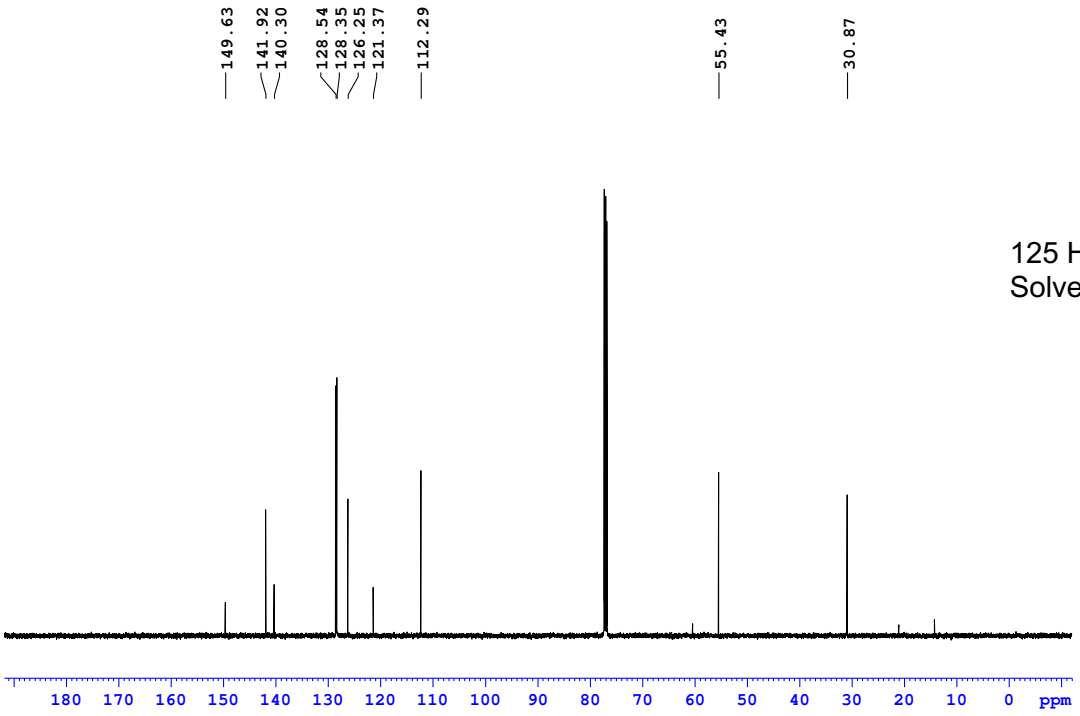


500 Hz
Solvent: $CDCl_3$



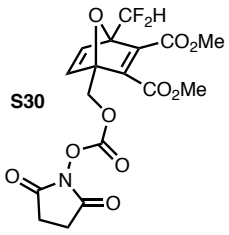


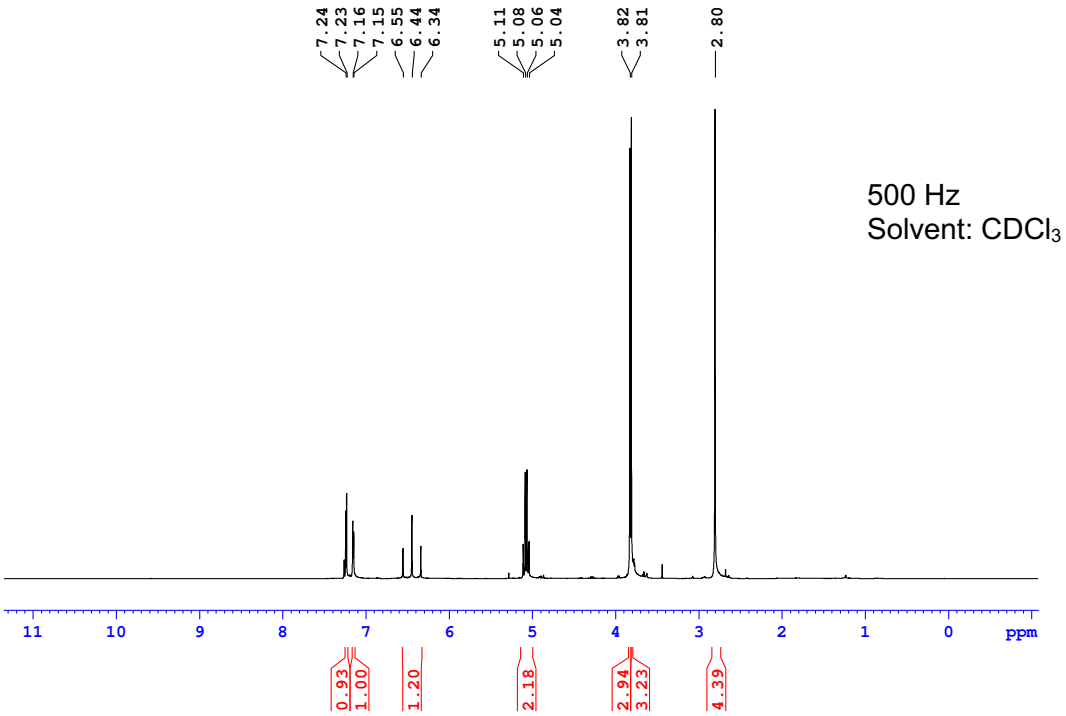
S29



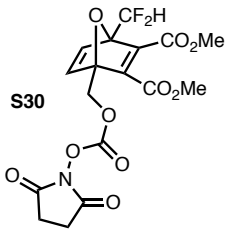
125 Hz
Solvent: $CDCl_3$

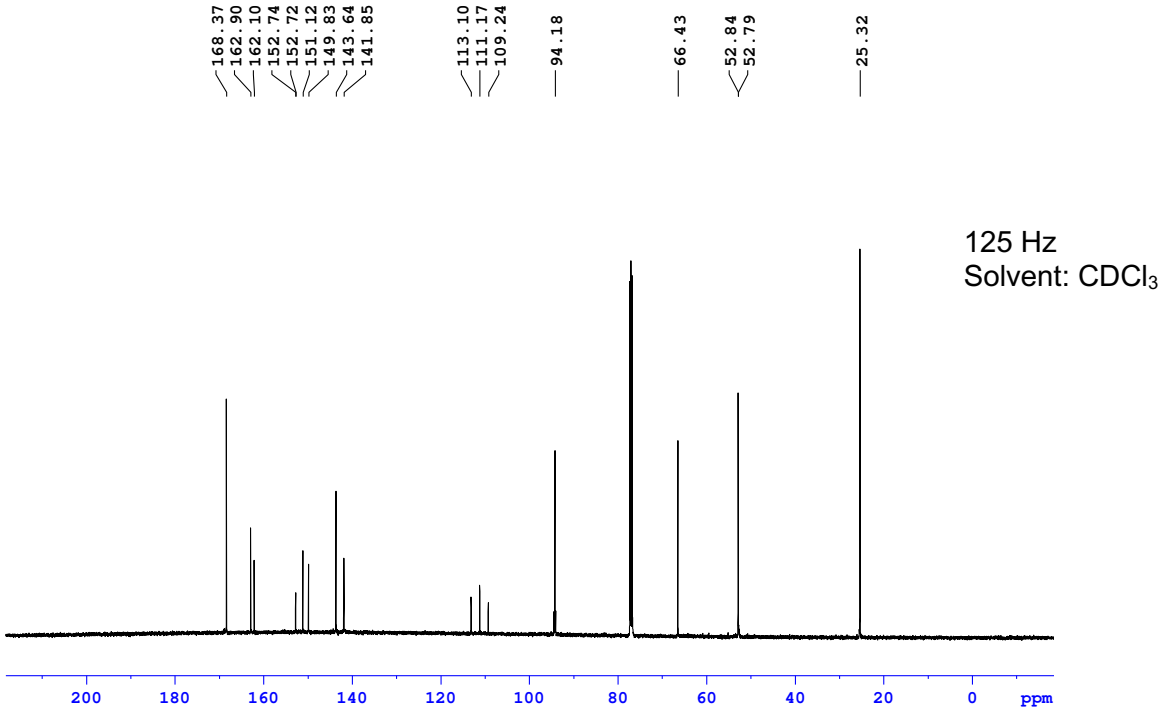
S30

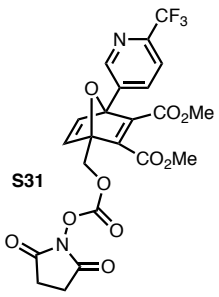

O
CF2H
CO2Me
CO2Me
O
O
O
O
N
O
O


7.24
7.23
7.16
7.15
6.55
6.44
6.34
5.11
5.08
5.06
5.04
3.82
3.81
2.80
500 Hz
Solvent: CDCl3
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
1.00
1.20
2.18
2.94
3.23
4.39

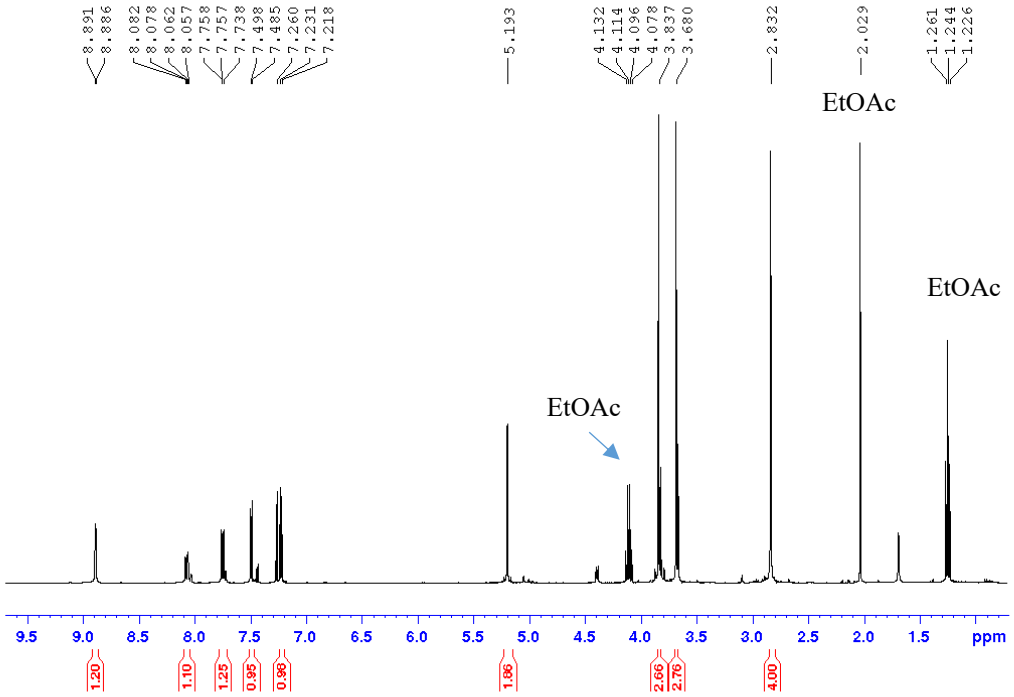
S30


O
CF2H
CO2Me
CO2Me
O
O
O
O
N
O

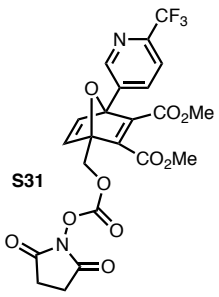

168.37
162.90
162.10
152.74
152.72
151.12
149.83
143.64
141.85
113.10
111.17
109.24
94.18
66.43
52.84
52.79
25.32
125 Hz
Solvent: CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm



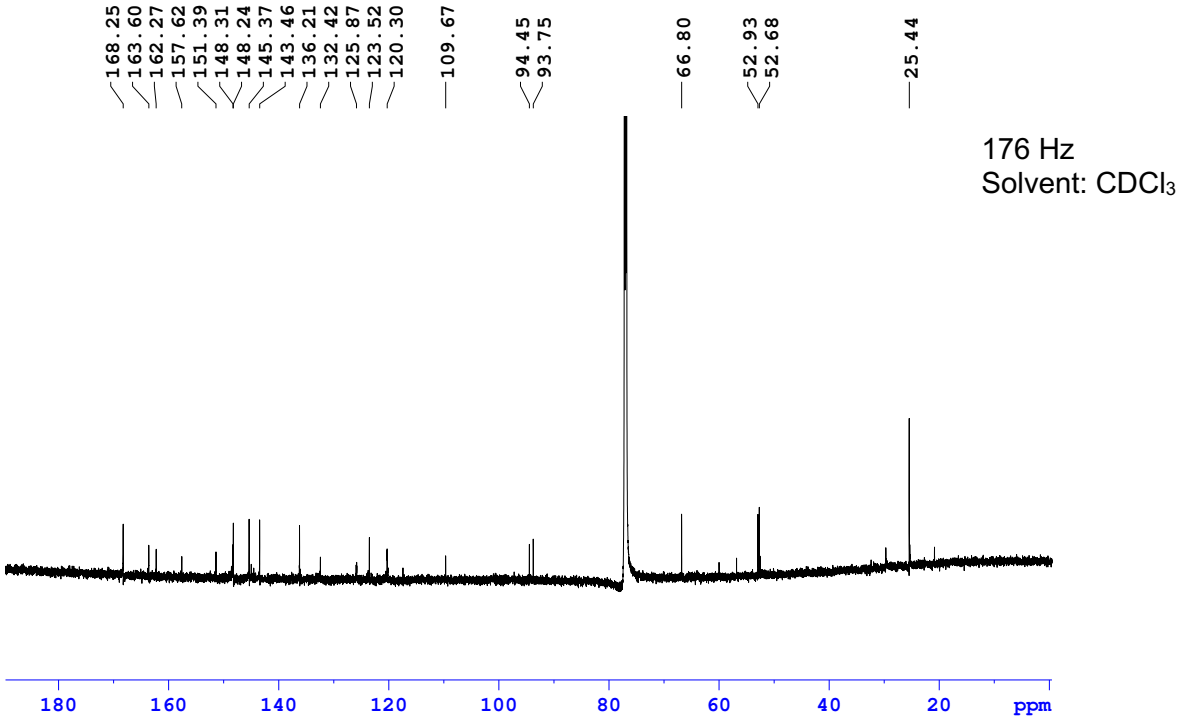
S31



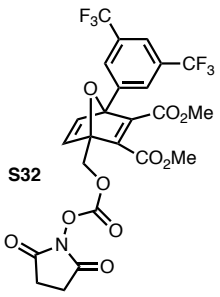
400 Hz
Solvent: $CDCl_3$

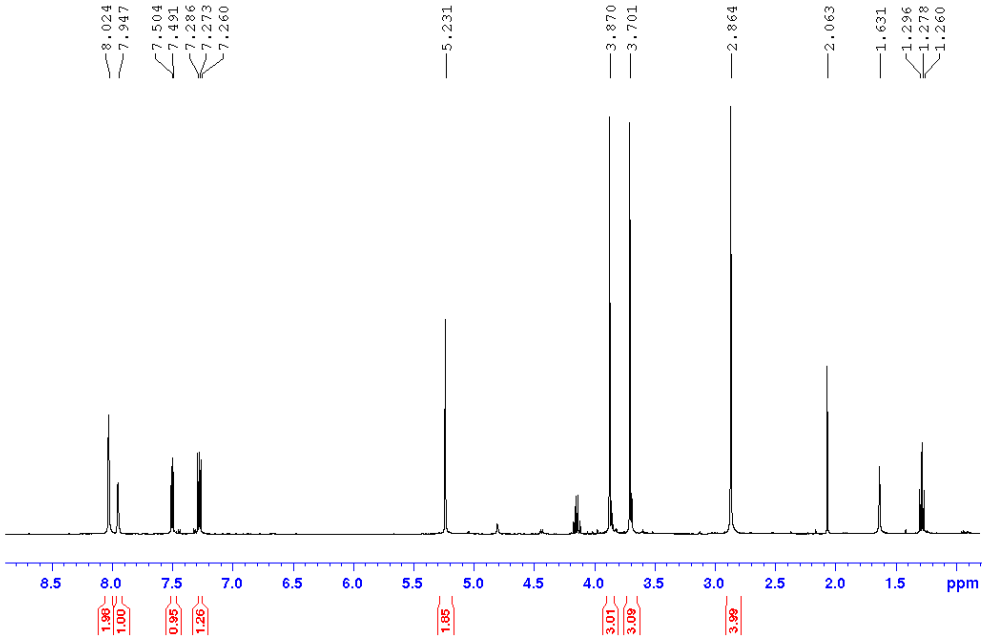

CF3
N
O
CO2Me
CO2Me
O
O
O
O
N
O
O

S31

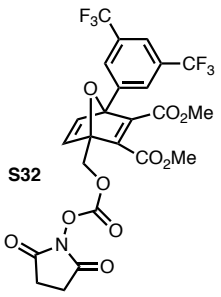

168.25
163.60
162.27
157.62
151.39
148.31
148.24
145.37
143.46
136.21
132.42
125.87
123.52
120.30
109.67
94.45
93.75
66.80
52.93
52.68
25.44
176 Hz
Solvent: CDCl3
180
160
140
120
100
80
60
40
20
ppm

S32

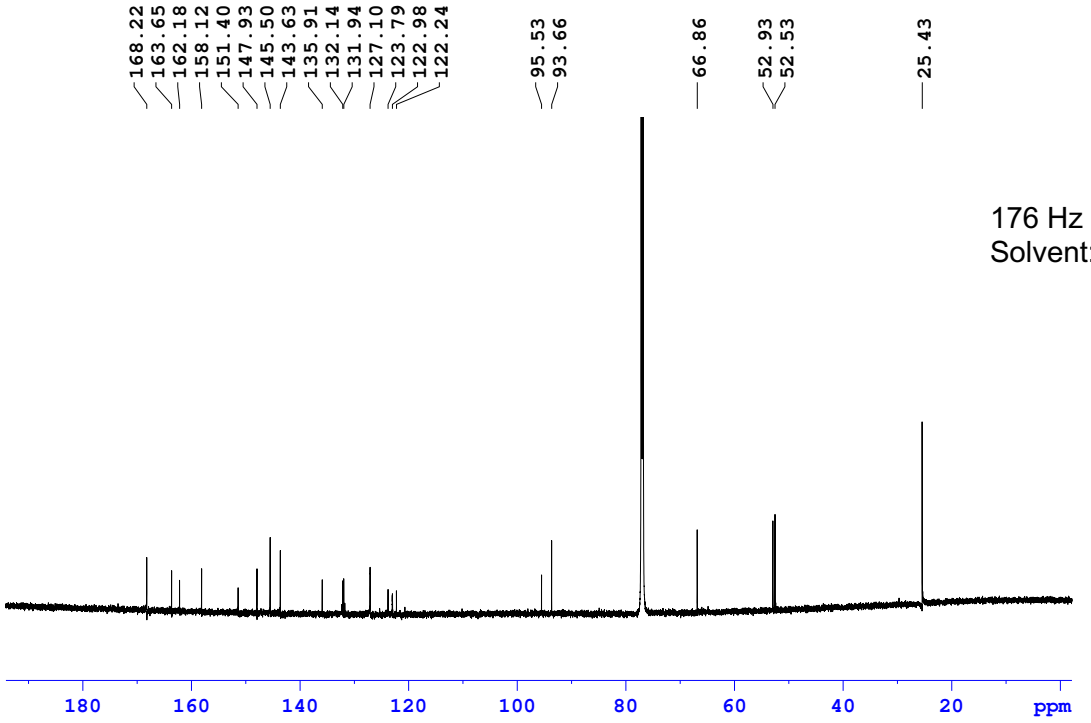




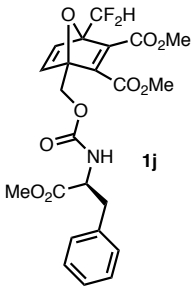
400 Hz
Solvent: $CDCl_3$



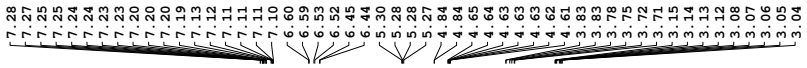
S32



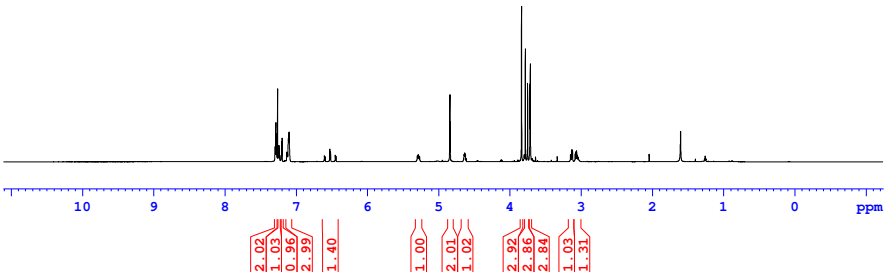
176 Hz
Solvent: $CDCl_3$

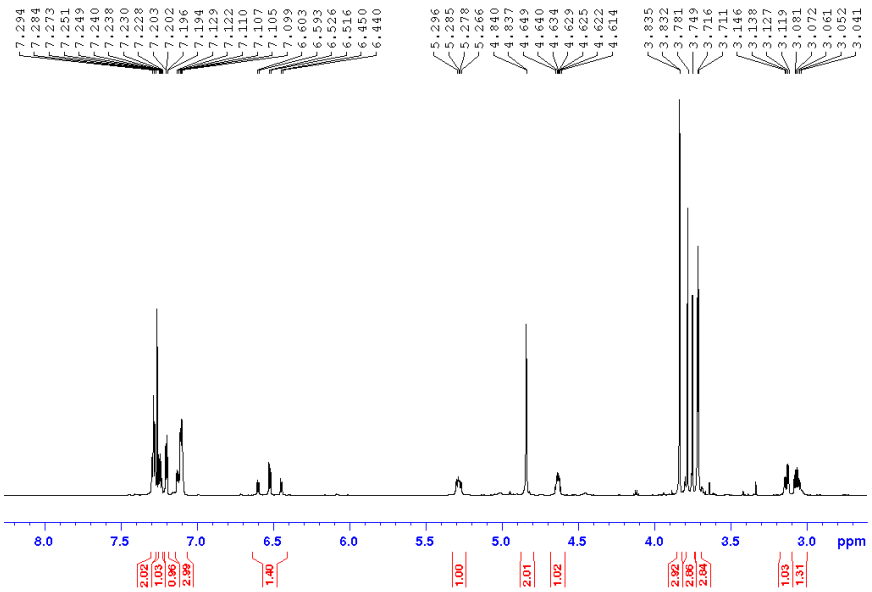


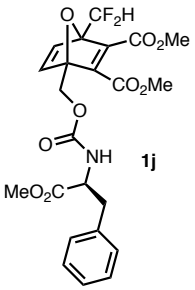
1j



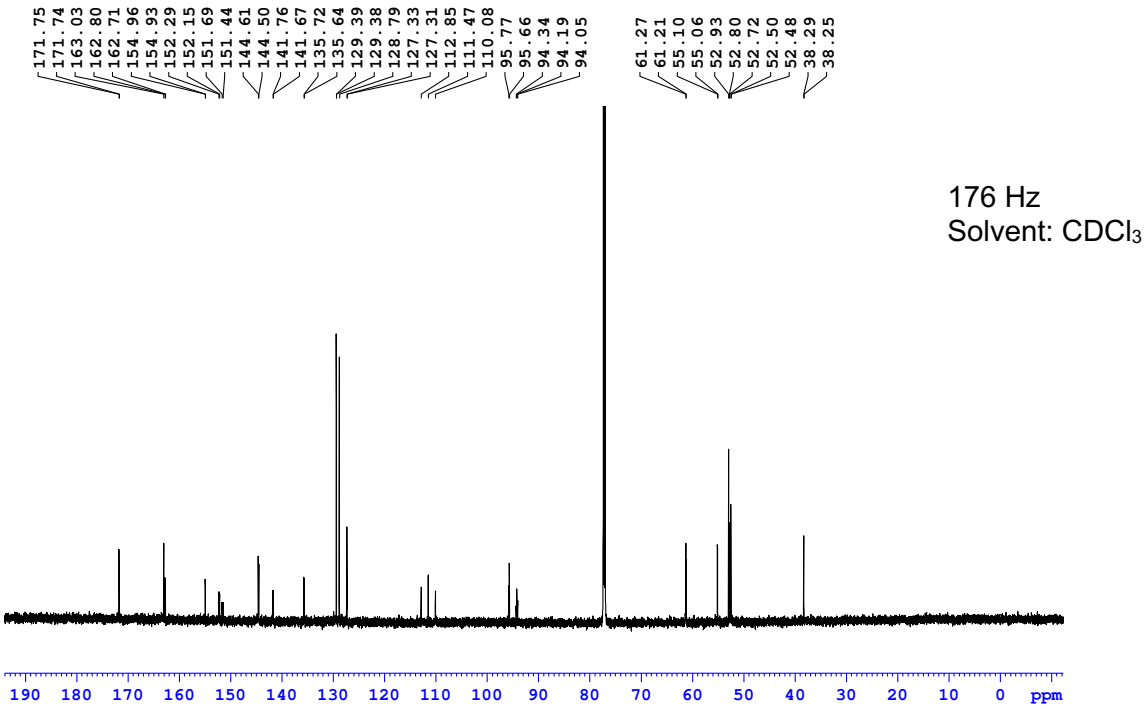
700 Hz
Solvent: $CDCl_3$



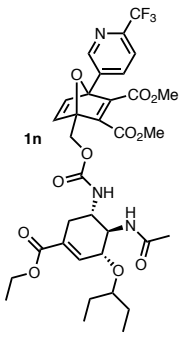




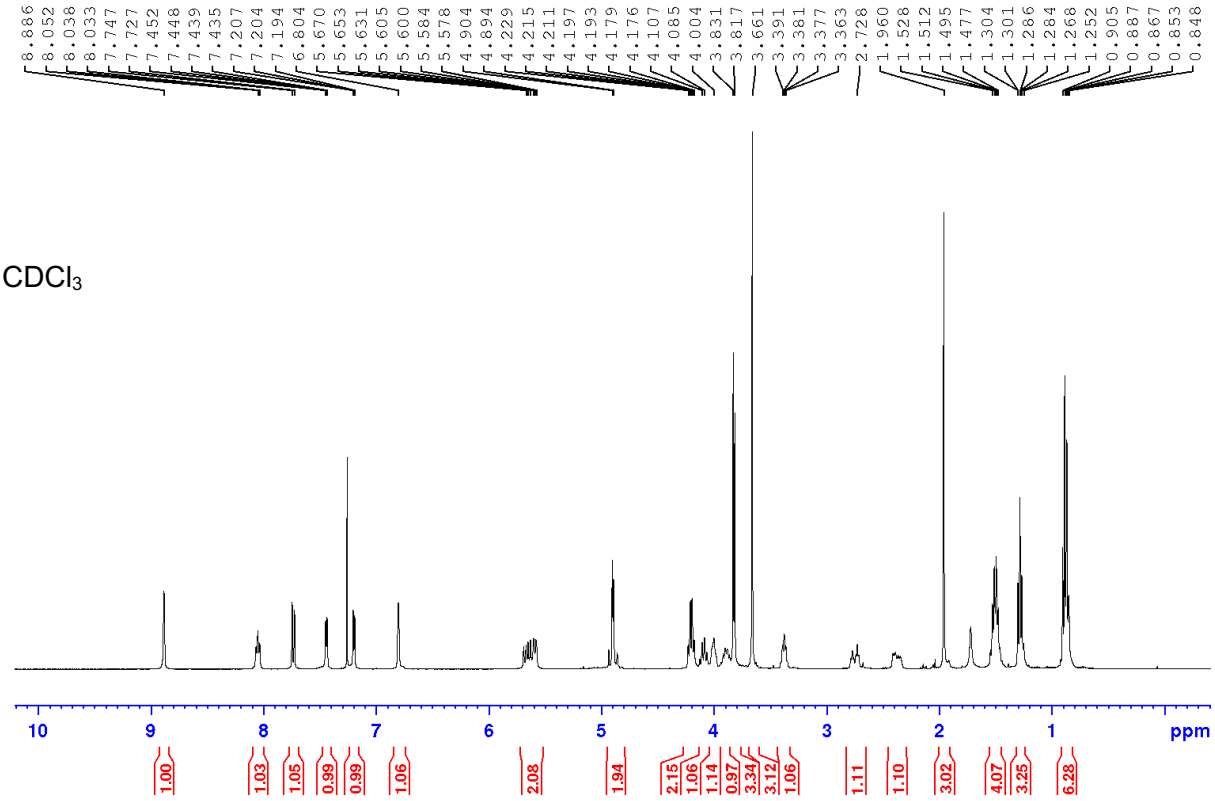
1j

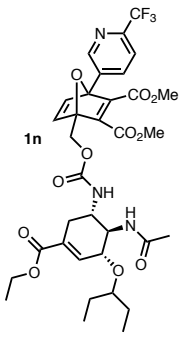


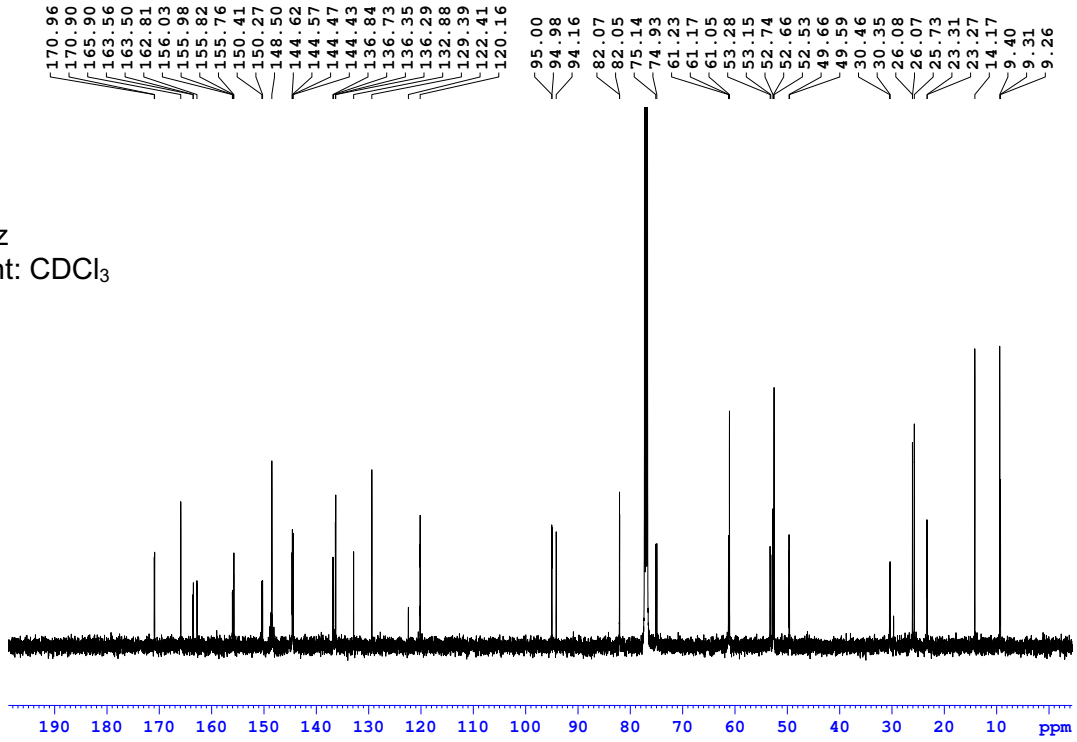
176 Hz
Solvent: $CDCl_3$



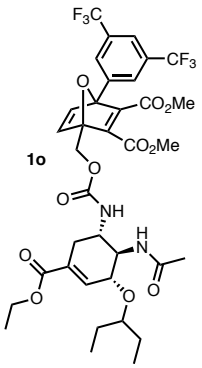
400 Hz
Solvent: $CDCl_3$



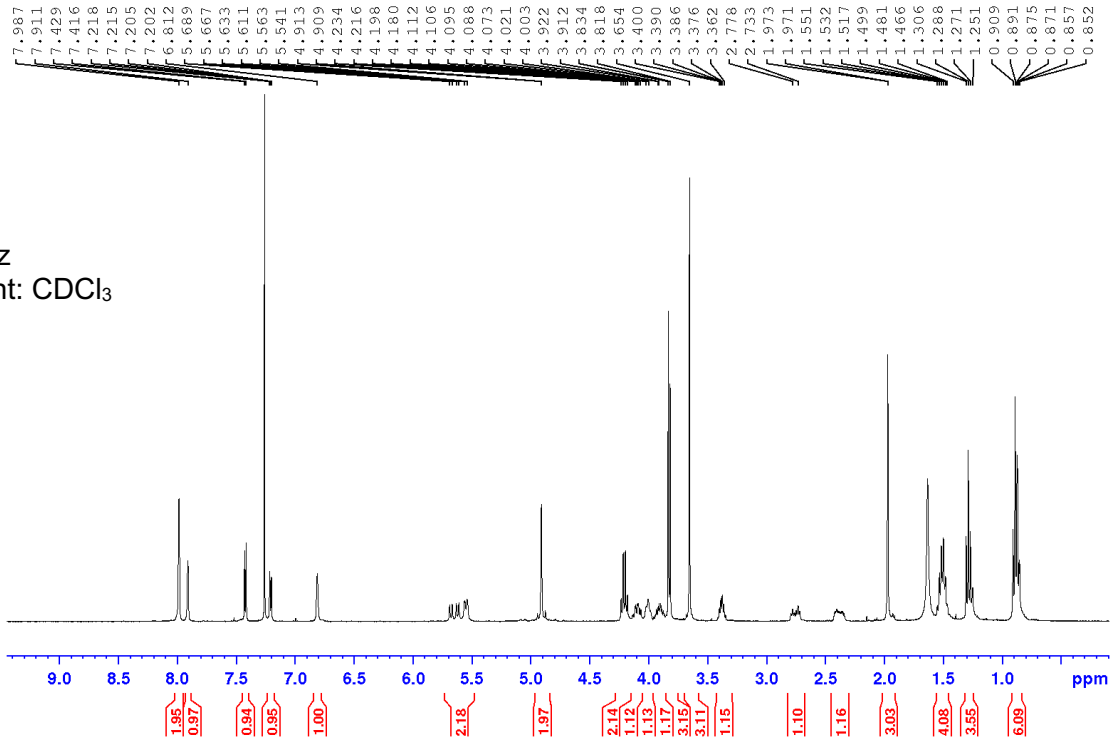


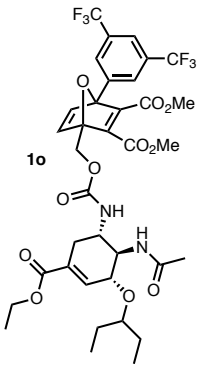


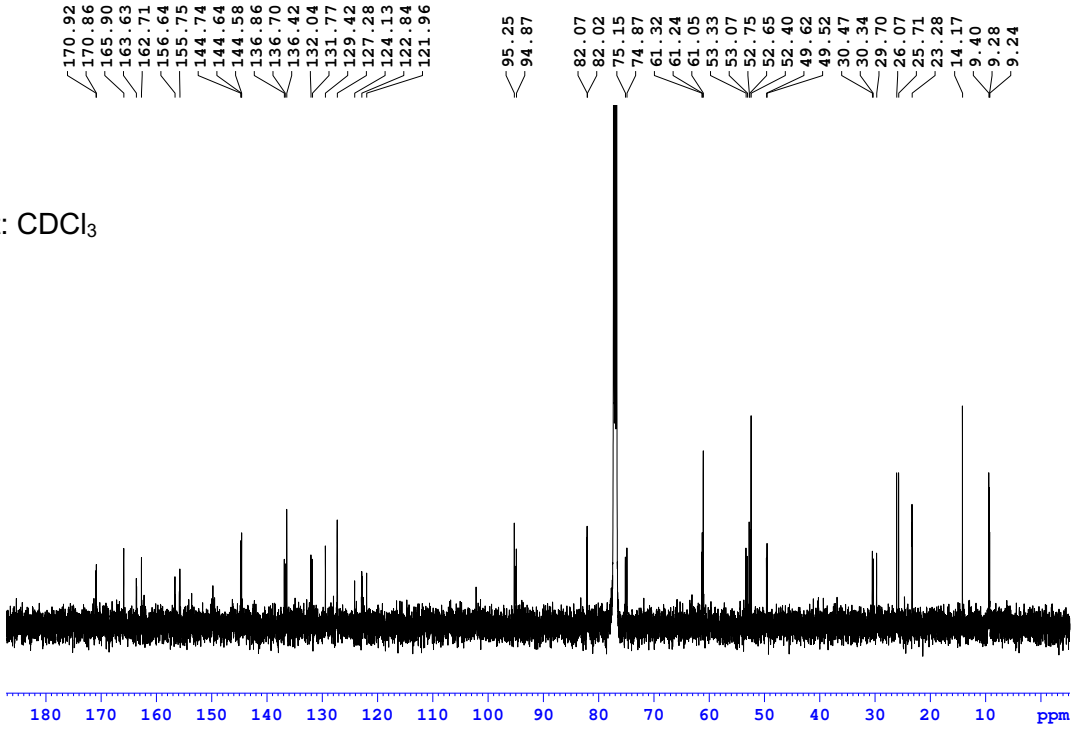
125 Hz
Solvent: $CDCl_3$



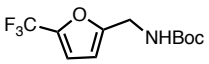
400 Hz
Solvent: $CDCl_3$



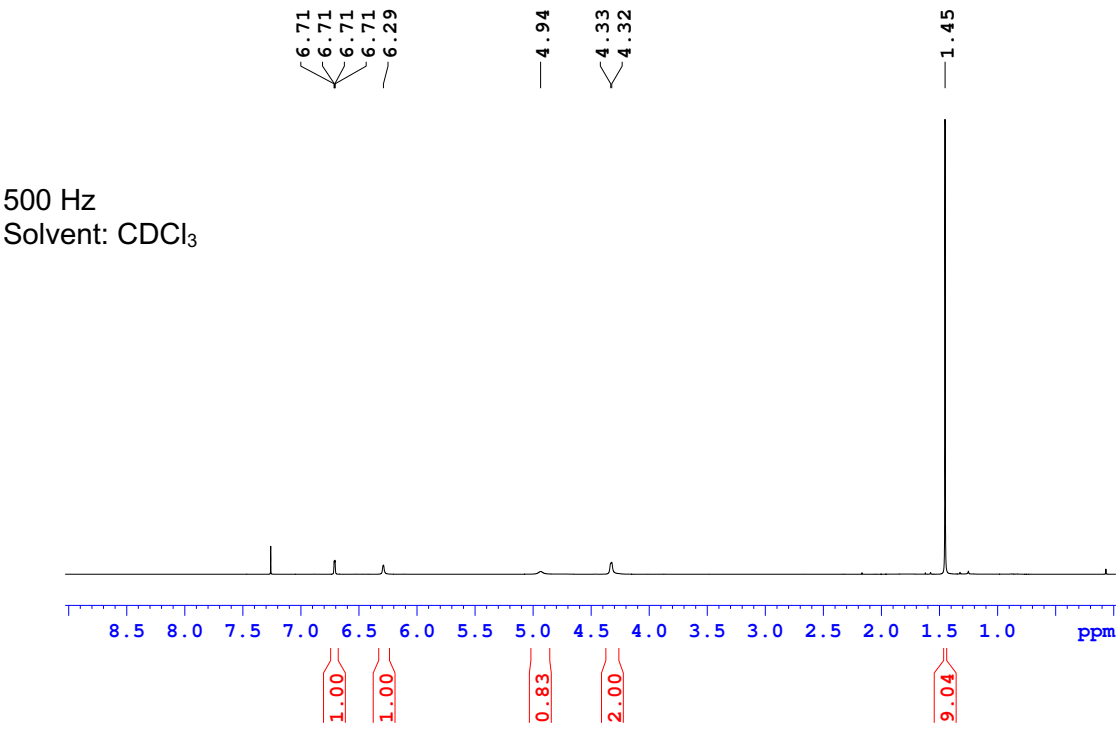


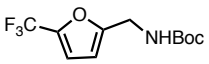


176 Hz
Solvent: $CDCl_3$

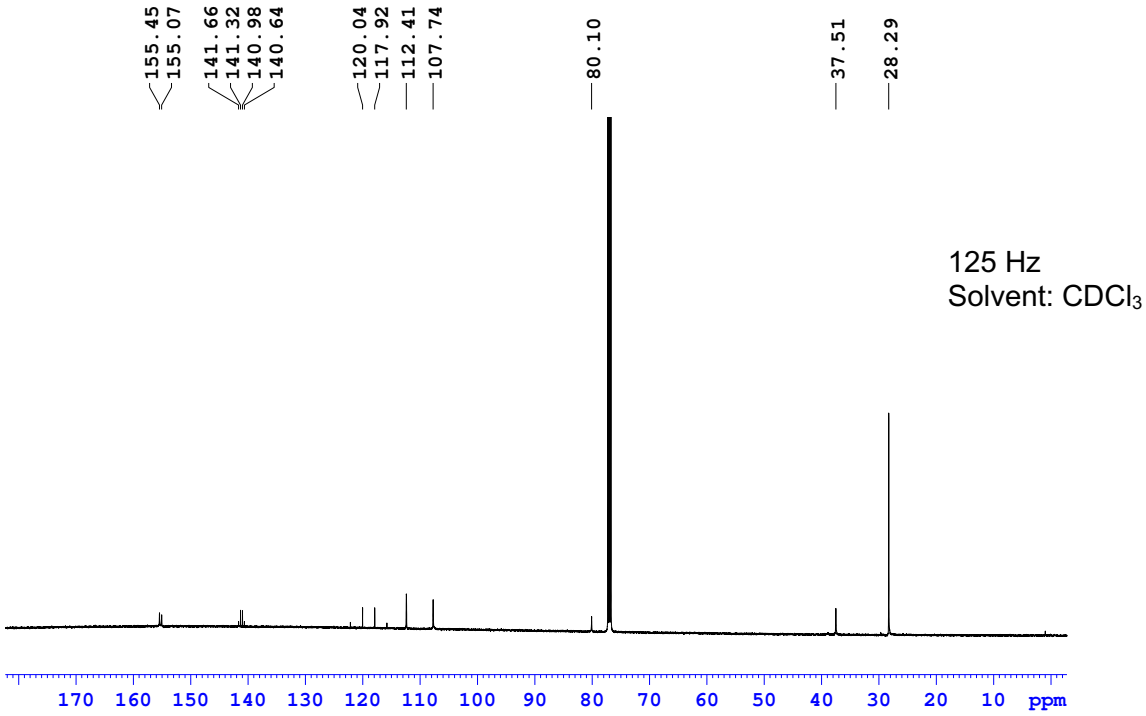

F3C
O
NHBoc

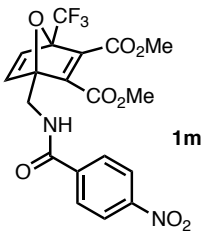
S35


6.71
6.71
6.71
6.71
6.29
4.94
4.33
4.32
1.45
500 Hz
Solvent: CDCl3
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 ppm
1.00
1.00
0.83
2.00
9.04


F3C
O
NHBoc

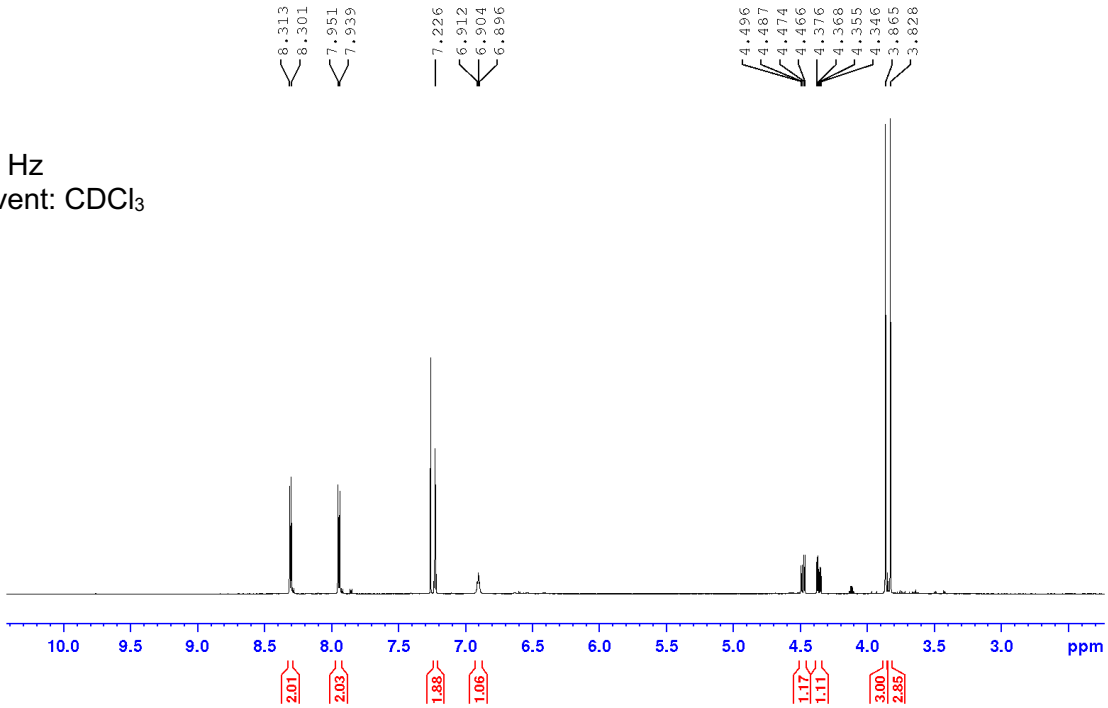
S35

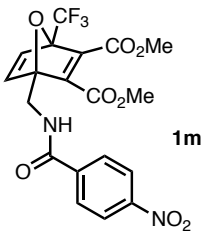

155.45
155.07
141.66
141.32
140.98
140.64
120.04
117.92
112.41
107.74
80.10
37.51
28.29
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



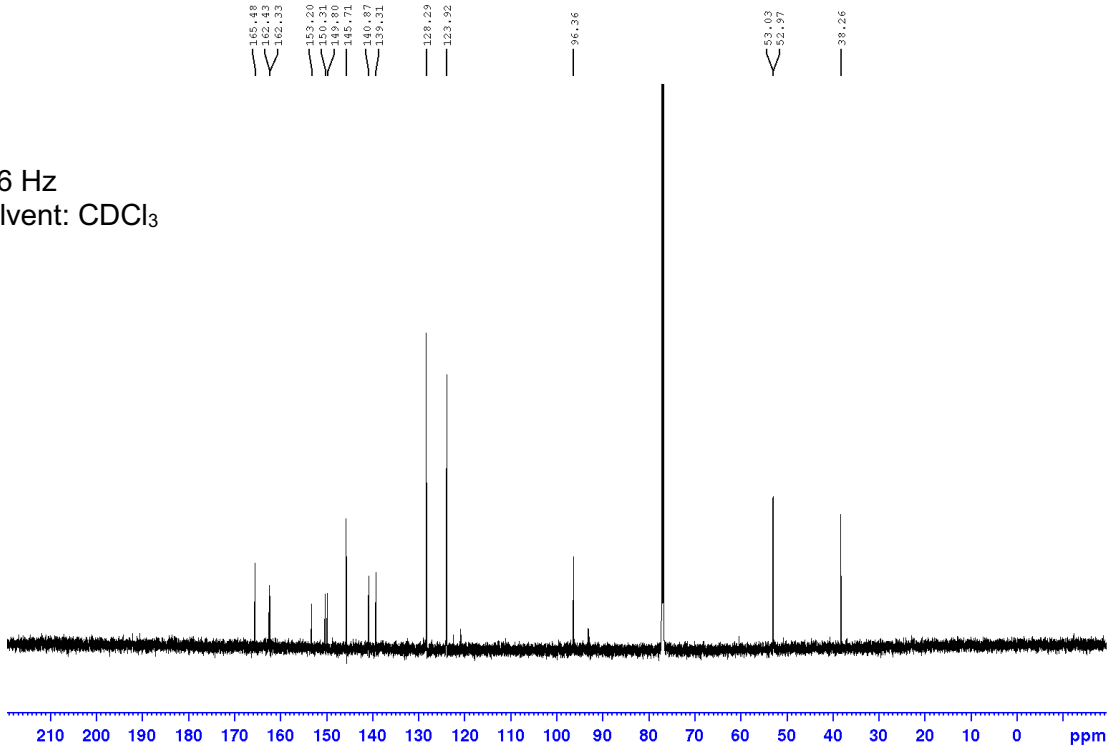
1m

700 Hz
Solvent: $CDCl_3$

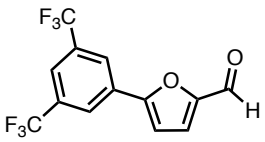




1m

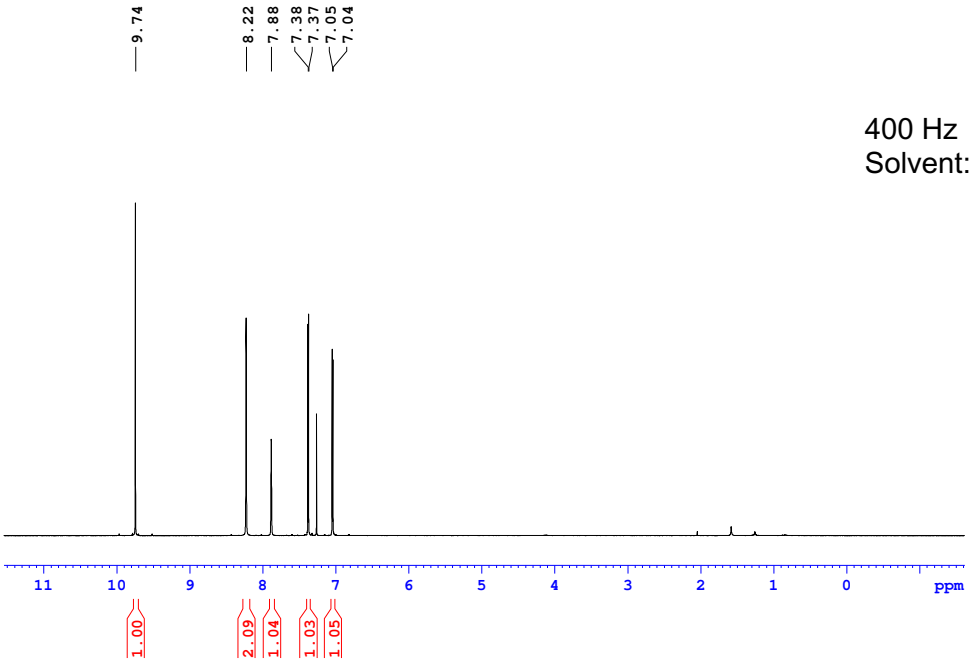


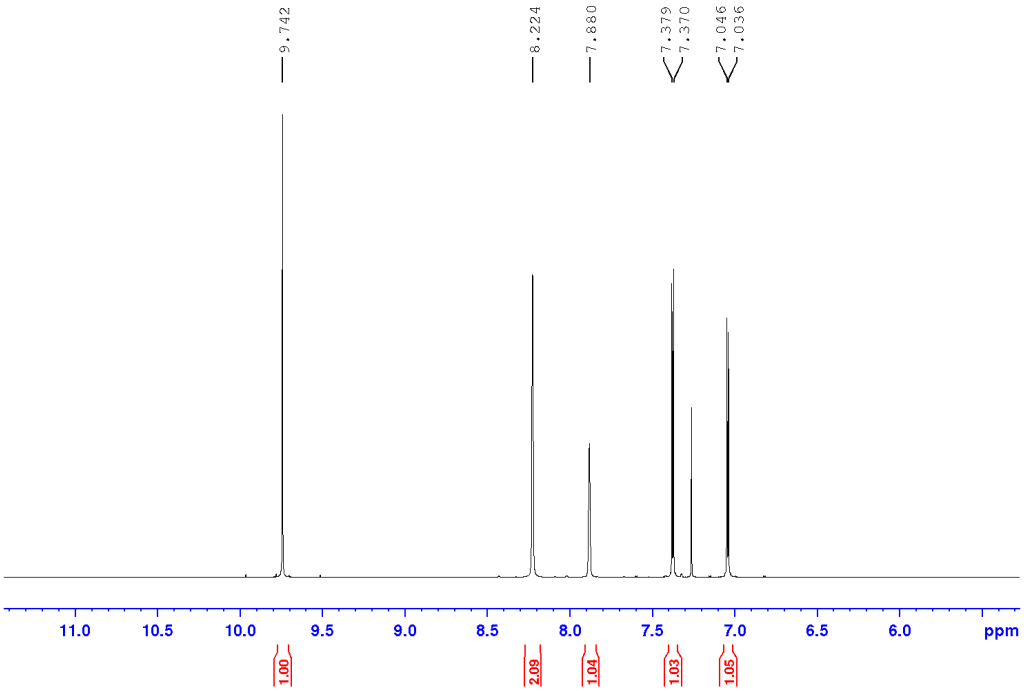
176 Hz
Solvent: $CDCl_3$

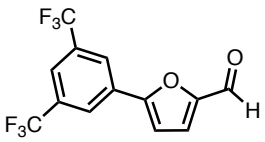


S37

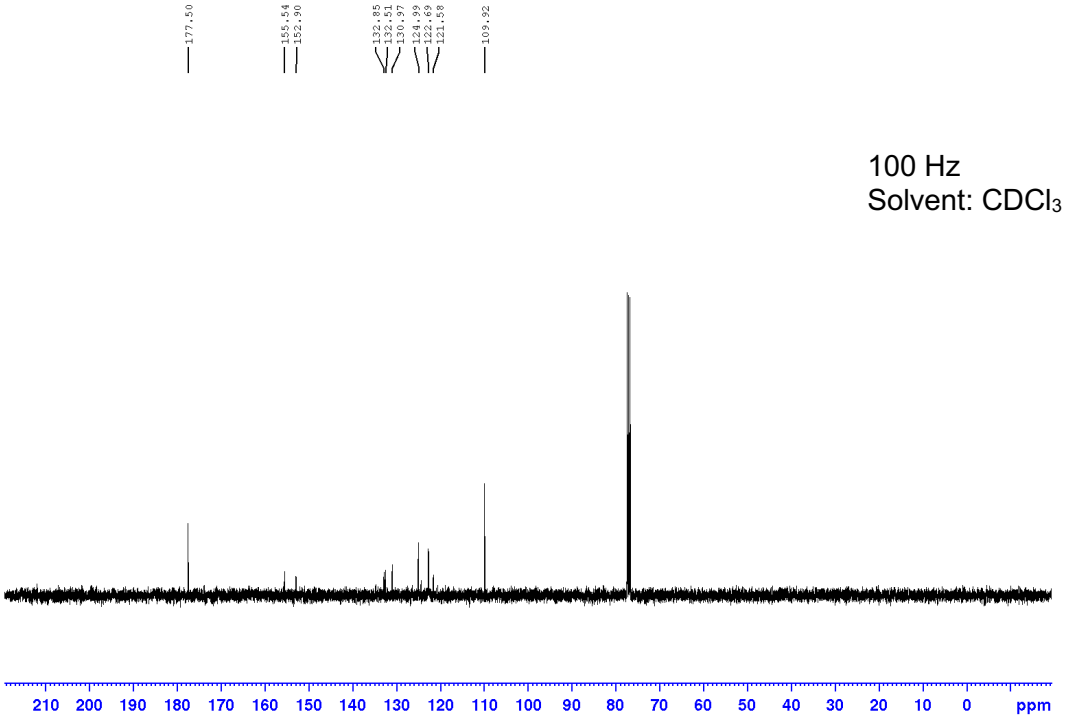
400 Hz
Solvent: $CDCl_3$

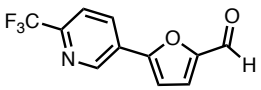




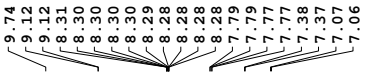

F3C
O
O
H
F3C

S37

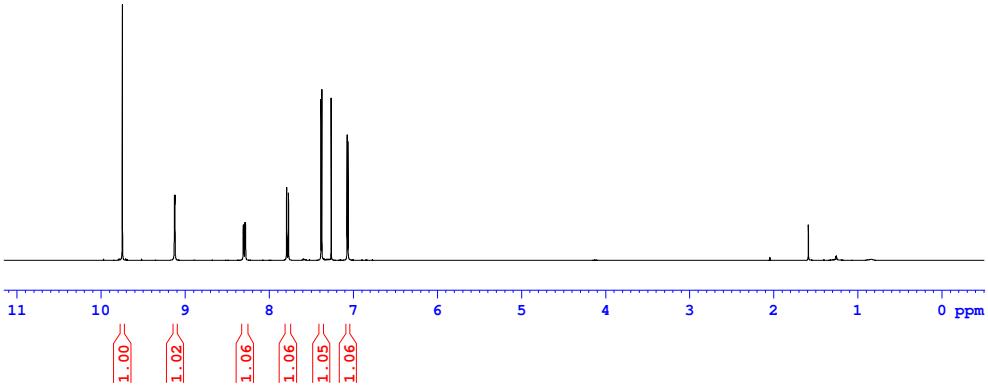

177.50
155.54
152.90
132.85
132.51
130.97
124.99
122.69
121.58
109.92
100 Hz
Solvent: CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

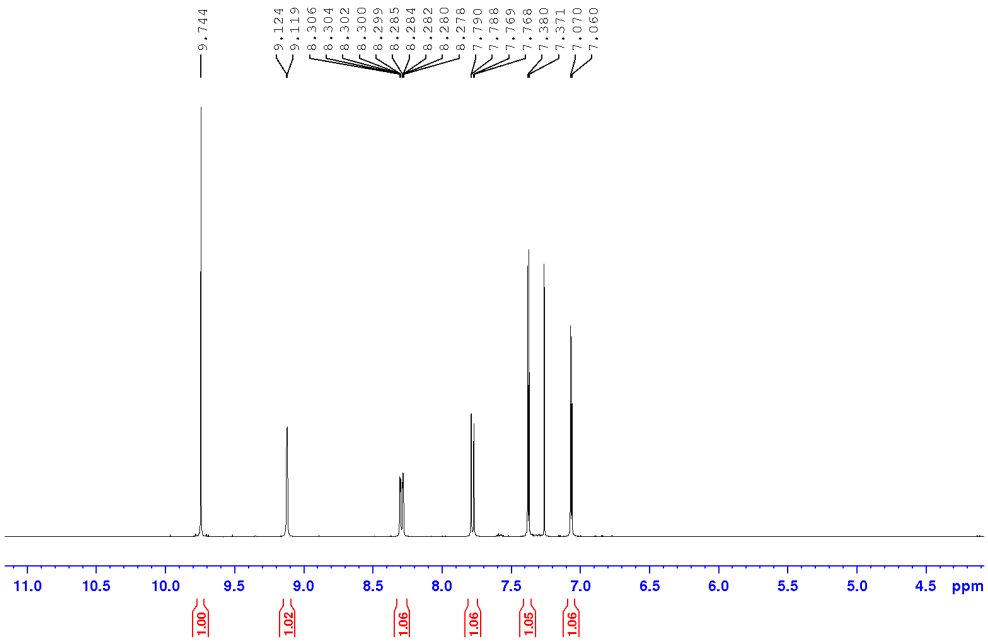


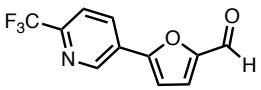
S38



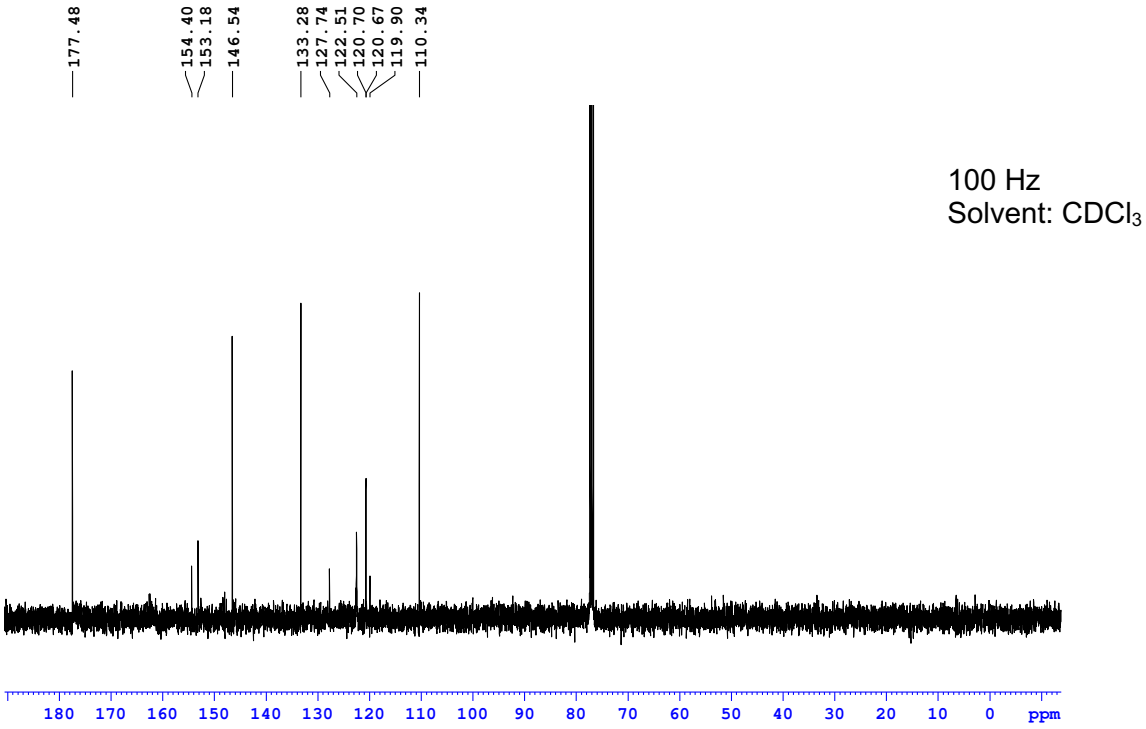
400 Hz
Solvent: $CDCl_3$

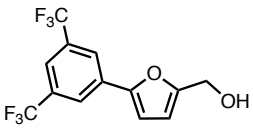




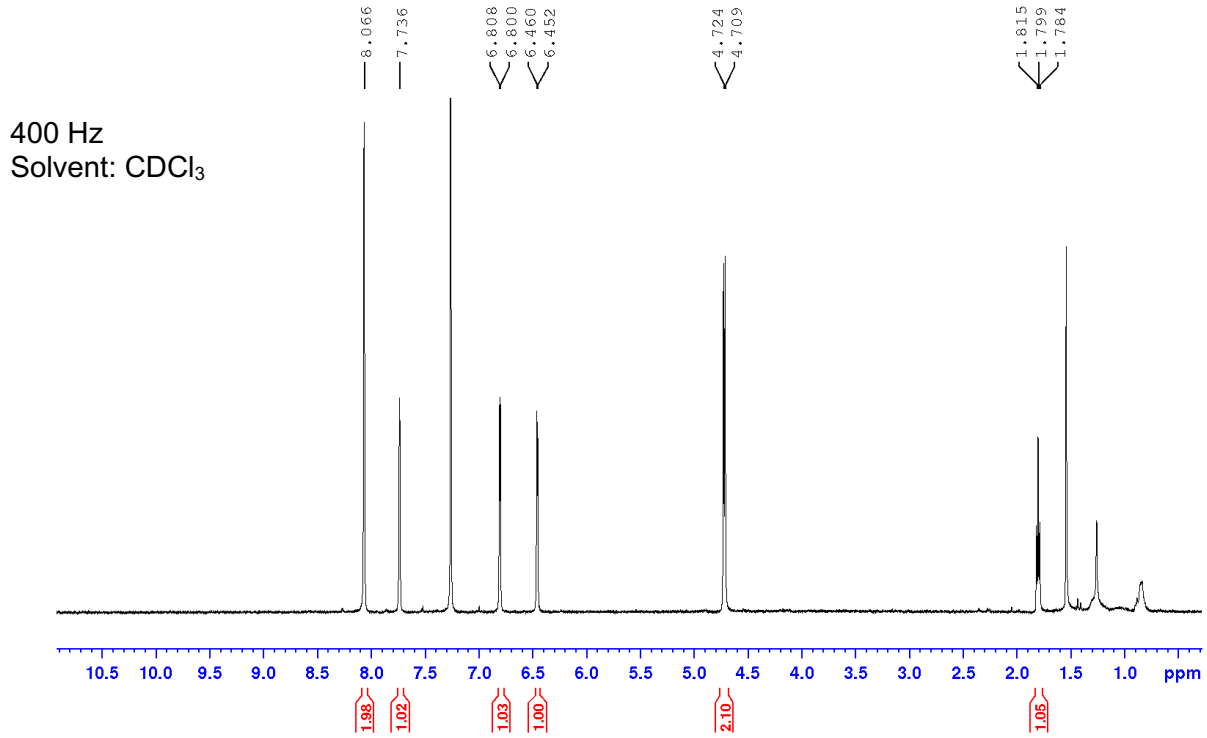

F3C
N
O
O
H

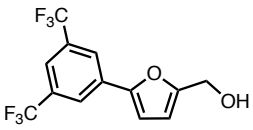
S38


177.48
154.40
153.18
146.54
133.28
127.74
122.51
120.70
120.67
119.90
110.34
100 Hz
Solvent: CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

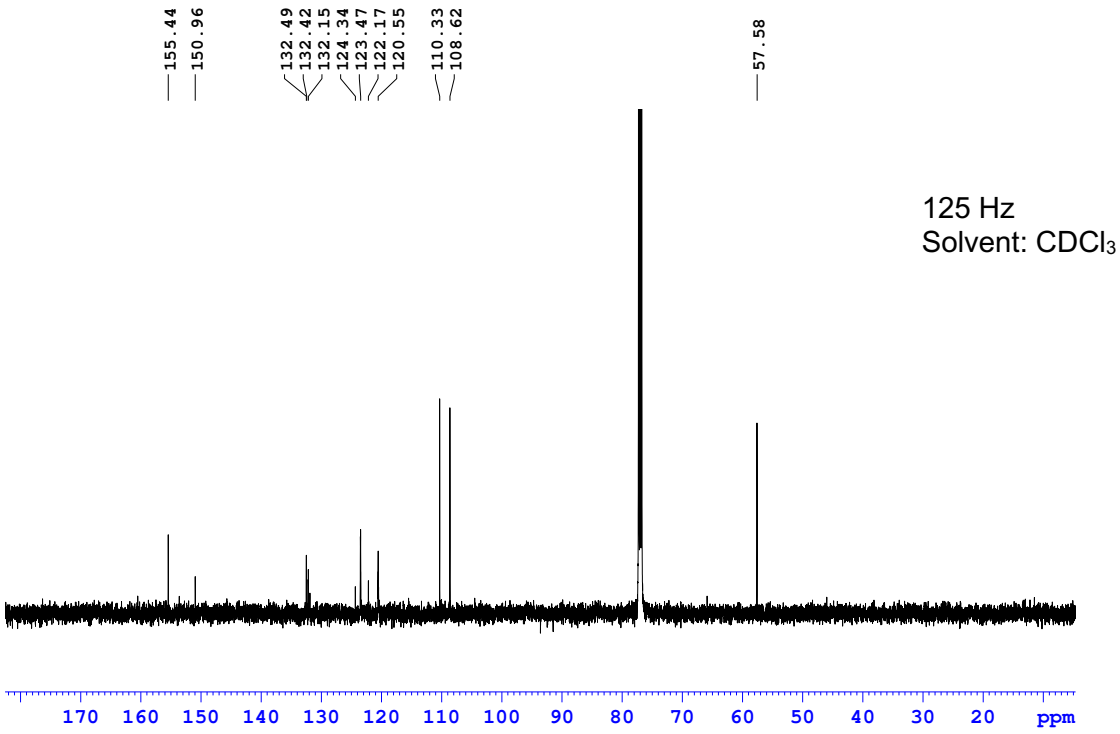

F3C
O
OH
F3C

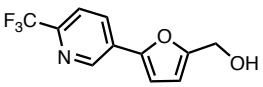
S39


8.066
7.736
6.808
6.800
6.460
6.452
4.724
4.709
1.815
1.799
1.784
400 Hz
Solvent: CDCl3
10.5 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 ppm
1.98
1.02
1.03
1.00
2.10
1.05

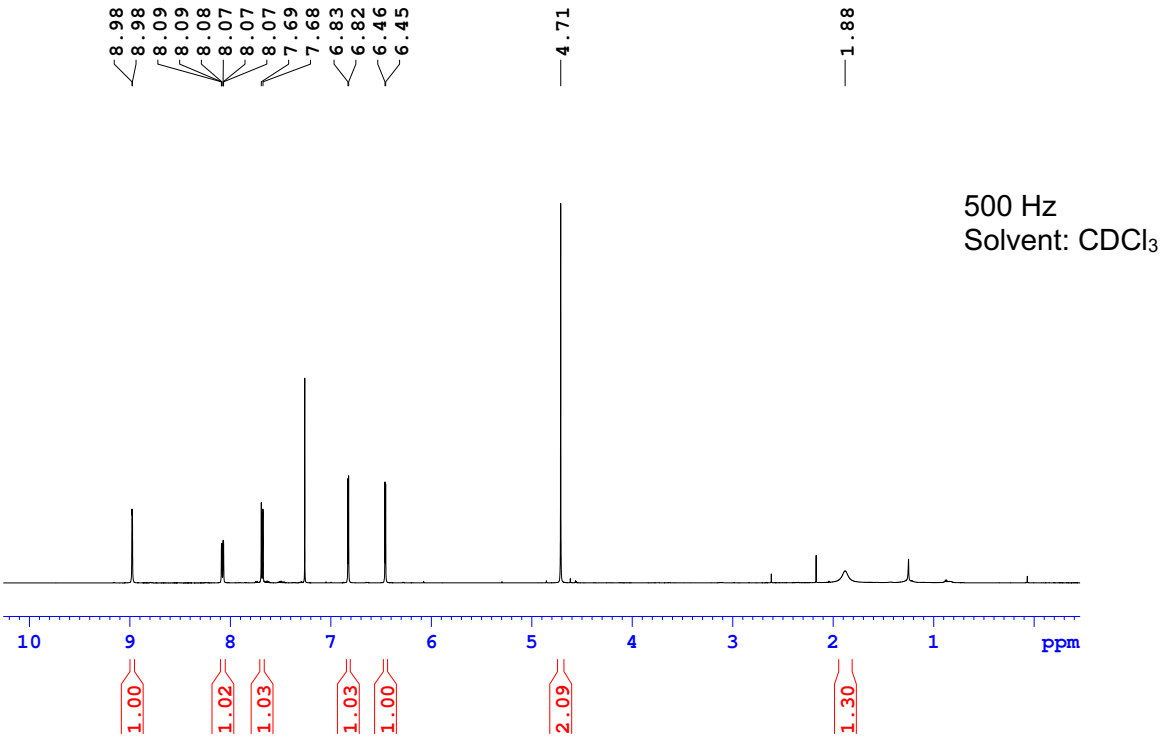

F3C
O
OH
F3C

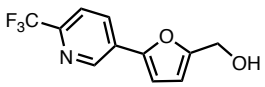
S39


155.44
150.96
132.49
132.42
132.15
124.34
123.47
122.17
120.55
110.33
108.62
57.58
125 Hz
Solvent: CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

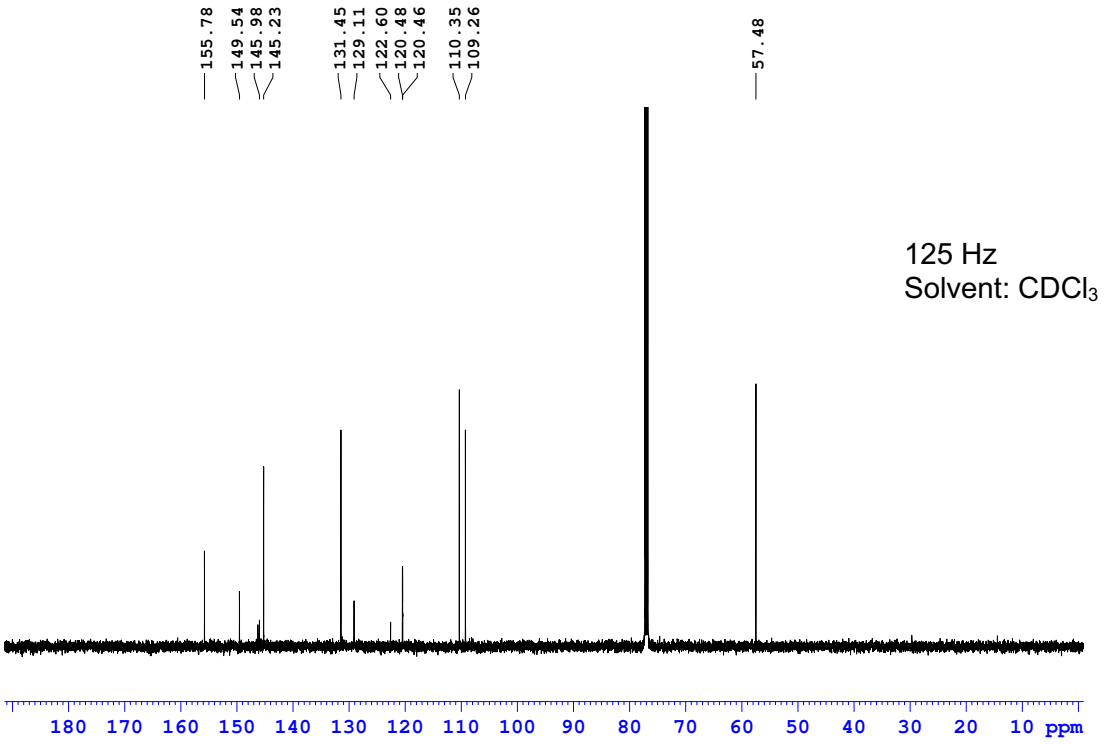

F3C
N
O
OH

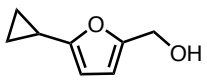
S40


8.98
8.98
8.09
8.09
8.08
8.07
8.07
8.07
7.69
7.68
6.83
6.82
6.46
6.45
4.71
1.88
500 Hz
Solvent: CDCl3
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.03
1.03
1.00
2.09
1.30

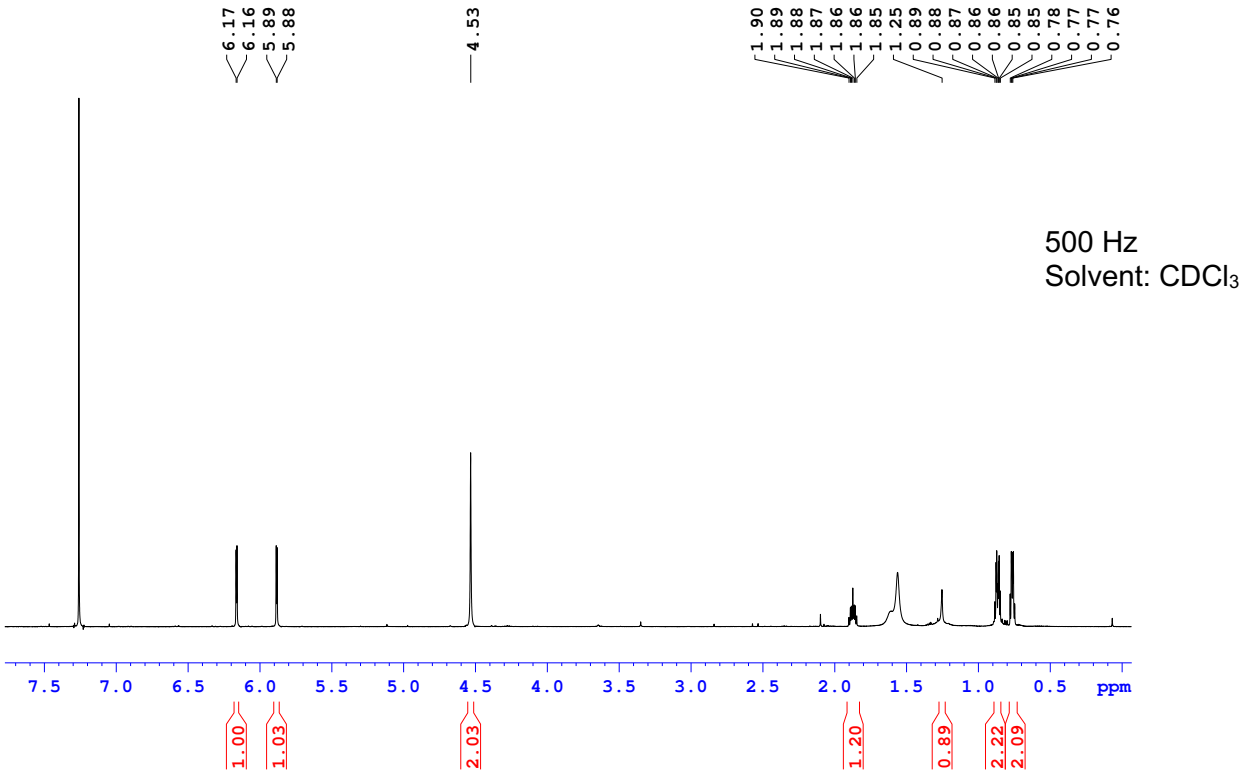

F3C
N
O
OH

S40

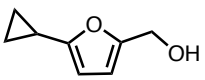

155.78
149.54
145.98
145.23
131.45
129.11
122.60
120.48
120.46
110.35
109.26
57.48
125 Hz
Solvent: CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



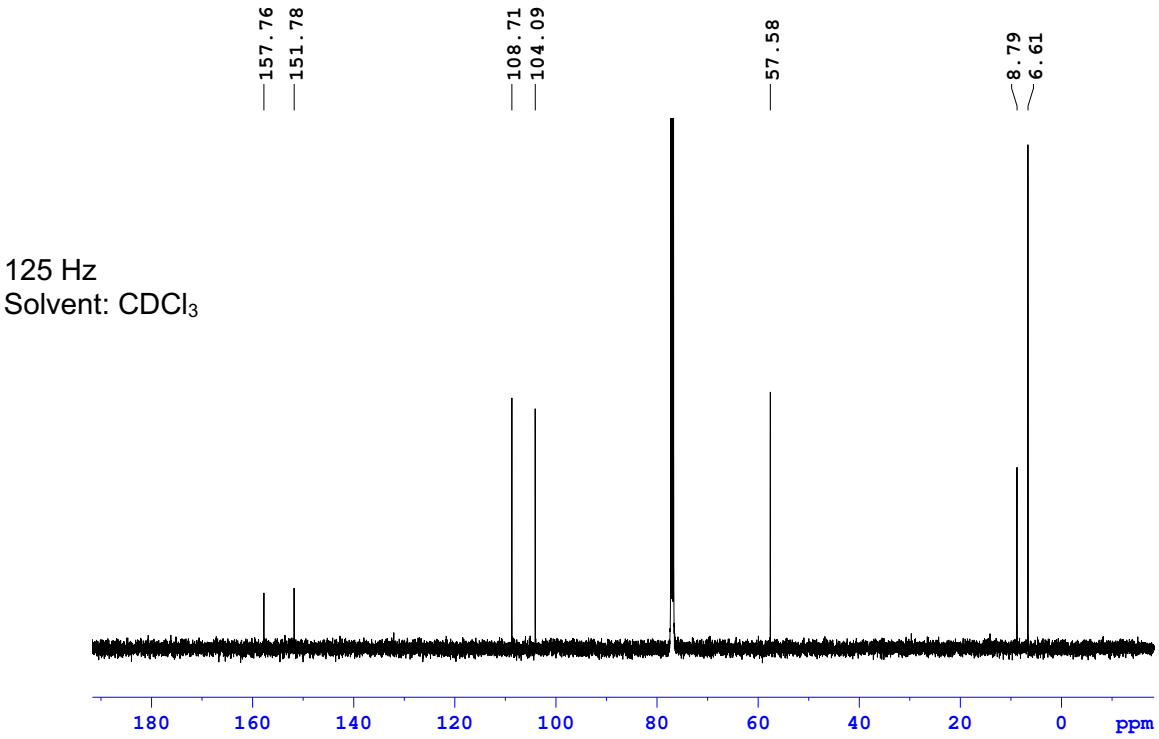
S41

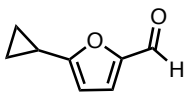


500 Hz
Solvent: $CDCl_3$


O
OH

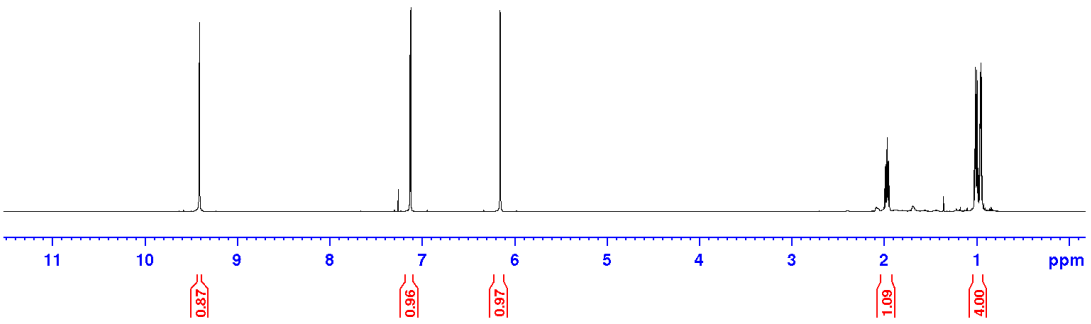
S41

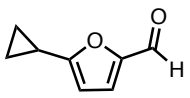

157.76
151.78
108.71
104.09
57.58
8.79
6.61
125 Hz
Solvent: CDCl3
180
160
140
120
100
80
60
40
20
0
ppm



S43

500 Hz
Solvent: $CDCl_3$





S43

125 Hz
Solvent: $CDCl_3$